SYNTHESIS OF COMPOUNDS OF THE PURINE SERIES

XXIV. 8-R-METHYL DERIVATIVES OF 2,3,7-TRIMETHYL HYPOXANTHINE

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In the course of the search for new, biologically active theobromine derivatives (substituted at the C_2 atom, i.e., compounds having quinone type distribution of double bonds in the pyrimidine ring) [1], there arose the problem of synthesis of 2-methyltheobromine derivatives (specifically 2,3,7-trimethyl-6-oxo-3,6-dihydropurine) substituted at the C_8 atom by the CH_2R group (I).

Attempts to use as the starting material 2,8-dimethyltheobromine, which has already been described by us in a previous article (1), and introducing one chlorine atom directly into the methyl group attached to the C_8, resulted in the formation of a mixture of chlorides, which were difficult to separate. Thus we have developed a method of synthesis of (I) from 8-chlorotheobromine (II), by reacting the latter compound with phosphoryl chloride. A compound shown to be 2,8-dichlorotheobromine was isolated from this reaction mixture in a yield of about 60%. Its structure was verified by reaction with 1 mole sodium ethoxide and identification of the reaction product as 2-ethoxy-8-chlorotheobromine (IV), which has already been described and was prepared by chlorination of 2-ethoxytheobromine [2].

This reaction indicates that differences in the mobility of the chlorine atoms of the dichloride (III) make it possible to introduce various substituents into the pyrimidine and imidazole parts of the molecule.

2-Methyl-8-chlorotheobromine (V) was obtained in high yields by substituting the C_2 attached chlorine atom of the dichloride (III) by a malonic residue and inducing hydrolytic cleavage. The condensation of compound (V) with sodium-ethyl malonate resulted in the formation of a malonic derivative (VI), which on being subjected to acid hydrolysis gave 2,3,7-trimethylhypoxanthinyl-8-acetic acid, which was converted into its ethyl ester (Ia) without any preliminary separation. Chlorination of (VI) with sulfuryl chloride gave chloromalonate (VII), which in contrast with (VI) was insoluble in alkali. It proved impossible to obtain correct analysis of this compound, and it was found to contain 1% more chlorine and 1% less nitrogen. It seemed probable that this excess of chlorine could be explained by the presence of some dichloride (VIII, R=Cl), but PMR spectra did not indicate presence of any of this compound in (VII). The presence of three separate peaks at 4.10, 3.78 and 2.57 ppm indicates the presence of two N-methyl and one C-methyl groups, and the triplet at 1.38 ppm and the quartet at 4.44 ppm indicate the presence of ethyl groups. Thus the PMR spectrum proves unequivocally the structure of (VII) and also indicates that this compound is free of any noticeable amounts of compound (VIII) (R=Cl or H).

The hydrolysis of (VII) with 18% hydrochloric acid gives 2-methyl-8-chloromethyltheobromine (IX), which is a key starting material for the synthesis of a number of compounds of general formula (I):

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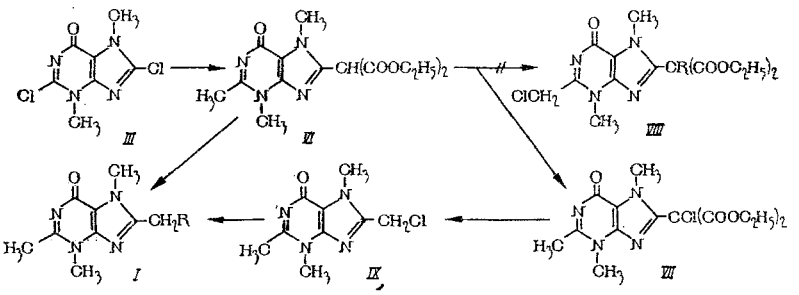
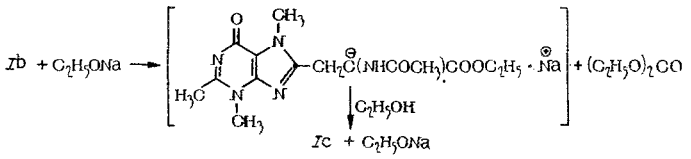


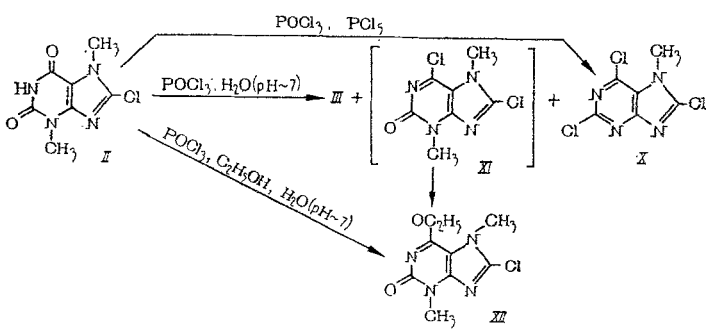
I: R = a) $COOC_2H_5$; b) $C(NHCOCH_3)(COOC_2H_5)_2$; c) $CH(NHCOCH_3)COOC_2H_5$; d) OH, e) $N(C_2H_5)_2$; f) $N(CH_2CH{=}CH_2)_2$; g) $N(CH_2CH_2OH)_2$; h) $N(CH_2CH_2Cl)_2$; i) $CH(NH_2)COOH$

Condensation of (IX) with sodiumacetylamino malonate gave the monoester (Ic) instead of the expected diester (Ib). This could be due to the presence of moisture in the reaction mixture, and consequent hydrolysis of one complex ester group during the decarboxylation of the diester. This hypothesis was shown to be incorrect, since the experiments carried out under conditions guaranteeing absence of moisture still gave the same results. It thus follows that the cleavage of the carbethoxyl groups does not involve their preliminary hydrolytic cleavage. It is well known that such cleavage takes place in the case of disubstituted malonic esters (3) and in particular in the case of purinyl malonates (4). It has been established that sodium ethoxide plays a part in such reactions and that there is formation of diethyl carbonate. In the current case this type of cleavage could be represented by the following reaction scheme:



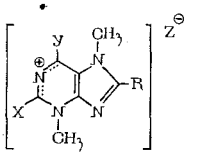
The explanation of the cleavage of (Ib) according to the proposed reaction scheme, is substantiated by the fact that the alcohol distilled off from the reaction mixture contains approximately 70% of the theoretical amount of diethyl carbonate.*

Thin layer chromatography on alumina of the products of chlorination of (II) has indicated that in addition to the dichloride (III) there are also present small amounts of two other compounds. One of these was found to be identical to 2,6,8,-trichloro-7-methylpurine (X), which we have prepared analogously to the preparation of 2,6-dichloro-7-methyl-purine from theobromine (5). In all probability the second compound is 6,8-dichlorotheobromine (XI), since the same type of reaction of 8-methyltheobromine gave two isomeric monochlorides, namely 2-chloro-8-methyltheobromine and 6-chloro-8-methyltheobromine (1). It was impossible to isolate pure (XI) from the mother liquors remaining after separation of (III), and the action of sodium ethoxide made it possible to isolate an individual compound, which was identical to 6-ethoxy-8-chlorotheobromine (XII) (2). This latter compound we prepared by reacting (II) with phosphoryl chloride, by a method analogous to the preparation of 6-ethoxytheobromine from theobromine (6, 7). The formation of (XII) on reaction with sodium ethoxide showed quite definitely that the mother liquors in question really contain (XI):



*Diethyl carbonate was determined quantitatively by heating the distilled alcohol for 30 min with an excess of 1 N solution of sodium hydroxide, titrating the excess of alkali with 1 N hydrochloric acid to phenolphthalein end point, and then titrating sodium bicarbonate to methyl orange end point.

It has already been established that the reaction of theobromine with phosphoryl chloride results in the formation of an intermediate, which is either an amido chloride (XIIa) or an adduct of 2- or 6-chlorotheobromine with phosphoryl chloride (XIIIb) (7), but this intermediate was not isolated from the reaction mixture in a crystalline state. In this case the reaction of (II) with phosphoryl chloride gave a good yield of crystalline compound, whose composition $C_7H_6Cl_5N_4O_2P$ corresponded to the structure of the adduct (XIV):



XIII: R=H, a) X=Y=Z=Cl;
b) X,Y,Z=Cl, ClOrOPOCl$_2$
XIV: R=Cl; X,Y,Z=Cl,
Cl$_u$ or OPOCl$_2$

Part of the synthesized compounds has been subjected to biological studies in order to evaluate some of their characteristics. The comparison of the pharmacological activity of the compound (Ie) with the activity of 8-diethyl-aminomethyltheobromine (8) has shown that it had lower blood vessel dilation activity and less effect on arterial pressure.

EXPERIMENTAL

The purity of the synthesized compounds has been evaluated chromatographically by using a free layer of alumina of degree of activity II. The solvent systems used included: chloroform–methyl acetate–ethanol (5 : 5 : 1) and chloroform–ethanol (9 : 1).

2,8-Dichloro-3,7-dimethylhypoxanthine (III). Sixty grams of (II) is boiled with 300 ml phosphoryl chloride until a solution is formed. Excess of phosphoryl chloride is distilled off, the viscous residue is added in batches to a mixture of 850 g ice and about 600 g sodium bicarbonate cooled in a salt bath. The mixture is stirred until evolution of carbon dioxide ceases, filtered, and the precipitate extracted with warm chloroform. Chloroform is removed by distillation and the residue is recrystallized from dry toluene. This gave about 43 g (~ 60%) of (III) of mp 225-227°C (decomp.). The compound (III) used for analysis is crystallized from dry toluene; mp 229-230°C. Found, %: Cl 30.86. $C_7H_6Cl_2N_4O$. Calculated, %: Cl 30.47.

The extraction of the filtrate with chloroform gives 5.8 g of a compound, which on being treated with sodium ethoxide solution (from 0.73 g sodium) gives ~ 0.75 g compound, which has mp 224-226°C and on being mixed with a sample of (XII) (2) does not depress its mp.

2-Ethoxy-8-chlorotheobromine (IV) (2). Two milliliters of sodium ethoxide solution (from 0.02 g sodium) is added dropwise to 0.2 g (III) in 2 ml absolute alcohol, the mixture is filtered through carbon and the alcohol is distilled off. The yield of (IV) is 0.2 g; mp 174-176°C; the mp of the sample mixed with a known sample of (IV) is 174-176°C.

Adduct of 2 (or 6), 8-Dichlorotheobromine with Phosphoryl Chloride (XIV). The reaction solution comprising (II) and phosphoryl chloride is evaporated under vacuum, the residue is allowed to crystallize out, a small amount of phosphoryl chloride is added, and then the crystals of (XIV) are washed with petroleum ether; mp 130-133°C (decomp.). Found, %: C 21.55; H 1.51; Cl 45.73; N 14.28; P 7.60. $C_7H_6Cl_5N_4O_2P$. Calculated, %: C 21.71; H 1.55; Cl 45.92; N 14.49; P 8.02.

6-Ethoxy-8-Chlorotheobromine (XII) (2). A reaction solution comprising 20 g (II) and 100 ml phosphoryl chloride is concentrated under vacuum. The residue is cooled with ice water, 200 ml of cold absolute alcohol are added, and the mixture is stirred until a solution is formed. On cooling, a precipitate of 2,6,8-trichloro-6-ethoxy-3,7-dimethyl-3,6-dihydropurine hydrochloride (XV) is formed and is washed with absolute alcohol and ether. The yield is 17.2 g; mp 201-204°C (decomp.). Found, %: C 32.70; H 3.75; Cl 42.76. $C_9H_{11}Cl_3N_4O \cdot HCl$. Calculated, %: C 32.34; H 3.59; Cl 42.51.

Seventeen grams of (XV) is mixed with a solution of 13.5 g sodium bicarbonate in 200 ml water until evolution of carbon dioxide ceases. The precipitate is separated off, the filtrate is extracted with chloroform and after crystallization from absolute alcohol, 10.5 g (XII) having mp 237-238°C are obtained. The mp of the mixture of this compound with a known sample of (XII) (2) was 233-234°C, and the mp of the sample was 232-234°C.

2,6,8-Trichloro-7-methylpurine (X) (9). A portion of phosphorous pentachloride (208 g) is added at ~20°C to a reaction solution comprising 107.2 g (II) and 500 ml phosphoryl chloride, and the mixture is boiled until complete dissolution takes place. Phosphoryl chloride is distilled off, the residue is decomposed with ice, neutralized with concentrated, aqueous ammonia (temperature <20°C), and filtered. The yield of (X) is ~99%; mp 158-160°;literature (9) mp 159-161°C.

3,7-Dimethyl-8-chlorohypoxanthinyl-2-malonate (XVI). A suspension of sodium-ethyl malonate (from 7.9 g sodium and 80 ml diethyl malonate) in 400 ml dry toluene is boiled for 30 min with 40 g of (III), water is added to dissolve the precipitate, the aqueous layer is filtered through carbon, and 40% sulfuric acid (to pH ca 5.0) is added gradually to precipitate the crystallizing oil. The yield of (XVI) is 58 g (~95%); mp 178-180°C and after crystallization from alcohol 183°C. Found, %: C 47.22; H 5.04; Cl 10.08. $C_{14}H_{17}ClN_4O_5$. Calculated, %: C 47.12; H 4.77; Cl 9.96.

2,3,7-Trimethyl-8-chlorohypoxanthine (V). A mixture of 50 g (XVI) and 200 ml 18% hydrochloric acid is boiled for about 1 h, decolorized with carbon, and the filtrate concentrated under vacuum. The residue is neutralized with 10% sodium hydroxide solution and then evaporated to dryness. The residue is extracted with hot chloroform to obtain (V). The yield is ~100%, mp 263-267°C (decomp.). If (V) is to be used for analysis it is recrystallized from alcohol; mp 272-274°C (decomp.). Found, %: C 44.81; H 4.22; Cl 16.24. $C_8H_9ClN_4O$. Calculated, %: C 45.18; H 4.24; Cl 16.70.

2,3,7-Trimethylhypoxanthynyl-8-malonate (VI). A suspension of sodium ethyl malonate (from 5.8 g sodium and 58 ml diethyl malonate in 300 ml dry toluene is heated with 25 g (V). In the course of 5-10 min a solidifying oil separates out from this reaction mixture. This material is comminuted under toluene and boiled for 8-10 h; water is added to dissolve the precipitate and the aqueous layer is decolorized with carbon, acidified with 40% sulfuric acid to pH 5.0-6.0, and extracted with chloroform. The extract is evaporated and the residue is ground with ether. The yield of (VI) is 37.5 g (95%), mp is 188-191°C and after crystallization from benzene 199-200°C. Found, %: C 53.59; H 6.08; N 16.63. $C_{15}H_{20}N_4O_5$. Calculated, %: C 53.57; H 5.95; N 16.67.

2,3,7-Trimethyl-8-chloromethylhypoxanthine (IX) and 2,3,7-Trimethylhypoxanthinyl-8-chloromalonate (VII). A solution of 45 g (VI) in 180 ml dry chloroform is mixed at ~20°C with 13.7 ml sulfuryl chloride in 25 ml chloroform and is left overnight. The chloroform is distilled off under vacuum, the residue is boiled with 250 ml of 18% hydrochloric acid, decolorized with carbon, concentrated under vacuum to a small volume, and neutralized with sodium bicarbonate. Water is eliminated under vacuum at a bath temperature <50°C. The residue is treated with hot, dry chloroform to extract (IX). After crystallization from absolute alcohol there is obtained 17.7 g of a compound having mp >200°C (yield of ~67%). For analysis this compound is crystallized from absolute alcohol. Found, %: C 47.68; H 5.18; N 24.64. $C_9H_{11}ClN_4O$. Calculated, %: C 47.68; H 4.86; N 24.72.

Part of the reaction solution (see above) is washed with 0.5 N sodium hydroxide and then with water; it is dried and the chloroform distilled off. The compound (VII) is ground with ether and is crystallized from carbon tetrachloride (1 : 30), mp 140-141°C. Found, %: C 48.41; H 5.06; Cl 10.63; N 14.01. $C_{15}H_{19}ClN_4O_5$. Calculated, %: C 48.54; H 5.14; Cl 9.58; N 15.11.

2,3,7-Trimethyl-8-hydroxymethylhypoxanthine (Id). Compound (IX) is boiled for 6 h in 100 volumes of water. The solution is neutralized with triethylamine, evaporated to dryness, and the residue recrystallized twice from 90% alcohol. This gave 75% (Id), mp 273-275°C. Found, %: Cl 51.68; H 6.26; N 26.69. $C_9H_{12}N_4O_2$. Calculated, %: C 51.92; H 5.77; N 26.92.

2,3,7-Trimethyl-8-diethylaminomethylhypoxanthine (Ie). A portion of (IX) (5.6 g) and 30 ml diethylamine are boiled for 4-5 h with stirring. Diethylamine is distilled off under vacuum, the residue is dissolved in benzene, is filtered, evaporated and ground with ether. The residue is dissolved in benzene and heated to ~70°C; then gradually 225 ml heptane followed by 40 ml of a mixture of heptane and benzene (9 : 2) are added, and the mixture is heated for several min at ~70°C and filtered. After some time the crystals are washed with ether and 4.8 g (74%) of analytically pure Ie, mp 98-100°C, are collected. Found, %: C 58.86; H 7.86; N 26.28. $C_{13}H_{21}N_5O$. Calculated, %: C 59.32; H 7.99; N 26.62.

2,3,7-Trimethyl-8-diallylaminomethylhypoxanthine Oxalate (If). A mixture of 4 g (IX) and 6 ml diallylamine in 15 ml absolute alcohol is boiled for 5 h. The solution is evaporated under vacuum and the

*It has been shown chromatographically that some (Id) is present.

residue is treated with water. The resulting crystals are put in water (if they are dried in air or in a vacuum desiccator an oil is formed), a solution of oxalic acid is added to the suspension, and the solution is filtered and evaporated to dryness. The residue is ground with ethyl acetate. The yield of the oxalate (If) is 5.3-5.4 g (80%); mp 118-121°C and after some time 152-154°C. Found, %: C 53.20; H 5.96; N 19.27. $C_{15}H_{21}N_5O \cdot H_2C_2O_4$. Calculated, %: C 54.11; H 6.10; N 18.57.

2,3,7-Trimethyl-8-bis-(β-hydroxyethyl)-aminomethylhypoxanthine Hydrochloride (Ig). A mixture of 5 g (IX) and 5 g diethanolamine in 40 ml absolute alcohol is boiled for 5 h, is decolorized with carbon and a solution of 1 g dry hydrogen chloride in 5 ml absolute alcohol is added. After washing of the residue with ether there are obtained 6.2 g (84%) hydrochloride (Ig), mp 215-218°C (decomp). For analysis this compound is crystallized from alcohol, mp 224-226°C. Found, %: C 47.30; H 6.95; N 21.02. $C_{13}H_{21}N_5O_3 \cdot HCl$. Calculated, %: C 47.05; H 6.64; N 21.20.

2,3,7-Trimethyl-8-bis-(β-chloroethyl)-aminomethylhypoxanthine (Ih). Five grams of compound (Ig) is added in batches to 40 ml thionyl chloride, the mixture is boiled for 15 min, and the excess of thionyl chloride is distilled off. First sodium carbonate and then water are added to the residue and the resulting oil is extracted with chloroform. The extract is decolorized with alumina and then evaporated. The residue (4 g Ie, mp 149-151°C) is dissolved in 25 ml absolute alcohol and alcoholic solution of hydrogen chloride is added to pH ~4.0. This gives 3.15 g (54%) of hydrochloride Ih, mp 142-145°C (decomp). Found, %: C 41.18; H 5.87; Cl 27.68; N 18.37; H_2O 2.43. $C_{13}H_{19}Cl_2N_5O \cdot HCl \cdot 0.5H_2O$. Calculated, %: C 41.32; H 5.56; Cl 28.21; N 18.54; H_2O 2.38.

For analysis (Ih) having mp 149-151°C is crystallized from benzene, and the product has mp 156-158°C (decomp.). Found, %: C 47.25; H 5.82; Cl 21.50. $C_{13}H_{19}Cl_2N_5O$. Calculated, %: C 46.69; H 5.72; Cl 21.39.

Ethyl ester of α-acetamido-β-(2,3,7-trimethylhypoxanthynyl-8)-propionic Acid (Ic). Thirty-eight grams of acetylamino malonate are added to a solution of 160 ml sodium ethoxide (from 3.7 g sodium). Then 12 g (IX) is added in the course of 30 min and the mixture is boiled for 4 h in the absence of atmospheric moisture. The reaction mixture is neutralized with an alcoholic solution of hydrogen chloride (pH 7.0) and the alcohol is distilled off under vacuum. The residue is dissolved in chloroform, the solution is filtered, evaporated water is added, and the solution is extracted with chloroform. The chloroform is distilled off and (Ic) is washed with warm ether. The yield is 8 g (~90%), mp 195-200°C. For analysis this compound is crystallized from alcohol; mp 205-207°C. Found, %: C 53.84; H 6.30; N 21.28. $C_{15}H_{21}N_5O_4$. Calculated, %: C 53.73; H 6.27; N 20.90.

β-(2,3,7-Trimethylhypoxanthynyl-8)-alanine (Ii). A portion of (Ic) (0.5 g, mp 195-200°C) and 50 ml of 18% hydrochloric acid are boiled for 2 h and the solution is decolorized with carbon and evaporated to dryness. The resulting dihydrochloride (Ii) is neutralized with a calculated amount of triethylamine in 30 ml absolute alcohol. The alcohol is distilled off, the residue is washed with chloroform to complete absence of chlorine ions, and then is washed with ether. The residue (4.7 g) is dissolved in ~15 ml water, the solution is decolorized with carbon, and gradually diluted with 75 ml alcohol. The reaction mixture is filtered and the residue is washed with a small amount of 70% alcohol and then with absolute alcohol and ether. This gives 3.7-3.9 g (Ii), mp 287-289°C (decomp) which gives violet coloration with ninhydrin. Found, %: C 49.35; H 5.72; N 26.05. $C_{11}H_{15}N_5O_3$. Calculated, %: C 49.31; H 5.71; N 26.15.

Ethyl ester of 2,3,7-trimethylhypoxanthynyl-8-acetic acid (Ia). A mixture of 3 g (VI) and 15 ml of 18% hydrochloric acid is boiled for 30 min and then is evaporated to dryness. Then 20 ml absolute alcohol and 0.5 ml concentrated sulfuric acid are added to the residue and the mixture is boiled for 2 h. The product is diluted with water, neutralized with sodium bicarbonate, and extracted with chloroform. This gives 1.6-1.7 g (~70%) (Ia); mp 153-156°C; after crystallization from alcohol mp 160-161°C. Found, %: C 54.85; H 6.51; N 21.51. $C_{12}H_{16}N_4O_3$. Calculated, %: C 54.55; H 6.06; N 21.21.

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