trioxymethylene were added and the formal derivative of D-(−)-2,3-butanediol was removed as formed by use of an esterification apparatus. The aqueous phase was saturated with potassium carbonate and the layer of D-(−)-4,5-dimethyl-1,3-dioxolane was separated, yield 1.9 g. (103%). This material was moist which accounts for the slightly high yield. Several runs gave crude yields of 100–105%. This crude material was dried over anhydrous potassium carbonate and distilled. The final product had the following physical constants: $n^{25}D$ 1.3952, d^{25}_4 0.933, $[\alpha]^{25}D$ −24.30°; b.p. 94–96° (760 mm.). Garner and Lucas[7] report $n^{25}D$ 1.3959, d^{25}_4 0.9346, $[\alpha]^{25}D$ −25.01, b.p. 95° (760 mm.).

Reaction of 1-Methyl-2-hydroxypropyl 1-Methyl-1-propenyl Methanephosphonate with Phosphorus Pentachloride.—1-Methyl-2-hydroxypropyl 1-methyl-1-propenyl methanephosphonate (33.2 g., 0.15 mole) was placed in a 200-cc. four-neck, round-bottom flask. The flask was equipped with a Trubore stirrer, thermometer, reflux condenser, nitrogen inlet tube and a worm-feed addition tube containing 93.5 g. (0.45 mole) of phosphorus pentachloride under anhydrous conditions. The reflux condenser was connected through a calcium chloride tube to a trap immersed in ice-water and then through a U-tube filled with calcium chloride to two gas washing bottles containing standardized 1 *N* sodium hydroxide solution. During the reaction, the equipment was swept with dry nitrogen.

Phosphorus pentachloride was added to the stirred solution at a sufficient rate to maintain a temperature of 50–60°. After the addition period of 55 minutes, the reaction mixture was held at 70° for a further period of 2.5 hours. This solution was allowed to stand overnight at room temperature.

Titration of the residual alkali in the gas washing bottles showed that 6.2 g. of hydrogen chloride was evolved from the reaction. The ice-water trap contained 5.5 g. of colorless liquid, which was identified as 2-chlorobutene-2, while the main liquid product in the reaction flask weighed 115 g. Fractionation of the latter product in a Todd column employing a stainless steel spiral packing and a reflux ratio of 10:20 gave 2.04 g. of 2-chlorobutene-2, 4.26 g. of phosphorus trichloride and 80.2 g. of a mixture of phosphorus oxychloride and 2,3-dichlorobutane.

2-Chlorobutene-2 was obtained as a colorless liquid, b.p. 62–68°, $n^{25}D$ 1.4231. The total yield was 7.54 g. (55.5%).

Anal. Calcd. for C_4H_7Cl: C, 53.07; H, 7.79; Cl, 39.16. Found: C, 53.43; H, 7.62; Cl, 38.80.

Gutner and Tischenko[10] reported the following physical properties for a mixture of *cis* and *trans* isomers of 2-chlorobutene-2, b.p. 62–67° and $n^{15}D$ 1.4232.

The phosphorus trichloride fraction (b.p. 73–77°) was hydrolyzed and oxidized to phosphoric acid. Then the aqueous solution was analyzed for phosphoric acid by the ammonium phosphomolybdate method.[11] This analysis confirmed the identity of this fraction.

In the third fraction phosphorus oxychloride and 2,3-dichlorobutane codistilled, b.p. 105–112°. This solution was hydrolyzed by addition of water and the 2,3-dichlorobutane extracted with ether. The ethereal extract was dried over anhydrous sodium sulfate and fractionated in the Todd column. This procedure gave 12.2 g. (64.0%) of D-(−)-2,3-dichlorobutane, b.p. 117–119.5°, $n^{25}D$ 1.4407, d^{25}_4 1.092 and $[\alpha]^{25}D$ −13.9°.

Anal. Calcd. for $C_4H_8Cl_2$: C, 37.83; H, 6.35; Cl, 55.84. Found: C, 38.11; H, 6.30; Cl, 56.07.

The aqueous fraction on analysis for phosphoric acid by the ammonium phosphomolybdate method[11] was found to contain phosphorus equivalent to 66.6 g. (96.7%) of phosphorus oxychloride.

The still residue (20.1 g.) from the original distillation in the Todd column on fractionation *in vacuo* gave 11.6 g. (58.2%) of methanephosphonyl dichloride, b.p. 49.5–53° (9 mm.) and $d^{25.3}_4$ 1.445. The methanephosphonyl dichloride was identified by a quantitative hydrolysis to methanephosphonic acid. After purification from methyl ethyl ketone, it melted at 108–109° alone and on admixture with an authentic sample of methanephosphonic acid.[2]

Acknowledgment.—The authors are grateful to Messrs. B. Sells and J. R. Gilpin for assistance with some of the experimental work. We also wish to thank Mr. L. J. Blondin of Defence Research Chemical Laboratories for measuring the infrared spectrum.

(10) B. A. Gutner and D. V. Tischenko, *J. Gen. Chem.* (*U.S.S.R.*), **6**, 1729 (1936).

(11) Scott's "Standard Methods of Chemical Analysis," Fifth Edition, Vol. 1, D. Van Nostrand Co., Inc., New York, N. Y., 1939, p. 694.

OTTAWA, ONTARIO, CANADA

[CONTRIBUTION NO. 1203 FROM THE STERLING CHEMISTRY LABORATORY, YALE UNIVERSITY]

Nitrogen-substituted-3,4-dihydroxypyrrolidines[1a]

BY ARTHUR J. HILL AND MARY-GERTRUDE MCKEON[1b]

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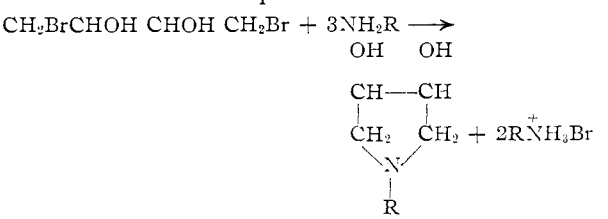
A series of nitrogen alkyl-, aryl- and arylalkyl-substituted 3,4-dihydroxypyrrolidines has been prepared by the action of *meso*-1,4-dibromobutanediol-2,3 with primary amines. Two methods of closure have been used, and derivatives, particularly dibenzoates, have been prepared for pharmacological testing.

The β-aminoethanol grouping appears frequently in a variety of pharmacologically active compounds. This fact suggested preparation of a series of N-substituted-3,4-dihydroxypyrrolidines, a type of amino alcohol which has received scant attention. Search of the literature made at the start of this investigation disclosed no reference to this type of pyrrolidine. A subsequent patent describes the preparation of some nitrogen aryl and nitrogen arylalkyl substituted 3,4-dihydroxypyrrolidines.[2]

Ring closure between a 1,4-dihalo entity and a primary amine is a common method for preparing pyrrolidines; in the study here reported, *meso*-1,4-dibromobutanediol-2,3 was treated with alkyl, aryl and alkylaryl primary amines to form N-substituted-3,4-dihydroxypyrrolidines. None of the compounds obtained has been reported previously, although certain of the aromatic and mixed alkyl-aryl series are stereoisomers of 3,4-dihydroxypyrrolidines described in the patent referred to above.



A satisfactory method for the preparation of the dibromobutanediol was developed by modification

(1) (a) Abstracted from the Dissertation submitted by Mary-Gertrude McKeon in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Yale University. (b) Connecticut College for Women, New London, Conn.

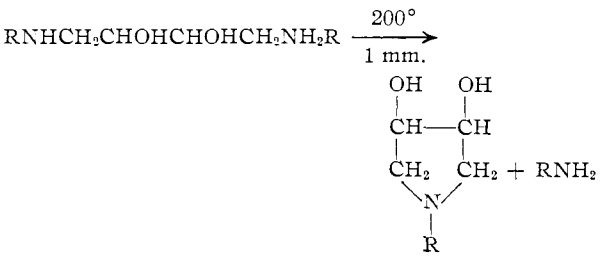
(2) German Patent 805,522 (March 15, 1951).

of previous methods,[3,4] and since it is more convenient than others described, the details are given in the Experimental section. For the ring closure of this entity with primary amines two procedures were used.

The aromatic amines investigated included aniline, *p*-carbethoxyaniline, *p*-toluidine, *p*-anisidine and β-naphthylamine. These reacted with 1,4-dibromobutanediol-2,3 during refluxing in absolute ethanol; three mole proportions of amine to one of dihalide were used. The 3,4-dihydroxypyrrolidines thus prepared were water-insoluble solids which were readily isolated from the reaction mixture.

This method of effecting closure was less satisfactory when applied to the preparation of N-benzyl-, N-β-phenylethyl- and N-cyclohexyl-3,4-dihydroxypyrrolidines. These could not be so readily isolated, partially at least because of their physical properties. None of the three crystallized from the reaction mixture, and since they were more water soluble than the N-aromatic dihydroxypyrrolidines and, like the latter, were sparingly soluble in organic solvents, separation from the primary amine hydrobromide formed during reaction was not efficient.

Lower alkylamines could not be condensed with 1,4-dibromobutanediol-2,3 during refluxing. Condensation was effected when a 1,4-diaminobutanediol-2,3 formed by treating dibromobutanediol with excess primary amine, was heated to high temperature (*ca.* 200°) in a system evacuated to 1 mm. Although the diamino intermediates were not isolated before closure, in each case a small amount was isolated from the final reaction mixture; these are listed in Table II, since they are previously unreported. The N-alkyl-dihydroxypyrrolidines, in contrast to the N-aromatic members of the series, were readily soluble in ether and were isolated by extraction and purified by distillation.



Reaction of the hydroxyl groups in the dihydroxypyrrolidines was effected with phenyl isocyanate and with benzoyl chloride. The former reagent formed mixtures of mono and diphenylcarbanilates in low yield with several N-aryl-3,4-dihydroxypyrrolidines; reaction with benzoyl chloride in pyridine solution was a generally useful method for obtaining dibenzoates of the N-alkyl-3,4-dihydroxypyrrolidines, which were viscous liquids. The dibenzoates were also of interest because their structure suggests possible local anesthetic activity.

Replacement of the hydroxyl groups by halogen could not be accomplished by use of the usual reagents. Contact with thionyl chloride promptly destroyed N-phenyl-3,4-dihydroxypyrrolidine, even when pyridine was present to remove acid formed during reaction. Phosphorus halides and halogen acids were also destructive, and in these reactions brightly colored blue tars were formed. Similar destruction occurred when pyridine was omitted during reaction of benzoyl chloride with this dihydroxypyrrolidine.

The most striking demonstration of the acid sensitivity of these compounds was observed during acetylation of N-phenyl-3,4-dihydroxypyrrolidine with acetic anhydride; when sulfuric acid was added to the acetylation mixture, the solution developed the blue color previously noted, and no acetylated product was obtained. When sodium acetate was used as catalyst, the reaction proceeded smoothly and the diacetate was obtained in good yield.

The N-substituted-3,4-dihydroxypyrrolidines and derivatives which have been prepared are indicated in Table I, which also indicates physical constants and general method of preparation. Details of typical procedures for each method of closure are described in the Experimental section; general procedures used in reaction with phenyl isocyanate and benzoyl chloride are described.

Experimental

1,4-Dibromobutanediol-2,3.—Sixty grams of *meso*-erythritol was fused in a three-neck flask provided with a condenser, thermometer immersed in the melt, and a delivery tube extending within 2 cm. of the bottom of the flask. A *Glas-col* mantle was used for heating. Hydrogen bromide was admitted through the tube at a rate which provided agitation of the fused material. The temperature rose spontaneously during the first few minutes of addition from 124–138°, and was maintained within these limits during addition of the gas; external heating was required toward the end of reaction. When there was no further gain in weight with addition of hydrogen bromide to the mixture (about one hour), the mixture was poured into a mortar and allowed to cool. The solidified mass was triturated with 50 ml. of water and filtered under suction. The air-dried crude dibromide was extracted with portions of benzene, during refluxing. Approximately 1.5 l. of solvent was used; a small amount of red-brown gum remained undissolved. The benzene solution deposited 56.5 g. of tan plates, m.p. 130–133°; an additional 5.0 g. was obtained when the mother liquor was concentrated; yield 51%. Recrystallization from water, norite being used to decolorize the solution, gave colorless plates, m.p. 136.5–137.5°. Champion[4] has reported a melting point of 134–135°. *Anal.* Calcd. for $C_4H_8O_2Br_2$: Br, 64.46. Found: Br, 64.27.

N-Phenyl-3,4-dihydroxypyrrolidine.—(This procedure was applied in the preparation of the N-aromatic pyrrolidines, and is referred to in Table I as method A.) Fifteen grams (0.06 mole) of 1,4-dibromobutanediol-2,3, 16.7 g. (0.18 mole) of aniline and 0.5 g. of KI were refluxed in absolute ethanol for 16 hours. After removal of the solvent under reduced pressure, the residue was suspended in 50 ml. of water, filtered and washed free of halide ion. Seven and four-tenths g. of amorphous N-phenyl-3,4-dihydroxypyrrolidine, m.p. 151–154°, was obtained; yield 74%. Crystallization from ethanol–water or dioxane–water and then from ethyl acetate gave 3.5 g. of light yellow needles, m.p. 156–157°. A diacetate, m.p. 102–103°, crystallized from absolute ethanol as colorless needles. *Anal.* Calcd. for $C_{13}H_{17}O_4N$: C, 63.84; H, 6.50; N, 5.31. Found: C, 63.42; H, 6.48; N, 5.36. The di-*p*-nitrobenzoate, m.p. 177–177.5°, formed orange needles from methanol. *Anal.* Calcd. for $C_{24}H_{19}O_8N_3$: C, 60.63; H, 4.01; N, 8.80. Found: C, 60.85; H, 4.21; N, 9.11. Data for the dibenzoate and phenylcarbanilates are recorded in Table I.

N-β-Phenylethyl-3,4-dihydroxypyrrolidine.—Twenty grams (0.08 mole) of 1,4-dibromobutanediol-2,3, 29.0 g. of β-phenylethylamine and 0.5 g. of KI were refluxed in

(3) P. Champion, *Z. Chem.*, 348 (1871).
(4) S. Przybytek, *Ber.*, **14**, 2072 (1881).

TABLE I

NITROGEN-SUBSTITUTED-3,4-DIHYDROXYPYRROLIDINES

Nitrogen substituent	Method of preparation	M.p., °C.	B.p., °C., 1 mm.	Yield, %	Calcd. C, %	Calcd. H, %	Calcd. N, %	Calcd. Cl, %	Found C, %	Found H, %	Found N, %	Found Cl, %
n-Butyl	B		100–105	53			8.79				8.55	
Isobutyl[a]	B		85–91	64	49.11	9.26	7.15	18.12	49.40	9.43	7.03	18.00
n-Amyl	B		101–106	63								
n-Hexyl[a]	B		114–120	70	53.68	9.91	6.25	15.84	53.83	9.67	6.52	16.02
Cyclohexyl	B	81.5–83		40	64.83	10.33	7.56		65.07	10.40	7.52	
n-Heptyl[a]	B		256–264	33			5.88	14.91			6.15	14.84
Benzyl	B	122–122.5		30			6.12				6.16	
β-Phenylethyl	B	71–72	171–173	23	69.54	8.26	6.75		69.66	8.39	6.44	
Phenyl	A	156–157		74	67.02	7.31	7.76		67.43	7.44	7.55	
p-Anisidyl	A	159–161		84	63.04	7.22	6.69		62.89	7.19	6.56	
p-Tolyl	A	169		57	68.37	7.82	7.24		68.53	8.00	6.97	
β-Naphthyl	A	139–140		56	73.35	6.59	6.14		73.34	6.68	6.06	

[a] Analyzed as hydrochloride.

NITROGEN-SUBSTITUTED-PYRROLIDINE-3,4-DIBENZOATES

Nitrogen substituent	M.p., °C.	Yield, %	N Calcd.	N Found	M.p., °C. chloroplatinate	Calcd. C, %	Calcd. H, %	Calcd. N, %	Found C, %	Found H, %	Found N, %
n-Butyl	155–157	93	3.81	3.69	160–161	46.10	4.58	2.44	46.58	4.76	2.18
Isobutyl		50			157–159	46.10	4.58	2.44	46.04	4.61	2.89
n-Amyl	139–140	55	3.66	3.34	162–163	47.13	4.81	2.38	46.91	5.02	2.22
n-Hexyl	125–126	81	3.54	3.38	127–129	48.04	5.04	2.33	47.89	5.05	3.03
n-Heptyl	123–124	33	3.42	3.20	127–129	48.90	5.25	2.28	48.73	5.37	2.26
Phenyl	123–125	78	3.61	3.66							

N-ARYL-3-HYDROXYPYRROLIDINE-4-PHENYLCARBANILATES

Nitrogen substituent	M.p., °C.	Yield, %	N Calcd.	N Found
Phenyl	166–167	45	9.38	9.65
p-Anisidyl	149–150	40	8.52	8.86
p-Tolyl	193–194	51	8.96	9.18

N-ARYL-PYRROLIDINE-3,4-DIPHENYLCARBANALATES

Nitrogen substituent	M.p., °C.	Yield, %	N Calcd.	N Found
Phenyl	222–223	24	10.06	9.90
p-Anisidyl	206–209	29	9.38	9.45
p-Tolyl	210–211	74	9.73	9.75

TABLE II

1,4-DIAMINOBUTANEDIOLS-2,3, $RNHCH_2CHOHCHOHCH_2NHR$

R	M.p., °C.	Calcd. C, %	Calcd. H, %	Calcd. N, %	Found C, %	Found H, %	Found N, %
n-Butyl	145–145.5	62.02	12.15	12.06	61.89	12.29	12.32
Isobutyl	135–136	62.02	12.15	12.06	61.92	11.71	11.80
n-Amyl	142–142.5	64.57	12.39	10.76	64.46	12.35	10.48
n-Hexyl	140–140.5	66.62	12.58	9.71	66.22	12.81	10.30
n-Heptyl	139.5–140	68.30	12.74	8.86	68.33	12.48	8.45

absolute ethanol for 12 hours in an atmosphere of nitrogen. The mixture was chilled and 10 g. of β-phenylethylamine hydrobromide was filtered off. The solvent was removed under reduced pressure, and the oily residue was extracted with chloroform; the extract was washed free of halide ion and dried over sodium sulfate. After removal of the solvent, the N-β-phenylethyl-3,4-dihydroxypyrrolidine was distilled at 2 mm., b.p. 171–173°, yield 3.8 g. (22%). The distillate crystallized on cooling, and recrystallization from benzene–petroleum ether gave silky needles, m.p. 71–72°. Analytical data are given in Table I.

N-Benzyl-3,4-dihydroxypyrrolidine.—Fifteen grams (0.06 mole) of 1,4-dibromobutanediol-2,3, 17.5 g. (0.18 mole) of benzylamine and 0.5 g. of KI were refluxed in absolute ethanol for 12 hours. The mixture was chilled, benzylamine hydrobromide was filtered off, solvent was removed under reduced pressure, the residue was extracted with ethyl acetate, the extract washed free of halide ion and dried over sodium sulfate. The residual oil after removal of solvent decomposed during distillation at 2 mm. In a second experiment, N-benzyl-3,4-dihydroxypyrrolidine was isolated as the hydrochloride by treating the dried ethyl acetate extract with hydrogen chloride in anhydrous ether. The hydrochloride separated as an oil, which crystallized after it had been dissolved in absolute ethanol and precipitated with petroleum ether. Recrystallization from the same solvents gave a microcrystalline powder, m.p. 122–122.5°. The yield before recrystallization was 30%. Analytical data are given in Table I.

N-Isobutyl-3,4-dihydroxypyrrolidine.—(This procedure was used in the preparation of N-alkyl-dihydroxypyrrolidines, and is indicated in Table I as method B.) 1,4-Dibromobutanediol-2,3 (12.4 g., 0.05 mole) was refluxed in isobutylamine (21.9 g., 0.3 mole) for 16 hours. Excess amine was removed at diminished pressure, the reaction flask was evacuated to 1 mm. and heated to 210–220° in a Wood's metal-bath for five hours. The dark, gummy residue was made distinctly basic with 20% sodium hydroxide and was extracted with 500 ml. of ether in three portions. During the first extraction a small amount of solid separated and was removed; crystallization of this solid from 95% ethanol gave 1.5 g. of 1,4-diisobutylaminobutanediol-2,3, m.p. 136.5–137°.

The ether extract contained the pyrrolidine, which boiled at 85–91° (0.5–1 mm.), after removal of the solvent. The originally light yellow viscous oil darkened rapidly; yield 5.0 g., 64%. The hydrochloride, prepared in anhydrous ether and crystallized from ethanol–ether after chilling and scratching, formed cubes, m.p. 95–97°.

Dibenzoates of N-Substituted-3,4-dihydroxypyrrolidines.—To the pyrrolidine in dry pyridine solution was added two mole proportions of benzoyl chloride and the mixture was refluxed for two hours and then poured into ice-water. The dibenzoate separated as an oil, which was taken up in ether, washed with 20% sodium carbonate and with water; 6 *N* hydrochloric acid was added to wash the ether solution, and the dibenzoate separated as an oil which crystallized with the evolution of heat. Treatment with norite during crystallization from benzene gave pure dibenzoate.

Phenylcarbanilates.—Two mole proportions of phenyl isocyanate reacted with the dihydroxypyrrolidine in refluxing benzene solution for 24 hours. After removal of the solvent by filtration and concentration of the mother liquor, the reaction product was separated into two fractions by extraction with boiling absolute ethanol. The less soluble, higher melting fraction gave the diphenylcarbanilate; after repeated crystallization the lower melting, more soluble fraction, gave a 3-hydroxy-4-phenylcarbanilate.

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