[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

Heterocyclic Basic Compounds. VI.[1] Dialkylaminoalkylamino-purines

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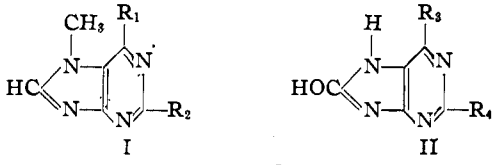
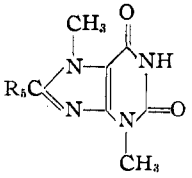
With the exception of the classical work of Emil Fischer and W. Traube on the synthesis of the natural occurring purines, very few new purines have been reported. It therefore seemed of interest, as an extension of our previous work on simple heterocyclic ring systems,[4] to prepare some (dialkylaminoalkylamino)-purines. The compounds which were synthesized correspond to the following general formulas:



I

II



III

In formula I, R_1 may be amino, diethylamino or γ-diethylaminopropylamino and R_2 is either chloro, diethylamino or γ-diethylaminopropylamino. In formula II, R_3 may be diethylamino or γ-diethylaminopropylamino and R_4 is either chloro, diethylamino or γ-diethylaminopropylamino. In formula III, R_5 is γ-diethylaminopropylamino.

The starting material for the synthesis of the methylpurines was theobromine which was readily converted to 2,6-dichloro-7-methylpurine by phosphorus oxychloride according to the method of Fischer.[5] It was found that prolonged heating of the theobromine with phosphorus oxychloride resulted in a yellowish product and in some cases the only material separated was completely soluble in dilute alkali, whereas the desired product is alkali-insoluble. This by-product, which has been mentioned by Fischer, was not investigated further.

Several unsuccessful attempts were made to aminate 2-chloro-6-(γ-diethylaminopropylamino)-7-methylpurine with aqueous ammonia at 145°,[6] with zinc ammonium chloride complex[7] and also by reaction with phenylhydrazine and subsequent reduction.[8] In the first case, 90% of the starting material was recovered unchanged while in the attempted reaction with phenylhydrazine only a red decomposition tar resulted.

The starting material for the synthesis of the 8-hydroxypurines was 2,6-dichloro-8-hydroxypurine which was prepared from the monopotassium salt of uric acid and phosphorus oxychloride according to the method of Fischer.[9]

The 2,6-dihydroxy-3,7-dimethyl-8-(γ-diethylaminopropylamino)-purine, which is represented by formula III, was made from 8-bromotheobromine. The 8-bromotheobromine was synthesized by the direct bromination of theobromine in chloroform solution.

All attempts to prepare 2-amino-6-chloropurine from guanine hydrochloride and phosphorus oxychloride at 150° and also at 175° in addition to phosphorus oxychloride–phosphorus pentachloride mixture at 145° were unsuccessful since no material containing chlorine was isolated from any of the reaction mixtures.

Acknowledgment.—The authors wish to thank Dr. H. S. Mosher for his interest and help and Parke, Davis and Company whose generous support made this work possible.

Experimental

2-Chloro-6-amino-7-methylpurine.[10]—A mixture of 12.0 g. of 2,6-dichloro-7-methylpurine and 100 ml. of concentrated aqueous ammonium hydroxide was heated in a bomb tube at 110° for eleven hours. The crystalline product was filtered, digested at room temperature with 200 ml. of 0.25 *N* potassium hydroxide solution for one-half hour, and washed with water; yield 9 g. (82.5%); m. p. over 250°. The product was easily recrystallized from water.

2-(γ-Diethylaminopropylamino)-6-amino-7-methylpurine Pentahydrochloride.—2-Chloro-6-amino-7-methylpurine, 4.2 g. (0.023 mole), and 10 g. (0.077 mole) of γ-diethylaminopropylamine were heated at 190° for seventeen hours in a bomb tube. The light yellow oil was taken up in 50 ml. of water, 3 g. of potassium carbonate added, the solution extracted with four 50-ml. portions of ether, the extracts discarded and the aqueous solution saturated with potassium carbonate. The oil layer which separated was removed and the solution extracted with two 50-ml. portions of chloroform. Anhydrous ether was added to the combined oil layer and extracts until the product just failed to separate from the solution. The solution was treated with charcoal, filtered and the filtrate saturated with dry hydrogen chloride. The precipitated, crude, white solid was washed with anhydrous ether and recrystallized from 60 ml. of *n*-propanol to which enough methanol was added to effect solution. The methanol was removed by distillation, after which the product crystallized from the boiling solution; it was washed with

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(4) (a) Whitmore, Mosher, Goldsmith, and Rytina, THIS JOURNAL, **67**, 393 (1945); (b) Mosher and Whitmore, *ibid.*, **67**, 662 (1945); (c) Yanko, Mosher and Whitmore, *ibid.*, **67**, 664 (1945); (d) Adams and Whitmore, *ibid.*, **67**, 735 (1945); **67**, 1159 (1945).

(5) Fischer, *Ber.*, **30**, 2402 (1897).

(6) Fischer and Ach, *ibid.*, **30**, 2214–2215 (1897).

(7) Diepolder, *J. prakt. Chem.*, **106**, 41 (1923).

(8) Backeberg and Marais, *J. Chem. Soc.*, 382 (1942).

(9) Fischer, *Ber.*, **28**, 2489 (1895); **30**, 2209 (1897).

(10) Fischer, *ibid.*, **31**, 117 (1898).

n-propanol–anhydrous ether mixture and finally with anhydrous ether; yield 4.95 g. (40.3%); m. p. over 225°.

Anal. Calcd. for $C_{13}H_{25}N_7Cl_5$: Cl, 38.60. Found: Cl, 38.62.

2-Chloro-6-diethylamino-7-methylpurine.—A mixture of 7.5 g. (0.037 mole) of 2,6-dichloro-7-methylpurine and 13.5 g. (0.185 mole) of diethylamine was heated in a sealed tube at 110° for five hours. The excess diethylamine was removed from the crystalline contents under reduced pressure, the residue suspended in 60 ml. of water and heated to boiling for one minute; an oil separated which crystallized on cooling and rubbing. The product was dissolved in 20% acetic acid, treated with charcoal and the solution filtered. Addition of ammonium hydroxide to the filtrate caused the separation of a brown oil which readily crystallized. Recrystallization from benzene–ligroin mixture yielded 5.3 g. (60%) of the pure white crystalline product; m. p. 107.0–107.5°.

Anal. Calcd. for $C_{10}H_{14}N_5Cl$: N, 29.20. Found: N, 28.85.

2-(γ-Diethylaminopropylamino)-6-diethylamino-7-methylpurine Pentahydrochloride.—A suspension of 4.5 g. (0.019) mole of finely powdered 2-chloro-6-diethylamino-7-methylpurine and 9.75 g. (0.075 mole) of γ-diethylaminopropylamine was placed in a bomb tube and heated at 195° for seventeen hours. The contents of the tube were treated with 110 ml. of 3% ammonium hydroxide, and the resulting milky solution was extracted with four 50-ml. portions of ether. The ether extracts were discarded and the aqueous solution saturated with potassium carbonate. The orange-red oil which separated was removed, the solution extracted with four 75-ml. portions of ether and the combined ether extracts and oil layer dried over potassium carbonate. The solvent was removed, the residue taken up in anhydrous ether and the hydrochloride precipitated as a white, finely divided powder by saturation of the solution with dry hydrogen chloride. The crude product was removed by filtration, washed with dry ether and recrystallized from 70 ml. of *n*-propanol to which enough methanol was added to effect solution. The methanol was removed by distillation and the product, which crystallized from the boiling solution, was filtered and washed first with *n*-propanol–anhydrous ether mixture and finally with anhydrous ether; yield 4.09 g. (42.1%); m. p. over 225°.

Anal. Calcd. for $C_{17}H_{35}N_7Cl_5$: Cl, 34.34. Found: Cl, 34.07.

2-Chloro-6-(γ-diethylaminopropylamino)-7-methylpurine.—To 15 g. (0.115 mole) of γ-diethylaminopropylamine, 10 g. (0.0493 mole) of 2,6-dichloro-7-methylpurine was added in small portions keeping the temperature below 125°. After all the purine had been added the solution was heated to 175° for three minutes, cooled and the red, semi-crystalline mass treated with 20 ml. of water, decolorized, filtered and 3 g. of potassium carbonate added to the resulting green solution. The solution was extracted with two 50-cc. portions of ether, the ether extracts discarded and the aqueous solution saturated with potassium carbonate. The oil layer which separated was removed and taken up in 50 ml. of benzene, the solution evaporated to 35 ml. and allowed to cool. The white crystalline product was washed with a small amount of benzene; yield 8.3 g. (56.7%), m. p. 131–133°.

The picrate was prepared in water and recrystallized from ethanol; m. p. 195–196°.

Anal. Calcd. for $C_{13}H_{21}N_5Cl\cdot 2C_6H_3O_7N_3$: N, 22.87. Found: N, 23.16.

2-Diethylamino-6-(γ-diethylaminopropylamino)-7-methylpurine Pentahydrochloride.—A mixture of 3.7 g. (0.0124 mole) of 2-chloro-6-(γ-diethylaminopropylamino)-7-methylpurine and 20 g. (0.274 mole) of diethylamine was heated in a bomb tube at 160° for twelve hours. The crystalline diethylamine hydrochloride, 0.85 g., was removed by filtration and the filtrate evaporated under reduced pressure to a red colored oil. The residue was taken up in benzene and the solution saturated with dry hydrogen chloride. The white powdery hydrochloride was washed with anhydrous ether and recrystallized from *n*-propanol–anhydrous ether mixture; m. p. over 255°, yield 2.28 g. (41.3%).

The picrate, prepared in water, was recrystallized from ethanol; m. p. 165.0–165.5°.

Anal. Calcd. for $C_{35}H_{40}N_{16}O_{21}$: N, 22.73. Found: N, 22.57.

2-Chloro-6-diethylamino-8-hydroxypurine.—A solution of 7.5 g. (0.036 mole) of 2,6-dichloro-8-hydroxypurine in 13.4 g. (0.184 mole) of diethylamine was heated at 110° for twenty-four hours in a sealed tube. The crystalline contents of the tube were boiled with 60 ml. of water, cooled and just acidified with acetic acid. The crude product was removed by filtration, dissolved in 2 *N* sodium hydroxide solution, decolorized, filtered and the product reprecipitated by the addition of acetic acid. The white crystalline product was removed by filtration and washed with water; yield 8.45 g. or 95.5%, m. p. over 225°. The product was insoluble in benzene, ethanol and water.

Anal. Calcd. for $C_9H_{12}N_5OCl$: N, 28.97. Found: N, 28.69.

2-(γ-Diethylaminopropylamino)-6-diethylamino-8-hydroxypurine.—A mixture consisting of 7.5 g. (0.031 mole) of finely powdered 2-chloro-6-diethylamino-8-hydroxypurine and 16 g. (0.123 mole) of γ-diethylaminopropylamine was heated in a bomb tube at 195° for seventeen hours. The crystalline contents of the tube were stirred with 70 ml. of cold water, filtered and washed with a small amount of water. The crude product, 7.0 g. (67.3%), was recrystallized from benzene to yield 6.25 g. (60.1%) of pure material; m. p. 222–224°.

This compound may also be isolated as the pentahydrochloride salt by the method previously described for 2-(γ-diethylaminopropylamino)-6-diethylamino-7-methylpurine but the yield is not as high (45%); m. p. over 225°.

Anal. Calcd. for $C_{16}H_{34}N_7OCl_5$: Cl, 34.27. Found: Cl, 34.25.

2-Chloro-6-(γ-diethylaminopropylamino)-8-hydroxypurine.—A mixture consisting of 7.5 g. (0.036 mole) of finely powdered 2,6-dichloro-8-hydroxypurine and 16 g. (0.123 mole) of γ-diethylaminopropylamine was heated at 100° for ten hours in a bomb tube. The clear, yellow, glassy solid was taken up in 60 ml. of water, 2 g. of potassium carbonate added and the solution extracted with four 50-ml. portions of ether. The ether extracts were discarded and the aqueous solution saturated with potassium carbonate causing a light yellow oil to separate which was insoluble in ether and ligroin. The water was decanted and the oil layer taken up in 100 ml. of *n*-propanol. The product was converted to the hydrochloride by addition of 50 ml. of *n*-butanol saturated with dry hydrogen chloride. Methanol, 150 ml., was added and the mixture heated to boiling to dissolve the solid. The methanol was removed by distillation, the solution cooled and the white, crystalline dihydrochloride removed by filtration, washed with *n*-propanol–anhydrous ether and finally with anhydrous ether; yield 8.7 g. (64.2%), m. p. over 225°.

Anal. Calcd. for $C_{12}H_{21}N_6OCl_3$: Cl, 19.15. Found: Cl, 19.14, 18.95.

This compound was also obtained as the free base by isolation of the silver salt and decomposition of the salt with hydrogen sulfide but the yield was considerably lower (29%). The base was recrystallized from ethanol–ethyl acetate mixture after which it melted at 150°.

The picrate was prepared in water and recrystallized from ethanol; m. p. 235.5°.

2-Diethylamino-6-(γ-diethylaminopropylamino)-8-hydroxypurine.—A mixture consisting of 5 g. (0.0135 mole) of 2-chloro-6-(γ-diethylaminopropylamino)-8-hydroxypurine dihydrochloride and 30 g. (0.41 mole) of diethylamine was heated in a bomb tube at 155° for twenty-four hours. When the tube was opened, the light yellow solution turned blood red in color. The diethylamine hydrochloride, 4.4 g., was removed by filtration and washed with two 25-ml. portions of ether. The ether washings and the filtrate were combined and evaporated to dryness on a

steam cone. The pink colored solid was digested in 40 ml. of water for one-half hour and filtered to give a crude yield of 4.45 g. (98.3%), m. p. 192–193°. The pink colored product was recrystallized three times from benzene to yield 3 g. (66.2%) of pure white crystalline material; m. p. 195–196°.

Anal. Calcd. for $C_{16}H_{20}N_7O$: N, 29.22; Found: N, 28.72.

8-Bromotheobromine.—Theobromine, 7.5 g. (0.0414 mole), was added to 42 g. (0.252 mole) of bromine and 25 ml. of chloroform with stirring. The mixture was allowed to stand at room temperature for one hour and then heated on a steam cone until all the bromine and chloroform had been expelled. The yellow solid was decolorized by digestion with acidified bisulfite solution, and washed with water. The crude product was dissolved in 5 *N* potassium hydroxide solution and the clear solution acidified with glacial acetic acid. The precipitated white product was removed by filtration, washed with water and dried in the air; yield 6.7 g. (62.1%), m. p. over 235°.

3,7-Dimethyl-2,6-dioxy-8-(γ-diethylaminopropylamino)-purine.—A mixture consisting 5.0 g. (0.019 mole) of 8-bromotheobromine and 7.5 g. (0.057 mole) of γ-diethylaminopropylamine was heated in a bomb tube at 165° for eight hours with no apparent change. The mixture was then heated first at 190° for six hours and finally at 200° for sixteen hours. In spite of the fact that the material appeared to be unchanged the contents of the tube were found to give a positive silver nitrate test for halogen. The white solid was boiled with 150 ml. of water, cooled, and the white crystalline product (2.8 g.) removed by filtration and washed with water. The combined filtrates were made exactly neutral with acetic acid and a second crop (1.17 g.) of the product separated; yield 3.97 g. (67%), m. p. 306°.

Anal. Calcd. for $C_{14}H_{24}O_2N_6$: N, 27.25. Found: N, 27.14.

The picrate was prepared in ethanol and after recrystallization the ruby red needles melted at 210–211°.

In a similar manner 1,3,7-trimethyl-2,6-dihydroxy-8-(γ-diethylaminopropylamino)-purine is obtained by the reaction of 8-chlorocaffeine and γ-diethylaminopropylamine;[11] m. p. of monohydrochloride 229–231°.

Anal. Calcd. for $C_{15}H_{26}O_2N_6 \cdot HCl$: N, 23.31. Found: N, 23.34, 23.37.

Summary

The synthesis of eleven new basically-substituted purine derivatives and their intermediates has been described.

(11) Walter F. Holcomb, private communication from the Research Laboratories of Parke, Davis and Company.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

The Synthesis of β-Keto Esters by the Decomposition of Acylated Malonic Esters

BY BYRON RIEGEL AND W. M. LILIENFELD[1]

For many types of synthetic problems, β-keto esters have been used as intermediates. For instance, in the Bardhan synthesis of polycyclic compounds β-ketoadipic ester is the most suitable starting material for the preparation of certain substituted 1,2-cyclopentenophenanthrenes. The original method[2] for the preparation of this ester was to acylate acetoacetic ester with the half ester acid chloride of succinic acid and then ammonolyze the resulting compound to remove the acetyl group. The yield is low and the method is difficult and tedious. To facilitate further studies in this field a better method for the preparation of β-ketoadipic ester was developed.

This new method involves the use of malonic ester in place of the acetoacetic ester. Lund and co-workers[3] reported that the magnesium enolate derivative of malonic ester, in an ether solution, is acylated very readily and in excellent yields. However, with β-carbethoxypropionyl chloride the acylation did not proceed as well as that reported by Lund for the simpler acid chlorides. The excess alcohol in the solution of the magnesium enolate interferes with the acylation and must be removed before adding the acid chloride.

The tricarboxylic ester thus obtained was converted into β-ketoadipic ester by heating it with β-naphthalenesulfonic acid. The mechanism of this reaction is not clearly understood and will require further study. Willstätter[4] found accidentally that a lower homolog, namely, acetone-1,1,3-tricarboxylic ester, underwent thermal decomposition quite readily to give the ester of acetone-1,3-dicarboxylic acid. More recently Breslow, Baumgarten and Hauser[5] have reported a new synthesis of β-keto esters by the thermal decomposition of the acylated ethyl *t*-butylmalonates using *p*-toluenesulfonic acid as a catalyst. The remarkable ease with which these esters gave off isobutylene and decarboxylated, presumably due to the acid catalyst, led to the development of their new method. Our method[6] is very similar to theirs except that it does not require the initial preparation of ethyl *t*-butylmalonate and thus can be carried out in much less time. Preliminary experiments were then made to see if our method could be used for the preparation of ethyl propionylacetate and ethyl benzoylacetate which were successful.

For the preparation of β-ketoadipic ester, β-

(1) Anna Fuller Fund Research Associate, 1943–1944.

(2) J. C. Bardhan, *J. Chem. Soc.*, 1848 (1936); P. Ruggli and A. Maeder, *Helv. Chim. Acta*, **25**, 936 (1942).

(3) H. Lund, *Ber.*, **67**, 935 (1934); "Organic Syntheses," Coll. Vol. II, p. 594; H. Lund, A. U. Hasnen and A. F. Voigt, *Kgl. Danske Videnskab, Selskab, Math.-fys. Medd.*, **12**, 1 (1933).

(4) R. Willstätter, *Ber.*, **32**, 1272 (1899).

(5) D. S. Breslow, E. Baumgarten and C. R. Hauser, THIS JOURNAL, **66**, 1286 (1944).

(6) At the time that the method described here was being developed we noted in an O.S.R.D. report that Dr. C. R. Hauser was also studying a similar method. We wish to thank him for sending to us portions of the experimental part of the manuscript he was submitting for publication. However, we did not know, until after publication, that they had tried an acid-catalyzed decomposition (steam distillation) of an acylated diethyl malonate with negative results.