hydroxylamine hydrochloride, pyridine, and ethanol. The yield was 10 g. (93%); recrystallization from methanol provided an analytical sample, m.p. 188–189°.

Anal. Calcd. for $C_{11}H_{11}O_3N$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.40; H, 5.40; N, 6.83.

Rearrangement of the Oxime VI.—A 2.0-g. sample of VI in 60 g. of polyphosphoric acid was heated at 105–110° for 5 minutes. A 0.4 g. (20%) yield of oxindole-3-propionic acid, m.p. 163–166°, was obtained. After recrystallization the m.p. and mixed m.p. was 167–169°.

Alkaline Hydrolysis of II.—A 0.4-g. sample of the methyl ester-lactam II in 10 ml. of methanol and 10 ml. of 10% sodium hydroxide solution was refluxed for 2 hours. The methanol was removed by distillation and the reflux period was continued for 0.5 hour. The acidic product was isolated and found to consist of 0.3 g. of oxindole-3-propionic acid.

Ethyl Oxindole-3-propionate. (A) By Esterification.—Oxindole-3-propionic acid (9.0 g.) was esterified in a mixture of 75 ml. of dry ethanol, 75 ml. of dry benzene and 3 drops of concd. hydrochloric acid, using an 11-hour reflux period. There was obtained 7.0 g. of ester, m.p. 67–69°. An analytical sample was recrystallized from pentane–benzene; m.p. 69.5–70°.

Anal. Calcd. for $C_{13}H_{15}O_3N$: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.97; H, 6.54; N, 5.93.

(B) **By Rearrangement.**—A solution of 1.5 g. of II in 50 ml. of dry ethanol and 50 ml. of dry benzene containing 3 drops of concd. hydrochloric acid was refluxed for 10 hours. The neutral product was isolated to yield 1.4 g. of ester, m.p. 65–67°, not depressed on mixture with the sample obtained by direct esterification.

Reduction-Cyclization of α-(*o*-Nitrophenyl)-glutaric Acid.—α-(*o*-Nitrophenyl)-glutaric acid[9] was prepared by the hydrolysis-decarboxylation of 1-(*o*-nitrophenyl)-propane-1,3,3-tricarboxylic acid triethyl ester with hydrobromic acid. The tricarboxylic ester was prepared by the Michael addition of diethyl methylenemalonate to ethyl *o*-nitrophenylacetate.

A mixture of 2.4 g. of the acid, 10 ml. of concd. hydrochloric acid and 2.4 g. of tin was heated at 100° for 2 hours and then allowed to stand overnight. The acid product was isolated and found to be 0.6 g. (31%) of oxindole-3-propionic acid.

(9) M. Kotake, T. Sakan and T. Miwa, THIS JOURNAL, **72**, 5086 (1950).

Oxindole-3,3-dipropionic Acid. A. From Oxindole.—The Michael addition of methyl acrylate and oxindole was carried out according to Horner.[6] The resulting ester was hydrolyzed in 2 *N* sulfuric acid to yield 66% of a colorless acid, m.p. 124–128°. This material was recrystallized from water and from pentane–ethyl acetate; m.p. 130–131°. Since the analytical data indicated water of hydration, attempts were made to obtain an anhydrous form by drying *in vacuo* over phosphorus pentoxide at 110°. The anhydrous acid of Horner[6] and Julian,[2] m.p. 152°, was not obtained.

Anal. Calcd. for $C_{14}H_{15}O_5N \cdot {}^1/_2H_2O$: C, 58.73; H, 5.63; N, 4.89. Found: C, 58.96; H, 5.64; N, 4.88.

B. From Methyl Oxindole-3-propionate.—From a 1.3-g. sample of methyl oxindole-3-propionate, by addition of methyl acrylate followed by acid hydrolysis, there was obtained 1.1 g. (66% over-all yield) of the same material described above.

1-Ethyloxindole-3,3-dipropionic Acid. (A) From Oxindole-3,3-dipropionic Acid.—A 1.2-g. sample of the oxindole-3,3-dipropionic acid described above was esterified in ethanol–benzene containing a few drops of concd. sulfuric acid. The ester was isolated in the usual way and was subjected to alkylation conditions using 0.1 g. of sodium, 15 ml. of dry ethanol and 1 ml. of ethyl iodide. After a 2-hour reflux period, the neutral product was isolated. Hydrolysis was effected with boiling 2 *N* sulfuric acid. The product crystallized from the solution in colorless form in 1.0 g. (75%) yield; m.p. 133–135°. Recrystallization from water and from ethyl acetate, followed by drying *in vacuo* at 110°, gave colorless hygroscopic needles with m.p. 137–138°.

Anal. Calcd. for $C_{16}H_{19}O_5N$: C, 62.94; H, 6.27; N, 4.59. Found: C, 62.92; H, 6.54; N, 4.61.

(B) **From 1-Ethyloxindole.**—Methyl acrylate (6.2 g.) was added to 1-ethyloxindole (3.2 g.) in a sodium ethoxide solution prepared from 0.46 g. of sodium and 20 ml. of dry ethanol. The neutral product was hydrolyzed in 10% sodium hydroxide solution, and the resulting acid was crystallized directly from the solution after acidification to yield 4.3 g. (71%) of 1-ethyloxindole-3,3-dipropionic acid; m.p. 135–137°. Recrystallization from water raised the m.p. to 137–138°, not depressed on mixture with the sample described above.

BETHESDA, MARYLAND

[CONTRIBUTION FROM THE COLLEGE OF PHARMACY, UNIVERSITY OF MICHIGAN]

Diuretics. I. 3-Substituted Paraxanthines

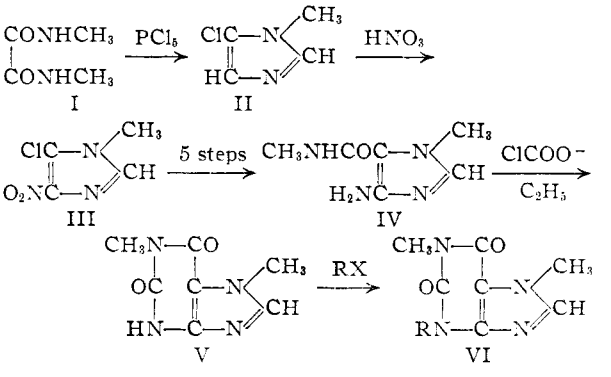
BY F. F. BLICKE AND H. C. GODT, JR.[1,2]

RECEIVED MARCH 15, 1954

Thirteen 3-substituted paraxanthines have been obtained by alkylation of paraxanthine, and their potency as diuretics has been reported.

The 3-substituted paraxanthines were obtained by heating an aqueous alcoholic solution of paraxanthine, potassium hydroxide and the required alkyl or aralkyl halide.

It was found that the necessary paraxanthine (V) could be obtained in adequate amounts by the following eight-step process. Diethyl oxalate was converted by methylamine into N,N'-dimethyloxamide (I) in the manner described by Wallach.[3,4] The amide reacted with phosphorus pentachloride to yield 1-methyl-5-chloroimidazole (II). This reaction has been described inadequately by Wallach.[3,4] Nitration of this imidazole gave 1-methyl-4-nitro-5-chloroimidazole (III) which reacted with sodium cyanide to produce 1-methyl-4-nitro-5-cy-



(1) This paper represents part of a dissertation submitted by H. C. Godt in partial fulfillment of the requirements for the Ph.D. degree in the University of Michigan, 1953.

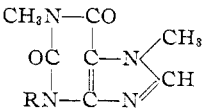
(2) Monsanto Chemical Company Fellow.

(3) O. Wallach and A. Boehringer, *Ann.*, **184**, 50 (1877).

(4) O. Wallach, *ibid.*, **214**, 257 (1882).

TABLE I

3-SUBSTITUTED PARAXANTHINES



Compound 1 was recrystallized from ethanol–ether, 2, 3 and 10 from ethyl acetate, 4, 5 and 6 from dilute ethanol, 7 and 8 from petroleum ether (90–100°), 9 from petroleum ether–ethyl acetate, 11 and 12 from ethanol and 13 from acetic acid.

	R	M.p., °C.	Yield, %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
1	Ethyl	128–130[a]	60	$C_9H_{12}O_2N_4$	51.92	52.08	5.81	5.31	26.91	26.67
2	*n*-Propyl	105–107	51	$C_{10}H_{14}O_2N_4$	54.04	54.35	6.35	6.30	25.21	25.20
3	Isopropyl	185–186	25	$C_{10}H_{14}O_2N_4$	54.04	54.01	6.35	6.20	25.21	25.12
4	*n*-Butyl	90–92	52	$C_{11}H_{16}O_2N_4$	55.91	56.14	6.83	6.88	23.71	23.67
5	Isobutyl	97–99	39	$C_{11}H_{16}O_2N_4$	55.91	55.56	6.83	6.51	23.71	23.59
6	*sec*-Butyl	98–99[b]	23	$C_{11}H_{16}O_2N_4$	55.91	56.32	6.83	6.84	23.71	23.85
7	Isoamyl	110–112	35	$C_{12}H_{18}O_2N_4$	57.58	57.73	7.25	7.16	22.39	22.50
8	*n*-Hexyl	101–102	46	$C_{13}H_{20}O_2N_4$	59.07	59.52	7.63	7.84	21.20	21.04
9	Allyl	114–116	49	$C_{10}H_{12}O_2N_4$	54.54	54.41	5.49	5.18	25.44	25.21
10	Benzyl	166–168	44	$C_{14}H_{14}O_2N_4$	62.21	62.09	5.22	4.94	20.73	20.84
11	β-Hydroxyethyl	156–158	60	$C_9H_{12}O_3N_4$	48.21	47.95	5.40	5.26	24.99	24.77
12	β-Diethylaminoethyl (HCl)	200–202	45	$C_{13}H_{22}O_2N_5Cl$	49.44	49.47	7.02	7.06	22.18	22.15[c]
13	Phenacyl	240–242	60	$C_{15}H_{14}O_3N_4$	60.39	60.00	4.73	4.62	18.78	18.88

[a] H. Biltz and E. Peukert (*Ber.*, **58**, 2190 (1925)), m.p. 128°. [b] A mixture of compounds 5 and 6 melted at a lower temperature. [c] Chlorine: calcd. 11.23, found 11.10.

anoimidazole. These two latter reactions have been carried out by Sarasin and Wegmann.[5] The 5-cyano compound was converted, successively, into the corresponding 5-carboxylic acid, 5-acid chloride and 5-methylcarbamyl derivative by processes reported by Mann and Porter.[6] We found that reduction of the nitro group in 1-methyl-4-nitro-5-methylcarbamylimidazole with the formation of the corresponding 4-amino compound IV could be effected successfully by the use of hydrogen and platinum oxide instead of Raney nickel.[6] In the final step, the 4-amino derivative was condensed with ethyl chlorocarbonate by Mann and Porter's process to produce paraxanthine (V). The 3-substituted paraxanthines (Table I) were prepared in the manner stated above.

Experimental

1-Methyl-5-chloroimidazole (II), Nitrate and Methobromide.—N,N'-Dimethyloxamide (I) (450 g., 3.88 moles) and 1,485 g. (7.13 moles) of phosphorus pentachloride were shaken thoroughly in a flask equipped with a wide-bore reflux condenser, and heated gently on a steam-bath until the reaction began. The flask was then removed from the bath. After completion of the reaction, the mixture was allowed to remain at room temperature for 12 hours. The phosphorus oxychloride was removed under reduced pressure. After the addition of 500 cc. of water to the tarry residue, it was cooled and 20% sodium hydroxide solution was added slowly until the mixture was distinctly basic. The inorganic salts were removed by filtration and the filtrate was extracted with chloroform. After removal of the solvent, the residue was distilled; b.p. 82–85° (11 mm.),[7] yield 258 g. (57%).

The nitrate was obtained by the described method.[5] It melted at 144–145° dec.[8] after recrystallization from absolute ethanol.

The methobromide was produced when a mixture of the base, dissolved in absolute ethanol and methyl bromide was allowed to remain at room temperature for 24 hours; m.p. 195–196° after recrystallization from ethyl acetate–ethanol.

Anal. Calcd. for $C_5H_8N_2ClBr$: N, 13.25; Br^-, 37.79. Found: N, 13.24; Br^-, 37.76.

1-Methyl-4-amino-5-methylcarbamylimidazole (IV).—A mixture of 5.0 g. of 1-methyl-4-nitro-5-methylcarbamylimidazole, 0.02 g. of platinum oxide catalyst and 100 cc. of absolute ethanol was hydrogenated under an initial pressure of 50 pounds. Reduction was completed in 1 hour. The mixture was filtered and the solvent removed from the filtrate under reduced pressure. The product was recrystallized from acetone–ether; m.p. 149–150°,[9] yield 3.1 g. (75%).

Paraxanthine (1,7-Dimethylxanthine).—The process of Mann and Porter[6] was carried out on a relatively large scale. When 15.4 g. of 1-methyl-4-amino-5-methylcarbamylimidazole, 44.0 g. of anhydrous potassium carbonate and 46.2 g. of freshly distilled ethyl chlorocarbonate were refluxed in 300 cc. of anhydrous dioxane for 2.5 days, 10.8 g. (60%) of product was obtained, m.p. 297–299°.[10] The unchanged amine was recovered.[6]

General Procedure for the Preparation of 3-Substituted Paraxanthines (VI).—Paraxanthine (9.0 g., 0.05 mole) and a solution of 3.9 g. (0.07 mole) of potassium hydroxide in 100 cc. of 95% ethanol were heated on a steam-bath and just enough water was added to bring all of the material into solution. The required alkyl or aralkyl halide (0.07 mole)[11] was added and the mixture heated in a citrate bottle at 100–120° for 24 hours. The cold mixture was made basic and extracted with chloroform. The solvent was removed from the dried extract under reduced pressure.

The first nine compounds (Table I) were purified by sublimation under 0.5 mm. pressure followed by recrystallization. Isopropyl alcohol, instead of ethanol, was used as a solvent for the preparation of the isopropyl derivative. The phenacyl derivative precipitated when the reaction mixture was cooled.

In order to obtain the β-diethylaminoethyl derivative, paraxanthine, potassium hydroxide, β-diethylaminoethyl chloride hydrochloride, an additional molecular equivalent of potassium hydroxide and ethanol were treated in the usual manner. The oily residue, obtained after removal of the chloroform, was distilled; b.p. 205–208° (1.2 mm.), yield 6.5 g. (46.5%). The hydrochloride precipitated when the base, dissolved in absolute ethanol, was treated with hydrogen chloride.

Some of the products listed in Table I were tested in dogs for diuretic activity in the Lilly Research Laboratories. Compounds 1 and 2, administered intravenously, produced moderate diuresis in 20 mg./kg. dose. Compounds 3, 4 and 5, administered orally, in a 250-mg. dose produced nausea

(5) J. Sarasin and E. Wegmann, *Helv. Chim. Acta*, **7**, 713 (1924).

(6) F. G. Mann and J. W. G. Porter, *J. Chem. Soc.*, 751 (1945).

(7) Reference 3 and 4, b.p. 205°.

(8) The melting point has not been reported previously.

(9) Reference 6, m.p. 149–150°.

(10) Reference 6, m.p. 297–299°.

(11) For the preparation of the ethyl, propyl and isopropyl derivatives, the alkyl iodides were used. The butyl, isobutyl, *sec*-butyl, isoamyl, hexyl and β-diethylaminoethyl derivatives were obtained by the use of the required bromide or chloride and the addition of 0.05 mole of potassium iodide to the mixture.

but no diuresis. Slight diuresis was observed in 1 of 2 dogs by a 200-mg. dose of 7. A 200-mg. oral dose of 9 caused moderate diuresis in 2 of 4 dogs. The same oral dose of 11 produced slight diuresis in 1 of 4 dogs. Compounds 6, 8, 10 and 13 were found to be inactive; 12 was slightly active in 10–20 mg./kg. dose.

ANN ARBOR, MICHIGAN

[CONTRIBUTION FROM THE COLLEGE OF PHARMACY, UNIVERSITY OF MICHIGAN]

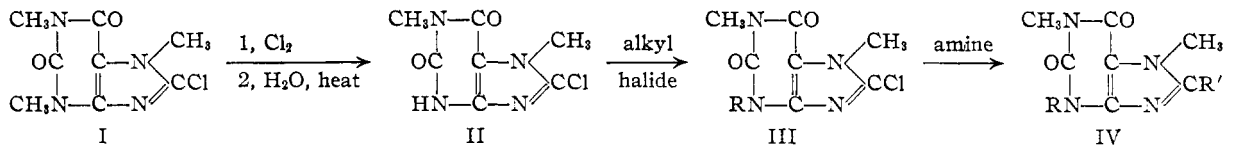
Diuretics. II. 3,8-Disubstituted Paraxanthines

BY F. F. BLICKE AND H. C. GODT, JR.[1,2]

RECEIVED MARCH 15, 1954

Eighteen 3,8-disubstituted paraxanthines were prepared by alkylation and then amination of 8-chloroparaxanthine, and the potency of some of them as diuretics has been reported.

The first step in the preparation of the 3,8-disubstituted paraxanthines IV consisted in the conversion of 8-chlorocaffeine (I) into 8-chloroparaxanthine (II). A stream of chlorine was passed into a boiling solution of 8-chlorocaffeine in *o*-dichlorobenzene. After the reaction mixture had been subjected to steam distillation, 8-chloroparaxanthine was obtained. This process has been described by Mann and Porter[3] who stated that the chlorine must be passed into the solution at such a rate that "excess chlorine" is present during the whole operation. In our initial attempts to repeat this process, we failed entirely to obtain 8-chloroparaxanthine or we were able to isolate it only in very poor yield. Since it seemed that the rate of flow of chlorine into the reaction mixture was an important factor, a flowmeter was employed in subsequent experiments. Even though many experiments were carried out with the use of this instrument, and the rate of flow of chlorine, the length of time of the introduction of chlorine and the temperature of the reaction mixture were varied, our yield of 8-chloroparaxanthine was never as high (37%) as that reported by Mann and Porter; we obtained a reproducible yield of 24%.



I II III IV

Alkylation of 8-chloroparaxanthine yielded the 3-alkyl derivatives III, and amination of these compounds produced the desired 3-alkyl-8-basically-substituted paraxanthines IV.

Experimental

8-Chloroparaxanthine (II).[4]—8-Chlorocaffeine (I)[5] (0.2 mole), 100 cc. of *o*-dichlorobenzene and a small crystal of iodine were heated at 165° for 1.5 hours while a stream of chlorine was passed into the reaction mixture at a rate which gave a meter pressure of 15 cm. of light liquid petrolatum on a flowmeter.[6] The mixture was cooled, 100 cc. of water was added and the mixture was steam distilled for 2 hours to remove the *o*-dichlorobenzene. The solution (about 500 cc.) in the distillation flask was concentrated to a volume of about 150 cc. and then cooled for 12 hours. The precipitated solid was filtered and dissolved in about 200 cc. of hot 2.5% sodium hydroxide solution. The hot solution was filtered and the sodium salt of 8-chloroparaxanthine was precipitated by the addition of 100 cc. of 30% sodium hydroxide solution. After refrigeration for several hours, the sodium salt was filtered, dissolved in about 300 cc. of hot water and the 8-chloroparaxanthine precipitated by acidification of the solution with 50% acetic acid. The filtered product was washed with ethanol and ether; m.p. 284°,[7] yield 10.4 g. (24%).

General Procedure for the Preparation of 3-Alkyl-8-chloroparaxanthines (III) (Table I).—8-Chloroparaxanthine (II, 12.0 g., 0.056 mole) and a solution of 4.2 g. (0.075 mole) of potassium hydroxide in 100 cc. of 95% ethanol were heated on a steam-bath; enough water was added to bring all of the material into solution. The required alkyl bromide[8] (0.075 mole) was added and the mixture was heated in a pressure bottle at 100° for 24 hours. The mixture was made basic with 10% potassium hydroxide solution and extracted with chloroform. The extract was dried over magnesium sulfate, the solvent was removed under reduced pressure and the product was recrystallized; yields 65–75%.

General Procedure for the Preparation of 3-Alkyl-8-basically-substituted Paraxanthines (IV) (Table I).—The required 3-alkyl-8-chloroparaxanthine (0.015 mole) and 50 cc. of a 10% solution of the required amine in absolute ethanol were heated in a pressure bottle at 155° for 24 hours. The solvent and unchanged amine were removed by distillation

(1) This paper represents part of a dissertation submitted by H. C. Godt in partial fulfillment of the requirements for the Ph.D. degree in the University of Michigan, 1953.

(2) Monsanto Chemical Company Fellow.

(3) F. G. Mann and J. W. G. Porter, *J. Chem. Soc.*, 751 (1945).

(4) Since Mann and Porter (ref. 3) gave only a sketchy outline for the preparation of this compound, the procedure used by us is written in detail.

(5) L. M. Long, THIS JOURNAL, **69**, 2939 (1947).

(6) A section of 0.5 mm. capillary tubing 2.5 inches in length was connected, end-to-end, between two T-tubes and placed in a horizontal position with the vertical ends of the T-tubes pointing downward. The two vertical ends were joined by fusion to the ends of a U-tube which was made of 1 mm. capillary tubing, the legs of the U being approximately 25 cm. in length. The junctions of the T-tubes and the U-tube may be blown into bulbs which will serve as safety devices. The 1 mm. capillary U-tube was half-filled with light liquid petrolatum which acted as a pressure meter. The apparatus was mounted on a vertical support with a centimeter scale placed between the side-arms of the U-tube. One end of the apparatus was connected to the reaction flask; the other end was attached to the chlorine tank. When chlorine was passed into the apparatus, the pressure which was built up was measured by the difference in the levels of the petrolatum in the U-tube. The pressure was an index of the rate of flow of the chlorine into the reaction vessel.

(7) E. Fischer and F. Ach (*Ber.*, **39**, 423 (1906)), m.p. 287°.

(8) In the preparation of the 3-*n*-butyl derivative, 1.0 g. of potassium iodide was also added.