6α-*p*-nitrobenzamido-3α,5α-cycloandrostan-17-one, m.p. 165–168°; $[\alpha]^{22}D$ +101° (1%, $CHCl_3$).

Anal. Calcd. for $C_{26}H_{32}N_2O_4$: C, 71.54; H, 7.39. Found: C, 71.78; H, 7.57.

6α-Acetamido-17-ethylenedioxy-3α,5α-cycloandrostane (IIb).—The ketal amine (1.62 g.), isolated as described above by separation as the water-soluble acetic acid salt from the products obtained by sodium–ethanol reduction of 6-oximino-17-ethylenedioxy-3α,5α-cycloandrostane, was dissolved in 36 ml. of pyridine and 12 ml. of acetic anhydride was added. The resulting solution was allowed to stand overnight at room temperature and then poured into 400 ml. of water. The sticky, white solid which separated was collected on a sintered glass funnel. This product was taken up in 200 ml. of chloroform, and the chloroform solution was dried over anhydrous magnesium sulfate. The chloroform was evaporated leaving a viscous, pale yellow glass. The product separated as a gel from acetone–ether–pentane solution, and was separated by filtration leaving a finely divided white solid, m.p. 157–186°. Two more such separations yielded 839 mg. of 6α-acetamido-17-ethylenedioxy-3α,5α-cycloandrostane, m.p. 192–197°, $[\alpha]^{23}D$ +53° (1%, $CHCl_3$), shown to be free of the 6β-acetamido epimer by vapor phase chromatography. For analysis 104 mg. was recrystallized twice from methanol–water solution to yield 66 mg., m.p. 198–200°.

Anal. Calcd. for $C_{23}H_{35}NO_3$: C, 73.95; H, 9.45; N, 3.75. Found: C, 73.82; H, 9.28; N, 4.02.

The ether–acetone–pentane filtrates from purification of the product were combined and the solvent was evaporated. The residue was dissolved in acetone, and the boiling solution was treated with carbon and filtered through Celite. The acetone was evaporated leaving 684 mg. of a rigid white glass. Vapor phase chromatography on both polar and nonpolar columns showed peaks of approximately equal area with retention times corresponding to those of the 6α- and 6β-acetamido-17-ethylenedioxy-3α,5α-cycloandrostanes (Table II) indicating a mixture of approximately equal amounts of the epimers.

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Notes

New Synthesis of Uric Acid and 1,7-Dimethyluric Acid[1]

C. WAYNE BILLS, STANLEY E. GEBURA, JOHN S. MEEK, AND ORVILLE J. SWEETING[2]

Department of Chemistry, University of Colorado, Boulder, Colorado

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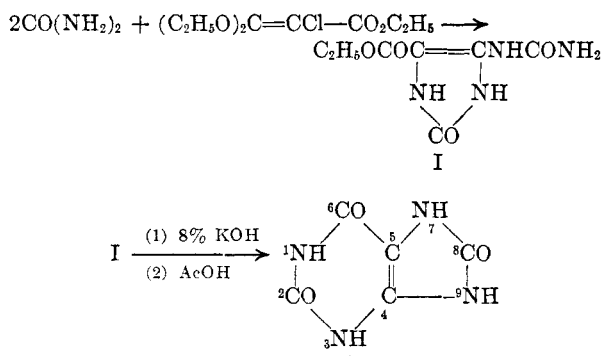
In the course of work on a new synthesis of pyrimidines of possible biological interest,[3] we sought to extend the reaction of ureas and β,β-diethoxyacrylic esters to include ethyl α-chloro-β,β-diethoxyacrylate in the expectation that such a reaction would yield with urea, ethyl α-chloro-β-ethoxy-β-ureidoacrylate, which then could be converted to 5-chloro-6-ethoxyuracil by ring closure. The unexpected occurred, however, and instead, two moles of urea interacted with one of ester to yield an imidazole (I), which by appropriate treatment with alkali followed by acid gave uric acid in good yield. This result affords a convenient tracer method for obtaining uric acid labeled with C^{14} in the 2 and 8 positions, starting with active urea, since the synthesis is conservative in the use of urea.

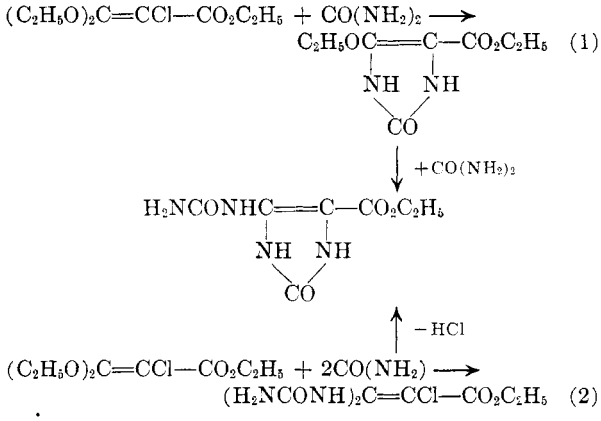


Two courses are possible, each capable of explaining the final result. One might suppose (1) that the first mole of urea reacting produces an imidazole, which reacts further to give the ureido imidazole, or (2) that the presence of a halogen atom in the acrylic ester promotes double replacement of the β-ethoxy groups followed by ring closure.

(1) This work was performed as part of a contract with the Division of Biology and Medicine of the U. S. Atomic Energy Commission, no. AT(29-1)-787.

(2) Present address: Film Research and Development Dept., Olin Mathieson Chemical Corp., New Haven, Conn.

(3) S. E. Gebura, O. J. Sweeting, and C. W. Bills, to be published.



There appears to be no counterpart of this reaction with urea and ethyl β,β-diethoxyacrylate. Ethyl β-ethoxy-β-ureidoacrylate does not react with urea under similar conditions.

Interaction occurred when methylurea was substituted for urea. The use of two moles of methylurea to one of the chloroacrylic ester gave a product of the formula $C_9H_{14}O_5N_3$ which remains to be identified; equimolar proportions of the reagents gave the desired intermediate, which gave 1,7-dimethyluric acid on proper treatment.

The synthesis of uric acid described is more direct and more suitable therefore for tracer synthesis than any of the other methods employed at present, such as those of Behrend and Roosen,[4] Fischer,[5] and Traube.[6] Extension of this method to other substituted ureas may lead to useful methods of preparing caffeine, theobromine, and other related purines.

Experimental

All melting or decomposition points were determined microscopically on a hot stage, and are uncorrected.

Ethyl Trichloroacrylate.—Preparation of this and the succeeding compound has been described by Fritsch,[7] but without much detail, and we therefore present our complete procedure. A solution of sodium ethoxide was prepared from 75 g. (3.07 moles) of sodium and 1 l. (17 moles) of absolute ethanol in a nitrogen atmosphere; 249 g. (1.0 mole) of hexachloropropene was added dropwise with stirring. It was necessary to moderate the exothermic reaction by cooling. The mixture was allowed to stand for 30 min., excess ethanol was removed at reduced pressure, cold water was added, and the product was extracted with ether. The ether solution, dried with anhydrous potassium carbonate, was distilled, yielding crude ethyl perchlorovinylorthoformate, $(C_2H_5O)_3CCCl{=}CCl_2$. To the crude ortho ester was added 300 ml. of concentrated hydrochloric acid dropwise during 1 hr. A dark oil which formed was separated and distilled at reduced pressure, yielding 138.5 g. (68.3%) of ethyl trichloroacrylate b.p. 112–114° (50 mm.).

Ethyl α-Chloro-β,β-diethoxyacrylate.—A solution of sodium ethoxide was prepared from 32 g. (1.4 moles) of sodium and 500 ml. of absolute ethanol, and to this was added dropwise with stirring 138 g. (0.68 mole) of ethyl trichloroacrylate. A violent reaction ensued that required severe cooling. The mixture was warmed for 30 min. on a water bath, excess ethanol was removed, and cold water was added. The oil which formed was extracted with ether, dried, and distilled at 50 mm. pressure to give 112.5 g. of ethyl α-chloro-β,β-diethoxyacrylate, 50.7%. The pure product was stored at 5° under nitrogen.

5-Carbethoxy-2-oxy-4-ureidoimidazole (I).—Ethyl α-chloro-β,β-diethoxyacrylate (3.7 g., 16.7 mmoles) was weighed into a 50-ml. distilling flask which had been flattened to facilitate magnetic stirring, 1.0 g. (16.7 mmoles) of dry urea and a magnetic slug were placed in the flask, the top was stoppered, and the side arm was fitted through a small stopper into a 10-ml. distilling flask, protected from air. Little indication of reaction was observed during the first 15 min. in an oil bath at 100°. The urea remained largely undissolved but finally melted, forming a two-phase system which persisted for about 2 min., finally becoming a homogeneous light yellow liquid, from which ethanol distilled rapidly. When distillation ceased, the slushy contents were poured into 25 ml. of water and cooled at 5° overnight. Filtration yielded 1.55 g. of I, 85.6% based on urea. The crude product was dried in air and washed with 10 ml. of ether. An analytical sample prepared by recrystallization twice from water and drying at 100°, melted at 195–196.5°.

Anal. Calcd. for $C_7H_6O_4N_4$: C, 39.24; H, 4.70; N, 26.16. Found: C, 38.82; H, 4.56; N, 25.90.

The structure of the imidazole was shown by its conversion to uric acid.

One gram (4.67 mmoles) of I was dissolved in 3.5 ml. of 8% potassium hydroxide solution (5.0 mmoles of KOH) and warmed at 60° for 1.5 min. The potassium salt precipitated and was redissolved by adding 5 ml. of water. Following cooling and acidification with glacial acetic acid, the precipitated uric acid was filtered, washed with ethanol and ether, and dried in air; it weighed 0.63 g., 81%. The product did not melt at temperatures up to 400°. A few milligrams dissolved in a few drops of concentrated nitric acid and evaporated on a water bath to dryness gave a deep red-purple color when exposed to ammonia vapor (the murexide test[8]).

Direct Preparation of Uric Acid.—In similar manner, 1.0 g. (16.7 mmoles) of dry urea was condensed with 3.7 g. (16.7 mmoles) of ethyl α-chloro-β,β-diethoxyacrylate by heating at 110° for 30 min.; 1.5 ml. of ethanol was collected. Following addition of 5 ml. of 8% aqueous potassium hydroxide at 50°, and stirring for 2 min., 15 ml. of water was added, the solution was acidified with glacial acetic acid and cooled, yielding 1.3 g., 92.6%, calculated as uric acid, based on urea taken. The compound failed to melt at temperatures up to 400° [9]; it appeared to be identical with the compound prepared from I and was identified as uric acid by conversion to allantoin and alloxan.

(a) **Allantoin.**—One-half gram (2.97 mmoles) of the preceding compound was suspended in 22.5 ml. of water at 75°, 0.5 g. of sodium hydroxide was added and the solution was stirred until the solid had dissolved. The solution was cooled to 30°, 0.25 g. of potassium permanganate was added, and the mixture was stirred for 20 min. The solution was filtered into 0.6 ml. glacial acetic acid, evaporated under reduced pressure to 4 ml., and held at 5° for 2 days. The crystals, filtered and recrystallized from water, melted at 234–236°, with decomposition, in good agreement with the melting point of allantoin, 230–236°.[10] A mixed melting point with an authentic sample of allantoin showed no depression.

(b) **Alloxan.**—One gram (5.94 mmoles) of the same compound was suspended in a mixture of 6 ml. of glacial acetic acid and 9 ml. of water. Chlorine was bubbled rapidly through the hot suspension, resulting in a clear

(4) R. Behrend and O. Roosen, *Ann.*, **251**, 235 (1889).
(5) E. Fischer, *Ber.*, **28**, 2473 (1895).
(6) W. Traube, *ibid.*, **33**, 3035 (1900).
(7) P. Fritsch, *Ann.*, **297**, 312 (1897).
(8) P. A. Levene and L. W. Bass, "Nucleic Acids," Chemical Catalog Co., New York, N. Y., 1931.
(9) F. Krafft and H. Weinlandt, *Ber.*, **29**, 2242 (1896).
(10) W. W. Hartman, E. W. Moffett, and J. B. Dickey, "Organic Syntheses," Coll. Vol. II, John Wiley, New York, N. Y. 1943, p. 21.

yellow solution after about 1 min. The solution was cooled in ice water, and the crystals which formed were filtered and dried in air (evaporation of the solution and addition of ether may be needed to promote crystallization). The rod-shaped crystals turned red at 100° and decomposed at 170°. These physical properties agree with those reported for alloxan.[11]

Further evidence of the product's being uric acid was obtained from positive color reactions observed, as follows. A sodium hydroxide solution of the compound gave a red-brown precipitate with phosphotungstic acid and hydrochloric acid.[12] A sodium carbonate solution of the compound reduced silver nitrate paper[13] and gave a blue precipitate with phosphomolybdic acid.[14] An authentic sample of uric acid was obtained and used as a comparison throughout this identification.

1-Methyl-5-carbethoxy-4-N′-methylureido-2-oxyimidazole.—Ethyl α-chloro-β,β-diethoxyacrylate (4.4 g., 20.0 mmoles) and 1.7 g. (23 mmoles) of dry methylurea in a 50-ml. flat-bottomed distilling flask protected from moisture were heated to 102°.

After having been stirred magnetically for approximately 5 min., the mixture became homogeneous, and after another 15 min., ethanol began to distill; reaction apparently was complete at the end of 0.5 hr. A clear light yellow oil remained which was poured into cold water and crystallized after standing for several hours at 5°. The product was filtered, washed with ether, and dried in air to give 2.0 g. of product, 72%, based on urea taken. An analytical sample, prepared by recrystallizing twice from water, melted at 158–159°.

Anal. Calcd. for $C_9H_{14}O_4N_4$: C, 44.62; H, 5.82; N, 23.12. Found: C, 44.53; H, 5.69; N, 23.24.

The structure of the imidazole was shown by its conversion to 1,7-dimethyluric acid. The imidazole (1.4 g., 5.8 moles) was dissolved in 6.5 ml. of 8% potassium hydroxide solution (9.3 mmoles of KOH). The solution was heated at 60° for 2 min., cooled, and diluted with 15 ml. water before acidification with glacial acetic acid. The white precipitate was filtered, washed with 10 ml. of ethanol, 10 ml. of ether, and dried in air. The yield was 0.65 g. (57%). The product sublimed rapidly at 360–365° and melted with decomposition about 382° (Biltz reports 287° as the melting point of 1,7-dimethyluric acid[15]); it had the same properties as 1,7-dimethyluric acid prepared in the next section.

Direct Preparation of 1,7-Dimethyluric Acid.—Ethyl α-chloro-β,β-diethoxyacrylate (4.4 g., 20.0 mmoles) and 1.7 g. (30.0 mmoles) of dry methylurea were condensed by heating at 105° for 25 min. (2 ml. of ethanol was collected). To the reaction mixture was added 21 ml. of 8% potassium hydroxide solution at 50°; the mixture was stirred 2 min. and added to 20 ml. of water. Cooling to room temperature and acidification with glacial acetic acid causes a colorless solid to separate which was filtered, washed with water, ethanol, and ether, and dried in air. The yield was 1.68 g. (74%, calculated as 1,7-dimethyluric acid, based on urea taken). This product sublimed rapidly at 350–365° and melted with decomposition at 382°.

Identification of the product as 1,7-dimethyluric acid was confirmed by analysis and by the preparation of the 5-chloro-1,7-dimethyl-$\Delta^{4,9}$-isouric acid derivative.

Anal. Calcd. for $C_7H_8O_3N_4$: C, 42.86; H, 4.11; N, 28.57. Found: C, 42.82 H, 4.11; N, 28.62.

5-Chloro-1,7-dimethyl-$\Delta^{4,9}$-isouric Acid.—One-half gram (2.5 mmoles) of dry dimethyluric acid was suspended in 7 ml. of dry chloroform. Chlorine gas was bubbled through the suspension at a rapid rate for 10 min. while cooling in an ice–salt bath. No solution occurred but a gradual transformation from the granular suspension to a white gummy solid occurred. Chlorine flow was discontinued, dry air was drawn through the mixture, and the product was filtered and washed with dry chloroform and ether. The yield was 0.2 g. of a solid which melted at 130° with decomposition, 34% of the expected isouric acid. Biltz and Damm report a melting point at 131° with decomposition for 5-chloro-1,7-dimethyl-$\Delta^{4,9}$-isouric acid.[16]

Anal. Calcd. for $C_7H_7O_3N_4Cl$: C, 36.45; H, 3.06; N, 24.29; Cl, 15.37. Found: C, 36.62; H, 2.98; N, 24.20; Cl, 15.26.

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(12) B. S. Schoendorff, *Pfluegers Arch. ges. Physiol.*, **62**, 30 (1896).

(13) H. Schiff, *Ann.*, **109**,65 (1859).

(14) Offer, *Zentr. Physiol.*, **8**, 801 (1894–1895) [Beilstein **26**, 521 (1937)].

(15) H. Biltz and P. Damm, *Ann.*, **413**, 142 (1916).

(16) H. Biltz and P. Damm, *ibid.*, **413**, 137 (1916).

A New Synthesis of Quinuclidine

STANLEY LEONARD AND SAMUEL ELKIN

Department of Chemistry, School of Pharmacy, Temple University, Philadelphia 40, Pennsylvania

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Quinuclidine (1-azabicyclo[2.2.2]octane) was first synthesized in 1909 by Löffler and Stiezel.[1] 4-Methylpyridine reacted with formaldehyde to form, among other substances, 4-(β-hydroxyethyl)-pyridine. Reduction and subsequent replacement of the hydroxyl group with iodine, using hydriodic acid, gave 4-(β-iodoethyl)piperidine; the latter was converted to quinuclidine by dilute alkali. However, the authors failed to isolate quinuclidine in a pure state.

Meisenheimer, *et al.*,[2] followed the same route and obtained quinuclidine in the form of colorless crystals, m.p. 154°; yielding a picrate, m.p. 275°.

Brown and Eldred[3] utilized the approach of Meisenheimer. The former started with 4-hydroxyethylpyridine rather than with γ-picoline. The authors also increased the yield of quinuclidine by improving the method of isolation.

Wawzonek, *et al.*,[4] converted N-bromo- and N-chloro-4-ethylpiperidine into quinuclidine by irradiating first with ultraviolet light in 85% sulfuric acid at temperatures ranging from 0–23° and then treating with alkali. This synthesis was simultaneously discovered by Lukes and Ferles.[5]

Clemo and Metcalfe[6] heated ethylpiperidine 4-carboxylate, ethyl chloroacetate, and potassium carbonate for four hours at 110–115° and obtained ethylpiperidine-1-acetate 4-carboxylate. The Dieckmann reaction followed by hydrolysis and decarboxylation gave 2-ketoquinuclidine. Wolff or Clemenson reduction gave quinuclidine.

(1) K. Löffler and F. Stiezel, *Ber.*, **42**, 124 (1909).

(2) J. Meisenheimer, J. Neresheimer, and W. Schneider, *Ann.*, **420**, 191 (1920).

(3) H. C. Brown and N. R. Eldred, *J. Am. Chem. Soc.*, **71**, 448 (1949).

(4) S. Wawzonek, M. F. Nelson, and P. S. Thelen, *ibid.*, **73**, 2806 (1951).

(5) R. Lukes and M. Ferles, *Collection Czech. Chem. Commun.*, **16**, 416 (1951); *Chem. Abstr.*, **47**, 2177g (1953).

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