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IODO- AND CHLORODEMERCURATION OF 5,5'-MERCURIBISURACILS

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The direct C mercuration in the 5 position of 1-acetyloracil by means of mercury(II) trifluoroacetate in anhydrous acetonitrile is described. The intermediately formed 1-acetyl-5-trifluoroacetoxymercuriuracil, without isolation, was subjected to symmetrization by the action of potassium iodide. The acetyl groups were then readily split out by the action of water. The resulting 5,5'-mercuribisuracil (50% yield) forms 5-iodo- or a 5-chlorouracil in 93% or 72% yields, respectively, under the influence of an aqueous KI₃ solution or excess pure liquid S₂Cl₂.

It is known that under the influence of mercury(II) acetate on caffeine [1, 2] or mercury(II) chloride on N₁,N₃-dimethyluracil [3] one observes the formation of their C-organomercury derivatives with substituents in the 8 or 5 positions, respectively. On the other hand, dimethyl-substituted xanthines [4, 5], imidazoles, uracils, etc. [6-8] generally give rather stable and, as a rule, slightly soluble metal complexes, or else the reaction stops at the stage involving the formation of slightly soluble N-organomercury derivatives (sometimes with admixed C-mercuri derivatives) [7, 8]. For example, uracil very rapidly forms a slightly soluble Hg complex [5, 6] in a ratio of 1:1; the latter is used in the syntheses of nucleosides [6, 9, 10]. Thus the fact is that, in the direct C mercuration of uracil, it is expedient to temporarily protect the N₁ position by means of some readily eliminable residue such as the very easily removable acyl group [17]. It has been demonstrated [11] that a methyl group is not at all applicable in this case and that benzyl and benzyloxy-

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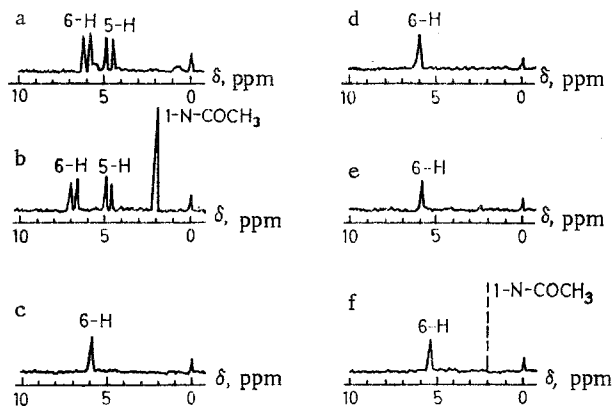
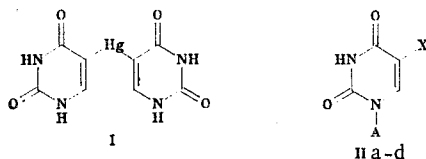


Fig. 1. PMR spectra: a) uracil; b) IIa; c) I; d) IIc; e) IIId (in CF_3COOD); f) IIb in CD_3CN [the signal of the 1-N-COCH₃ group is absent; this evidently due to exchange of the hydrogen atom of this group for deuterium upon prolonged (10 h) refluxing of the reaction mixture].

methyl groups, although they are eliminated by the action of BBr_3 , are mercurated more easily than the uracil residue.

In [4] we reported the preparation of 8-trifluoroacetoxymercuri derivatives of theophylline and theobromine (in 53% and 56% yields, respectively) from the N-acetyl derivatives of both alkaloids by the action of mercury(II) trifluoroacetate in an anhydrous $\text{CF}_3\text{COOH} + (\text{CF}_3\text{CO})_2\text{O}$ mixture.* However, we initially made an unsuccessful attempt to subject to direct mercuration (under various conditions) theophylline and theobromine with the well-known [12, 14] mercurating reagents HgCl_2 , $\text{Hg}(\text{OCOCH}_3)_2$, and $\text{Hg}(\text{OCOCF}_3)_2$, and then their N-acyl derivatives (but only in anhydrous media) by the action of less electrophilic reagents such as HgCl_2 and $\text{Hg}(\text{OCOCH}_3)_2$. The structures of the C-trifluoromercuri derivatives that we obtained were also confirmed by chemical transformations, i.e., by the known [12-14] reactions involving their bromo- and iodomercuration. However, an attempt to subject these substances to chlorodemercuration with excess amounts of pure SCl_2 and S_2Cl_2 did not lead to the desired chloro derivatives. Here, one must once again recall that these relatively little-studied, as yet, reactions give 8-chlorocaffeine (in high yields) only with the more reactive symmetrical 8,8'-mercuribiscaffeine, but they were inapplicable to 8-acetoxymercuricaffeine [2].

In the present research we were also initially unsuccessful in an attempt to obtain C-mercuri derivatives of unsubstituted uracil under various conditions and subsequently to subject its 1-N-acyl derivatives to C-mercuration (only in anhydrous media) by the action of HgCl_2 and $\text{Hg}(\text{OCOCH}_3)_2$. In all cases only the above-indicated mercury complex of uracil was formed. Finally, we were able to obtain the reactive (from the point of view of its subsequent demercurations for the syntheses of various 5-substituted uracils) symmetrical 5,5'-mercuribisuracil (I) in 50% yield based on the converted starting 1-acetyluracil (IIa) but only by the prolonged action of the strongly electrophilic mercury(II) trifluoroacetate in refluxing anhydrous acetonitrile.



II a, b A = COCH₃; c, d A = H; a X = H; b X = HgOCOCF₃; c X = I; d X = Cl

It might be assumed that the substance that is initially formed is the less reactive (see above) intermediate 1-acetyl-5-trifluoroacetoxymercuriuracil (IIb). However, we did not isolate this intermediate, which is a readily hydrolyzable compound; immediately after completion of the direct mercuration of uracil IIa (which we monitored by PMR spectroscopy and TLC) to the resulting reaction mixture we added two equivalents of a solution of potas-

*We subsequently were able to raise the yields to 70% by using N-trichloroacetyl derivatives of theophylline and theobromine as the substrates. When we used a solution of N₇-trifluoroacetyltheophylline (obtained *in situ* [4]), we obtained 8-trifluoroacetoxymercuritheophylline in 64% overall yield.

sium iodide in anhydrous acetonitrile and continued heating of the mixture up to the point of completion of the known [12-14] symmetrization of trifluoroacetyl derivative IIb, as a result of which, the diacetyl derivative of I is probably formed. The latter derivative is subsequently readily hydrolyzed in the presence of water. The iodomercuriation of the isolated pure bisuracil I by the action of an aqueous solution of KI_3 leads to the formation of the previously described [15] 5-iodouracil (IIc), whereas the chlorodemercuration of I with pure liquid S_2Cl_2 leads to the known [16] 5-chlorouracil (IIId). The same IIc is formed after the addition of iodine immediately to the above-mentioned reaction mixture containing IIb in acetonitrile.

The compositions and structures of all of the synthesized compounds were confirmed by the melting points, the results of elementary analysis, and the PMR spectra (Fig. 1). In the PMR spectra of uracil and IIa one observes the presence of signals of 5-H and 6-H protons, in contrast to the spectra of I and IIb-d, which contain only signals of the 6-H protons. This demonstrates that the X group ($-Hg-$, I, Cl) is located in the 5 position of the pyrimidine ring. The broad signals of the N-H group are usually not observed at room temperature.

EXPERIMENTAL

The melting points of all of the substances synthesized in this research were not corrected. The PMR spectra of solutions of the compounds in CF_3COOD , CD_3CN , and d_6 -DMSO at room temperature were recorded with a Tesla BS-487C spectrometer (80 MHz) with hexamethyldisiloxane (HMDS) as the internal standard.

The starting 1-N-acetyluracil IIa, with mp 190-191°C, was obtained in 86% yield from uracil and acetic anhydride by the standard method [17].

1-Acetyl-5-trifluoroacetoxymercuriuracil (IIb). A hot solution of 12.2 g (28.6 mmoles) of mercury(II) trifluoroacetate [18] in 50 ml of dry acetonitrile was added with stirring to a refluxing solution of 2.0 g (13 mmoles) of acetyluracil IIa in 80 ml of dry acetonitrile, after which the mixture was refluxed for 10 h. The resulting light-yellow solution of IIb was used for the subsequent reactions.

In continuing the mercuriation (more than 10 h) we obtained an increasingly more slightly soluble white precipitate, which was evidently the 5-trifluoroacetoxymercuri derivative of the above-mentioned Hg complex (1:1) of uracil. This was confirmed by the results of elementary analysis (found: Hg 72.0%. $C_6H_2F_3Hg_2N_2O_4$. Calculated: Hg 70.8%), as well as by the PMR spectra in CF_3COOD of this substance, which do not contain a signal of a 5-H proton but do retain unchanged the signal of the 6-H protons (at 6.3 ppm). The Lossen test demonstrated the presence of nitrogen and fluorine (in the form of CaF_2), as well as mercury (in the form of HgS).

5,5'-Mercuribisuracil (I). A solution of 4.3 g (26 mmoles) of potassium iodide in 80 ml of dry acetonitrile was added with stirring to a refluxing solution of IIb (obtained from 2.0 g of IIa), and the mixture was refluxed for 4 h (it began to become turbid after 15 min). The mixture was then cooled, and the white gelatinous precipitate was removed by filtration and then heated for 30 min at 60°C with an almost saturated aqueous solution of 4.3 g (26 mmoles) of potassium iodide. The white precipitate was removed by filtration, washed with hot water, dried, and ground up to give 3.5 g (50%) of white I, which decomposed (without melting) at a temperature above 300°C. Found: Hg 49.2%. $C_8H_6HgN_4O_4$. Calculated: Hg 47.2%. The Lossen test demonstrated the presence of nitrogen and mercury (in the form of HgS), as well as the absence of fluorine (in the form of CaF_2).

5-Iodouracil (IIc). A) To a refluxing solution of IIb (obtained from 2.0 g of IIa), we added, in small portions with stirring, ~ 2 g (7.8 mmoles) of finely crystalline iodine until the solution no longer took on a persistent light-yellow color. During this time, we observed the copious precipitation of a white substance, which was removed by filtration and then refluxed again with stirring for 30 min with an almost saturated aqueous solution of 3.0 g of potassium iodide. The solution was cooled, and the resulting colorless crystals were removed by filtration and recrystallized repeatedly from water to give 1.85 g (60%, based on the unchanged IIa) of colorless lustrous needles with mp 272-273°C (dec.) [according to the data in [15], this compound had mp 273-274°C (dec)]. Found: C 20.3; H 1.3; N 11.7%. $C_4H_3IN_2O_2$. Calculated: C 20.2; H 1.3; N 11.8%. The Lossen test demonstrated the presence of iodine (in the form of AgI).

B) A 1.25-g (4.6 mmoles) sample of finely crystalline iodine was added with stirring in small portions to a suspension of 1.0 g (2.3 mmoles) of finely ground I in 100 ml of a saturated aqueous solution of potassium iodide, and the mixture was heated with stirring at 80°C for 30 min. The color of the solution, which was initially dark red, became yellow at the end of the reaction. The excess iodine was removed by steam distillation, and the residue produced in the flask after cooling was removed by filtration and recrystallized from absolute alcohol to give 1.0 g (93%, based on the unchanged I) of iodide IIc in the form of colorless lustrous needles with mp 272-273°C (dec.). No melting-point depression was observed for a mixture of the samples obtained by methods A and B. Found: C 20.3; H 1.3; N 11.7%.

The Lossen test demonstrated the presence of iodine (in the form of AgI).

5-Chlorouracil (IIId). A 10-ml (124 mmoles) sample of sulfur monochloride (bp 135-136°C) was added slowly dropwise with stirring to 1.0 g (2.3 mmoles) of finely ground dry I, after which the reaction mixture was allowed to stand overnight at room temperature. The resulting precipitate was removed by filtration, washed with dry acetonitrile until the S₂Cl₂ was removed, and recrystallized from ethanol to give 0.45 g (72%, based on the unchanged I) of pure IIId; after yet another crystallization, from ethanol (with activated charcoal), the yield of an analytically pure sample in the form of colorless plates was 0.41 g (65%), the product had mp 320-321°C (dec.) [according to [16], this product had mp 321°C (dec.)]. Found: C 32.4; H 2.4; N 18.7%. C₄H₃ClN₂O₂. Calculated: C 32.8; H 2.1; N 19.1%.

The Lossen test demonstrated the presence of chlorine (in the AgCl form).

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