[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, OREGON STATE COLLEGE]

Purines. I. The Chlorination of Certain Purinones with Phosphorous Oxychloride in the Presence of Aliphatic Tertiary Amines[1]

BY ROLAND K. ROBINS AND BERT E. CHRISTENSEN

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The reaction of uric acid, xanthine and hypoxanthine with phosphorus oxychloride in the presence of various aliphatic tertiary amines has been shown to result in the replacement of the "hydroxy" group in the 6- and in some cases the 2- and 6-positions of the purine nucleus to give the corresponding dialkyl- or bis-(dialkyl)- aminopurine in good yield. The structures of a number of the dialkylaminopurines have been established by syntheses. 8-Chloroxanthine has been prepared in good yield from the monopotassium salt of uric acid by the action of phosphorus oxychloride and a limited amount of triethylamine. An excess of triethylamine in the same reaction has been found to yield 2,8-dichloro-6-diethylaminopurine.

Since Baddiley and Topham[2] first chlorinated barbituric acid in the presence of dimethylaniline, the use of this tertiary amine and phosphorus oxychloride has found extensive application in the preparation of numerous chloropyrimidines. It would seem logical that this reaction may well be expanded to the preparation of the rather rare chloropurines, which could serve as valuable intermediates in the preparation of synthetic nucleosides.[3] For this reason a study of the behavior of dimethylaniline in a reaction mixture of phosphorus oxychloride and several purinones was undertaken.

Preliminary experiments with uric acid were not promising; short periods of reaction time commonly employed in the preparation of chloropyrimidines were found to have little effect in chlorinating the purine ring. Longer periods of reaction time resulted in considerable phosphorylation of the dimethylaniline[4] as well as in the production of a large amount of a phosphorylated, partially chlorinated derivative of uric acid and in isolation of very little of the desired trichloropurine. Recently, Davoll and Lowy[5] reported an isolation of 16–25% yield of trichloropurine from uric acid using dimethylaniline and phosphorus oxychloride.

In view of these results several routine chlorinations using other tertiary amines were attempted. In the course of this work it was discovered that in the presence of a limited amount of triethylamine uric acid was converted to 8-chloroxanthine in yields of from 30–40%; by the substitution of monopotassium salt of uric acid the yields were consistently above 80%. These results were interesting since in the usual chlorination procedure it is the 8-position which is the last to be chlorinated.[6]

When these experiments were extended to the use of excess triethylamine coupled with longer reaction time, it was discovered that the reaction not only chlorinated the purine ring but the triethylamine proceeded to ammonate the ring. Uric acid under these conditions gave a product $C_9H_{11}Cl_2N_5$ (I, R = C_2H_5) instead of the expected trichloropurine; this indicated that the product contained a diethylamino-substituent.

In order to determine the position of this substituent, trichloropurine was treated with diethylamine; this gave a product which was found to be identical to (I, R = C_2H_5). The reaction of a secondary amine with trichloropurine has not been previously described, but 2,6-dichloro-7-methylpurine[7] has been reported to yield 2-chloro-6-diethylamino-7-methylpurine. Thus it would indicate that the 6-position may be the more reactive one in trichloropurine. This opinion was confirmed, and the structure of (I) proven when the reduction product of (I) with hydriodic acid was found to be 6-diethylaminopurine (II) which was identical to the reaction product of hypoxanthine, triethylamine and phosphorus oxychloride. Xanthine with phosphorus oxychloride and triethylamine gave 2,6-bis-(diethylamino)-purine.

To establish the generality of this reaction the study was expanded to the use of other tertiary amines in the reaction mixture. Trimethylamine, xanthine and phosphorus oxychloride yielded a product 2,6-bis-(dimethylamino)-purine (III, R = CH_3). It is interesting to note that these reactions can be operated at atmospheric pressures; this would suggest some type of salt formation in the reaction mixture. When tri-*n*-propylamine was used, the reaction product was not the expected 2,6-di-*n*-propylamino derivative but a compound having the empirical formula $C_{11}H_{17}N_5O$ (IV, R = C_3H_7); with tri-*n*-butylamine, $C_{13}H_{21}N_5O$ (IV, R = C_4H_9) was obtained. It thus appears that only one of the "hydroxy" groups in xanthine had been replaced by the dialkylamino radical in each case. In order to prove this and to establish the position of the dialkylamino group, the unambiguous synthesis of 6-di-*n*-butylamino-2-purinone was undertaken.

Using trichloropurine and di-*n*-butylamine, 2,8-dichloro-6-di-*n*-butylaminopurine (I, R = C_4H_9) was prepared by a similar procedure to that previously employed to synthesize (I, R = C_2H_5) by the second method. I (R = C_4H_9) was then treated with sodium ethoxide which gave 8-chloro-2-ethoxy-6-di-*n*-butylaminopurine (V) by a procedure similar to that employed by Fischer[6] to prepare 8-chloro-2-ethoxy-6-aminopurine from 2,8-dichloro-6-aminopurine. (V) in turn was treated with hydrogen iodide which cleaved the ethoxy group and removed the chlorine atom to give 6-di-*n*-butylamino-2-purinone (IV). This compound

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(2) J. Baddiley and A. Topham, *J. Chem. Soc.*, 678 (1944).

(3) J. Davoll, B. Lythgoe and A. R. Todd, *ibid.*, 833 (1946).

(4) R. Robins and B. E. Christensen, *J. Org. Chem.*, **16**, 324 (1951).

(5) J. Davoll and B. A. Lowy, THIS JOURNAL, **73**, 2936 (1951).

(6) E. Fischer, *Ber.*, **30**, 2220 (1897).

(7) R. R. Adams and F. C. Whitmore, THIS JOURNAL, **67**, 1272 (1945).

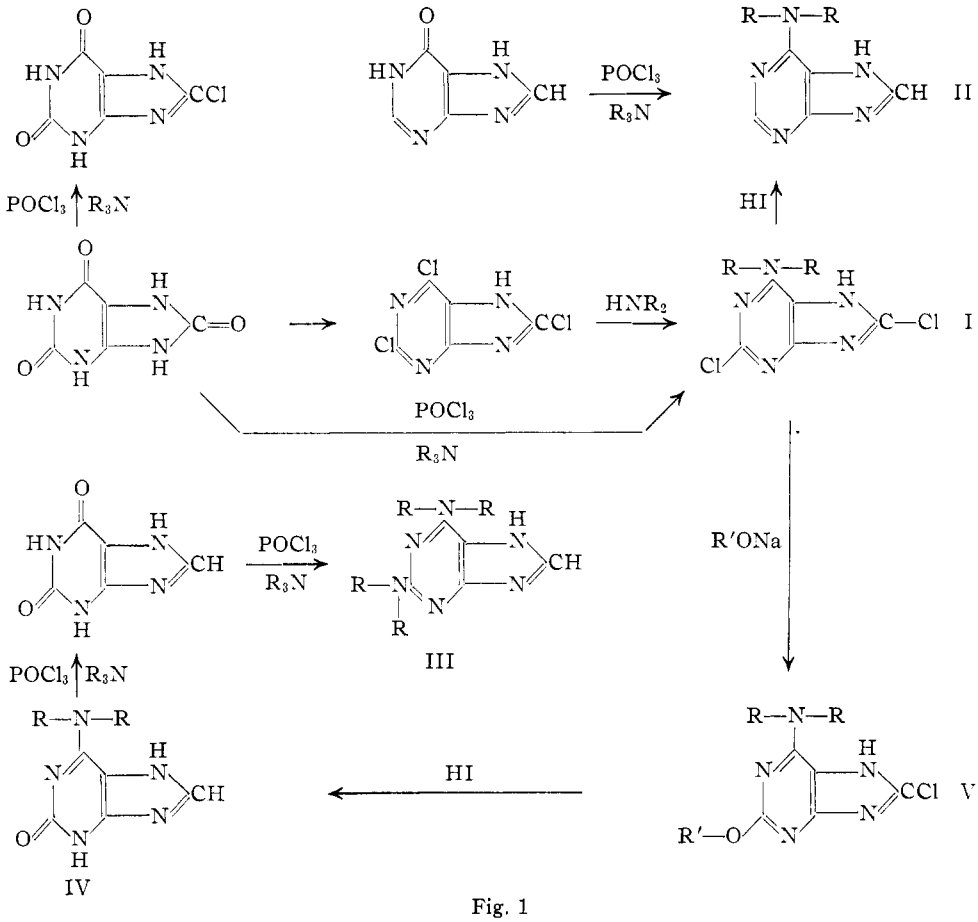

Fig. 1

was found to be identical with the product $C_{13}H_{21}N_5O$ obtained from the reaction mixture of tri-*n*-butylamine, xanthine and phosphorus oxychloride.

That the compound $C_{11}H_{17}N_5O$ obtained with tri-*n*-propylamine is 6-di-*n*-propylamino-2-purinone (IV, R = C_3H_7) seems highly probable judging from analogous properties and the method of preparation similar to (IV, R = C_4H_9).

In order to exclude the possibility that the dialkylamination of the purine rings may have been due to the presence of a secondary amine contaminant (in tertiary amine) only best available grades of tertiary amines were used in these experiments, and only after distillation using a ten-plate column.

These purified tertiary amines gave a negative Hinsberg test for presence of secondary or primary amine contaminants.

Similar reactions involving pyrimidone have been reported. King and co-workers[8] have isolated 4,6-dichloro-2-methylanilinopyrimidine from the reaction mixture of barbituric acid, phosphorus oxychloride and dimethylaniline; 2(4)-chloro-6-methyl-4(2)-methylanilino-5-nitropyrimidine[9] has been prepared from 6-methyl-5-nitrouracil in an analogous manner.

Kawai and Miyoshi[10] heated 2,4,6-trichloropyrimidine with dimethylaniline and isolated 2,4,6-tris-(methylanilino)-pyrimidine. In principle these reactions appear to be the same. It seems quite probable that the reaction proceeds through the formation of a quaternary salt which decomposes to give the new tertiary amine.

(8) F. E. King, T. J. King and P. C. Spensley, *J. Chem. Soc.*, 1247 (1947).

(9) J. R. Marshall and J. Walker, *ibid.*, 1016 (1951).

(10) S. Kawai and T. Miyoshi, *Sci. Papers Inst. Phys. Chem. Research (Tokyo)*, **16**, 20 (1931).

Experimental[11]

8-Chloroxanthine (8-Chloro-2,6-purinedione).—To 250 ml. of redistilled phosphorus oxychloride was added 30 g. of the monopotassium salt of uric acid,[3] and 35 ml. of triethylamine which had been refractionated and dried over sodium. The solution was refluxed for 4.5 hours during which time all the monopotassium urate went into solution. The excess phosphorus oxychloride was then removed using a steam-bath and reduced pressure until a light tan sirup remained which was poured onto 200 g. of cracked ice. The solution was then allowed to *stand at room temperature for three hours* and refrigerated overnight to complete precipitation. The precipitate was removed by filtration, washed with cold water, acetone, and finally dried at 110°. The yield of crude slightly yellow 8-chloroxanthine was 23.1 g. (85.5%).

Further purification was effected by crystallization of the ammonium salt.[12] Two grams of crude 8-chloroxanthine was suspended in 30 ml. of water containing 5 ml. of concd. ammonium hydroxide and the mixture brought to boiling to effect complete solution. The product was decolorized with charcoal and then refrigerated at 4° for 24 hours, and filtered. The white ammonium salt was washed with 5 ml. of ice-water and again dissolved in 30 ml. of boiling water. The hot solution was acidified with dilute hydrochloric acid which precipitated the white 8-chloroxanthine. The product was filtered, washed with cold water and dried for one hour at 130°; yield 1.7 g.

(11) All melting points are corrected and were taken on a Fischer-Johns block unless otherwise stated.

(12) E. Fischer, *Ber.*, **30**, 2336 (1897).

Anal. Calcd. for $C_5H_3ClN_4O_2$: C, 32.10; H, 1.61; Cl, 19.1. Found: C, 32.06; H, 2.11; Cl, 19.0.

The compound thus obtained was established as 8-chloroxanthine by methylation of the crude product with methyl iodide in the manner employed by Fischer.[12] One gram of crude 8-chloroxanthine gave 0.61 g. of 8-chlorocaffeine, m.p. 188°.

The 8-chloroxanthine was also reduced to xanthine by a modification of the Fischer[12] procedure. Two grams of crude 8-chloroxanthine was suspended in 30 ml. of hydroiodic acid (sp. gr. 1.50, preserved by the addition of hypophosphorous acid) and the solution was boiled gently until the 8-chloroxanthine dissolved (5 min.). The xanthine was then isolated as described by Fischer.[12] The crude yield of white xanthine was 1.7 g. This material was purified by recrystallization of the sodium salt according to the procedure of Biltz and Beck.[13]

Anal. Calcd. for $C_5H_4N_4O_2$: N, 36.85. Found: N, 36.8.

2,8-Dichloro-6-diethylaminopurine (I, R = C_2H_5). **Method** (1).—A mixture of 100 ml. of redistilled phosphorus oxychloride, 5.0 g. of monopotassium urate and 30 ml. of triethylamine was refluxed for 13 hours. The excess phosphorus oxychloride was removed under reduced pressure and the brown sirupy residue poured slowly with vigorous stirring onto 150 g. of cracked ice. The aqueous solution was cooled at 0° for one-half hour and then filtered. The precipitate was partially dried using a hot air fan until nearly all of the water had been removed. The rather gummy precipitate was then extracted in a soxhlet extractor with 250 ml. of ether for five hours. Evaporation of the ether left a residue which was dissolved in 100 ml. of boiling heptane; upon cooling 2.5 g. of white needles was isolated, m.p. 210–220°. Recrystallization from 95% ethanol gave 2.1 g. of colorless needles, m.p. 224–225°. A final recrystallization from heptane raised the m.p. to 225–225.5°.

2,8-Dichloro-6-diethylaminopurine was insoluble in dilute hydrochloric acid but soluble in dilute sodium hydroxide.

Anal. Calcd. for $C_9H_{11}Cl_2N_5$: C, 41.55; H, 4.23; N, 26.9. Found: C, 41.86, 40.96; H, 4.43, 3.89; N, 26.7.

2,8-Dichloro-6-diethylaminopurine (I, R = C_2H_5). **Method** (2).—To a solution of 5 ml. of diethylamine in 25 ml. of water was added 1.0 g. of trichloropurine,[5] and the mixture refluxed for one-half hour. The condenser was then removed and the excess diethylamine was allowed to evaporate slowly. The solution was then cooled and acidified to congo red paper with dilute hydrochloric acid. An immediate white precipitate was noted, which was filtered, washed with water and recrystallized from 95% ethanol; yield 0.8 g. of colorless needles, m.p. 225°. A mixed m.p. of this compound with (I) obtained by method (1) was 225–225.5°.

2,8-Dichloro-6-diethylaminopurine (I, R = C_2H_5). **Method** (3).—A mixture of 40 ml. of phosphorus oxychloride, 2.5 g. of trichloropurine and 15 ml. of triethylamine was refluxed for 13 hours. The product was isolated as described in method (1), yield 1.1 g. of 2,8-dichloro-6-diethylaminopurine. One recrystallization from 95% ethanol gave a m.p. of 225°. The product was identical with (I) prepared by both methods (1) and (2) as judged by mixed melting points.

6-Diethylaminopurine (II). Method (1).—A solution containing 4 g. of colorless hypoxanthine prepared from adenine by the method of Kruger,[14] 75 ml. of redistilled phosphorus oxychloride and 20 ml. of triethylamine was vigorously refluxed for four hours. After removing the excess phosphorus oxychloride the remaining brown sirup was poured onto 200 g. of chopped ice. After 30 minutes the mixture was brought to a *p*H of 9 with concentrated ammonium hydroxide, and then placed in a refrigerator overnight to effect crystallization. The yield was 3.8 g. of tan colored needles which were recrystallized from an ethanol-water mixture to yield 3.0 g. of a colorless product, m.p. 222–223°. A second recrystallization from benzene did not raise the m.p.

Anal. Calcd. for $C_9H_{12}N_5$: C, 56.6; H, 6.81; N, 36.7. Found: C, 56.7; H, 6.89; N, 36.7.

6-Diethylaminopurine (II). **Method** (2).—2,8-Dichloro-6-diethylaminopurine (0.5 g.) together with 10 g. of hydroiodic acid (sp. gr. 1.5), was placed in a small beaker. The solution was slowly heated to boiling and then boiled gently for ten minutes, cooled, diluted with 5 ml. of water and made slightly basic with concd. ammonium hydroxide. The precipitate which formed was collected, washed with water, dried and recrystallized from benzene to yield 0.15 g. of a crystalline product, m.p. 220–221°. A second recrystallization from benzene raised the m.p. to 221–223°. A mixed m.p. of this product with 6-diethylaminopurine (II) method (1) was 221–223°.

2,6-Bis-(diethylamino)-purine (III, R = C_2H_5).—Xanthine (6.0 g.) and 35 ml. of triethylamine and 100 ml. of phosphorus oxychloride were refluxed for 210 minutes. After the removal of the excess phosphorus oxychloride the sirupy residue was poured onto 300 g. of chopped ice. The aqueous solution was made ammoniacal, brought to a *p*H of 9, and placed in a refrigerator for 24 hours. The hardened gummy precipitate was then removed by filtration, washed with water and dried. The crude product (5.1 g.) was recrystallized from ligroin yielding 4.8 g. of a light tan powder, m.p. 112–115°. This material was readily purified by sublimation under reduced pressure. A pure white product was obtained in this manner, m.p. 114–116°. The sublimed material was again recrystallized from ligroin to give a product, m.p. 116.5–117.5°.

Anal. Calcd. for $C_{13}H_{22}N_6$: C, 59.60; H, 8.41; N, 32.05. Found: C, 59.55, 59.39; H, 8.69, 8.36; N, 32.23, 31.68.

A picrate, recrystallized twice from ethanol, gave m.p. 173–174°.

Anal. Calcd. for $C_{19}H_{25}N_9O_7$: C, 46.43; H, 5.12. Found: C, 46.67; H, 5.34.

2,6-Bis-(dimethylamino)-purine (III, R = CH_3).—Four grams of xanthine was suspended in 60 ml. of phosphorus oxychloride and the solution was cooled to 0°. Anhydrous trimethylamine, 20 ml., was added and the mixture was gradually allowed to warm up to room temperature then refluxed for 15 minutes. The solution was again cooled to 0°, an additional 10 ml. of trimethylamine added, and the solution was again refluxed for a total of four hours. The reaction product was then isolated in the manner used in the preparation of (III, R = C_2H_5). The crude product, 2.5 g. of a gray powder, was sublimed under reduced pressure to yield 2.1 g. of a colorless product. Recrystallization from xylene gave 2.0 g., m.p. 252–254°; a second recrystallization from 95% ethanol, m.p. 254–255°.

Anal. Calcd. for $C_9H_{14}N_6$: C, 52.40; H, 6.80; N, 40.77. Found: C, 52.36; H, 7.03; N, 40.68.

6-Di-*n*-propylamino-2-purinone (IV, R = *n*-C_3H_7).—Xanthine (1.5 g.), 13 ml. of tri-*n*-propylamine and 50 ml. of phosphorus oxychloride were vigorously refluxed for 4.5 hours. The phosphorus oxychloride was then removed under reduced pressure and the sirupy residue poured onto 200 g. of cracked ice. The aqueous solution was brought to a *p*H of 9 with concd. ammonium hydroxide and the solution was concentrated (using a heating fan) until the layer of excess tripropylamine had evaporated, then cooled, filtered, and the precipitate washed with water. The yield was 1.5 g. of a white powder which was recrystallized first from ethanol, then from methanol, to give 1.1 g. of colorless fine needles, m.p. 290.5–291.5° (m.p. taken with a copper block).

Anal. Calcd. for $C_{11}H_{17}N_5O$: C, 56.20; H, 7.23; N, 29.0. Found: C, 56.75; H, 7.33; N, 29.0.

6-Di-*n*-butylamino-2-purinone (IV, R = *n*-C_4H_9). **Method** (1).—A mixture containing 1 g. of xanthine and 15 ml. of tri-*n*-butylamine and 45 ml. of phosphorus oxychloride was refluxed for 3.5 hours. The product was isolated in a manner identical with that used in the preparation of (IV, R = *n*-C_3H_7), yield 0.6 g. Recrystallization first from ethanol and then from methanol gave 0.3 g. of colorless crystals, m.p. 279–280° (m.p. taken with a copper block).

Anal. Calcd. for $C_{13}H_{21}N_5O$: C, 59.3; H, 7.97; N, 26.6. Found: C, 59.3; H, 7.93; N, 26.3.

2,8-Dichloro-6-di-*n*-butylaminopurine (I, R = C_4H_9).—To a solution consisting of 10 ml. of di-*n*-butylamine, 30 ml. of water and 20 ml. of ethanol was added 3.0 g. of trichloropurine. The solution was refluxed for an hour, cooled and acidified with dilute hydrochloric acid. The crude white precipitate was washed with water, dried and recrystallized from 95% ethanol to yield 2.2 g. of white needles, m.p.

(13) H. Biltz and A. Beck, Jr., *J. prakt. Chem.*, **118**, 166 (1928).

(14) M. Kruger, *Z. physiol. Chem.*, **18**, 444 (1894).

165–167°. A second recrystallization from heptane raised the m.p. to 168–169°.

Anal. Calcd. for $C_{13}H_{19}Cl_2N_5$: C, 49.40; H, 6.02. Found: C, 49.45; H, 6.47.

8-Chloro-2-ethoxy-6-di-*n*-butylaminopurine (V).—One gram of 2,8-dichloro-6-di-*n*-butylaminopurine (I) was dissolved in an alcoholic solution of sodium ethoxide, prepared by dissolving 1.0 g. of sodium in 10 ml. of absolute ethanol. This solution was placed in a sealed glass tube and heated in an oven (temperature 130°) for 3.5 hours. The contents of the tube were diluted with 10 ml. of water and then acidified with acetic acid. The white solid was collected, washed with a little cold water, and recrystallized from an ethanol–water mixture yielding 0.8 g., m.p. 162–164°. A small amount was recrystallized from 95% ethanol for analytical purposes, m.p. 164–165°. A mixed m.p. of this product and the starting material (V) was 125°.

Anal. Calcd. for $C_{13}H_{24}N_5ClO$: C, 55.4; H, 7.40. Found: C, 55.4; H, 7.56.

6-Di-*n*-butylamino-2-purinone (IV, R = n-C_4H_9). **Method (2).**—To 10 ml. of hydroiodic acid (sp. gr. 1.5, preserved with hypophosphorous acid) was added 0.6 g. of 8-chloro-2-ethoxy-6-di-*n*-butylaminopurine (V). The solution was boiled gently for five minutes, and then vigorously boiled for an additional ten minutes. The cooled reaction mixture was then diluted with 5 ml. of cold water and made slightly alkaline with concd. ammonium hydroxide. The white precipitate thus obtained was washed several times with cold water and then recrystallized from methanol, yield 0.3 g. of product, m.p. 275–277° (m.p. taken with a copper block). A second recrystallization from methanol raised the m.p. 278.5–279.5°. A mixed m.p. of this product and 6-di-*n*-butylamino-2-purinone (IV, R = n-C_4H_9) prepared by method (1) was 278.5–280°.

2(6)-Chloro-6(2)-diethylaminopurine.—Into a 500-ml. flask was placed 15.0 g. of xanthine, 200 ml. of phosphorus oxychloride and 10 ml. of triethylamine. The solution was refluxed; every 20 minutes 10 ml. of additional triethylamine was added until a total of 65 ml. had been used. The solution was then refluxed 12 hours more and the reaction mixture processed in the usual manner. The crude product, 6.5 g. of brown gum, was extracted with heptane using a soxhlet extractor. Upon cooling the heptane solution 0.4 g. of crude material separated from the more heptane-soluble 2,6-bis-(diethylamino)-purine (III, R = C_2H_5). The crude product was dissolved in a propanol-2–water mixture, decolorized with charcoal and allowed to crystallize. A second recrystallization from the same solvent gave a white product of m.p. 224–226°. A final recrystallization from heptane gave fine needles, m.p. 225–227°.

Anal. Calcd. for $C_9H_{12}ClN_5$: C, 47.89; H, 5.34. Found: C, 47.62, 47.58; H, 5.44, 5.39.

The isolation of this product from subsequent similar runs could not be consistently repeated. None of this material could be isolated when the preparation of 2,6-bis-(diethylamino)-purine (III, R = C_2H_5) was carried out in the usual manner.

CORVALLIS, OREGON

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

"Enamine" Derivatives of Steroidal Carbonyl Compounds. I

BY M. E. HERR AND F. W. HEYL

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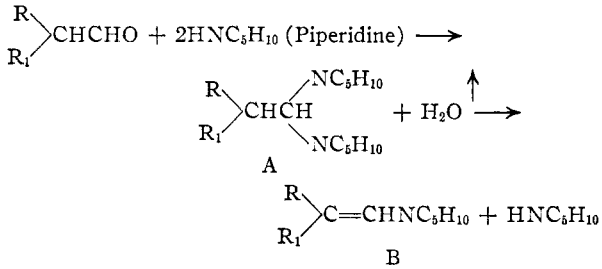
Representative steroidal aldehydes have been treated with secondary amines under conditions chosen to facilitate the formation of α,β-unsaturated amines—"enamines." This reaction affords an improved method of degrading the side chain of bisnorcholenaldehydes to 20-ketopregnenes. Isomers of 3-ketobisnor-4-cholenaldehyde and 3-ketobisnor-4-cholenic acid have been prepared and characterized.

It has recently been shown that enol acetates, readily prepared from bisnorcholenaldehydes, in which a double bond is introduced at C-20(22) in the side chain, are converted upon ozonolysis into the corresponding C_{20}-ketones.[1] 3-Ketobisnor-4-cholenaldehyde was readily prepared in good yield by the selective ozonization of stigmastadienone. When, however, this ketoaldehyde was enolized with acetic anhydride and sodium acetate, the resulting mixture of enol acetates proved to be an oil.

A new type of steroidal carbonyl derivative is now reported. It is prepared by a reaction described by Mannich and Davidsen[2] in which a secondary amine, preferably piperidine, reacts with an aldehyde in the presence of potassium carbonate, splitting out a molecule of water to produce in the first phase a dipiperidyl derivative (A). The subsequent loss of one molecule of piperidine in the second phase leads to an α,β-unsaturated amine (B), designated as an "enamine." The aldehydes used by Mannich and Davidsen were liquids and the enamines were isolated from the reaction mixture by fractional distillation at various pressures, which were selected in order to facilitate the splitting out of one mole of the secondary amine.



Since the steroidal carbonyl compounds were crystalline solids, modification of the conditions employed by Mannich and Davidsen[2] was necessary. 3β-Acetoxybisnor-5-cholenaldehyde[3] gave 22-(N-piperidyl)-bisnor-5,20(22)-choladien-3β-ol acetate (I) in 84% yield, when the aldehyde and a small excess of piperidine in benzene were heated under reflux, using a Bidwell–Sterling moisture trap to collect the water of reaction. Under similar conditions 3β-hydroxybisnor-5-cholenaldehyde gave 22-(N-piperidyl)-bisnor-5,20(22)-choladien-3β-ol (II); 3-ketobisnor-4-cholenaldehyde[1] gave 22-(N-piperidyl)-bisnor-4,20(22)-choladien-3-

(1) F. W. Heyl and M. E. Herr, THIS JOURNAL, **72**, 2617 (1950).

(2) C. Mannich and H. Davidsen, *Ber.*, **69B**, 2106 (1936). In a recent paper, P. L. deBenneville and J. H. Macartney, THIS JOURNAL, **72**, 3073 (1950), a wide range of yields has been reported for a number of examples of this reaction.

(3) A. P. Centolella, F. W. Heyl and M. E. Herr, *ibid.*, **70**, 2953 (1948).