XII was acetylated under conditions similar to those recorded by de Arce, Greene and Capps[6] for the acetylation of 5-amino-8-bromo-6-methylquinoline; yield 67%, m.p. >330° (uncor.) from 95% ethanol.

Anal. Calcd. for $C_{12}H_{12}N_2O_2$: N, 12.96. Found: N, 13.11.

XII was benzoylated under conditions similar to those used by de Arce, Greene and Capps[6] for the benzoylation of 5-amino-8-bromo-6-methylquinoline; yield 42%, m.p. > 315°.

Anal. Calcd. for $C_{17}H_{14}N_2O_2$: N, 10.07. Found: N, 10.00.

8-Methyl-5-quinolinearsonic Acid (XV), 2-Chloro-8-methyl-5-quinolinearsonic Acid (XVIII) and 2-Hydroxy-8-methyl-5-quinolinearsonic Acid (XXI).—The hydrochlorides of X (12.0 g.), XI (9.0 g.) and XII (10.0 g.) were diazotized and converted into arsonic acids according to the procedure reported by Capps and Hamilton[11] for changing certain 2-chloroaminoquinolines into 2-chloroquinolinearsonic acids. XV, XVIII and XXI resulted in yields of 12.8, 11.9 and 14.8%, respectively. XV melted at 224–226° while XVIII and XXI melted above 315° (uncor.).

Anal. Calcd. for $C_{10}H_{10}AsNO_3$: As, 28.05; N, 5.27. Found: As, 27.92; N, 5.09. Calcd. for $C_{10}H_9AsClNO_3$: As, 24.84; N, 4.65. Found: As, 24.69; N, 4.75. Calcd. for $C_{10}H_{10}AsNO_4 \cdot H_2O$: As, 24.87; N, 4.65. Found: As, 24.79; N, 4.67.

(11) J. D. Capps and C. S. Hamilton, THIS JOURNAL, **60**, 2105 (1938).

ROSS CHEMICAL LABORATORY
ALABAMA POLYTECHNIC INSTITUTE
AUBURN, ALABAMA

Seroflocculating Steroids. I. Ethyl 3β-Chloro-Δ¹¹-cholenate[1]

BY FREDERIC C. CHANG AND DOUGLAS H. SPRUNT

RECEIVED APRIL 2, 1954

During the course of our study of the relationship of steroids[2] to immunological phenomena associated with injury, we have had the occasion to investigate the seroflocculating reagents described by Penn and his associates.[3] These reagents[4] cause flocculation in a high percentage of the sera of patients with cancer and other diseases.

Our investigation of the flocculating reaction led us to prepare ethyl 3β-chloro-Δ¹¹-cholenate (I) which in preliminary testing we have found to be a very satisfactory flocculating reagent. The compound is crystalline and stable under ordinary conditions. We will discuss in detail elsewhere implications of general significance in this field suggested to us by this finding.

Treatment of ethyl 3α-hydroxy-Δ¹¹-cholenate (II) with phosphorus pentachloride in chloroform at 0° yielded ethyl 3β-chloro-Δ¹¹-cholenate (I), which could be quantitatively hydrogenated to ethyl 3β-chlorocholanate (III). The latter was found to be identical by melting point comparison with the product of reaction between ethyl lithocholate and phosphorus pentachloride.

(1) Aided in part by a grant from the United States Public Health Service.

(2) D. H. Sprunt, A. D. Dulaney and R. P. Conger, *Cancer Research*, **2**, 282 (1951).

(3) H. S. Penn, *J. Natl. Cancer Inst.*, **12**, 1389 (1952); A. H. Dowdy, H. S. Penn, C. Hall and A. Bellamy, *Proc. Am. Assoc. for Cancer Research*, **1**, 12 (1954).

(4) We wish to thank Drs. Dowdy and Penn and their group for their coöperation in making available to us procedures for preparing and testing both the liver and desoxycholic acid-derived flocculating reagents which they designate as "antigens."

Testing data on I and current studies on related compounds with flocculating activity will be reported in forthcoming publications.

Experimental[5,6]

Ethyl 3α-Hydroxy-Δ¹¹-cholenate (II).—3α-Hydroxy-Δ¹¹-cholenic acid[7,8] was esterified with absolute ethanol essentially according to the method used by Kendall and his associates for the preparation of the methyl ester.[9] However, whereas esterification with methanol is complete in less than an hour, with ethanol 27% of unreacted acid was recovered even after 22 hours. The ethyl ester did not crystallize from aqueous ethanol, but separated satisfactorily from purified Skellysolve F as colorless needles melting at 81–82°, $[\alpha]^{26}D$ + 30° (*c* 2.01, chf.). *Anal.* Calcd. for $C_{26}H_{42}O_3$: C, 77.56; H, 10.52. Found: C, 77.3; H, 10.6.

Ethyl 3β-Chloro-Δ¹¹-cholenate (I).[10]—To a stirred solution of 500 mg. of II in 28 ml. of chloroform, in a flask equipped with a drying tube and immersed in an ice-bath maintained at 0°, 800 mg. of powdered calcium carbonate and, in two portions with a 20-minute interval, 1.2 g. of phosphorus pentachloride were added. Stirring was continued for 100 minutes at 0°. The reaction product was poured into 200 ml. of 5% sodium bicarbonate solution containing ice, and ether was added. The resulting mixture was stirred until the ice had melted, transferred to a separatory funnel and shaken thoroughly. The organic layer, which still retained a small amount of an insoluble, colorless, inorganic solid, was washed with water, dried (Drierite), filtered and evaporated (reduced pressure) to a colorless residual oil. This oil dissolved in the minimum amount of warm methanol, on refrigeration for 2 hours yielded 380 mg. (73%) of colorless crystals m.p. 69–73°. Two recrystallizations from methanol gave thin plates melting at 74–76°, $[\alpha]^{26}D$ + 25° (*c* 2.05, chf.). *Anal.* Calcd. for $C_{26}H_{41}O_2Cl$: C, 74.16; H, 9.82; Cl, 8.42. Found: C, 74.3; H, 9.8; Cl, 8.8.

Catalytic Hydrogenation.—I in acetic acid solution and the presence of Adams catalyst absorbed 1.03 moles of hydrogen within 20 minutes. After removal of catalyst and solvent, two crystallizations of the product from methanol gave colorless, feathery crystals, m.p. 59–60.5°, which did not depress the melting point of ethyl 3β-chlorocholanate (III) prepared from ethyl lithocholate[11,12] by the same method as used for the unsaturated derivative, crystallizing in methanol as colorless needles, m.p. 59–61.5°, $[\alpha]^{26}D$ +18.5° (*c* 1.27, chf.). *Anal.* Calcd. for $C_{26}H_{43}O_2Cl$: C, 73.81; H, 10.24; Cl, 8.38. Found: C, 73.5; H, 10.5; Cl, 8.2.

(5) Microanalyses by the Microchemical Laboratory of New York University.

(6) Melting points were taken on an electrically heated micro hot-stage and are uncorrected.

(7) J. Press and T. Reichstein, *Helv. Chim. Acta*, **25**, 878 (1942); B. F. McKenzie, W. F. McGuckin and E. C. Kendall, *J. Biol. Chem.*, **162**, 555 (1946).

(8) Generously supplied by Merck and Co. through the kindness of Dr. Max Tishler.

(9) L. L. Engle, V. R. Mattox, B. F. McKenzie, W. F. McGuckin and E. C. Kendall, *J. Biol. Chem.*, **162**, 565 (1946).

(10) Although a double bond shift is considered unlikely under the conditions of this reaction, experiments are under way to confirm the position of unsaturation.

(11) F. Reindel and K. Niederländer, *Ber.*, **68**, 1969 (1935).

(12) We are indebted to Ciba Pharmaceutical Products, Inc., and Dr. H. B. MacPhillamy for a supply of lithocholic acid.

DIVISION OF CHEMISTRY, AND
DIVISION OF PATHOLOGY AND BACTERIOLOGY
UNIVERSITY OF TENNESSEE
MEMPHIS, TENNESSEE

The Preparation of Sarcosine and Methyl α-Methylamino-β-(3-indolyl)-propionate

BY F. F. BLICKE AND PAUL E. NORRIS

RECEIVED FEBRUARY 15, 1954

The preparation of methyl α-methylamino-β-(3-indolyl)-propionate was undertaken since a supply of this ester was required as an intermediate.

1-Methylhydantoin,[1] which had been synthesized from sarcosine (N-methylglycine) and potassium cyanate, was condensed with indole-3-aldehyde[2] to form 1-methyl-5-(3′-indolal)-hydantoin.[1] This hydantoin had been heated with ammonium sulfide in a sealed tube at 100° for 3 days, by Miller and Robson,[1] in order to reduce it to 1-methyl-5-(3′-indolylmethyl)-hydantoin. We found that this reduction could be carried out at 40–50° by the use of Raney nickel, and could be completed in 5–6 hours.

When the last-mentioned hydantoin was refluxed with barium hydroxide, according to the directions in the literature,[1] α-methylamino-β-(3-indolyl)-propionic acid was obtained. We converted this acid into the methyl ester hydrochloride, in quantitative yield, by the use of methanol and hydrogen chloride. The ester base was formed when the salt was treated with ammonia.

It was discovered that sarcosine could be prepared by a much simpler method than that which has been described,[3] namely, by interaction of chloroacetic acid and methylamine.

Experimental

Sarcosine.—Two liters of 30% aqueous methylamine was stirred and 47.5 g. of chloroacetic acid, dissolved in 30 cc. of water, was added slowly. After 24 hours, the solution was concentrated under reduced pressure to a thick sirup which was diluted with absolute ethanol until the volume was about 240 cc. The alcoholic solution was then kept at about −10° for 15 hours, the crystalline precipitate was removed by filtration and the filtrate was diluted with absolute ethanol until the volume was about 225 cc. When the solution was cooled to −10°, and maintained at that temperature, more crystalline material deposited. The combined precipitates were recrystallized twice from 95% ethanol; m.p. 212–215°,[4] yield 18.0 g. (40.5%).

1-Methyl-5-(3′-indolylmethyl)-hydantoin.—Five grams of activated Raney nickel[5] was added to a mixture of 5.0 g. of 1-methyl-5-(3′-indolal)-hydantoin[1] and 100 cc. of 1 *N* sodium hydroxide solution. The mixture was hydrogenated at 40–50° under an initial pressure of 40 pounds. After completed reduction (5–6 hours), the catalyst was removed by filtration and the filtrate was adjusted to a *p*H of 6.5 with 1:1 hydrochloric acid. The product, which separated from the cooled mixture, weighed 4.5 g. (90%); m.p. 212–213°.[6]

α-Methylamino-β-(3-indolyl)-propionic Acid.[7]—This substance was obtained by treatment of 1-methyl-5-(3′-indolylmethyl)-hydantoin with barium hydroxide solution by the procedure of Miller and Robson[1] in 80% yield; m.p. 272–275° dec.[8]

Anal. Calcd. for $C_{12}H_{14}O_2N_2$: C, 65.53; H, 6.46. Found: C, 65.19; H, 6.63.

The hydrochloride, prepared according to the directions in the literature,[1] melted at 220–222°.[9]

The picrate, prepared by a described method,[10] melted at 185–186° dec.[11]

Methyl α-Methylamino-β-(3-indolyl)-propionate and Hydrochloride.—A mixture of 5.0 g. of the propionic acid and 50 cc. of absolute methanol was cooled in an ice-bath and saturated with hydrogen chloride. The mixture was allowed to remain at room temperature whereupon the acid slowly dissolved. By slow evaporation of the solvent from the solution, under reduced pressure in a desiccator which contained calcium chloride, a crystalline residue was obtained. It was covered with methanol and the solvent was removed in the manner just described. If necessary, this process was repeated in order to remove the odor of hydrogen chloride. The hydrochloride, which was slightly contaminated by a light violet impurity, melted at 185–188°.

Anal. Calcd. for $C_{13}H_{17}O_2N_2Cl$: N, 10.42; Cl, 13.20. Found: N, 10.41; Cl, 13.56.

The finely powdered hydrochloride was suspended in absolute ether, the mixture was cooled and saturated with dry, gaseous ammonia. After 10 minutes, the mixture was filtered through a sintered glass funnel and the solvent was removed from the filtrate in the manner described above; the residue, the ester base, melted at 70–72°; yield 2.3 g. (45%).

Anal. Calcd. for $C_{13}H_{17}O_2N_2$: C, 67.21; H, 6.94; N, 12.06. Found: C, 67.34; H, 6.84; N, 12.28.

The picrate was obtained when the ester was treated with an alcoholic solution of picric acid; m.p. 180–182°.

The hydrobromide precipitated when an ethereal solution of the ester was treated with hydrogen bromide; m.p. 163–165° after recrystallization from absolute ethanol–ether.

COLLEGE OF PHARMACY
UNIVERSITY OF MICHIGAN
ANN ARBOR, MICHIGAN

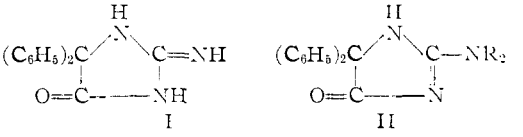
(1) E. J. Miller and W. Robson, *J. Chem. Soc.*, 1910 (1938).
(2) J. Elks, D. F. Elliot and B. A. Hems, *ibid.*, 629 (1944).
(3) W. Cocker, *ibid.*, 1693 (1937).
(4) Reference 3, m.p. 211–212°.
(5) A. A. Pavlic and H. Adkins, THIS JOURNAL, **68**, 1471 (1946).
(6) Reference 1, m.p. 211–212°.
(7) The name N-methyltryptophan, which has been used for this compound, is an unsatisfactory one as has been pointed out by Miller and Robson.[1]
(8) Reference 1, m.p. 245°; W. G. Gordon and R. W. Jackson (*J. Biol. Chem.*, **110**, 154 (1935)), m.p. 297° dec.
(9) Reference 1, m.p. 192–193°; N. Ghatak (*Bull. Acad. Sci. United Provinces Agra Oudh, India*, **3**, 295 (1934); *C. A.*, **29**, 3344 (1935)), m.p. 221–222°.
(10) W. M. Cahill and R. W. Jackson, *J. Biol. Chem.*, **126**, 29 (1938).
(11) Reference 10, m.p. 185–186° dec.

The Preparation of 2-Disubstituted Amino-5,5-diphenyl-4(5H)-imidazolones[1]

BY C. K. CAIN AND SARA K. NAEGELE

RECEIVED DECEMBER 4, 1953

In spite of the large number of 5,5-disubstituted hydantoins which have been prepared and studied pharmacologically, the corresponding 2-imino compounds (glycocyamidines) have received little attention. Recently Hoffmann[2] reported the preparation of 5,5-diphenyl-2-iminohydantoin (5,5-diphenylglycocyamidine) (formula I) and Deliwala and Rajagopalan[3] described the synthesis of a few related compounds. No examples could be found in the literature of compounds containing a disubstituted amino group attached to the carbon atom between the two nitrogen atoms of the ring (formula II). Such a structure is of interest since the existence of the tautomeric form involving a double bond between carbon atom 2 and the exocyclic atom attached to it is not possible, at least in neutral or basic medium.



Several 2-disubstituted amino-5,5-diphenyl-4(5H)-imidazolones have been prepared in good yields by the reaction of 2-methylmercapto-5,5-diphenyl-4(5H)-imidazolone with an excess of a secondary amine (Table I). Diisopropylamine failed to give any detectable reaction under the conditions tried.

(1) Presented before the Division of Medicinal Chemistry at the 124th Meeting of the American Chemical Society, Chicago, Ill., September, 1953.
(2) C. Hoffmann, *Bull. soc. chim. France*, 659 (1950).
(3) C. V. Deliwala and S. Rajagopalan, *Proc. Indian Acad. Sci.*, **31A**, 107 (1950).