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

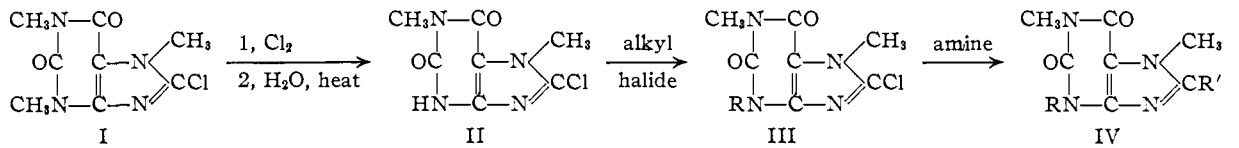
BY F. F. BLICKE AND H. C. GODT, JR.[1,2]

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%.

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.



I II III 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).

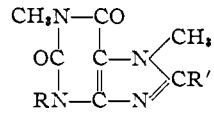
(6) A section of 0.5 mm. capillary tubing 2.5 inches in length was connected, end-to-end, between two T-tubes and placed in a horizontal position with the vertical ends of the T-tubes pointing downward. The two vertical ends were joined by fusion to the ends of a U-tube which was made of 1 mm. capillary 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.

TABLE I

3,8-DISUBSTITUTED PARAXANTHINES



Compounds 1, 15 and 16 were recrystallized from isopropyl alcohol, 2 from water, 3–13 from dilute ethanol, 14, 17 and 18 from dilute methanol, and 15 and 16 from isopropyl alcohol

	R	R'	M.p., °C.	Yield, %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Diuresis
1	Ethyl	Chloro	111–112[a]	68	$C_9H_{11}O_2N_4Cl$	44.54	44.82	4.57	4.52	23.09	22.78[b]	Slight in 1 of 4 dogs
2	Ethyl	Amino	293–294	82	$C_9H_{12}O_2N_5$	48.42	48.35	5.87	5.91	31.38	31.20	
3	Ethyl	Methylamino	267–269	85	$C_{10}H_{14}O_2N_5$	50.62	50.55	6.37	6.43	29.52	29.50	None
4	Ethyl	Ethylamino	240–242	78	$C_{11}H_{17}O_2N_5$	52.57	52.39	6.82	6.73	27.87	27.67	Marked in 2 of 4 dogs
5	Ethyl	Dimethylamino	130–132	73	$C_{11}H_{17}O_2N_5$	52.57	52.55	6.82	6.84	27.87	27.99	None
6	Ethyl	Diethylamino	125–127	68	$C_{13}H_{21}O_2N_5$	55.89	56.10	7.58	7.81	25.07	25.03	Mild in 2 of 4 dogs
7	Ethyl	Piperidino	127–129	68	$C_{14}H_{21}O_2N_5$	57.71	58.19	7.27	7.45	24.04	23.97	Mild in 3 of 4 dogs
8	*n*-Butyl	Chloro	69–70	74	$C_{11}H_{15}O_2N_4Cl$	48.80	49.25	5.58	5.73	20.70	20.68[c]	Slight
9	*n*-Butyl	Amino	249–250	76	$C_{11}H_{17}O_2N_5$	52.57	52.56	6.82	6.63	27.87	27.76	
10	*n*-Butyl	Methylamino	230–232	85	$C_{12}H_{19}O_2N_5$	54.32	54.59	7.22	7.00	26.40	26.44	None
11	*n*-Butyl	Ethylamino	206–207	78	$C_{13}H_{21}O_2N_5$	55.89	55.84	7.58	7.61	25.07	25.05	Moderate to marked in all 4 dogs
12	*n*-Butyl	Dimethylamino	69–70	70	$C_{13}H_{21}O_2N_5$	55.89	56.14	7.58	7.63	25.07	24.98	Moderate in 4 dogs
13	*n*-Butyl	Diethylamino	82–83	71	$C_{15}H_{25}O_2N_5$	58.61	58.98	8.20	8.39	22.79	22.76	Mild in 2 of 4 dogs
14	*n*-Butyl	Piperidino	92–93	70	$C_{16}H_{25}O_2N_5$	60.16	60.20	7.89	7.40	21.92	22.07	None
15	Allyl	Chloro	112–114	74	$C_{10}H_{11}O_2N_4Cl$	47.16	47.69	4.35	4.43	22.00	21.89[d]	Mild in 4 of 6 dogs
16	Allyl	Methylamino	233–235	79	$C_{11}H_{15}O_2N_5$	53.00	53.22	6.07	6.32	28.10	28.17	
17	Allyl	Dimethylamino	126–127	68	$C_{12}H_{17}O_2N_5$	54.74	54.69	6.51	6.78	26.60	26.57	
18	Allyl	Piperidino	99–101	65	$C_{15}H_{21}O_2N_5$	59.38	59.99	6.98	6.89	23.09	22.93	Mild in 2 of 4 dogs

[a] H. Biltz and E. Peukert (*Ber.*, **58**, 2109 (1925)), m.p. 112°. [b] Chlorine: calcd. 14.61, found 14.80. [c] Chlorine: calcd. 13.10, found 13.10. [d] Chlorine: calcd. 13.92, found 13.90.

under reduced pressure and the product was recrystallized; yields 65–85%.

Some of the compounds listed in Table I were tested for diuretic activity by oral administration to dogs in the Lilly Research Laboratories. The dose was 200 mg. except in the case of compound 5; in this instance, it was 400 mg.

ANN ARBOR, MICHIGAN

[CONTRIBUTION FROM THE ABBOTT LABORATORIES]

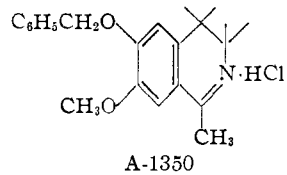
Local Anesthetics. IV.[1] The Synthesis of Local Anesthetic 3,4-Dihydroisoquinolines[2]

BY M. B. MOORE, H. B. WRIGHT, MAYNETTE VERNSTEN, M. FREIFELDER AND R. K. RICHARDS

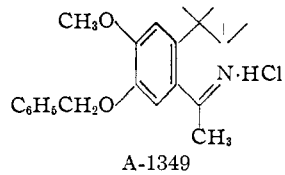
RECEIVED FEBRUARY 27, 1954

Because of the excellent local anesthetic properties of 6(7)-benzyloxy-7(6)-methoxy-3,4-dihydroisoquinolines, their synthesis and pharmacology were extensively studied. Other 3,4-dihydroisoquinolines containing one, two or three substituents, many of them new compounds, were compared with these, but none was found to be superior.

In the course of a pharmacological screening program 6-benzyloxy-7-methoxy-1-methyl-3,4-dihydroisoquinoline hydrochloride (A-1350) originally



A-1350



A-1349

synthesized as an intermediate[3] was shown to have powerful local anesthetic properties. It is effective topically as well as by infiltration and is not irritating in the concentrations needed for anesthesia. The isomer (A-1349) in which the positions of the benzyloxy and methoxy groups are interchanged showed only slightly less desirable properties.

Compounds A-1350 and A-1349 were synthesized by Späth, *et al.*,[4] during their proof of structure of salsoline, but neither the bases nor their salts were purified; the crude materials were reduced. The yields by their method are poor, one of the most unsatisfactory reactions being the two-step reduction of the nitrostyrene to the phenethylamine. Other types of hydrogenation were tried here, including a few unsuccessful attempts at one-step electrolytic reduction.[5] A modification of the method of Hahn and Schales[6,7] first applied by Hahn and Rumpf[8] to 3-hydroxy-4-methoxy-ω-nitrostyrene was successful; but the large volumes and careful technique required make it an impractical method for use with large quantities.

The possible routes for synthesis of dihydroiso-

(1) Paper III, THIS JOURNAL, **75**, 1770 (1953).

(2) Presented before the Division of Medicinal Chemistry, 124th Meeting of the American Chemical Society, Chicago, Ill., September 6–11, 1953.

(3) By E. J. Matson, in these laboratories.

(4) E. Späth, A. Orechoff and F. Kuffner, *Ber.*, **67B**, 1214 (1934).

(5) R. Robinson and S. Sugasawa, *J. Chem. Soc.*, 3163 (1931). Since this investigation was carried out, two publications have appeared describing successful reductions of nitrostyrenes by lithium aluminum hydride: (a) K. E. Hamlin and A. W. Weston, THIS JOURNAL, **71**, 2210 (1949); (b) F. A. Ramirez and A. Burger, *ibid.*, **72**, 2781 (1950).

(6) G. Hahn and O. Schales, *Ber.*, **67B**, 1486 (1934).

(7) O. Schales, *ibid.*, **68B**, 1579 (1935).

(8) G. Hahn and F. Rumpf, *ibid.*, **71B**, 2141 (1938).