

Review

Some Heteroaromatic Organomercurials, Their Syntheses and Reactions: A Review of Our Research (1980-2000)

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Abstract: This review reports some *novel* (or improved) synthetic methods for preparing a number of aromatic (carbocyclic and predominantly heterocyclic) organomercurials, particularly those derived from *theophylline*, *theobromine* and *uracil*, as well as some *novel* halo- and cyano-demercuration reactions. We have also synthesized the first *stable* organic derivative of mercury(I), viz. *1,8-bis(acetoxy-dimercurio)theobromine*, and studied its novel reactions. We have also improved the old Willgerodt method (1897), applicable for preparing various diaryliodonium chlorides from appropriate (dichloroiodo)arenes and *symmetric aromatic mercurials*. A full list of our works, published over the past twenty years (1980-2000), is also provided (see Refs. 1-16).

Keywords: heteroaromatic organomercurials, halo-demercuration reactions, cyano-demercuration reaction, heteroaromatic halides and nitriles

Contents

1. Introduction
2. Early Results: 8-Substituted Caffeine Mercurials and Their Demercuration Reactions
 - 2.1. Halo-demercuration Reactions of Caffeine Mercurials
 - 2.2. Cyano-demercuration Reaction of Caffeine Mercurials
 - 2.3. Unsuccessful Reactions with Caffeine Mercurials and Conclusions
3. "Model" Monosubstituted Benzene Mercurials and Their Demercuration Reactions
4. "Model" 2-Substituted Furan and Thiophene Mercurials and Their Demercuration Reactions
5. 6-Substituted 2,3-Diphenyl-5-methoxybenzo[b]furan Mercurials and Their Demercuration Reactions
6. 5-Substituted 1,3-Dimethyluracil and 1-Methyluracil Mercurials and Their Demercuration Reactions
7. 5-Substituted 2,4-Dimethoxypyrimidine Mercurials and Their Demercuration Reactions as well as an Indirect Method for Preparing 5-Halogeno-substituted Uracils
8. 5-Substituted Uracil Mercurials and Their Demercuration Reactions
9. 8-Substituted Theophylline Mercurials and Their Demercuration Reactions
10. 8-Substituted Theobromine Mercurials and Their Demercuration Reactions
11. Preparation of 1,8-*bis*(Acetoxymethyl)theobromine and Its Reactions
12. Further Studies on Some Heteroaromatic Mercurials
13. Final Results of Our Halo- and Cyano-demercuration Reactions
 - 13.1. Aromatic Iodides from Aromatic Organomercurials
 - 13.2. Aromatic Bromides from Aromatic Organomercurials
 - 13.3. Aromatic Chlorides from Aromatic Organomercurials
 - 13.4. Aromatic Fluorides from Aromatic Organomercurials
 - 13.5. Aromatic Nitriles from Aromatic Organomercurials
14. Improved Syntheses of Some Diaryliodonium Salts from Symmetric Diarylmercurials and (Dichloroiodo)arenes (Willgerodt's method)
15. Conclusions

1. Introduction

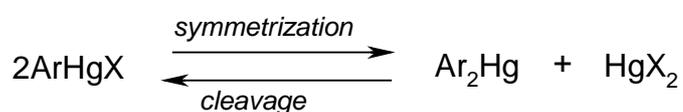
The first organomercury(II) compound (organomercurial) was reported by E. Frankland (1850), who synthesized *dimethylmercury*, Me_2Hg , by the action of methyl iodide on mercury metal under sunlight irradiation. The number of structurally diverse organomercurials that were later synthesized for pharmacological purposes is very large, but their role in chemotherapy has now been completely superseded and their applications as fungicides are also on the decline, owing to their *toxicity* towards human beings and animals. Nevertheless, numerous organomercurials have found increasing applications as useful *reagents* for the synthesis of many other organometallics via metal exchange reactions, and they are still attractive as *synthetic intermediates* which are usually readily available,

accommodate essentially all functional groups and possess remarkable thermal and chemical stability towards air, water, dilute acids and bases. These valuable features allow synthetic reactions employing organomercurials to be run under a wide variety of reaction conditions. The major disadvantage of these compounds is the **high toxicity** of more volatile mercurials. In fact, all heterocyclic (lactamic) organomercurials prepared by us during the course of our research (1980-2000) were nonvolatile and either slightly soluble or practically insoluble in common solvents, hence they were notably *less hazardous* than e.g. many aliphatic organomercurials. However, due to their very limited solubility in boiling common solvents, they often could not be purified satisfactorily or not be purified at all. This made it difficult (or even impossible) to analyze them reliably for the purpose of making proper structural assignments. Therefore, their possible structures were deduced from subsequent, well known and effective, chemical reactions (usually *iodo-demercuration* and/or *bromo-demercuration reactions*) followed by chemical and spectral analysis of the resulting products (i.e. monoiodo and/or monobromo derivatives of the parent aromatics), often also produced in the other known routes, for the sake of a better comparison.

There are a large number of different methods for preparing **unsymmetric aromatic** organomercurials, ArHgX, but the **direct mercuration** of aromatic systems is evidently the most simple of them and is thus very often used. Its proper and effective application strongly depends on: (i) the relative reactivity of the reacted aromatic system towards the *electrophilic* attack by a mercuric salt; (ii) the relative electrophilicity of the mercuric salt applied, e.g. $\text{HgCl}_2 < \text{Hg}(\text{OCOCH}_3)_2 < \text{Hg}(\text{OCOCF}_3)_2 < \text{Hg}(\text{ClO}_4)_2$; (iii) the applied reaction conditions: the use of a proper solvent, temperature and reaction time. This is an ordinary *electrophilic* aromatic substitution and takes place via the arenium ion mechanism to form the corresponding *unsymmetric* aromatic mercurials, e.g. $\text{ArHgCl} < \text{ArHgOCOCH}_3 < \text{ArHgOCOCF}_3 < \text{ArHgClO}_4$ (their relative reactivities towards the subsequent reactions with various *electrophilic* reagents being precisely in this order).

Although more or less effective depending on the particular case considered, several **symmetrization methods** are known to convert *unsymmetric* compounds ArHgX to the corresponding *symmetric* ones, Ar₂Hg (usually *more reactive* than ArHgX). It must be borne in mind that the following equilibrium should be displaced far to the right to cause effective symmetrization:

Scheme 1

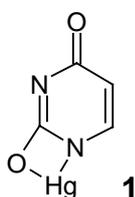


From a practical point of view, this may be attained either (i) by removal of the mercuric salt HgX₂ by *strong complexation* with e.g. sodium or potassium iodide, sodium thiosulfate, ammonia or EDTA, potassium cyanide, potassium thiocyanate, etc. or (ii) by *reduction* of HgX₂ with hydrazine, sodium stannite, by electrolysis, or otherwise. Consequently, there is no single general procedure applicable to effectively symmetrize the various types of ArHgX, as certain types of ArHgX compounds are symmetrized with great ease and give high yields of Ar₂Hg, while others are resistant to particular

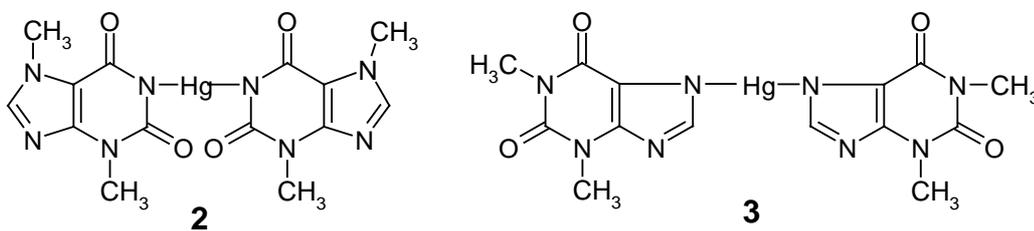
symmetrization agents, and the desirable Ar_2Hg can only be obtained by changes in the applied procedure(s).

In 1979, when we started our preliminary experiments in this area, the direct mercuriation with mercuric salts of some important "model" *lactamic* heterocycles, e.g. uracil, theobromine and theophylline, had not been previously reported in the literature. The attempted mercuriation reactions of these compounds at their C_5 or C_8 positions, respectively, resulted only in the formation of their *insoluble* N-Hg salts **1** - **3** (named also 1:1 or 1:2 mercuric "complexes"), which were precipitated out in full from the mercurating reaction mixtures – this impeded attempts to obtain their *true organomercurials*, i.e. their mercurated derivatives with the mercury atom joined to the organic residues via C_5 or C_8 carbon atoms.

Scheme 2



a 1:1Hg mercuric complex (N-Hg salt)



2:1Hg mercuric complexes (N-Hg salts)

In contrast, heterocycles devoid of any *acidic* N-H group(s), e.g. caffeine (see Section 2), 1,3-dimethyluracil (see Section 6), 2,4-dimethoxypyrimidine (see Section 7), or 2,3-diphenyl-5-methoxybenzo[b]furan (see Section 5) were readily mercurated directly to form the respective *unsymmetric* organomercurials, ArHgX , which were often *symmetrized* to form Ar_2Hg . Next, the mercurials of the two types were always *iodo-demercurated* and/or *bromo-demercurated* to form the corresponding iodides or bromides, ArI or ArBr , which after their purification were analyzed and studied by $^1\text{H-NMR}$ and other techniques to confirm the chemical structures of the starting mercurials.

Generally, it is known that mercury(II) ions, consistent with their pronounced electrophilic character, can effectively mercurate a large number of aromatics at their carbon atom(s) to form the corresponding *true organomercurials* if they are inherently devoid of any *acidic* S-H, O-H, N-H, Se-H, and sometimes P-H groupings. Otherwise, Hg(II) ions reveal a *greater tendency* to combine with those electronegative heteroatoms bearing lone pair(s) of electrons, forming thus some seemingly

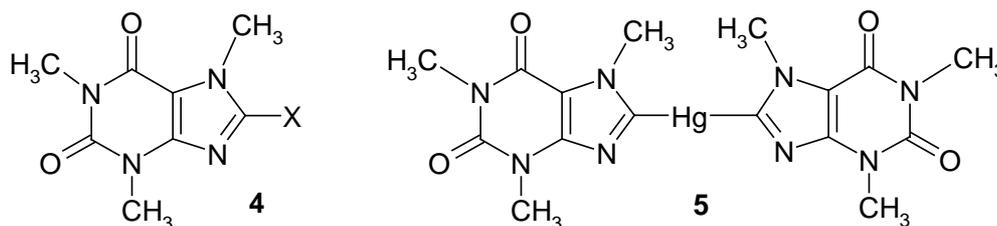
“mercurated”, sparingly soluble final products or intermediates – which are *not* true organomercurials, since the mercury atom therein is joined to the organic residue not via carbon atom but via the respective heteroatom. Those containing the O-Hg bond are the least stable. Compounds with the S-Hg linkage are formed very readily and exhibit particular stability. The strength of the N-Hg bond varies between wide limits, but in most cases it does not exceed that of the S-Hg bond. Organic compounds containing O-Hg, N-Hg, and sometimes even S-Hg bonds are often the first intermediates formed during the direct mercurations of oxygen-, nitrogen-, and some sulfur-containing compounds, and are transformed more or less readily into compounds mercurated at the carbon atom (true organomercurials), when this process is carried out under more vigorous conditions, e.g. at a higher temperature or at a lower pH. For example, thioanisole can be C-mercurated in 36.6% yield by means of $\text{Hg}(\text{OCOCH}_3)_2$ on a steam bath, giving thus 4-(acetoxymercurio)thioanisole; for more such examples see Ref. 23, p. 93.

During the course of our systematic, multi-year studies of various *aromatic* (carbo- and predominantly heterocyclic) true organomercurials and their reactions, we successfully synthesized *novel* organomercurials derived from *theobromine* and *theophylline* (Sections 9 and 10), *uracil* (Section 8), and also some other mercurials, though mostly in *indirect* routes. We also isolated (in ca 28% yield) the supposed-to-be *1,8-bis(acetoxymercurio)theobromine*, which seemingly represents the first *stable* organic derivative of **mercury(I)**, and we subsequently studied its chemical properties (Section 11). We also discovered several *novel halo-* and *cyano-demercuration* reactions; in our opinion, our novel fluoro-, chloro-, and cyano-demercuration reactions are particularly interesting and useful. We also extended, improved and better substantiated Willgerodt's old method (1897), which enables to synthesize diaryliodonium chlorides by reacting (dichloroiodo)arenes with *symmetric aromatic organomercurials*, in stirred hot aqueous suspensions (Section 14). For more information on our own *published* achievements [1-16] see the sections that follow.

2. Early Results: 8-Substituted Caffeine Mercurials and Their Demercuration Reactions [1, 2, 11 and 12]

Previously, Rosenthaler [43] had mercurated *caffeine* (**4a**) to afford *8-(acetoxymercurio)caffeine* (**4b**) in 90% crude yield, on boiling **4a** for 48 hours with an aq. $\text{Hg}(\text{OCOCH}_3)_2$ solution acidified with $\text{CH}_3\text{CO}_2\text{H}$. Next, he symmetrized **4b** with a boiling aq. KI solution for 30 minutes, to give *8,8'-mercuriobis(caffeine)* (**5**) in 50% crude yield; he did not carry out any further reactions with **4b** and **5**. In our laboratory, we improved the above synthesis of **4b**, by adding a few drops of conc. aq. HClO_4 , a recommended catalyst [23, 24, 26-28], to the mercurating reaction mixture, which shortened considerably the mercuration time to only four hours, while preserving the same 90% crude yield; we also established that the mercurating solutions may be prepared *in situ* by dissolving the freshly prepared yellow HgO in hot aq. $\text{CH}_3\text{CO}_2\text{H}$.

Scheme 3



X = H (**a**); HgOCOCH₃ (**b**); I (**c**); Br (**d**); Cl (**e**); F (**f**); CN (**g**).

We also improved the crude yield of the symmetrization of **4b** from 50% to 83% by using a hot (ca. 90°C) aqueous Na₂S₂O₃ solution, instead of aq. KI. We also *metathesized* **4b** into sparingly soluble 8-(chloromercurio)caffeine (83% crude yield) by adding excess aq. NaCl solution to a boiling solution of **4b** in water [1, 11]. On heating with an aq. Na₂S solution, the black precipitate of HgS conclusively proved the presence of mercury in the three aforementioned caffeine mercurials; their chemical structures were confirmed by their ¹H-NMR solution spectra as compared with that of caffeine [1, 11], as well as by subsequent *halo-* and *cyano-demercuration reactions* discussed below (see also Ref. 11).

Finally, it should be recalled that our many attempts to synthesize either 8-(trichloroacetoxymercurio)caffeine or the *more thermostable* 8-(chloromercurio)caffeine by a one-pot method suitable for preparing the *thermostable* phenylmercury(II) chloride were without success: the latter benzene mercurial was obtained in 70% yield when yellow HgO and CCl₃CO₂H were stirred in thiophene-free benzene for ca one hour at 65-70°C; for the explanation see Ref. 11 as well as Section 3.

2.1. Halo-demercuration Reactions of Caffeine Mercurials [1, 2, 11 and 12]

Gomberg [44] had reported the failure to iodinate *caffeine* (**4a**) with diiodine in chloroform; later on, 8-iodocaffeine (**4c**) was obtained in ca 40% yield by heating *caffeine* (**4a**) with diiodine in a sealed tube at 150°C [45]. In our laboratory, at first we *iodo-demercurated* caffeine mercurials **4b** and **5** by applying a widely used procedure [17, 23-28]; on heating these mercurials with hot (80°C) aq. KI₃ solutions for 30 minutes, we obtained **4c** in the same 95% yield (after purification) from the both substrates **4b** and **5** [1, 2]. Similarly, the sparingly soluble 8-(chloromercurio)caffeine (**4**, X = HgCl) was iodo-demercurated to give pure **4c** in 65% yield [11]. The same pure **4c** was also obtained by us [1, 2] in 90% yield from the both substrates **4b** and **5**, by heating them with a hot (80°C) aq. solution of the freshly sublimated ICN [**Caution:** ICN is highly toxic]; in fact, it is an effective, though less convenient and *unsafe*, iodo-demercuration method.

Previously, *caffeine* (**4a**) was directly brominated to give 8-bromocaffeine (**4d**) in high yields [45, 46]. In our laboratory, the two mercurials **4b** and **5** were effectively *bromo-demercurated*, by applying the widely-used procedure [17, 23-28]; the reactions took place in hot (80°C) aq. KBr₃ solutions

previously adjusted to pH 7, for 30 minutes, to give **4d** (purified) in the same 83% yields from the both substrates **4b** and **5**. We also bromo-demercurated **4b** and **5** (at 60°C, for 2 hours) with an aq. slurry of a labile complex (or adduct) of unknown composition, $(\text{KBr}\cdot\text{BrCN})_x$ [**Caution:** highly toxic], obtained by adding Br_2 to a cooled saturated aq. KCN solution [47]; this gave compound **4d** (purified) in 85% yields from the both substrates **4b** and **5**. In fact, this represents an effective, albeit less convenient and *unsafe, novel bromo-demercuration method*.

The direct chlorination of *caffeine* (**4a**) to *8-chlorocaffeine* (**4e**) had been reported as early as 1850; fairly high yields of **4e** (ca 80%) were later reported in the literature [45, 48]. In our laboratory, we obtained the purified compound **4e** in 27-90% yields, but only from the *more reactive* symmetric mercurial **5** [mercurial **4b** did *not* react under the same reaction conditions]. At first, we reacted **5** with *neat liquid* S_2Cl_2 or SCl_2 at room temperature for 4 hours to afford **4e** in 80% or 70% yields, respectively; though the yield of the latter reaction with SCl_2 was lower, nevertheless the crude **4e** thus obtained was easier to purify. When mercurial **5** was similarly suspended in *neat boiling* SO_2Cl_2 for 2 hours, then compound **4e** (after its isolation and purification) was obtained in only 27% yield. These *novel chloro-demercuration methods* were later on also applied by us to other mercurials (Section 13.3). Finally, we must admit that we *failed* to obtain compound **4e** upon passing gaseous Cl_2 through solutions or suspensions of mercurials **4b** or **5** in water, aq. KCl solutions, formamide, dimethyl sulfoxide, benzene, etc. The same was true for the action of chlorine *in statu nascendi* (generated in reaction: $6\text{HCl} + 2\text{KClO}_3 \rightarrow 6\text{Cl} + 2\text{KCl} + 3\text{H}_2\text{O}$) upon **4b** or **5** in aqueous media. For some more reactive organomercurials these chloro-demercuration reactions were successful [17, 23, 24, 26, 28]; see also Section 3.

8-Fluorocaffeine (**4f**) was not reported in the literature before 1981/1982 [1, 2]; until then very few organomercurials have been fluoro-demercurated, but only with difluorine diluted with nitrogen gas [26]. In our laboratory, we suspended the *more reactive* mercurial **5** [mercurial **4b** did *not* react under the same reaction conditions] in liquefied, *neat* SF_4 (b.p. -40.4°C . **Caution:** highly toxic) at -70°C (solid CO_2 + acetone) *for 16 hours*. After evaporating SF_4 , crude **4f** was purified to give 30% yield (after 8 hours only 15%); an increase in the reaction temperature (in an autoclave) considerably diminished the given yield. This *novel* and interesting *fluoro-demercuration reaction* was later on applied in our laboratory to other *symmetric* mercurials; see Ref. 12, where we summarized and commented *all our fluoro-demercuration experiments*; see also Section 13.4.

2.2. Cyano-demercuration Reaction of Caffeine Mercurials [1, 2]

Previously, *8-bromocaffeine* (**4d**) in the presence of KCN in 80% ethanol yielded *caffeine-8-carboxamide*, which by treatment with POCl_3 yielded *8-cyanocaffeine* (**4g**) [45, 49]; it is worth mentioning that ICN, when reacted at 110°C with dimethylmercury, yielded mercuric iodide and methyl isocyanide [50]. In our laboratory, we reacted the *more reactive*, symmetric mercurial **5** with freshly purified BrCN [**Caution:** highly toxic] *in water*, at 60°C for 2 hours (at higher temperatures some decomposition of **5** was observed, whereas at 40°C the reaction did *not* proceed); after purification of the crude product, we obtained pure **4g** in 50% yield; the same reaction with

unsymmetric mercurial **4b** gave pure compound **4g** in only 25% yield. It was surprising that by using aq. KBr solutions instead of pure water for dissolving BrCN, the same compound **4g** was obtained, instead of the expected **4d** (*vide supra*). By using aq. KCN solutions instead of water for dissolving BrCN, the yield of this *cyano-demercuration reaction* was evidently lowered. We applied this interesting but *unsafe* reaction also for *more reactive* “model” benzene mercurials (see Section 3). It should be noted that when we reacted **4b** or **5**, under widely varied conditions, with (CN)₂ or ClCN solutions, we failed to obtain compound **4g**; the latter reagent *decomposed* vigorously both **4b** and **5** in their solutions or suspensions.

2.3. Unsuccessful Reactions with Caffeine Mercurials and Conclusions [1, 2]

The preparative demercuration methods discussed above show the usefulness of organomercurials in organic synthesis. There are, however, *noticeable differences* in the reactivity of the various organomercurials. It has been mentioned several times in the literature [23-28, 34] that Ar₂Hg compounds are usually *more reactive* as compared with ArHgX. It is seen that *unsymmetric* mercurial **4b** does *not* react with S₂Cl₂, SCl₂, SO₂Cl₂, and SF₄ under the same experimental conditions as does *symmetric* **5**. The cyano-demercuration reaction of symmetric mercurial **5** furnished twice as much of **4g** as compared with unsymmetric mercurial **4b**. Only the iodo- and bromo-demercuration reactions furnished *the same yields* of **4c** and **4d** from both **4b** and **5**. We have also established experimentally that both **4b** and **5** *did not* undergo several well-known demercuration reactions [23-28, 34] with HNO₃, (CN)₂, (SCN)₂, Cl₂ or chlorine *in statu nascendi*, SOCl₂, and aryldiazonium cations, which were successful with some other, more reactive, organomercurials. Thus, it seems to us that both the caffeine mercurials **4b** and **5** are noticeably *less reactive* in a number of demercuration reactions as compared with some corresponding organomercurials, ArHgX or Ar₂Hg, in which Ar represent e.g. *o*-nitrophenyl, thienyl or furyl moieties [23-28, 34]; cf. particularly our results presented in Sections 3 and 4.

3. “Model” Monosubstituted Benzene Mercurials and Their Demercuration Reactions [7, 11 and 12]

A survey of methods applied so far for the *halo-demercuration* of various organomercurials [17, 24-28, 34] reveals that dihalogens do decompose them in two stages: (1) R₂Hg + X₂ → RHgX + RX, followed (with an excess of halogens) by (2) RHgX + X₂ → R-X + HgX₂; it has been pointed out [23] that *symmetric* R₂Hg react *more readily* than RHgX. In 1870 Dreher and Otto [51] reacted cold solutions of *diphenylmercury*, Ph₂Hg (in ethanol or better in CS₂), with equimolar amounts of I₂ or Br₂, and they obtained the respective halogenomercurio- or halogeno-benzenes, whereas with an excess of the halogens the former were changed into the respective halogenobenzenes and mercuric salts (with necessary heating).

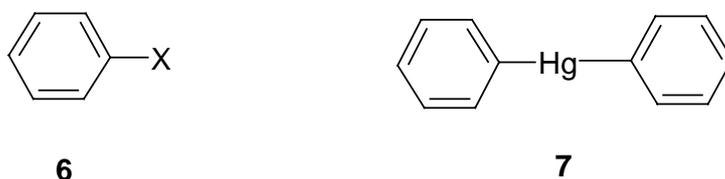
Dry dichlorine gives a vigorous reaction with Ph₂Hg yielding PhHgCl, PhCl and HgCl₂; when Cl₂ is bubbled through a hot aq. suspension of Ph₂Hg or (better) through its hot solution in CS₂, at first

PhHgCl, and then more and more PhCl and HgCl₂ are obtained. The German authors [51] have also remarked that PhHgCl seems to be *less reactive* towards the action of Cl₂ than the corresponding PhHgBr and PhHgI towards the action of Br₂ and I₂. A concentrated solution of hypochlorous acid acts like free Cl₂, forming PhHgCl and PhCl from Ph₂Hg. An aqueous solution of PhHgOCOCH₃ heated with an excess of I₂ gives PhI, HgI₂ and CH₃CO₂H [51].

Later on, the iodo- and the bromo-demercuration reactions have vastly been *improved* [24-28, 34, 52], e.g. by using KI₃ or KBr₃ solutions, mostly aqueous (cf. Ref. 2), but also with a wide variety of solvents, e.g. alcohols, acetonitrile, DMF, DMSO, pyridine, dioxane or their mixtures with water. Even *permercurated* arenes are readily cleaved in this way [52] by NaI₃ in DMF at room temperature for 3-14 days, by KBr₃ aq. methanolic solutions at room temperature for 1 – 24 hours, or by Cl₂ in DMF at room temperature for 3-8 hours, giving thus the respective periodo-, perbromo-, and perchloro-arenes in good yields. It is also necessary to recall that on a prolonged heating Ph₂Hg with TeCl₂, mercuric telluride and PhCl are formed unexpectedly [23, 53]. Iodine monochloride reacts according to the reactions: R₂Hg + 2ICl → 2RI + HgCl₂ and RHgX + ICl → RI + HgXCl [23, 28]; the same diiodocamphor is obtained when mercurated camphor reacts with I₂ or with ICl or with IBr in benzene [17]. **ICN** acts preferably as a *iodo-demercuration agent*, whereas **BrCN** may act *both* as a *bromo-demercuration agent* as well as a *cyano-demercuration agent* depending on the reaction conditions (*vide infra*, as well as Section 2.2). ClCN has been reported to give *no reaction* at all with some organomercurials [17]; cf. however Section 2.2.

It is of interest to mention that ICN and Me₂Hg in ethereal solution give MeCN at 50°C, and HgI₂ and methyl isonitrile at 110°C [17, 23, 50]. It has also been reported [23] that **BrCN** does *not* cleave the C-Hg bond, but only replaces e.g. the acetoxy group by bromine in α-acetoxymercurio-β-methoxy-β-phenylethane. Pseudohalogenes, X₂ = (CNS)₂ and (CN)₂, do react with some *symmetric* organomercurials, R₂Hg, giving the respective RX and RHgX compounds; we failed, however, to replace mercury atoms in the *less reactive* caffeine mercurials on acting upon them with (CNS)₂ and (CN)₂ (see Ref. 2 as well as Section 2.3). The reaction with ClN₃ undergoes similarly, viz. R₂Hg + ClN₃ → RHgN₃ + RCl, and it was applied as well with Ph₂Hg (R = C₆H₅) [17, 24-28, 34].

Scheme 4



X = HgOCOCH₃ (**a**); HgOCOCF₃ (**b**); HgOCOCCl₃ (**c**);
 HgCl (**d**); I (**e**); Br (**f**); Cl (**g**); F (**h**); CN (**i**).

In our next paper of the series [7], we reported the application of several halo- and cyano-demercuration procedures to the *more reactive* “model” benzene mercurials **6a**, **6b** and **7**; cf. our

results discussed in Section 2. Thus, *diphenylmercury*, Ph_2Hg (**7**), dissolved in ethanol smoothly gave only PhI (**6e**) in 72% yield (purified product) on adding pure **ICN** and then refluxing the mixture for 3 hours. On refluxing for 3 hours a mixture of **7** with pure **BrCN** in *benzene*, only PhCN (**6i**) was produced in 86% yield – whereas when **7** was refluxed for 3 hours in an ethanolic solution containing $(\text{BrCN}\cdot\text{KBr})_x$, a complex of unknown structure [47], only PhBr (**6f**) was formed in 79% yield. The reaction of **7** with **ClCN**, carried out under widely-varied experimental conditions, gave some *composite* mixtures, which were not subjected to closer study.

By reacting **7** with large excesses of neat liquid either S_2Cl_2 or SO_2Cl_2 [SCl_2 was not studied], and leaving overnight at room temperature, we obtained pure PhCl (**6g**) in 78% or 47% yields, respectively. The former reaction was also carried out at first at -10°C , and next it was left overnight at room temperature: we obtained PhCl (**6g**) in 35% yield together with 30% of isolated PhHgCl (which throws some light on its mechanism). The second reaction was considerably accelerated by a Friedel-Craft catalyst, viz. AlCl_3 . Both the symmetric mercurial **7** as well as the two unsymmetric ones, **6a** and **6b**, *did react* with an excess of neat S_2Cl_2 (under the same experimental conditions) to afford PhCl (**6g**) in 78%, 50% and 69% yields, respectively; previously (Section 2), it was supposed that this *new chloro-demercuration procedure* was characteristic only of the symmetric organomercurials.

The *novel fluoro-demercuration* procedure, applicable only for the *symmetric* organomercurial **7**, was reported in our other paper [12]; cf. also Section 2.1. On reacting **7** with a large excess of neat liquid SF_4 , for 8 hours at $-(60-70^\circ\text{C})$, it was possible to obtain PhF (**6h**; purified product) in 58% yield; its structure was confirmed by microanalyses and its $^1\text{H-NMR}$ spectrum. In this publication we made the following remark (footnote on p. 26): “The calculated yields [for ArF] correspond to “ideal” reactions: $\text{Ar}_2\text{Hg} + \text{SF}_4 \rightarrow \text{HgF}_2 + 2\text{ArF}$ (soluble in organic solvents; often volatile), whereas the “real” reactions probably are *terminated* either in full or in part at the *intermediate stage* yielding $\text{ArF} + \text{ArHgF}$ (sparingly soluble in organic solvents; nonvolatile). Since the aim of our investigation [12] was to obtain the possible highest yields of ArF , therefore we did *not* scrutinize the nonextractable residues composed of mercuric salts heavily contaminated by some sulfur-containing side-products and, probably, by the *less-reactive* (under the given low-temperature conditions) fluoromercurials, ArHgF .” In fact, all our fluoro-demercuration procedures, applicable only for Ar_2Hg mercurials, resulted in *moderate* yields for the purified ArF , viz. 28-58% [12].

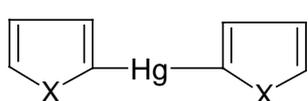
In our next work [11] we attempted to mercurate *benzene* and caffeine by means of *mercury(II) trichloroacetate*; and we submitted therein a *detailed review* of the prior attempts to prepare this *thermally unstable* mercuric salt. We have come to the conclusion that it is reasonable to prepare this mercuric salt *in situ* to obtain appropriate mercurating reaction mixtures. When we suspended yellow HgO in thiophene-free benzene containing $\text{Cl}_3\text{CCO}_2\text{H}$ (a 1:1 molar proportion of $\text{Cl}_3\text{CCO}_2\text{H}$ to HgO seems to be optimal) and the reaction mixture thus obtained was heated for ca one hour at $65-70^\circ\text{C}$, then we unexpectedly isolated PhHgCl (**6d**) in 70% yield (purified product), *instead of* the thermolabile mercurial **6c**. This method was quite unsuitable for the mercuration of less reactive caffeine. Next, mercurial **6d** was readily *iodo-demercurated* to give **6e** (purified product) in 59% yield, with a hot (80°C) aq. KI_3 solution, for 30 minutes.

4. "Model" 2-Substituted Furan and Thiophene Mercurials and Their Demercuration Reactions [5]

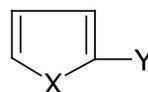
In order to extend the scope of the aforementioned (Sections 2 and 3) *novel chloro-demercuration procedure* [the action of neat, liquid S_2Cl_2 on mostly *symmetric* organomercurials, yielding effectively the corresponding chloro derivatives, $ArCl$; see however Section 3], we first synthesized (by the known methods) *2,2'-difurylmercury* (**8**) and *2,2'-dithienylmercury* (**9**) (Scheme 5).

We had expected in advance that they would be *more reactive* than those symmetric organomercurials discussed in Sections 2 and 3. However, in our attempted chloro-demercuration reactions we had to use only *freshly-redistilled* S_2Cl_2 to remove the accompanying SCl_2 ; the latter is known [54] to equilibrate as follows: $2SCl_2 \rightleftharpoons S_2Cl_2 + Cl_2$, which is very inconvenient due to the known high sensitivity of furan and thiophene towards the action of free dichlorine; see also our paper [5] where various chlorinating procedures applicable for furan and thiophene were briefly reviewed, with the relevant references.

Scheme 5



X = O (**8**);
X = S (**9**);



X = O, Y = Cl (**10a**); I (**10b**);
X = S, Y = Cl (**11a**); I (**11b**);

At first, we reacted solid finely-powdered mercurials **8** or **9** as well as 2-(chloromercurio)furan or 2-(chloromercurio)thiophene with an excess, as previously (see Sections 2 and 3), of *neat* liquid S_2Cl_2 with *no solvent*, over a wide temperature range from $-70^\circ C$ up to room temperature. Even at $-70^\circ C$ the reactions were *extremely vigorous* and could hardly be controlled. Colorless oils, in nearly quantitative yields, were isolated from the reaction mixtures, which were composite mixtures of several highly chlorinated compounds, in part also of open-ring structures, with only small admixtures of 2-monochloro and 2,5-dichloro derivatives of furan or thiophene, respectively. After several attempts we achieved a proper and effective method of *chloro-demercuration* mercurials **8** and **9**, but only using *carbon disulfide* as an *inert diluent* – the reactions were completed after two days either at room temperature with *more reactive* **8** or, with *less reactive* **9**, on boiling under a reflux condenser; with still *less reactive* 2-(chloromercurio)furan or 2-(chloromercurio)thiophene the reactions did *not* proceed under the same experimental conditions. From the reaction mixtures we isolated either pure 2-chlorofuran (**10a**) in 60% yield or pure 2-chlorothiophene (**11a**) in 70% yield, with *no trace* of higher-boiling 2,5-dichlorinated admixtures. Later on, we *considerably simplified* the syntheses of compounds **10a** and **11a** just by mixing together pure furan or thiophene with $HgCl_2$ previously dissolved in an excess of the freshly-redistilled S_2Cl_2 , followed by keeping the mixtures overnight at room temperature. Most likely, the reactions proceeded via some 2-mercurio intermediates, since no 2-chloro derivatives were formed in the *absence* of $HgCl_2$. From the reaction mixtures we isolated pure compounds **10a** or **11a** in 50% or 60% yields, respectively; see Ref. 5 for experimental details.

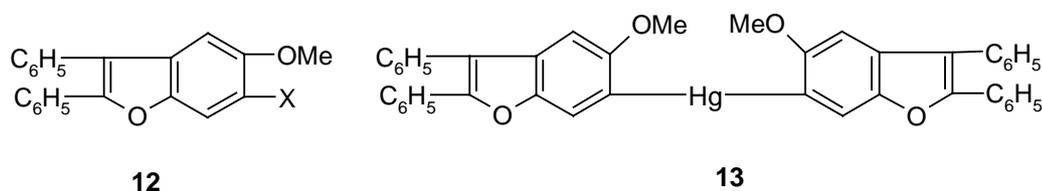
The various methods for the *direct iodination* of furan and thiophene (and also other heterocycles) were very extensively reviewed in Ref. 55; they were also briefly reviewed in our paper [5]. We reacted *symmetric* mercurials **8** and **9** with the well-known [23, 26, 28, 34] iodo-demercuration agent, viz. an aq. KI₃ solution, for 30 minutes at 80°C, which gave pure **10b** or **11b** in 60% or 65% yields, respectively. These yields are considerably *higher* than those previously reported, when the same iodo-demercuration method was applied with either 2-(chloromercurio)furan (32% yield was reported [56]) or 2-(chloromercurio)thiophene (a low yield was reported [57]). Our *iodo-demercuration* reactions confirmed the structures of the starting mercurials **8** and **9** as well as their *higher reactivities* as compared with the respective 2-chloromercurio derivatives.

In our paper [5] we offered the following *general remark* (footnote on p. 445): “It is rather a common procedure that after completing several direct mercuriation reactions with more electrophilic (than HgCl₂) mercuric acetate or trifluoroacetate, the *less soluble*, but least reactive, *chloromercurio derivatives* are precipitated out with aq. NaCl or CaCl₂ solutions, in order to increase the *isolated yields* of desirable mercurials. In our opinion, it is often more advantageous to collect the respective *symmetric mercurials* (usually less soluble as well), which may be obtained by *subsequent addition* – if possible – of symmetrizing agents (e.g. KI, Na₂S₂O₃, etc.) directly to the said reaction mixtures, and then to complete the symmetrization reaction in order to obtain the resulting, *more reactive* Ar-Hg-Ar compounds”. In fact, we applied this approach *in practice* in our works [6] and [9]; see Sections 7 and 8 for details.

5. 6-Substituted 2,3-Diphenyl-5-methoxybenzo[b]furan Mercurials and Their Demercuration Reactions [10]

Egyptian chemists [58] had synthesized a number of derivatives of heterocyclic compound **12a**, and later they studied their biological activities. They established that in various reactions obeying the S_E-type mechanism, the respective derivatives of **12a** were predominantly substituted at its C₆ carbon atom. However, bromination of **12a** with Br₂ in CCl₄ gave the 4,6-dibromo derivative of **12a**. In cooperation with the Egyptian chemists we decided to synthesize in our laboratory the two mercurials **12b** and **13** (Scheme 6), and then study their bromo- and iodo-demercuration reactions.

Scheme 6



X = H (a); HgOCOCH₃ (b); I (c); Br (d).

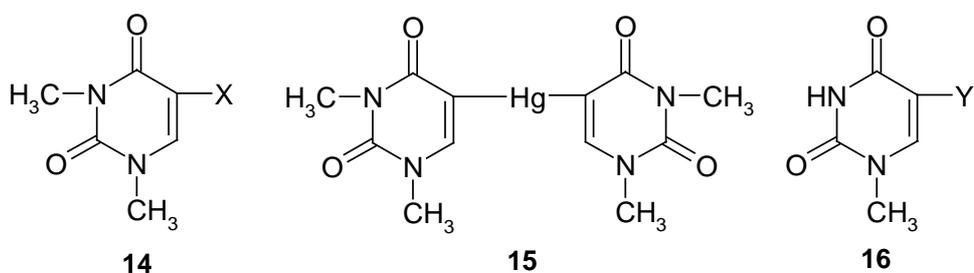
The *direct mercuration* of **12a** with $\text{Hg}(\text{OCOCH}_3)_2$ in boiling ethanol, for 2 hours, gave *unsymmetric* mercurial **12b** in ca 70% crude yield, which next was readily symmetrized by a hot (90°C) $\text{KI}/\text{EtOH}/\text{H}_2\text{O}$ solution, for 2 hours, to afford *symmetric* mercurial **13** in 60% crude yield. Further proof of the structures of **12b** and **13** was given by their routine bromo- and iodo-demercuration reactions, carried out for ca 30 minutes in hot (80°C) aq. KBr_3 or KI_3 solutions, respectively. These two reactions furnished the respective 6-bromo or 6-iodo derivatives of **12a**, i.e. pure compounds **12c** and **12d**, in 70% yield, the same for the two mercurials **12b** and **13**, and the same for the two different reactions.

The above syntheses of the mercurials **12b** and **13** may open up an easy way for preparing many other 6-substituted derivatives of **12a** (e.g. **12**, $\text{X} = \text{F}, \text{Cl}, \text{CN}$) by the well-checked by us demercuration procedures explained in Sections 2-4, or otherwise. It would also be possible to prepare readily from **12b** and/or **13** many metallo- and metalloido-organic derivatives of compound **12a**, by using known [23, 26, 28, 34] methods applicable for ArHgX and/or Ar_2Hg mercurials.

6. 5-Substituted 1,3-Dimethyluracil and 1-Methyluracil Mercurials and Their Demercuration Reactions [6, 8 and 12]

Uracil [pyrimidine-2,4(1*H*,3*H*)-dione] cannot be directly C-mercurated, since it forms at once a sparingly soluble 1:1 mercury complex (N-Hg salt; formula **1** in Section 1) [59] (see however Ref. 60, which will be discussed in Section 8). Contrariwise, *1,3-dimethyluracil* (**14a**, Scheme 7) can be readily directly C-mercurated in its 5-position.

Scheme 7



$\text{X} = \text{H}$ (a); HgOCOCH_3 (b); HgCl (c); $\text{Y} = \text{H}$ (a); HgOCOCH_3 (b); Br (c)
 I (d); Br (e); Cl (f); F (g)

We applied routine [23, 24, 26, 28, 34] mercurating procedures by reacting **14a** either with a boiling aq. $\text{Hg}(\text{OCOCH}_3)_2$ solution containing $\text{CH}_3\text{CO}_2\text{H}$, for 4 hours (which gave pure mercurial **14b** in 52% yield), or with a boiling buffered $\text{C}_2\text{H}_5\text{OH}/\text{H}_2\text{O}$ solution of HgCl_2 , for 4 hours, which gave pure mercurial **14c** in 64% yield. The same compound **14c** was also obtained in 45% yield on adding NaCl to a hot aq. solution of **14b**. Subsequently, we prepared *symmetric* pure mercurial **15** by reacting **14b** with a hot boiling aq. KI solution, for 0.5 hour, in 89% yield, after recrystallization from water.

Subsequently, continuing our previous studies related in Sections 2 - 4, we carried out the following chemical experiments on *halo-demercuration* of the 1,3- dimethyluracil mercurials **14b** and/or **15**, viz.

- i) on reacting **14b** or **15** with hot aq. KI₃ solutions, we obtained known pure *5-iodo-1,3-dimethyluracil* (**14d**) in 88% or 83% yields, respectively;
- ii) on reacting **14b** or **15** with hot (80°C) aq. KBr₃ solutions (adjusted in advance to pH = 7), we obtained known pure *5-bromo-1,3-dimethyluracil* (**14e**) in the same 82% yield;
- iii) on reacting only dry **15** with a large excess of pure liquid S₂Cl₂, we obtained known pure *5-chloro-1,3-dimethyluracil* (**14f**) in 74% yield;
- iv) on reacting only dry **15** with a large excess of neat liquefied SF₄ for 48 hours at -(60-70°C), and following workup explained in Ref. 12, pure compound **14g** was produced in 30.3% yield [12].

So far, there is no easy method of removing N-methyl group(s) from the uracil ring system. Therefore, there is (so far) no easy way of transforming compounds **14d-g**, into the respective non-methylated analogues. See however Section 7, where such the demethylation was possible for 5-substituted 2,4-dimethoxypyrimidines.

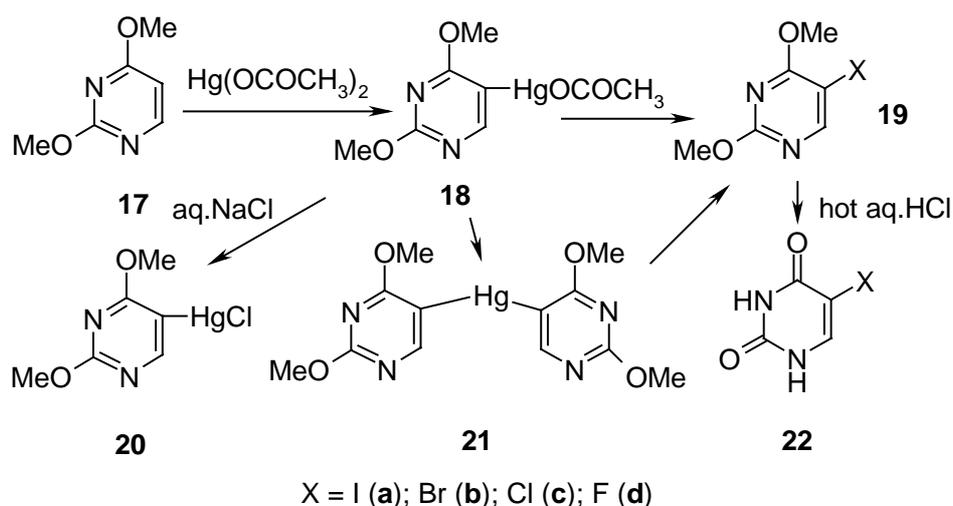
Uracil has two N-H groups, which differ chemically and otherwise, e.g. at 25°C [61]: pK_a (1-N-H) = 9.43; pK'_a (3-N-H) ca. 13.2 (*estimate*). In order to check whether or not the 1-N-H group alone must be blocked to accomplish a successful direct mercuration in position 5, we synthesized *1-methyluracil* (**16a**), and we subsequently carried out its routine mercuration with a boiling, slightly acidified with CH₃CO₂H, aq. Hg(OCOCH₃)₂ solution, for 3.5 hours, which resulted in the formation of mercurial **16b** (purified) in 49% yield; by its bromo-demercuration, similarly to that of **14b**, we obtained *5-bromo-1-methyluracil* (purified) in 78% yield. In fact, also other 1-N-substituted uracils, e.g. uridine [62] and 2'-deoxyuridine [63] were readily mercurated in their positions 5 with buffered aq. Hg(OCOCH₃)₂ solutions.

7. 5-Substituted 2,4-Dimethoxypyrimidine Mercurials and Their Demercuration Reactions as well as an Indirect Method for Preparing 5-Halogeno-substituted Uracils [6, 9 and 12]

2,4-Dimethoxypyrimidine (**17**, Scheme 8) was readily mercurated with a boiling aq. Hg(OCOCH₃)₂ solution acidified with CH₃CO₂H, for 2 hours, and this *hot solution containing 18* was applied at once in subsequent reactions (*vide infra*) [only a small isolated sample of **18** was recrystallized from ethanol, and its ¹H-NMR spectrum was run for identification purposes].

By adding an aq. NaCl solution to the aforementioned hot solution containing **18**, the *metathesized, insoluble* mercurial **20** was precipitated out and collected to give 48% crude yield (Scheme 8). By adding dropwise a nearly saturated aq. KI solution to the afore-said hot solution containing **18**, and refluxing for 0.5 hour, the *symmetrized* mercurial **21** (recrystallized from water) was isolated in 79% yield.

Scheme 8



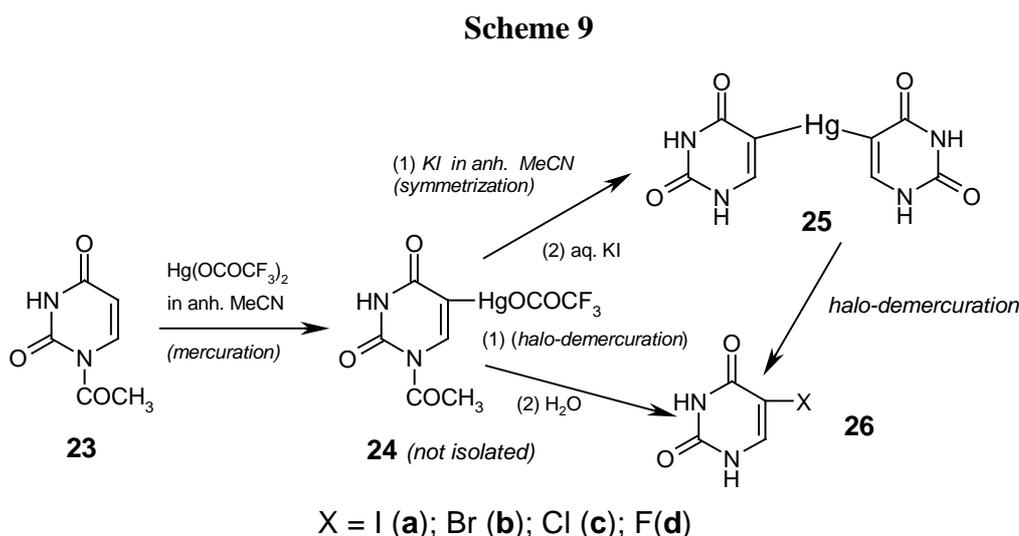
Similarly, an appropriate amount of I_2 was added to the boiling aforementioned solution containing **18**, which resulted (after cooling) in the isolation of iodo derivative **19a** in 58% yield (purified); alternatively, the same compound **19a** (purified) was obtained from solid organomercurial **21** by its *iodo-demercuration* with a saturated hot (60°C) aq. KI_3 solution, for 45 minutes, which resulted in 52% yield of **19a**. *Bromo-demercuration* of **18** was attained by adding a *neutralized* aq. KBr_3 solution to the afore-said solution containing **18**, and next the reaction was carried out at $60\text{--}80^\circ\text{C}$ for 45 minutes – isolation of bromo derivative **19b** (purified) resulted in 51% yield; also solid organomercurial **21** was similarly *bromo-demercurated* to give **19b** (purified) in 55% yield. Solid organomercurial **21** was *chloro-demercurated* with excess of *freshly redistilled* liquid S_2Cl_2 (to avoid the undesirable presence of SCl_2 ; see Section 4 for the explanation). The reaction transpired for 8 hours at 20°C , and the reaction mixture was then left overnight – after its two-step workup, pure 5-chloro-2,4-dimethoxypyrimidine (**19c**) was produced in 49% yield. On reacting *symmetric* mercurial **21** with a large excess of *neat* liquefied SF_4 at $(-60\text{--}70)$ for 48 hours and the following workup explained in Ref. 12, pure compound **19d** was obtained in 32.6 % yield.

5-Halogeno-2,4-dimethoxypyrimidines **19a**, **19b**, **19c**, and **19d**, were readily *demethylated* by adding them to a 10% aq. hydrochloric acid (used in a large excess), and by evaporating the solutions to dryness on a boiling water bath; the reactions were accompanied by *vigorous foaming*. The residues were recrystallized to give pure 5-halogeno-substituted uracils **22a**, **22b**, **22c**, and **22d** in 69%, 83%, 69% and 81% [12] yields, respectively. The title method is called *indirect*, because compound **17** is prepared from *uracil*, converted first by POCl_3 into 2,4-dichloropyrimidine, which next is reacted upon with CH_3ONa , yielding finally compound **17** [64]. In reverse, also the direct *demethylation* of 2,4-dimethoxypyrimidine (**17**) was easily accomplished on heating **17** with hot hydrochloric acid [65].

8. 5-Substituted Uracil Mercurials and Their Demercuration Reactions [4, 6, 9, 12 and 14]

In Section 6 we reported that 1-methyluracil (**16a**) may be readily C-mercurated to give 5-(acetoxymercurio)-1-methyluracil (**16b**) which next was bromo-demercurated to give 5-bromo-1-methyluracil (**16c**). There is (so far) no easy and effective method for removing N-methyl group(s) in the uracil ring system, hence it is not possible to obtain e.g. 5-bromouracil (**26b**) from compound **16c**. However, it is known [66] that 1-acetyluracil (**23**) is readily *deacetylated* even by cold water to form the initial uracil. We made numerous attempts to mercurate **23** in various *anhydrous* solvents with the less reactive mercurating agents, viz. HgCl_2 or $\text{Hg}(\text{OCOCH}_3)_2$ (Scheme 9). On prolonged heating only the sparingly soluble N-Hg salt of uracil (formula **1** in Section 1) was precipitated out in excellent yields, probably with a negligible C-mercuration in position 5.

Finally, we effectively C₅-mercurated **23** in boiling *anhydrous* acetonitrile, for 10 hours, but only with the *strongly electrophilic* $\text{Hg}(\text{OCOCF}_3)_2$. We did *not* isolate the intermediate mercurial **24**, but rather its yellowish, clear hot solutions were applied as such in the following reactions (*vide infra*); when the same mercuration was carried out, quite similarly, in CD_3CN , then the presence of the soluble mercurial **24** was confirmed by $^1\text{H-NMR}$ spectroscopy.



If we *prolonged* for more than ten hours the above mercuration reaction, a white solid was precipitated out in still increasing amounts, and it represented the N-Hg salt **1**, but substituted with the HgOCOCF_3 group in its position 5 (which was confirmed chemically, spectrally, and in part, analytically). The desirable 5,5'-mercuriobis(uracil) (**25**) was obtained in 50% crude yield by adding excess KI dissolved in *dry* acetonitrile to the afore-said yellowish solution of **24**. This mixture was refluxed for 4 hours, cooled, and filtered. The collected white precipitate was heated for 30 minutes at 60°C with a saturated aq. KI solution [which also *split off* the 1-N-acetyl groups] and after cooling, the collected white precipitate was washed well with boiling water, dried, and analyzed. Its structure was confirmed by the routine *iodo-demercuration* reaction with a hot aq. KI_3 solution to give known compound **26a** (purified) in 93% yield; see Ref. 4 for details. Alternatively, the same *iodo-*

demercuration reaction was carried out but with using the aforementioned yellowish boiling solution of **24**, which was treated at first with diiodine and next the collected white precipitate was heated for 30 minutes, at 60°C, with an aq. KI solution to give finally **26a** (purified) in 60% yield.

The respective routine *bromo-demercuration* reactions with hot aq. KBr₃ solutions (prior adjusted to pH = 7) of either solid **25** or **24** (in its CH₃CN solution) were reported elsewhere [9], and gave known purified 5-bromouracil (**26b**) in 84% and 77% yields, respectively. The above results confirm a somewhat *lesser reactivity* of unsymmetric mercurial **24** as compared with symmetric mercurial **25**.

The *chloro-demercuration* of symmetric mercurial **25** was reported in our paper [4]. Solid **25** was slowly added to the *freshly-redistilled* S₂Cl₂ (used in excess), and this was left overnight at room temperature. The collected precipitate was washed with dry CH₃CN, recrystallized from ethanol to give known purified 5-chlorouracil (**26c**) in 65% yield.

The *novel fluoro-demercuration procedure*, presented in Ref. 12, gave 5-fluorouracil (**26d**) in 27.1% yield, by reacting *symmetric* mercurial **25** with a large excess of *neat* liquid SF₄ for 48 hours at ca -60°C, and the subsequent workup; see Section 7 for another method of preparing compound **26d**.

Note. The *electron-donating* groups, viz. the methyl or methoxy groups in caffeine, 2,3-diphenyl-5-methoxybenzo[b]furan, 1,3-dimethyluracil and 1-methyluracil, and 2,4-dimethoxypyrimidine do *increase* more or less an electron density in the substituted parent heterocyclic systems, facilitating thus their *direct mercuration* even with *less electrophilic* mercuric salts, viz. mercuric acetate, sometimes also with HgCl₂ in its buffered aq. solutions. In contrast, any *electron-withdrawing* N-acyl groups (e.g. the acetyl, trichloroacetyl or trifluoroacetyl groups), which were introduced by us into the uracil, theophylline or theobromine parent ring systems, render considerably more difficult their direct mercurations with Hg(OCOCH₃)₂, and completely eliminate the use of HgCl₂. It is why we had to use the *strongly electrophilic* Hg(OCOCF₃)₂, usually prior prepared *in situ*, to effectively mercurate N-acylated uracil (Section 8), theophylline (Section 9), and theobromine (Section 10) in *anhydrous* solvents to obtain possibly highest yields of the desired C-substituted *unsymmetric* mercurials.

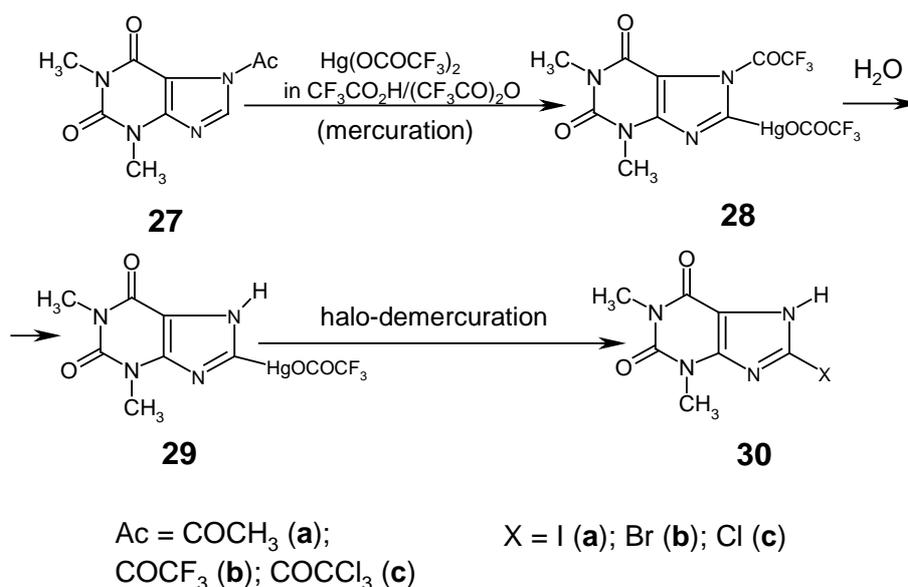
Visser et al. [60] have succeeded to synthesize *microquantities* of radioactive 5-X-uracils (X = ²¹¹At or ¹³¹I) by reacting 45 μmol of *uracil*, dissolved in 1 ml of 0.2 M aq. H₂SO₄, with HgSO₄ (40 μmol), for 3 hours at room temperature, followed with NaCl (90 μmol). *Without isolating* the intermediate 5-(chloromercurio)uracil, they added subsequently 0.9 equivalent of ²¹¹At/I₂ or ¹³¹I/I₂, which resulted in very good *radiochemical yields* of final radioactive products. Similar approaches were used, with varying reaction times and temperatures, e.g. for imidazole, thyrosine, phenylalanine, etc. We *scaled up* [14] the aforementioned procedure a *thousandfold* (i.e. to the *millimolar* scale) as to *directly* C₅-mercurate *uracil* as well as, for the sake of comparison, 2-thiouracil and theobromine. Only *uracil* gave 5-(chloromercurio)uracil in 85% crude yield; its following routine *iodo-demercuration* with a hot (80°C) aq. KI₃ solution led to 5-iodouracil in ca 61% crude yield. All our attempts to symmetrize 5-(chloromercurio)uracil by means of hot aq. KI, Na₂S₂O₃ or KSCN solutions as well as by a methanolic solution of hydrazine were not successful. Therefore, the *symmetric* mercurial **25** should be prepared in the way explained above. Theobromine reacted as above [60] but in the millimolar scale, furnished *1-N-(chloromercurio)theobromine* in ca 77% crude yield, which being iodo-demercurated gave the initial theobromine in ca 72% yield, with no detectable amount of the expected

8-iodotheobromine; see also Section 12. Similarly, 2-thiouracil reacted as above [60] but on a millimolar scale, forming nearly quantitatively an insoluble crude mercurial, which after its demercuration with an aq. KI solution, yielded solely the initial 2-thiouracil with no detectable amount of any C-mercurated product. We *concluded* [14] the above experiments as follows: “the direct mercuration procedure offered in **Ref. 60** should always be tried in the future, since it is relatively simple and less hazardous than the other ones (cf. Section 11), though it is *less general* than it has been expected and wanted”.

9. 8-Substituted Theophylline Mercurials and Their Demercuration Reactions [3, 4]

When *theophylline* as well as theobromine and uracil, all having *acidic* N-H groups, are reacted with Hg(II) salts, then their sparingly soluble N-Hg salts (see formulae **1 – 3** in Section 1) are immediately precipitated out from the mercurating solutions [63, 66], and their effective C-mercuration cannot be performed; see Section 8, where this topic is discussed. N-Acetyl derivatives of theophylline and theobromine [67], are *easily hydrolyzable* by the action of water, likewise as does *1-acetylmuracil* (Section 8).

Scheme 10



We made many attempts to mercurate *7-acetyltheophylline* (**27a**) in various *anhydrous* media, e.g. in CH₃CO₂H/(CH₃CO)₂O mixtures, with *less reactive* mercurating agents, viz. HgCl₂ or Hg(OCOCH₃)₂, but all our experiments were unsuccessful for the same reasons as those explained for 1-acetylmuracil (Section 8). We succeeded in C-mercurating the theophylline system in its 8-position (which is somewhat more reactive than the same position in theobromine and caffeine), but only by using the *strongly electrophilic* Hg(OCOCF₃)₂ dissolved in boiling *anhydrous* mixtures made of CF₃CO₂H and (CF₃CO)₂O. The reaction was complete after 10 hours, the resulting reaction mixture was concentrated under diminished pressure, *water* was added to the viscous residue, and a white

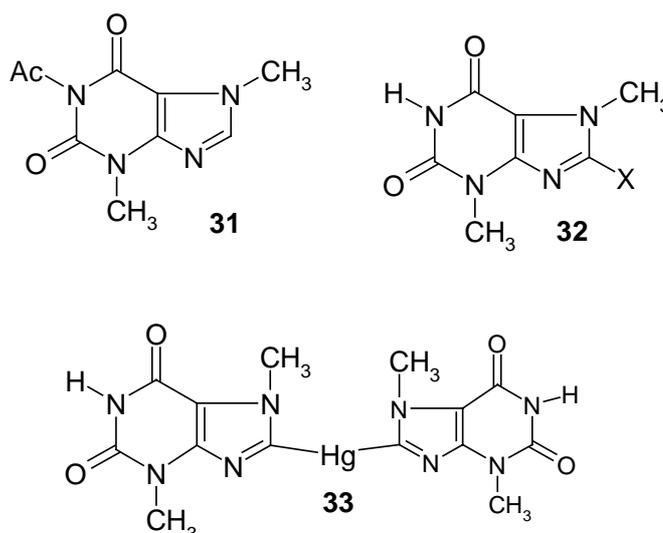
precipitate collected was recrystallized from water to give *8-(trifluoroacetoxymercurio)theophylline* (**29**) in 53% yield. We also *simplified* the above procedure as follows. Theophylline was refluxed with $(\text{CF}_3\text{CO})_2\text{O}$ for 2 hours [thus, *7-(trifluoroacetyl)theophylline* (**27b**) was produced there *in situ*], then a solution of $\text{Hg}(\text{OCOCF}_3)_2$ in $\text{CF}_3\text{CO}_2\text{H}/(\text{CF}_3\text{CO})_2\text{O}$ was added, and the same mercuriation reaction was carried out under a reflux condenser for 10 hours; the subsequent workup was the same as previously described to afford mercurial **29** in 64% yield. This yield was later increased to 70%, when *7-(trichloroacetyl)theophylline* (**27c**) was used as the starting substrate (Ref. 4; see footnote on p. 386).

Next, we carried out the routine *iodo-* and *bromo-demercuration* reactions with mercurial **29** in hot aq. KI_3 or KBr_3 solutions (previously adjusted to $\text{pH} = 7$), at 80°C for 30 minutes, which gave the purified compounds **30a** and **30b** in 95% and 96% yields, respectively. However, our attempts to prepare *8-chlorotheophylline* (**30c**) from dry *unsymmetric* mercurial **29**, using pure liquid S_2Cl_2 or SCl_2 as the chloro-demercuration agents, were unsuccessful.

10. 8-Substituted Theobromine Mercurials and Their Demercuration Reactions [3, 4 and 13]

Since all our experiments on the C-mercuriation of *theobromine* and *theophylline*, published in [3], were performed in parallel and were very close ones to the others, hence there is no need to relate here all our unsuccessful preliminary experiments aimed at the preparation of the desired theobromine mercurial(s). As previously, we succeeded in the mercuriation of *1-acetyltheobromine* (**31a**) only with $\text{Hg}(\text{OCOCF}_3)_2$ in boiling *anhydrous* $\text{CF}_3\text{CO}_2\text{H}/(\text{CF}_3\text{CO})_2\text{O}$ mixtures, for 10 hours. The following workup was practically the same as that for preparing mercurial **29**, which gave *8-(trifluoroacetoxymercurio)theobromine* (**32a**) in 56% yield (Scheme 11). Later (Ref. 4; see footnote on p. 386), we increased this yield to 70% by using *1-(trichloroacetyl)theobromine* (**31c**) as the starting substrate.

Scheme 11



Analysis: For $\text{C}_{14}\text{H}_{14}\text{HgN}_8\text{O}_4$ Calc. 35.9% Hg, Found: 35.8% Hg(II)

Ac = COCH_3 (a); COCF_3 (b); COCCl_3 (c)

X = HgOCOCF_3 (a); I (b); Br (c);

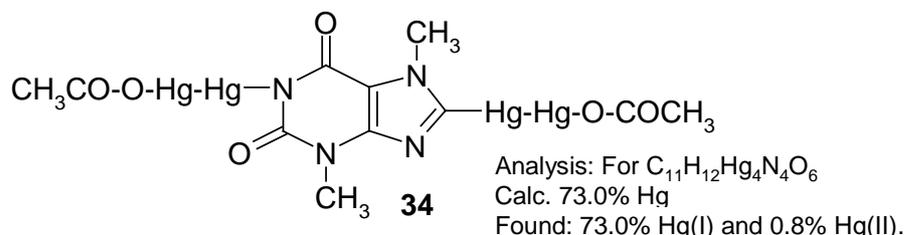
As previously, the solid *unsymmetric* mercurial **32a** was next *iodo-* and *bromo-demercurated* with hot (80°C) aq. KI₃ or aq. KBr₃ (pH = 7) solutions, under nearly the same reaction conditions as those related in Section 9, which resulted in the purified *8-iodo-* (**32b**) and *8-bromo-theobromine* (**32c**) obtained in 95% and 92% yields, respectively. Our attempted *chloro-demercuration experiments* with mercurial **32a** upon reaction with neat S₂Cl₂ or SCl₂ were quite unsuccessful as well.

Later [13], we prepared pure *8,8'-mercuriobis(theobromine)* (**33**) in 88% yield, though only from *1,8-bis(acetoxydimercurio)theobromine* (**34**). Using the routine *iodo-* and *bromo-demercuration* methods with the *symmetric* mercurial **33**, we obtained the purified either *8-iodo-* (**32b**) or *8-bromo-theobromine* (**32c**) in 97% and 92% yields, respectively. However, the contents of our paper [13] will be discussed more extensively in Section 11 below.

11. Preparation of 1,8-bis(Acetoxydimercurio)theobromine and Its Reactions [13]

Australian chemists [52] have prepared numerous fully mercurated (permercurated) arenes by the reaction of an excess of *molten* Hg(OCOCH₃)₂ with suitable arenes at ca 180-245°C; the reaction temperature used depended on the reactivity of a given starting arene. The *crude* (i.e. *not analyzed*) *permercurated arenes* were subsequently halo-demercurated to give the corresponding *perhalogenated arenes*. Therefore, we expected that the same *melting chemical procedure* would be suitable for the direct permercuration of several fairly stable, N-H acidic, *lactamic heterocycles*, e.g. theobromine, theophylline, xanthine, hypoxanthine, uracil, etc. For our preliminary study we chose *theobromine*, whose mercurials are discussed in Section 10.

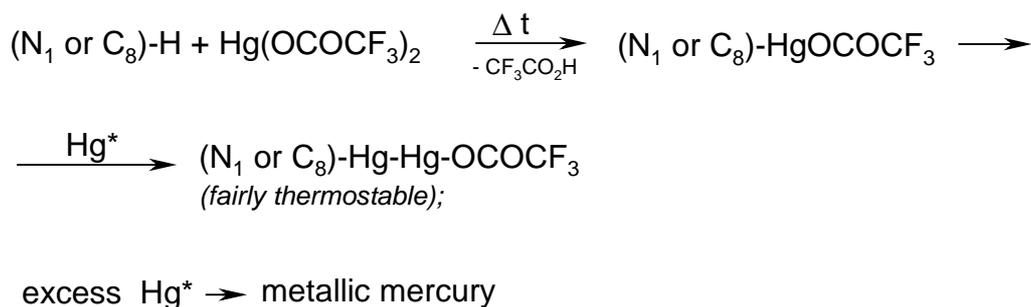
Scheme 12



In order to accomplish the said melting chemical procedure, we intimately mixed pure theobromine with an excess of molten Hg(OCOCH₃)₂ (prepared *in situ*). A vigorous reaction was observed with the evolution of gaseous, *strongly toxic* products as well as *tiny droplets of metallic mercury*. This is why, in our opinion, the organic derivatives of *mercury(I)* would readily be formed in the hot reaction mixture.

Note. We submitted in our paper [13] the following *assumption* (see footnote on p. 30): Mercury *in statu nascendi* (Hg*), probably formed during the thermal decomposition of Hg(OCOCH₃)₂, would, at a guess, react readily with intermediates of mercury(II), forming the resulting compounds of mercury(I), viz.

Scheme 13



The main problem was how to properly control the reaction temperature, since the aforementioned reaction mixture thickened continuously, until it had solidified. In hindsight, it would probably be desirable in the future to identify some suitable *inert solvents*, e.g. some highly boiling hydrocarbons or perfluorinated hydrocarbons, in order to better control the reaction. For the time being, we obtained some *crude melt*, evidently containing tiny droplets of metallic mercury as well as some highly mercurated products, most likely *1,8-bis(trifluoroacetyldimercurio)theobromine*. The latter tentative opinion was further indirectly supported by the subsequent reaction. *On boiling* the powdered *crude melt* with glacial acetic acid – where the following *metathesis* would take place: $\text{-Hg-Hg-OCOCF}_3 + \text{excess CH}_3\text{COOH} \rightarrow \text{-Hg-Hg-OCOCH}_3 + \text{CF}_3\text{CO}_2\text{H}$ – a considerably purer **yellow** product was obtained (after the concentration of the $\text{CH}_3\text{CO}_2\text{H}$ extract under reduced pressure) in 28% yield calculated with respect to the starting theobromine. Its analysis is given in the Scheme above. Its $^1\text{H-NMR}$ spectrum (in CF_3COOD) shows the absence of any 8-*H* low-field proton signal at ca. 8.5 ppm, and the presence of two N- CH_3 three-proton signals (at 3.38 and 4.08 ppm) characteristic of theobromine [3]. At ca 1.8 ppm there is, however, an additional and intense six-proton *singlet* derived from two, apparently spectrally equivalent, CH_3COO groups. Thus, it may be guessed that the two assumed -Hg-Hg-OCOCH_3 groups are substituted in mercurial **34** in its 1 and 8 positions. The lack of any 1-*NH* proton signal is insignificant, since it might have been due to a quick isotopic exchange with the deuterated solvent. Hence, the said substitution in position 1 is better explained by the full absence of any characteristic N-H absorption band over the $3070\text{-}3150\text{ cm}^{-1}$ IR range which, in contrast, is found at 3120 cm^{-1} in the comparative IR spectrum of theobromine taken also in Nujol.

This considerably purified product **34** was used *as such* in the following reactions without further purification. Compound **34** was readily *iodo-* and *bromo-demercurated* with either a boiling I_2 solution in dry CH_3CN , for 1.5 hours, or by an aq. KBr_3 solution, at 80°C for one hour, to give finally either *8-iodotheobromine (32b)* (purified) in 97% yield, or *8-bromotheobromine (32c)* (purified) in 92% yield; in the course of both demercuration procedures, the $(N_1)\text{-Hg-Hg-OCOCH}_3$ groups are exchanged in full by the hydrogen atoms (proto-demercuration), whereas those attached to the C_8 atom of **34** are replaced by the respective halogen atoms (halo-demercuration). The same difference was observed in the course of our attempted symmetrization of compound **34** by a hot ethanolic solution of

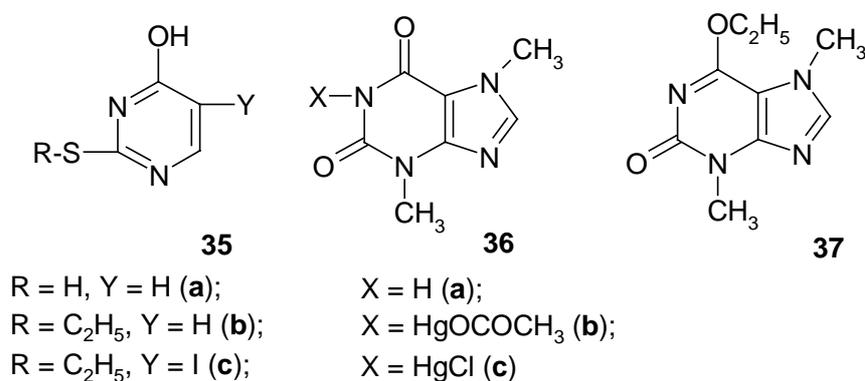
hydrazine (the other symmetrizing agents tried were either ineffective or gave worse results). Only the C₈-substituted –Hg-Hg-OCOCH₃ groups were all engaged in the formation of -Hg- bridging present in the formed 8,8'-mercuriobis(theobromine) (**33**), which was obtained, after its purification, in 88% yield [its structure was confirmed analytically, spectrally as well as by its subsequent iodo- and bromo-demercuration reactions; see Section 10], whereas those groups substituted in 1-N position were readily split off in favor of the hydrogen atom. All these reactions are new in the field of organic derivatives of mercury(I) – to the best of our knowledge (**Note:** Organic C-derivatives of mercury(I) so far are rare and generally regarded as *unstable*. For example, controlled electrolysis of 1,6-dibromohexane with a mercury cathode gives the dimer [Me(CH₂)₅Hg]₂ [68]).

It is impossible not to mention that the permercurated arenes prepared by the Australian chemists [52] had been neither purified nor analyzed, but they were immediately used as such in the subsequent halo-demercuration reactions, resulting in numerous, purified and analyzed, perhalogenated arenes. Nobody knows whether the said intermediate permercurated arenes were, in fact, the derivatives of mercury(II), mercury(I) or, possibly, were composite mixtures of both; this should be elucidated in future.

12. Further Studies on Some Heteroaromatic Mercurials [14]

Using various known methods of *direct C-mercuration* we attempted to mercurate *uracil*, *thiouracil* (**35a**), *S-ethyl-2-thiouracil* (**35b**), *theobromine* (**36a**) and *6-O-ethyltheobromine* (**37**). Only *uracil* was effectively C₅-mercured giving the crude 5-(chloromercurio)uracil (Section 8) in ca 85% crude yield, whereas the rest formed (in good yields) either S-Hg bonds (compounds **35a** and **35b**) or N-Hg bonds (compounds **36a** and **37**); in the latter its 6-O-ethyl groups were *completely split off* under the reaction conditions. All the newly obtained *crude* mercurials were next *iodo-demercurated* by the routine methods [23-25, 34, 42]. This furnished from S-ethyl-2-thiouracil mercurial the corresponding C-iodinated product, i.e. *S-ethyl-5-iodo-2-thiouracil* (**35c**) in ca 64% crude yield.

Scheme 14



The other mercurials were mostly *proto-demercurated*, though with some noticeable exceptions which are discussed below. The main purpose of our work [14] was to detect whether the

aforementioned *crude* mercurials do contain (or not) any detectable amounts of C-mercurated admixtures, which would then have been transformed into recognizable *C-iodinated* derivatives formed in the subsequent iodo-demercuration reactions.

It has been shown in Section 7 that *2,4-dimethoxypyrimidine* (**17**) was effectively C₅-mercurated on boiling with an aq. Hg(OCOCH₃)₂ solution acidified with CH₃CO₂H, for 2 hours. Hence, we *did* expect that compound **37** would behave similarly to give a *true mercurial* C-substituted in position 8. Thus, compound **37** was refluxed for 55 hours with a Hg(OCOCH₃)₂ solution in boiling glacial acetic acid (the reaction was monitored with TLC). Quite unexpectedly, we obtained a *new mercurial* **36b**, i.e. *1-(acetoxymercurio)theobromine*, in 83% yield, whose structure was confirmed by chemical tests and its IR and ¹H-NMR spectra; no ¹H-NMR spectral evidence was found for any C₈-mercuration. The 6-O-ethyl groups in compound **37** were *completely split off* under the reaction conditions, momentarily forming the parent *tautomeric* theobromine (**36a**), which *immediately* reacted with Hg(OCOCH₃)₂ to give the new mercurial **36b**.

Our assumption was supported as follows: when compound **37** was refluxed for 48 hours with *neat* CH₃CO₂H; after cooling, we isolated *theobromine* (**36a**) in 83% yield, which was proven chemically and spectroscopically. We also obtained another *new mercurial* **36c**, i.e. *1-(chloromercurio)-theobromine* in ca 77% crude yield (Section 8). The two crude mercurials **36b** and **36c** were refluxed for 2 hours with excess diiodine dissolved in *dry* CH₃CN; after workup this furnished *theobromine* (**36a**) in 76% and 72% yields, respectively. No detectable amounts of known 8-iodotheobromine – which would have supported the sought C₈-mercuration – were found in the both reaction mixtures which furnished only theobromine.

It should be added that, so far, only one *theobromine* mercurial with a 2:1 Hg ratio has been reported [69]; its structure is shown in Section 1. In the same paper [69] other N-Hg mercurials prepared from *theophylline*, *hypoxanthine*, *xanthine*, *guanine* and *uracil* (the latter is a 1:1 Hg complex as shown in Section 1) were also reported.

The *new S-ethylthiouracil mercurial* (supposedly a 1:1 Hg complex) was synthesized as follows: compound **35b** was dissolved in CH₃OH acidified with two drops of added conc. aq. HClO₄. Then a solution of Hg(OCOCH₃)₂ in methanol was added to the former solution, the mixture was refluxed for 8 hours, and then left overnight. The collected white precipitate was practically insoluble in common solvents, and was obtained in ca 42% crude yield. When this *novel* crude mercurial was boiled with a conc. aq. KI solution until the combined solution was clear and slightly yellowish, then after cooling we isolated the recovered compound **35b** in 99% yield. But the same crude mercurial upon refluxing with an aq. KI₃ solution for 30 – 40 minutes, unexpectedly gave (after cooling) the *iodo derivative* **35c** in ca 64% crude yield; it was recrystallized from ethanol and 2-propanol yielding pure **35c**.

13. Final Results of Our Halo- and Cyano-demercuration Reactions [1-15]

13.1. Aromatic Iodides from Aromatic Organomercurials

It is known [23, 26, 28, 34, 42] that *aromatic iodides* and *bromides* may be obtained from both symmetric and unsymmetric aromatic organomercurials, by reacting them with either hot aq. KI₃ and

KBr₃ neutralized solutions or with hot solutions of diiodine and dibromine in acetonitrile, DMF, etc. We have repeatedly applied these “classic” *iodo-demercuration* and *bromo-demercuration* reactions to better elucidate the chemical structures of organomercurials prepared by us in various ways. Thus, we synthesized (the yields are given in brackets) the following *aromatic iodides* and *bromides*, viz.

- i) 8-iodocaffeine (95%) from 8-(*acetoxymercurio*)caffeine and 8,8'-*mercuriobis*(caffeine) [1, 2];
- ii) 8-iodotheophylline (95%) from 8-(*trifluoroacetoxymercurio*)theophylline, and 8-iodotheobromine (95%) from 8-(*trifluoroacetoxymercurio*)theobromine [3];
- iii) 5-iodouracil (60 or 93%, resp.) from either 1-acetyl-5-(*trifluoroacetoxymercurio*)uracil or 5,5'-*mercuriobis*(uracil) [4];
- iv) 2-iodofuran (60%) from 2,2'-*difurylmercury*, and 2-iodothiophene (65%) from 2,2'-*dithienylmercury* [5];
- v) 5-iodo-1,3-dimethyluracil (87.5 or 82.5%, resp.) from either 5-(*acetoxymercurio*)-1,3-dimethyluracil or 5,5'-*mercuriobis*(1,3-dimethyluracil) [8];
- vi) 5-iodo-2,4-dimethoxypyrimidine (58 or 52%, resp.) from either 5-(*acetoxymercurio*)-2,4-dimethoxypyrimidine or 5,5'-*mercuriobis*(2,4-dimethoxypyrimidine); the acid hydrolysis of pure 5-iodo-2,4-dimethoxypyrimidine afforded 5-iodouracil (69%) [9];
- vii) 6-iodo-2,3-diphenyl-5-methoxybenzo[*b*]furan (70%) from both 6-(*acetoxymercurio*)-2,3-diphenyl-5-methoxybenzo[*b*]furan and 6,6'-*mercuriobis*(2,3-diphenyl-5-methoxybenzo[*b*]furan) [10];
- viii) iodobenzene (59%) from (*chloromercurio*)benzene, and 8-iodocaffeine (65%) from 8-(*chloromercurio*)caffeine [11];
- ix) 8-iodotheobromine (97%) from 1,8-bis(*acetoxymercurio*)theobromine; the latter compound was the first *stable* organic derivative of **mercury(I)** [13]
- x) 5-iodouracil (61% crude yield) from 5-(*chloromercurio*)uracil, and 2-ethylthio-4-hydroxy-5-iodopyrimidine (64% crude yield) from crude 2-ethylthio-4-hydroxypyrimidine mercurial [14].

Note. We also applied twice another *iodo-demercuration* method, by reacting two *symmetric* organomercurials with hot either aqueous [1, 2] or ethanolic [7] solutions of cyanogen iodide, **ICN**. In this way we synthesized:

- xi) 8-iodocaffeine (90%) from 8,8'-*mercuriobis*(caffeine) [1, 2], and
- xii) iodobenzene (72%) from *diphenylmercury* [7].

13.2. Aromatic Bromides from Aromatic Organomercurials

- i) 8-bromocaffeine (83% or 85%, resp.) from either 8-(*acetoxymercurio*)caffeine or 8,8'-*mercuriobis*(caffeine) [1, 2];
- ii) 8-bromotheophylline (96%) from 8-(*trifluoroacetoxymercurio*)theophylline [3];
- iii) 8-bromotheobromine (96%) from 8-(*trifluoroacetoxymercurio*)theobromine [3, 13];
- iv) 5-bromo-1,3-dimethyluracil (82% or 84.5%, resp.) from either 5-(*acetoxymercurio*)-1,3-dimethyluracil or 5,5'-*mercuriobis*(1,3-dimethyluracil) [8];

- v) 5-bromo-2,4-dimethoxypyrimidine (51% or 55%, resp.) from either 5-(*acetoxymercurio*)-2,4-dimethoxypyrimidine or 5,5'-*mercuriobis*(2,4-dimethoxypyrimidine); the acid hydrolysis of pure 5-bromo-2,4-dimethoxypyrimidine afforded 5-bromouracil (83%) [9];
- vi) 5-bromouracil (77% or 84%, resp.) from either 5-(*trifluoroacetoxymercurio*)uracil or 5,5'-*mercuriobis*(uracil) [9];
- vii) 6-bromo-2,3-diphenyl-5-methoxybenzo[*b*]furan (70%) from both 6-(*acetoxymercurio*)-2,3-diphenyl-5-methoxybenzo[*b*]furan or 6,6'-*mercuriobis*(2,3-diphenyl-5-methoxybenzo[*b*]furan) [10].
- viii) 8-bromotheobromine (92%) from both 8,8'-*mercuriobis*(*theobromine*) or 1,8-*bis*(*acetoxymercurio*)*theobromine* [13].

Note. We also applied twice our *novel bromo-demercuration* method, with applying a labile complex (or adduct) of an unknown composition, (**BrCN·KBr**)_x, suspended either in hot water [1, 2] or dissolved in boiling ethanol [7]. In this way we obtained:

- ix) 8-bromocaffeine (85%) from both 8-(*acetoxymercurio*)*caffeine* or 8,8'-*mercuriobis*(*caffeine*) [1, 2];
- x) *bromobenzene* (79%) from *diphenylmercury* [7].

13.3. Aromatic Chlorides from Aromatic Organomercurials

During our studies we discovered three *novel chloro-demercuration* reagents, viz. S₂Cl₂, SCl₂, or (the least reactive) SO₂Cl₂. Mostly, they were applied as pure liquids, but for furan and thiophene mercurials, S₂Cl₂ had to be *diluted* with CS₂ (Section 4). Thus, we obtained the following results:

- i) 8-chlorocaffeine (90%) from 8,8'-*mercuriobis*(*caffeine*), using neat liquid S₂Cl₂, or (70%), using neat liquid SCl₂, or (27%) using neat liquid SO₂Cl₂ [1, 2];
- ii) 5-chlorouracil (65%) from 5,5'-*mercuriobis*(uracil), using neat liquid S₂Cl₂ [4];
- iii) 2-chlorofuran (60%) from 2,2'-*difurylmercury*, using S₂Cl₂ diluted with CS₂, or (50%) from a mixture of *furan* and dry finely-powdered HgCl₂ dissolved in excess S₂Cl₂ [5];
- iv) 2-chlorothiophene (70%) from 2,2'-*dithienylmercury*, using S₂Cl₂ diluted with CS₂, or (60%) from a mixture of *thiophene* and dry finely-powdered HgCl₂ dissolved in excess S₂Cl₂ [5];
- v) *chlorobenzene* (78%) from *diphenylmercury*, using neat liquid S₂Cl₂, or (69%) from (*trifluoroacetoxymercurio*)*benzene*, using neat liquid S₂Cl₂, or (50%) from (*acetoxymercurio*)*benzene*, using neat liquid S₂Cl₂, or (47%) from *diphenylmercury*, using neat liquid SO₂Cl₂ [5];
- vi) 5-chloro-1,3-dimethyluracil (74%) from 5,5'-*mercuriobis*(1,3-dimethyluracil), using neat liquid S₂Cl₂ [8];
- vii) 5-chloro-2,4-dimethoxypyrimidine (49%) from 5,5'-*mercuriobis*(2,4-dimethoxypyrimidine), using neat liquid S₂Cl₂; the acid hydrolysis of pure 5-chloro-2,4-dimethoxypyrimidine afforded 5-chlorouracil (69%) [9].

13.4. Aromatic Fluorides from Aromatic Organomercurials

By successively reacting (at ca - 60°C) several symmetric organomercurials (*vide infra*) with a great excess of *neat liquid SF₄* (b.p. - 40.4°C) the following monofluorinated products were obtained:

- i) 8-fluorocaffeine (30%) from 8,8'-mercuriobis(caffeine) [1, 2];
- ii) fluorobenzene (58%) from diphenylmercury [12];
- iii) 5-fluoro-1,3-dimethyluracil (30.3%) from 5,5'-mercuriobis(1,3-dimethyluracil) [12];
- iv) 5-fluoro-2,4-dimethoxypyrimidine (32.6%) from 5,5'-mercuriobis(2,4-dimethoxypyrimidine); the former compound was demethylated to give 5-fluorouracil in 81.3% yield [12].
- v) 5-fluorouracil (27.1%) from 5,5'-mercuriobis(uracil) [12].

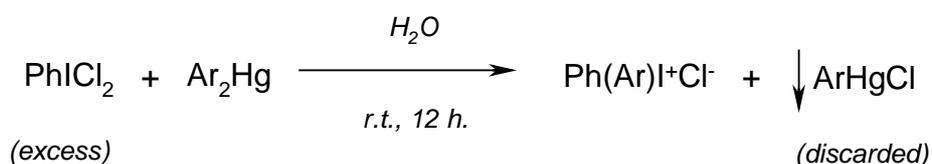
13.5. Aromatic Nitriles from Aromatic Organomercurials

- i) 8-cyanocaffeine (50% or 25%, resp.) from either 8,8'-mercuriobis(caffeine) or 8-(acetoxymercurio)caffeine, with freshly purified **BrCN** in hot (60°C) water [1, 2];
- ii) benzonitrile (86%) from diphenylmercury, with freshly purified **BrCN** in boiling dry benzene [7].

14. Improved Syntheses of Some Diaryliodonium Salts from Symmetric Diarylmercurials and (Dichloroiodo)arenes (Willgerodt's Method) [16]

Willgerodt [70-72] had reacted cold (or hot [71]) aqueous suspensions of *equal masses* [in practical terms this means that the mercurials were used *in a deficit*] of powdered PhICl₂ with powdered Ar₂Hg (where Ar = phenyl, 2- and 4-tolyl, and 2-naphthyl) to afford the respective diaryliodonium chlorides (yields were not reported); sparingly soluble ArHgCl and other admixtures, e.g. PhIO [73], were hot-filtered off and discarded, viz.

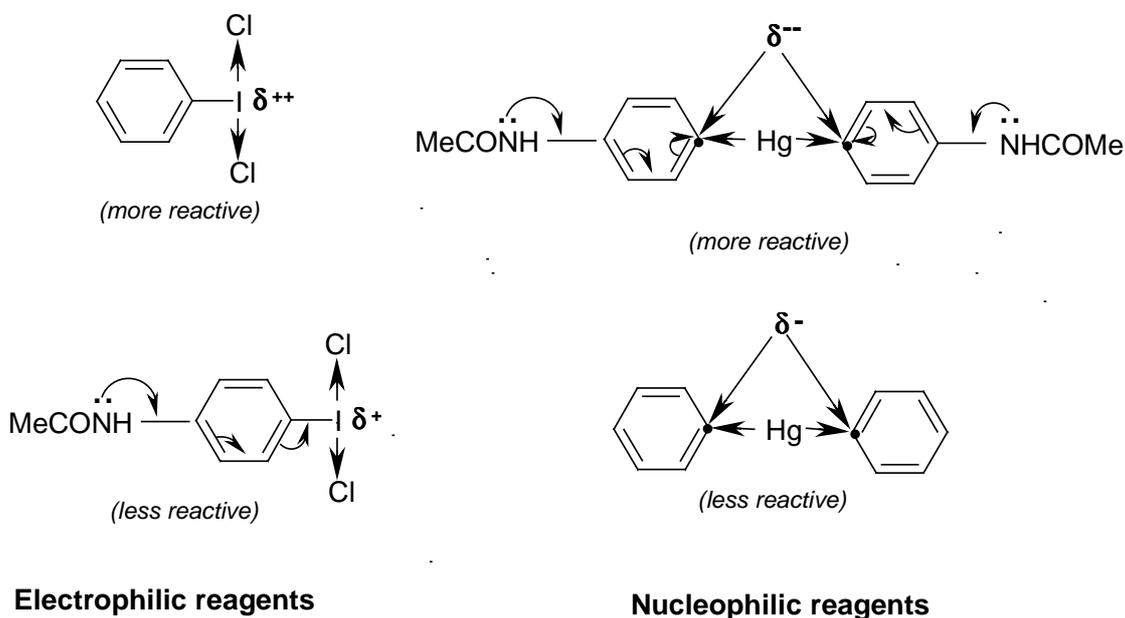
Scheme 15



Beringer and Lillien [74] applied the Willgerodt method to obtain three unsymmetric diaryliodonium chlorides. They obtained only 4-acetamidophenyl(phenyl)iodonium chloride (which was precipitated out as its sparingly soluble iodide, isolated in **10%** crude yield) by reacting *equimolar amounts* of Ph₂Hg with 4-AcNHC₆H₄ICl₂ in hot water (40-50°C) for 12 hours. We obtained [16] the same iodide, but in **80%** crude yield, by reacting *equal masses* of PhICl₂ with symmetric 4,4'-

mercuriobis(acetanilide) suspended in stirred hot water (40-50°C) for 12 hours. We explained this evident yield increase as follows:

Scheme 16



Consequently, by reacting *equal masses* of PhICl_2 with symmetric 4,4'-mercuriobis(*N,N*-dimethylaniline), suspended in stirred hot water (40-50°C) for 12 hours, we isolated from the hot filtrate, after its cooling, 4-dimethylaminophenyl(phenyl)iodonium chloride in **60%** crude yield. Previously, Beringer and Lillien [74] failed to obtain this iodonium salts, *para*-substituted with only one NMe_2 group; the same failure was also reported by Neiland [75]. A similar iodonium salt bearing the two *p,p'*-substituted NMe_2 groups was synthesized by quite a different route [76]; this synthesis is shown (Scheme 7) in our paper [16].

We also attempted, *without effect*, to synthesize various 8-(aryliodonio)caffeine halides with using the Willgerodt method. Hence, we used our short-cut, oxidative method [77] to obtain 8-(4-methoxyphenyliodonio)caffeine bromide (49% crude yield) by acidic coupling of the previously oxidized 8-iodocaffeine with anisole. This is, in fact, the first *iodine(III)* derivative of caffeine, which may open up novel routes for preparing 8-substituted caffeines by its reactions with various nucleophiles [78].

16. Conclusions

This review shows our small research group's main interests in developing *novel* (or considerably improved) preparative procedures, mainly in the class of aromatic heterocyclic mercurials, which afforded a number of both unsymmetric, ArHgX , and symmetric, Ar_2Hg , C-mercured compounds, mostly *not reported* in the former literature. In our opinion, most interesting are those *indirect* preparative C-mercuration methods, which made possible the syntheses of organomercurials derived from *uracil*, *theophylline*, and *theobromine*; they also open up new ways for preparing other similar

organomercurials from many aromatic activated systems having N-H *acidic* groups, which when reacted with mercuric salts, usually form at once the *insoluble* N-Hg salts that precipitate out from the reaction mixtures, *instead of* forming the expected *true organomercurials* (with the mercury atoms joined to the organic residues via carbon atoms). In order to better confirm the chemical structures of the new organomercurials synthesized by us, they were next *iodo-* and/or *bromo-demercurated* (by known halo-demercuration procedures) to form in high yields a considerable number of the respective (purified) iodo and bromo derivatives (Section 13), whose structures were well established chemically, spectrally, and by comparison with the available literature data. We also discovered some *novel halo-* and *cyano-demercuration* procedures, which enabled us to obtain a number of the corresponding (purified) aromatic halides and nitriles in high yields (Section 13). Also very interesting is our synthesis of *1,8-bis(acetoxymercurio)theobromine*, seemingly the first *stable* organic derivative of **mercury(I)**, as well as its novel reactions (Section 11). Finally, we considerably *improved* the old Willgerodt method (1897), which enables to synthesize in high yields diaryliodonium chlorides from appropriate (dichloriodo)arenes and symmetric aromatic organomercurials (Section 14). We hope that our preparative procedures, discussed and explained in the present review, will be applied either *as such*, or they would be further improved and extended in other organic chemical laboratories.

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