BROMO- AND IODODEMERCURATION OF 8-TRIFLUOROACETOXYMERCURI DERIVATIVES OF THEOPHYLLINE AND THEOBROMINE

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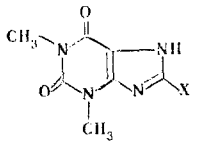
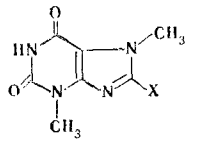
Direct C-mercuration in the 8 position of N-acyl derivatives of theophylline and theobromine with mercury(II) trifluoroacetate in a mixture of anhydrous trifluoroacetic acid and trifluoroacetic anhydride is described. 8-Bromo and, respectively, 8-iodo derivatives of both dimethylxanthines were obtained in high yields from 8-trifluoroacetoxymercuri derivatives by the action of an aqueous solution of potassium tribromide or a solution of iodine in acetonitrile.

It is known that C-organomercuri derivatives are obtained by the action of mercury(II) acetate on caffeine [1, 2] or 8-methylcaffeine, 8-chloromethylcaffeine, etc. [3]. On the other hand, dimethyl-substituted xanthine [4], imidazole, uracil, etc. [5-7] generally do not undergo direct C-mercuration because either rather stable complexes are obtained with mercury(II) salts or the reaction stops at the stage involving N-organomercuri derivatives, sometimes admixed with C-mercuri isomers [6, 7]. We have also previously made an unsuccessful attempt under various conditions to synthesize C-mercuri derivatives of the compounds mentioned above. It is apparent from this that one must temporarily protect the NH group of these compounds with some readily eliminatable residue such as an acyl group (see below).

We have previously reported [2] that the corresponding 8-halo- or 8-cyano-substituted caffeines are obtained (sometimes in high yields) by the action of aqueous solutions of KI_3 and KBr_3 (the widely known iodo- and bromodemercuration reactions [8-10]) or aqueous solutions of ICN, BrCN, and the BrCN·KBr complex, as well as by the action of excess pure liquid SO_2Cl_2, SCl_2, S_2Cl_2, and SF_4 (new halo- and cyanodemercuration reactions [2]), on 8-acetoxymercuricaffeine or the more reactive 8,8'-mercuribiscaffeine. We therefore recently began a new series of experiments in order to develop a new reliable method for the synthesis of 8-X-organomercuri derivatives (X = HgCl, $HgOCOCH_3$, $HgOCOCF_3$) of theophylline (Ia) and theobromine (IIa) as substrates for their subsequent demercuration. In the present paper we report the successful preparation (although by an indirect method) from theophylline (I) and theobromine (II) of their 8-trifluoroacetoxymercuri derivatives Ib and IIb, as well as successful attempts to bromo- and iododemercurate the latter:



I a-d



II a-d

I–II a X=H; b X=$HgOCOCF_3$; c X=Br; d X=I

It is known that N-acyl derivatives are obtained by the action of acid chlorides on Ia and IIa or acid anhydrides on the more reactive theophylline (Ia). However, the N-acetyl derivatives [11, 12] are hydrolyzed very rapidly even by the action of water. Their direct C-mercuration by mercury(II) salts must therefore be carried out in an anhydrous medium such as in a mixture of the corresponding dehydrating anhydride and anhydrous acid (the mercury salts are usually only slightly soluble in the pure anhydrides). We initially made

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TABLE 1. Characteristics of the Compounds Obtained

Compound	mp, °C	Found, %			Empirical formula	Calc., %			Yield, %
		C	H	N		C	H	N	
Ib	300—340[b]	21,9	1,4	11,4	$C_9H_7F_3N_4O_4$	22,4	1,6	11,7	53
IIb	320—360[b]	21,9	1,4	11,4	$C_9H_7F_3N_4O_4$	22,0	1,5	11,5	56
Ic	320—321 [13]	32,5	2,7	21,6	$C_7H_7BrN_4O_2$	32,8	2,8	21,9	96
IIc	341—342 [14]	32,5	2,7	21,6	$C_7H_7BrN_4O_2$	32,2	2,8	21,7	92
Id	280—285[b] [15]	27,5	2,3	18,3	$C_7H_7IN_4O_2$	27,7	2,4	18,7	95
IId	290—295[b] [16]	27,5	2,3	18,3	$C_7H_7IN_4O_2$	27,3	2,3	18,5	95

[a]Lossen tests showed the presence of the corresponding halogens in each case: fluorine (in the form of CaF_2) and bromine or iodine (in the form of AgBr or AgI). [b]With decomposition.

an unsuccessful attempt to mercurate the N-acetyl derivatives of Ia and IIa by the action of $HgCl_2$ or $Hg(OCOCH_3)_2$ in an anhydrous medium (a mixture of acetic anhydride and glacial acetic acid). We were able to obtain mercuri derivatives Ib and IIb only by the prolonged action of the more active [13] mercury(II) trifluoroacetate in a refluxing mixture of trifluoroacetic acid and its anhydride on N-acetyl derivatives of Ia and IIa. The initial products were the corresponding N-acetyl-8-trifluoroacetoxymercuri derivatives, which, however, are completely hydrolyzed during their recrystallization from water to give pure C-organomercuri compounds Ib and IIb in 53 and 56% yields, respectively. The more reactive theophylline (Ia) can also be initially N-trifluoroacetylated, and the resulting product can then be mercurated with $Hg(OCOCF_3)_2 + CF_3COOH + (CF_3CO)_2O$ to give, after recrystallization from water, the same mercuri derivative Ib.

We then checked the lability of the $HgOCOCF_3$ group in Ib and IIb under the influence of halodemercurating agents such as aqueous solutions of KBr_3 and KI_3. We found that bromodemercuration leads to the formation of the recently discovered [14, 15] bromo derivatives Ic and IIc in 96 and 92% yields, respectively. Compounds Ib and IIb did not, unexpectedly, undergo iododemercuration in aqueous KI_3 solution, despite the fact that C-organomercuri derivatives of caffeine are iododemercurated effectively by this reagent [2]. However, we were able to demercurate Ib with a solution of iodine in acetonitrile. Mercuri derivative IIb is also demercurated in this solution but only in the presence of an equivalent of potassium iodide. As a result, we obtained the recently discovered [16, 17] iodo derivatives Id and IId in high yields.

An attempt to chlorodemercurate Ib and IIb by the action of excess amounts of pure liquid SCl_2 and S_2Cl_2 did not lead to the desired chloro derivatives. However, it must be recalled that these little-studied reactions give 8-chlorocaffeine in high yields only with the more reactive 8,8'-mercuribiscaffeine and are inapplicable to 8-acetoxymercuricaffeine [2]. The results of our further studies of the demercuration of C-organomercuri derivatives of Ia and IIa, uracil, imidazole, etc. will be reported upon their completion.

The compositions and structures of all of the compounds that we obtained were confirmed by their melting points, the results of elementary analysis (Table 1), and their PMR spectra (Fig. 1). As compared with starting dimethylxanthines Ia and IIa, the one-proton signal of the 8-H proton at 8.4 ppm vanishes in the PMR spectra of Ib-d and IIb-d, but the three-proton signals of the N-methyl groups are retained. This constitutes unambiguous proof that the X group ($HgOCOCF_3$, Br, and I) is in the 8 position. Broad signals of NH groups are virtually absent in the spectra of solutions in CF_3COOH at room temperature. The PMR spectra of Ia, IIa, and some of their 8-substituted derivatives are described in [18, 19].

EXPERIMENTAL

The melting points of the compounds were not corrected. The PMR spectra of solutions of the compounds in CF_3COOH were recorded with a Tesla BS-487C spectrometer (80 MHz) at room temperature with hexamethyldisiloxane as the internal standard.

8-Trifluoroacetoxymercuritheophylline (Ib). A) A solution of 4.2 g (0.01 mole) of mercury(II) trifluoroacetate [20] in a mixture of 20 ml (0.14 mole) of trifluoroacetic

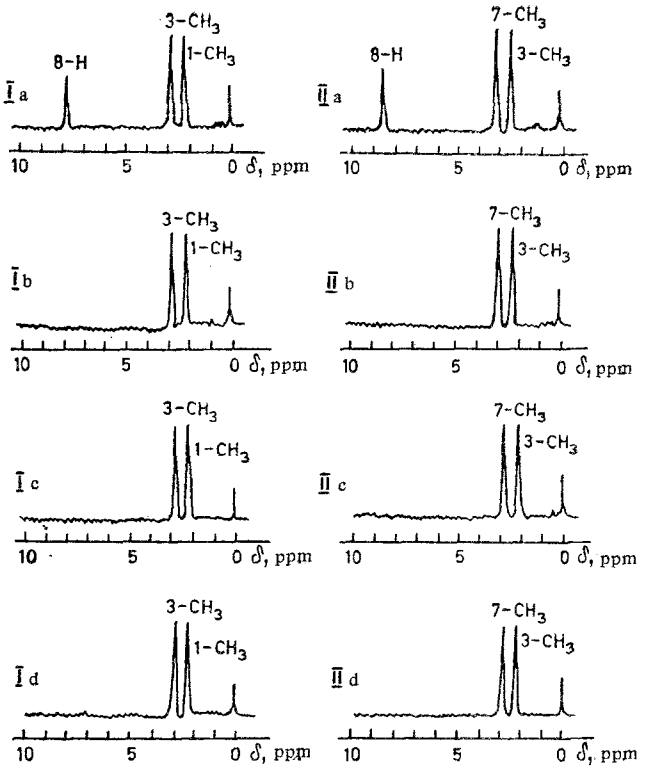

Fig. 1. PMR spectra of theophylline (Ia) and theobromine (IIa) and their 8-substituted derivatives.

anhydride with 10 ml (0.13 mole) of anhydrous trifluoroacetic acid was added to a solution of 2.2 g (0.01 mole) of 7-acetyltheophylline [11] in 20 ml (0.14 mole) of trifluoroacetic anhydride, and the mixture was refluxed for 20 h. The small amount of white precipitate that was liberated during the reaction was removed at the end of the reaction. The solvent was removed from the filtrate by distillation in vacuo until a viscous sticky mass of the mercuration product (7-acetyl-8-trifluoroacetoxymercuritheophylline) was obtained. This product was treated with stirring with 50 ml of water, and the colorless precipitate was recrystallized from water to give colorless rods of 8-trifluoroacetoxymercuritheophylline (Ib).

B) A solution of 1.8 g (0.01 mole) of theophylline (Ia) in 20 ml (0.01 mole) of trifluoroacetic anhydride was refluxed for 2 h, after which a solution of 4.2 g (0.01 mole) of mercury(II) trifluoroacetate in a mixture of 20 ml (0.14 mole) of trifluoroacetic anhydride and 10 ml (0.13 mole) of anhydrous trifluoroacetic acid was added dropwise with heating and stirring. Mercuration was then carried out for 20 h as described above (method A), and the reaction product (7-trifluoroacetyl-8-trifluoroacetoxymercuritheophylline) was crystallized from water to give Ib in the form of colorless rods. No melting-point depression was observed for a mixture of this product with a sample of the compound obtained by method A.

8-Trifluoroacetoxymercuritheobromine (IIb). A 2.2-g (0.01 mole) sample of 1-acetyltheobromine [12] was mercurated with 4.2 g (0.01 mole) of mercury(II) trifluoroacetate in a mixture of 20 ml of $(CF_3CO)_2O$ and 10 ml of CF_3COOH as described above (method A for the preparation of Ib). Recrystallization of the initially obtained white reaction product (7-acetyl-8-trifluoroacetoxymercuritheobromine) from water gave pure mercury derivative IIb in the form of colorless rods.

8-Bromotheophylline (Ic). A 1.6-g (0.01 mole) sample of bromine was added dropwise with stirring to a suspension of 4.9 g (0.01 mole) of 8-trifluoroacetoxymercuritheophylline (Ib) in 20 ml of a saturated aqueous solution of potassium bromide, and the mixture was neutralized carefully to pH 7 with sodium bicarbonate or carbonate and then heated with stirring at 80°C for 30 min. The resulting almost colorless solution was cooled, and the white precipitate was removed by filtration, washed with water, and crystallized from ethanol to give bromo derivative Ic in the form of colorless needles.

8-Bromotheobromine (IIc). Pure bromide IIc was obtained in the form of colorless needles (from ethanol) from 4.9 g (0.01 mole) of 8-trifluoroacetoxymercuritheobromine (IIb) by the method used to bromodemercurate Ib.

8-Iodotheophylline (Id). A 2.53-g (0.01 mole) sample of iodine was added to a solution of 4.9 g (0.01 mole) of 8-trifluoroacetoxymercuritheophylline (Ib) in 20 ml of acetonitrile, and the mixture was heated with stirring at 80°C for ∿30 min until the color due to iodine vanished almost completely. Product IId was obtained in the form of a white precipitate after dilution of a cold solution in acetonitrile with ether. The precipitate was washed with ether and recrystallized from ethanol to give colorless needles.

8-Iodotheophylline (IId). A 1.66-g (0.01 mole) sample of potassium iodide and 2.53 g (0.01 mole) of iodine were added to a solution of 4.9 g (0.01 mole) of 8-trifluoroacetoxymercuritheobromine (IIb) in 20 ml of acetonitrile, after which iododemercuration was carried out as described above (see the synthesis of Id) to give iodide IId in the form of colorless needles (from ethanol).

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