droxide. The dry, crude 6-chloromethylquinoline was dissolved in 35 ml. of hot ligroin (b.p. 63–93°) and the solution was cooled to −15°. A yield of 2.3 g. (83%) of short white needles was obtained, m.p. 70.5–71°.

Anal. Calcd. for $C_{10}H_8ClN$: Cl, 19.96. Found: Cl, 19.86.

The hydrochloride was prepared and recrystallized from absolute ethyl alcohol; m.p. 183.5–184.5°.

Anal. Calcd. for $C_{10}H_9Cl_2N$: Cl, 33.28. Found: Cl, 33.51.

6-Bromomethylquinoline.—A stream of dry hydrogen bromide was directed at the surface of a solution of 5 g. (0.031 mole) of 6-quinolinemethanol dissolved in 75 ml. of glacial acetic acid, which was contained in a 500-ml. flask, until a gain in weight of 15 g. was attained. The temperature rose to 40°. The solution was heated on a steam-bath at 70° for 20 minutes, then cooled and the solution was diluted with 300 ml. of dry ether. The solid was collected on a filter and was washed with dry ether. The yield of the crude hydrobromide was 9 g. (95%). The crude solid was dissolved in 125 ml. of water, cooled to 10° and carefully neutralized with 1 *N* sodium hydroxide. The solid was filtered immediately and dried in a desiccator. The dried solid was dissolved in 150 ml. of ligroin (b.p. 63–93°) at room temperature, filtered and the clear solution was cooled in a Dry Ice–acetone-bath. The yield of slightly yellow short needles was 4.7 g. (68%), m.p. 74–75°. This substance is a strong irritant and a lachrymator.

Anal. Calcd. for C_9H_8BrN: Br, 35.98. Found: Br, 35.73.

6-Quinolineacetonitrile.—A solution of 3 g. (0.017 mole) of 6-chloromethylquinoline and 1.2 g. (0.0185 mole) of potassium cyanide in 150 ml. of absolute ethyl alcohol was refluxed for ten hours then the alcohol was removed by evaporation in a vacuum and the residue extracted with three 50-ml. portions of ether. The ether was allowed to evaporate leaving an oil which congealed after standing overnight. The crude solid was extracted with two 75-ml. portions of ligroin (b.p. 63–93°), the solution was treated with Norite, filtered and evaporated to about 75 ml. After cooling to −15° and recrystallization a second time, a yield of 0.8 g. (28%) of white platelets was obtained, m.p. 80–81.5°.

Anal. Calcd. for $C_{11}H_8N_2$: N, 16.66. Found: N, 16.86.

6-Quinolineacetic Acid.—A mixture of 0.7 g. of 6-quinolineacetonitrile and 10 ml. of 10% sodium hydroxide was refluxed for 25 minutes then diluted with 10 ml. of water. The cold solution was extracted with 10 ml. of benzene. The aqueous layer was heated to boiling, then it was made slightly acidic (*p*H 4–5) with acetic acid. After cooling in ice-water for one hour, the white granular solid was collected on a filter, washed and dried. The yield was 0.64 g. (78%); it melted with decomposition at 220°. After solution in dilute alkali and reprecipitation, the melting point was raised to 225° dec.

Anal. Calcd. for $C_{11}H_9NO_2$: N, 7.48. Found: N, 7.62.

Ethyl 6-Quinolylmethyl Ether.—Sodium (0.5 g., 0.022 mole) was dissolved in 40 ml. of absolute ethyl alcohol, 3 g. (0.017 mole) of 6-chloromethylquinoline was added and the solution was refluxed for three hours. After the solution was filtered, the volume was reduced to about 12–15 ml., then four drops of water was added and the solution filtered again. After removal of the alcohol, the residue was vacuum distilled at 0.4 mm. yielding 2.4 g. (76%) of the ether which came over at 101–102°. The liquid was redistilled at 0.05 mm., b.p. 82–83°.

Anal. Calcd. for $C_{12}H_{13}NO$: N, 7.48. Found: N, 7.71.

4-(6-Quinolyl)-2-butanone.—To a cooled solution of 0.68 g. (0.03 mole) of sodium in 80 ml. of absolute ethyl alcohol was added 3.66 g. (0.036 mole) of ethyl acetoacetate. After the solution was stirred for a few minutes, a solution of 5 g. (0.028 mole) of 6-chloromethylquinoline in 25 ml. of absolute alcohol was added and the mixture heated on a steam-bath for three hours. At the end of this time, most of the alcohol was removed by distillation then 100 ml. of water was added and the aqueous portion extracted with two 100-ml. portions of ether. The ether layer was extracted with three 100-ml. portions of 0.5 *N* hydrochloric acid, then the acid solution was neutralized with 10% sodium hydroxide and the alkaline solution extracted with three 100-ml. portions of ether. After evaporation of the ether, the oil was refluxed with 50 ml. of 5% sodium hydroxide then acidified while hot with dilute sulfuric acid. After cooling, the solution was made slightly alkaline, extracted with three 100-ml. portions of ether and the latter dried with magnesium sulfate. After removal of the ether, a viscous yellow oil remained which congealed after standing for several days. The crude solid was recrystallized from 200 ml. of petroleum ether (b.p. 30–60°) by cooling the solution in Dry Ice–acetone. The yield of long white needles was 1.5 g. (28%), m.p. 56–57°.

Anal. Calcd. for $C_{13}H_{13}NO$: N, 7.03. Found: N, 7.06.

The 2,4-dinitrophenylhydrazone was prepared in the customary manner and recrystallized from a 1:1 solution of ethyl alcohol–pyridine as yellow platelets, m.p. 197–198.5°.

Anal. Calcd. for $C_{19}H_{17}N_5O_4$: N, 18.46. Found: N, 18.62.

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11-Deoxycorticosterone. The Aqueous Sulfuric Acid Hydrolysis of 21-Diazoprogesterone

BY CHARLES G. SALEM[1] AND W. WERNER ZORBACH[2]

RECEIVED AUGUST 23, 1954

Reichstein and von Euw[3] have studied 21-diazoprogesterone (II) and some of its transformation products, and have established the constitution of II in part by the action of aqueous sulfuric acid which converts it into 11-deoxycorticosterone (III). Yields and experimental details were not furnished. It was of interest, therefore, to reinvestigate this hydrolysis as a possible method for the preparation of III. It was gratifying to have available a more recent, improved synthesis whereby 3-oxo-Δ^4-etiocholenic acid (I)[4,5] may be converted in two steps and in good yield to 21-diazoprogesterone (II).[6]

Preliminary hydrolyses of II according to the directions of Steiger and Reichstein[7] yielded oils which were only weakly reducing with ammoniacal silver oxide. It was found, however, that by increasing considerably the temperature and time of reaction, an oily product was obtained which gave a strong reducing test with this reagent, and which on chromatography on silicic acid gave pure, crystalline 11-deoxycorticosterone (III) in 62% yield, considerably above our expectations.

Experimental

11-Deoxycorticosterone (III).—A mixture of 680 mg. (2.0 mmoles) of 21-diazoprogesterone (II), 20 ml. of pure dioxane and 7.6 ml. of 2 *N* sulfuric acid was maintained at 75° for four hours. The material was then extracted with 300 ml. of ether, the ether extract washed with two 100-ml. portions of 5% potassium carbonate, and dried over anhydrous magnesium sulfate. The filtered extract was concentrated *in vacuo* at 55° and the small amount of residual dioxane aspirated on a steam-bath by means of a current of

(1) In partial fulfillment of requirements for the degree of Master of Science.

(2) Communications should be addressed to the senior author.

(3) T. Reichstein and J. von Euw, *Helv. Chim. Acta*, **23**, 137 (1940).

(4) K. Miescher and A. Wettstein, *ibid.*, **22**, 1262 (1939).

(5) We are indebted to Dr. A. C. Shabica, Ciba Pharmaceutical Products, Inc., Summit, N. J., for supplying us with methyl 3β-hydroxy-Δ^5-etiocholenate from which this acid was prepared.

(6) A. L. Wilds and C. H. Shunk, THIS JOURNAL, **70**, 2427 (1948).

(7) M. Steiger and T. Reichstein, *Helv. Chim. Acta*, **20**, 1164 (1937).

dry nitrogen. This treatment gave 596 mg. of a clear, neutral oil which was chromatographed in benzene on 18 g. of Fisher reagent grade silicic acid previously wetted with *n*-pentane. Elution (employing 50-ml. eluates throughout) was initiated with benzene, followed by benzene–ether mixtures in which the increment of ether added each time the solvent was changed amounted to 2.5. Benzene–ether (95.0–5.0 and 92.5–97.5) eluates furnished 422 mg. (62%) of crystalline 11-deoxycorticosterone (III) which melted at 138–142°. One recrystallization from ether gave pure III, m.p. 141.5–142.5° cor., $[\alpha]^{25}D$ +184 ± 6° (*c* 0.20, $CHCl_3$), λ_{max}^{alc} 240 mμ (4.3).

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2-Guanidino-4(5)-*p*-chlorophenylimidazoles

BY TERRY O. NORRIS AND R. L. MCKEE

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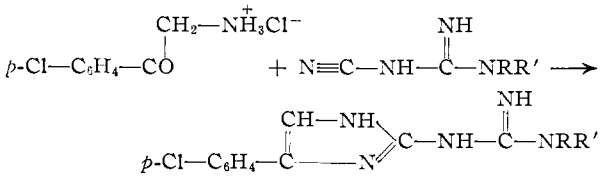
In continuation of a program of synthesis of heterocyclic guanidines,[1,2] imidazole analogs have been prepared as indicated



Although successful condensations were effected with derivatives of dicyandiamide, we were unable to obtain satisfactory condensations from *p*-chlorophenacylamine hydrochloride with cyanamide, dicyandiamide or sodium dicyanamide.

In addition, *p*-chlorophenacylamine hydrochloride was converted into 2-mercapto-4(5)-*p*-chlorophenylimidazole by the procedure of Wohl and Marckwald.[3] However, a marked improvement in yields was obtained in this reaction by using glacial acetic acid in place of aqueous ethanol as the reaction medium. Oxidation of the mercapto compound to 4(5)-*p*-chlorophenylimidazole was effected in rather poor yield with nitric acid.

Experimental

p-Chlorophenacylamine hydrochloride has been prepared[4] by reduction of isonitroso-*p*-chloroacetophenone. For the present work it was prepared conveniently by the procedure of Long and Troutman[5] and melted with decomposition at 290°.[4]

N-Cyano-N'-*p*-hydroxyphenylguanidine was prepared from *p*-aminophenol and sodium dicyanamide according to published procedure.[6] After crystallization from butyl alcohol and from butyl cellosolve, it melted at 269–270°.

Anal. Calcd. for $C_8H_8N_4O$: C, 54.6; H, 4.6; N, 31.8. Found: C, 54.2; H, 4.4; N, 31.7.

2-Guanidino-4(5)-*p*-chlorophenylimidazoles all were prepared by a reasonably standardized procedure in which *p*-chlorophenacylamine hydrochloride and the appropriate cyanoguanidine[6] were mixed in equimolar (usually 0.01 mole) amounts in a test-tube and placed in an oil-bath at 180°. The mixture fused and evolved steam after which it was maintained at 150–200° for about 30 minutes and allowed to cool. The resulting brown glassy material was extracted with acetone which removed tarry matter. The residual hydrochlorides[7] of the desired products were dissolved in hot water and the free bases liberated with ammonium hydroxide, filtered and crystallized to constant melting point. The yields of purified material, which were in all cases about 30%, cannot be considered particularly significant because of losses encountered in finding suitable solvents for crystallization.

The compounds so prepared (Table I) are readily soluble in dilute hydrochloric acid and the resulting solutions can be boiled extensively without decomposition.

2-Mercapto-4(5)-*p*-chlorophenylimidazole.—Five grams (0.035 mole) of *p*-chlorophenacylamine hydrochloride and 3.9 g. (0.035 mole) of potassium thiocyanate were refluxed in 100 ml. of glacial acetic acid for 10 minutes. Addition of water and thorough chilling resulted in the separation of 5 g. (97% yield) of material melting at 285–291° dec. A sample was recrystallized from absolute ethanol to a melting point of 293–295° dec.

Anal. Calcd. for $C_9H_7ClN_2S$: N, 13.2; S, 15.2. Found: N, 13.1; S, 15.2.

4(5)-*p*-Chlorophenylimidazole.—To 100 ml. of boiling 10% nitric acid was added 3 g. of powdered 2-mercapto-(45)-*p*-chlorophenylimidazole over a period of 5 minutes. Heating was continued for 10 minutes and the solution was filtered while hot. Upon cooling, the filtrate deposited a small amount of material melting at 179–180°.[8] Neutralization of the filtrate produced a material melting at 140–143°. The substance was crystallized from hot water giving a white product, m.p. 145–147°. During several preparations, the yields of purified material varied from 10–30%.

Anal. Calcd. for $C_9H_7ClN_2$: C, 60.5; H, 4.0; N, 15.7. Found: C, 60.7; H, 4.0; N, 15.7.

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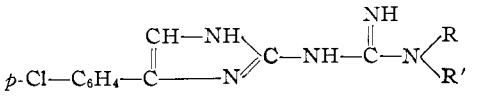
TABLE I



R	R'	M.p., °C.	Cryst. solvent	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
H–	$-CH(CH_3)_2$	163–165	Benzene	$C_{13}H_{16}ClN_5$	56.2	56.0	5.9	6.1	25.1	25.0
C_2H_5–	$-C_2H_5$	102.5–104.5	Benzene–pet. eth.	$C_{14}H_{18}ClN_5$	57.6	57.5	6.2	6.1	24.0	24.0
H–	$-CH_3$	214–216	50% Alcohol	$C_{11}H_{12}ClN_5$	52.9	53.2	4.9	5.1	28.1	27.9
CH_3–	$-CH_3$	186–188	50% Alcohol	$C_{12}H_{14}ClN_5$	54.7	54.7	5.4	5.1	26.6	26.6
H–	$-C_4H_9(n)$	187.5–189.5	80% Alcohol	$C_{14}H_{18}ClN_5$	57.6	57.5	6.2	6.1	24.0	24.0
H	$-C_6H_5$	171–173	95% Alcohol	$C_{16}H_{14}ClN_5$	61.6	61.5	4.5	4.5	22.5	22.4
H–	$-C_6H_4-OH(p)$	222–224	80% Alcohol	$C_{16}H_{14}ClN_5O$	58.6	58.7	4.3	4.4	21.4	21.3

(1) L. Theiling and R. McKee, THIS JOURNAL, **74**, 1834 (1952).
(2) R. L. McKee and J. D. Thayer, *J. Org. Chem.*, **17**, 1494 (1952).
(3) A. Wohl and W. Marckwald, *Ber.*, **22**, 568, 1353 (1889).
(4) R. P. Edkins and W. H. Linnell, *Quart. J. Pharm. Pharmacol.*, **9**, 75 (1936).
(5) L. Long and H. Troutman, THIS JOURNAL, **71**, 2473 (1949)
(6) T. S. Kenny and A. G. Murray, British Patent 599,722.
(7) The crude salts were obtained in yields of 46–79%. They were not characterized by analysis due to their hygroscopic nature.
(8) This material had approximately the nitrogen content (17.4%) to be expected from the *nitrate* of *p*-chlorophenylimidazole (17.7%). Upon treatment with sodium carbonate, the latter was formed.