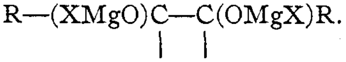
Summary

The unsaturated halogeno-magnesium glycolates obtained by reduction of various aromatic diketones have been prepared and their reactions studied. Several new benzils and benzoins necessary for this work have been prepared and described.

It has been found that magnesium iodide alone, even in the absence of metallic magnesium, has a decided reducing action on the diketone; the amount of glycolate formed is dependent upon the equilibrium: diketone + $MgI_2 \rightleftharpoons$ glycolate + I_2. The amount of iodine thus set free is from 16 to 50% of the theoretical.

The characteristic color changes during and at the end of the reduction process suggest the probability of the existence in the unsaturated glycolates of molecules containing each two trivalent carbon atoms



$$R\text{—}(XMgO)\underset{|}{C}\text{—}\underset{|}{C}(OMgX)R.$$

ANN ARBOR, MICHIGAN

[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

THE SYNTHESIS OF SOME ALKYLXANTHINES[1,2]

BY D. W. MACCORQUODALE

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In view of the valuable therapeutic properties of the naturally occurring xanthine bases theophylline, theobromine and caffeine, it seems desirable that a study be made of the relation between the pharmacological action and the nature of the alkyl groups attached to the xanthine nucleus. This work was undertaken at the suggestion of the late Dr. A. S. Loevenhart in order to make available some of the homologs of these alkaloids for such a study.

A consideration of the various syntheses devised for the preparation of compounds of this type finally led to the selection of a series of reactions worked out by Emil Fischer during his researches on the purines and used by him for the preparation of caffeine.

Potassium urate when heated with phosphorus oxychloride yields 8-hydroxy-2,6-dichloropurine (I) which in turn is converted into trichloropurine when heated with a large excess of the same reagent.

The chlorine atom at position eight being much more firmly attached than those in the other positions, does not react with sodium ethoxide,

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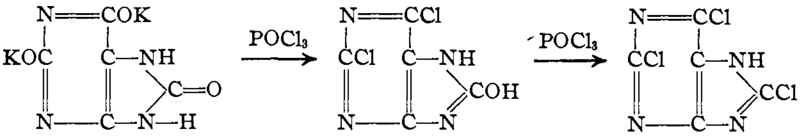
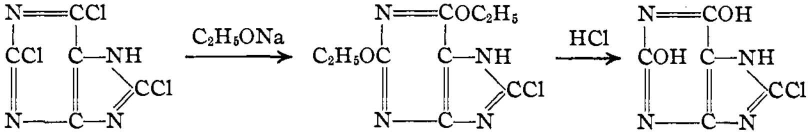
[1] This paper is constructed from a thesis submitted to the Graduate School of the University of Wisconsin in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Chemistry.

[2] Read before the Regional Meeting of the American Chemical Society at Minneapolis on June 19, 1928.



I

while the others are readily replaced by ethoxyl groups forming 2,6-diethoxy-8-chloropurine (II). The ethoxyl groups are easily replaced by hydroxyl groups by heating the compound with concentrated hydrochloric acid.



II III

The 8-chloroxanthine (III) thus obtained is dissolved in aqueous potassium hydroxide solution and heated with two moles of alkyl iodide to form the 3,7-dialkyl-8-chloroxanthine, which can be reduced to the 3,7-dialkylxanthine or can be further alkylated to the 1,3,7-trialkyl-8-chloroxanthine, which upon reduction yields the 1,3,7-trialkylxanthine. It was found that the 1,3,7-trialkyl-8-chloroxanthine cannot be readily obtained in one operation from the 8-chloroxanthine, for even when a considerable excess of the alkylating agents is used the yield of trialkylchloroxanthine is small and the yield of dialkylchloroxanthine relatively large. This is in agreement with the work of Biltz and Peukert,[3] who found that the ethylation of 3-ethyl-8-chloroxanthine produced 3,7-diethyl-8-chloroxanthine, but they did not attempt to ethylate this compound further. Other evidence to show that xanthine and its substitution products are most readily alkylated in the 3- and 7-positions is found in the work of Fischer, who showed that theobromine is formed by the methylation of xanthine,[4] that the methylation of 3-methylxanthine also produces theobromine[5] and that chlorotheobromine can be obtained by the methylation of 3-methyl-8-chloroxanthine.[6]

By the ethylation of 8-chloroxanthine (III) a compound was obtained which analysis showed to be a diethylchloroxanthine. That it was the 3,7-isomer which would be expected was shown by its reduction to 3,7-diethylxanthine,[3] but its melting point (207°) did not agree with that of the 3,7-diethyl-8-chloroxanthine obtained by Biltz and Peukert, who give its melting point as 238°. They proved the structure of their compound by hydrolyzing it with alkali and obtaining 3,7-diethyluric acid,

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[3] Biltz and Peukert, *Ber.*, **58**, 2198 (1925).

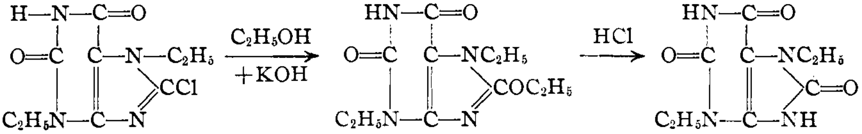
[4] Fischer, *Ann.*, **215**, 311 (1882).

[5] Fischer and Ach, *Ber.*, **31**, 1987 (1898).

[6] Ref. 5, p. 1984.

which had previously been prepared by Biltz and Sedlatschek.[7] We attempted to hydrolyze our compound both by boiling with normal potassium hydroxide solution and by heating to 125–130° with concentrated hydrochloric acid for five hours; in both cases the substance was recovered unchanged.

The diethylchloroxanthine was finally converted into 3,7-diethyluric acid (IV) by treatment with potassium hydroxide in absolute alcohol solution. 3,7-Diethyl-8-ethoxyxanthine was thus obtained and this compound, upon heating with concentrated hydrochloric acid, readily yielded the 3,7-diethyluric acid prepared by Biltz and Sedlatschek.



IV

Contrary to statements of these authors it was found that this compound suffers decomposition at its melting point and so it proved unsuited for identification of the diethylchloroxanthine. This was accomplished, however, by methylation of the diethyl-8-chloroxanthine, treatment of the methyldiethyl-8-chloroxanthine with alcoholic potassium hydroxide to form methyldiethyl-8-ethoxyxanthine, and hydrolysis of this with concentrated hydrochloric acid to form a compound identical with the 1-methyl-3,7-diethyluric acid of Biltz and Sedlatschek,[7] thus proving the structure of the 3,7-diethyl-8-chloroxanthine, and also of each of the intermediate compounds.

By application of these methods the ethyl and normal butyl analogs of theobromine and caffeine were obtained as well as a number of other new purine derivatives.

Experimental Part

2,6-Dichloro-8-hydroxypurine.—This was prepared by Fischer's[8] method, the yields varying from 42 to 48% of the theoretical. It was partly purified by boiling with three times its weight of concentrated nitric acid, further purification being found unnecessary for the preparation of trichloropurine.

Trichloropurine.—This was prepared as described by Fischer[9] and yields of 46 to 50% of the theoretical were obtained.

2,6-Diethoxy-8-chloropurine.—The method described by Fischer[10] was followed except that it was found unnecessary to heat the reactants in a sealed vessel. The reaction takes place readily when a hot solution of trichloropurine in absolute alcohol is added slowly to a boiling alcoholic solution of sodium ethoxide under a reflux condenser; yield, 64–73% of the theoretical.

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[7] Biltz and Sedlatschek, *Ber.*, **57**, 179 (1924).

[8] Fischer and Ach, *ibid.*, **30**, 2209 (1897).

[9] Fischer, *ibid.*, **30**, 2221 (1897).

[10] Fischer, *ibid.*, **30**, 2234 (1897).

8-Chloroxanthine.—This was prepared exactly as described by Fischer,[10] the yield of crude product being 91% of the theoretical. It was purified by crystallization of the ammonium salt from dilute ammonia solution and subsequent decomposition of the salt with hydrochloric acid.

3,7-Diethyl-8-chloroxanthine.—Five grams of 8-chloroxanthine was dissolved in 68.5 cc. (2.25 molecular equivalents) of 0.917 *N* potassium hydroxide solution and shaken in a closed vessel with 9.4 g. (2.25 molecular equivalents) of pure ethyl iodide for one and one-half hours at 90–95°. The light yellow, crystalline product was filtered off, washed with water and then treated with very dilute potassium hydroxide solution whereupon it readily passed into solution, leaving practically no residue. In the cases of those runs in which larger proportions of alkali and ethyl iodide were used a small amount of alkali-insoluble material was obtained which proved to be triethylchloroxanthine but its amount was never very great. Upon addition of a slight excess of dilute hydrochloric acid to the filtrate the product was precipitated as a white crystalline solid which was filtered off, washed with cold water and dried at 110°. The yield was 1.6–2.0 g. For the analysis it was crystallized from a large volume of hot water and dried at 110°.

Anal. Calcd. for $C_9H_{11}O_2N_4Cl$: Cl, 14.62. Found: Cl, 14.40, 14.23.

The compound dissolves in hot alcohol, benzene, ethyl acetate and acetone, and separates in white needles on cooling. It is very soluble in chloroform. It is difficultly soluble in hot water and the solution on cooling deposits beautiful white needles. After one such crystallization the substance melted at 201–202° (207° corrected) and a recrystallization did not raise the melting point. Biltz and Peukert give the melting point of this substance as 238° but this is evidently a typographical error and probably 208° is intended. Upon reduction with hydriodic acid and phosphonium iodide it yields 3,7-diethylxanthine melting at 183°.

3,7-Diethyl-8-ethoxyxanthine.—One gram of 3,7-diethyl-8-chloroxanthine was heated for two hours under reflux with 15 cc. of a 10% solution of potassium hydroxide in absolute alcohol. A precipitate of potassium chloride began to separate soon after the heating was started. The alcoholic solution was evaporated to about 3 cc. and then was diluted with 20 cc. of water. The solution was acidified with hydrochloric acid and the voluminous white precipitate filtered off, washed with water and dried at 110°; yield, 0.93 g. After being recrystallized from alcohol the melting point was 207° (212° corrected). The analysis for nitrogen was by the Kjeldahl method.

Anal. Calcd. for $C_{11}H_{16}O_3N_4$: N, 22.22. Found: N, 22.12, 22.39.

The 3,7-diethyl-8-ethoxyxanthine is easily soluble in benzene, chloroform, acetone and glacial acetic acid. It dissolves sparingly in ether. Strong acids and dilute alkali solutions dissolve it easily. In hot water it dissolves only very slightly and separates again on cooling in fine, short, white needles. It is readily soluble in hot alcohol–water mixtures and these solutions on cooling deposit long, closely matted, hair-like needles.

3,7-Diethyluric Acid.—One tenth of a gram of 3,7-diethyl-8-ethoxyxanthine was dissolved in 2 cc. of concentrated hydrochloric acid (sp. gr. 1.19) and heated on the water-bath for twenty minutes. White crystals began to separate from the clear solution almost immediately. A little water was added and after the mixture had been cooled to 5° the product was filtered off and washed with a little cold water. The crystals were dissolved in 5 cc. of hot water to which had been added a drop of concentrated hydrochloric acid and 2 cc. of 95% alcohol. The solution was filtered and upon cooling and standing the diethyluric acid separated in small white crystals which were filtered off, washed with water and dried in the oven at 110°. The melting point was 360–365° (371–376° corrected) with decomposition. Biltz and Sedlatschek give the melting point as 350–355° without decomposition.

1-Methyl-3,7-diethyl-8-chloroxanthine.—Two grams of 3,7-diethyl-8-chloroxanthine was dissolved in 100 cc. of 0.917 *N* potassium hydroxide solution and 2 g. (excess) of pure methyl iodide was added. This was sealed in a pyrex bomb tube and shaken at 80–85° for two and one-half hours. When cool the crystalline product was filtered off and washed with very dilute potassium hydroxide solution to remove any unchanged diethylchloroxanthine and free iodine. After washing with water and drying at 105° it weighed 1.78 g. For the analysis it was recrystallized from 50% alcohol, from which it separated in beautiful white needles which melted at 113° (114.5° corrected).

Anal. Calcd. for $C_{10}H_{13}O_2N_4Cl$: Cl, 13.82. Found: Cl, 13.97, 13.73.

The compound is insoluble in water and in alkali but dissolves readily in strong hydrochloric acid. It dissolves in acetone, chloroform, benzene, ether and glacial acetic acid.

1-Methyl-3,7-diethyl-8-ethoxyxanthine.—Seven-tenths of a gram of 1-methyl-3,7-diethyl-8-chloroxanthine was heated under a reflux condenser with a 10% solution of potassium hydroxide in absolute alcohol for forty minutes. Potassium chloride separated rapidly during the heating. Most of the alcohol was removed by evaporation and the solution was acidified with dilute acetic acid. The voluminous white product was filtered off, washed with water and dried; yield 0.43 g. It was recrystallized from 50% alcohol; m. p. 111° (112° corrected).

Anal. Calcd. for $C_{12}H_{18}O_3N_4$: N, 21.05. Found: N, 20.68.

The compound is insoluble in water and in alkali but dissolves readily in strong hydrochloric acid. It is readily soluble in alcohol, ether, benzene, acetone and chloroform.

1-Methyl-3,7-diethyluric Acid.—Fifty milligrams of 1-methyl-3,7-diethyl-8-ethoxyxanthine was dissolved in 3 cc. of concentrated hydrochloric acid and heated on the water-bath for fifteen minutes, the solution being allowed to evaporate to dryness at the end of this period. The white crystalline residue was dissolved in 1.5 cc. of boiling 95% alcohol and chilled to −10°. The white crystalline product was filtered off and washed with a few drops of alcohol. It melted sharply without decomposition at 258° (266° corrected). Biltz and Sedlatschek obtained this compound by heating 1-methyl-3,7,9-triethyluric acid with hydrochloric acid and found it to have a melting point of 257–258°.

1,3,7-Triethyl-8-chloroxanthine.—Four grams of 3,7-diethyl-8-chloroxanthine was dissolved in 18.4 cc. of 0.895 *N* potassium hydroxide and 5.0 g. of pure ethyl iodide added. The mixture was shaken in a closed vessel at 90–95° for two hours. The solid product was filtered off and leached with very dilute potassium hydroxide solution and then washed with water. The air-dried product weighed 2.05 g. Upon acidification of the potassium hydroxide solution with hydrochloric acid, 0.48 g. of unchanged diethylchloroxanthine was obtained. The product was recrystallized from 50% alcohol; m. p. 79–80°.

Anal. Calcd. for $C_{11}H_{15}O_2N_4Cl$: Cl, 13.10. Found: Cl, 12.89, 12.81.

The triethyl-8-chloroxanthine is insoluble in water and alkali but dissolves readily in hydrochloric acid. It is also soluble in alcohol, ether, acetone, benzene, chloroform and glacial acetic acid.

1,3,7-Triethylxanthine.—Four grams of pure 1,3,7-triethyl-8-chloroxanthine was dissolved in 20 cc. of fuming hydriodic acid (sp. gr. 1.96) and heated on the water-bath with the occasional addition of small amounts of finely pulverized phosphonium iodide. When iodine was no longer liberated the reduction was over. This required about eight hours. The solution was evaporated on the water-bath until only a thick paste of crystals of the hydriodide of triethylxanthine remained. The crystals were dissolved in 15 cc. of water and dilute ammonium hydroxide solution added to liberate the base. The solution was chilled and the white crystalline product filtered off, washed and dried in the air; wt. 3.05 g. From the mother liquor a small crop of crystals was obtained upon concentration. The compound was purified by recrystallization from dilute alcohol; m. p. 113°.

Triethylxanthine was first obtained by Scarlat[11] by means of Traube's synthesis. He gives the melting point as 115°. Like caffeine it has no acid properties but acts as a weak base. It is difficultly soluble in water but dissolves readily in strong hydrochloric acid. It also dissolves in alcohol, ether, acetone, benzene, chloroform and glacial acetic acid. It can be volatilized undecomposed at atmospheric pressure.

3,7-Dibutyl-8-chloroxanthine.—The butylation of 8-chloroxanthine was found to proceed in exactly the same manner as the ethylation, that is, upon shaking the chloroxanthine with an excess of alkali and butyl iodide at 130°, the main product obtained was a dibutylchloroxanthine, only a very small amount of the tributyl derivative being formed. For the preparation of 3,7-dibutyl-8-chloroxanthine, 10.0 g. of 8-chloroxanthine was dissolved in 126 cc. of 0.895 *N* potassium hydroxide and 20.8 g. of pure *n*-butyl iodide was added. This was shaken in a closed vessel for two hours at 130°. The solid product was filtered from the well-cooled reaction mixture and purified in the manner described for 3,7-diethyl-8-chloroxanthine. The yield of crude product was 7.9 g. After recrystallization from 60% alcohol the melting point was 142.5 (145° corrected).

Anal. Calcd. for $C_{13}H_{19}O_2N_4Cl$: Cl, 11.87. Found: Cl, 11.86.

The 3,7-dibutyl-8-chloroxanthine is very slightly soluble in boiling water and separates in crystals on cooling. It dissolves readily in dilute alkali and in strong hydrochloric acid. It is readily soluble in alcohol, acetone, benzene, chloroform and glacial acetic acid, and somewhat less readily soluble in ether.

3,7-Dibutylxanthine.—This was prepared by the reduction of 3,7-dibutyl-8-chloroxanthine in a manner precisely the same as that described for the preparation of triethylxanthine. From 1 g. of 3,7-dibutyl-8-chloroxanthine 0.83 g. of dibutylxanthine was obtained which after recrystallization from dilute alcohol had a melting point of 124–125° (127° corrected).

Anal. Calcd. for $C_{13}H_{20}O_2N_4$: N, 21.20. Found: N, 21.11, 21.24.

The 3,7-dibutylxanthine is very sparingly soluble in boiling water, from which it crystallizes on cooling. Dilute alkali and strong hydrochloric acid dissolve it readily. It dissolves with ease in alcohol, acetone, benzene, chloroform and glacial acetic acid, and a little less readily in ether.

1,3,7-Tributyl-8-chloroxanthine.—Six grams of 3,7-dibutyl-8-chloroxanthine was dissolved in 28.2 cc. (25% excess) of 0.895 *N* potassium hydroxide solution and 4.7 g. (25% excess) of pure *n*-butyl iodide added. The mixture was shaken in a closed vessel at 125–130° for two hours. When the vessel was allowed to cool the product remained as a viscous brown oil. The reaction mixture was shaken with 20 cc. of pure redistilled benzene to dissolve the oil and the benzene solution was shaken three times with 5% potassium hydroxide solution. From this alkaline solution there was recovered 0.4 g. of dibutylchloroxanthine by acidification with dilute hydrochloric acid. The benzene solution was washed three times with water and then dried over anhydrous sodium sulfate. The benzene solution was filtered into a small distilling flask and the solvent distilled off, the last traces being removed at 10-mm. pressure and the temperature of the boiling water-bath. The flask was then heated strongly, the pressure being maintained at 10 mm., and the product began to distil at 232° (uncorrected), about 80%

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[11] Scarlat, *Bull. Sciences Bucarest,* **13,** 155–159 (1903).

of it distilling before the temperature reached 240°. The distillate was light yellow in color and weighed 4.2 g.

Anal. Calcd. for $C_{17}H_{27}O_2N_4Cl$: Cl, 9.99. Found: Cl, 9.92, 9.98.

The 1,3,7-tributyl-8-chloroxanthine is a viscous oil, soluble in alcohol, ether and benzene. An unsuccessful attempt was made to form the hydrochloride salt by precipitation from dry ether and benzene solutions with dry hydrogen chloride.

1,3,7-Tributylxanthine.—This compound, which is the butyl analog of caffeine, was prepared by the reduction of 1,3,7-tributyl-8-chloroxanthine with fuming hydriodic acid and phosphonium iodide in the manner already described. The free base was obtained as a colorless oil which solidified when chilled with ice and salt. It was filtered off and washed with water, and after drying thoroughly was dissolved in 155 cc. of absolute alcohol and the solution was saturated with dry hydrogen chloride gas. Then 30 cc. of dry ether was added and the solution cooled to 0° whereupon the hydrochloride of tributylxanthine separated almost completely in white crystals which were filtered off and washed with dry ether. The yield was 2.20 g. from 3.30 g. of tributylchloroxanthine. The salt was recrystallized from an alcohol–ether solution (1:2) saturated with hydrogen chloride and after being washed with dry ether was dried in a vacuum desiccator over calcium chloride and solid caustic potash. The melting point was 131–134°.

Anal. Calcd. for $C_{17}H_{29}O_2N_4Cl$: Cl, 9.94. Found: Cl, 9.75, 9.51.

The free base was liberated from the salt by dissolving the latter in a few cc. of 95% alcohol and adding dilute ammonium hydroxide solution. Upon chilling the solution in ice and salt the tributylxanthine separated as a colorless oil which gradually crystallized and was filtered off and washed with dilute alcohol. It was recrystallized again from alcohol, being obtained as pure white crystals which melted at 41–42°.

Anal. Calcd. for $C_{17}H_{28}O_2N_4$: N, 17.56. Found: N, 17.56.

The 1,3,7-tributylxanthine is a white crystalline solid which is practically insoluble in water and alkali. It dissolves readily in strong acids, forming salts which are hydrolyzed upon dilution. It can be volatilized at atmospheric pressure without decomposition. It dissolves easily in the common organic solvents such as alcohol, ether, acetone, benzene, chloroform and glacial acetic acid.

To Dr. Homer Adkins, under whose supervision this work was carried out, the author wishes to express his thanks for many valuable suggestions made during the course of this investigation.

Summary

1. The ethyl and the *n*-butyl analogs of caffeine and theobromine have been prepared, the latter for the first time and the former by a method not heretofore used for the preparation of these compounds.

2. A number of other new derivatives of xanthine have been synthesized and described.

MADISON, WISCONSIN