The Effect of Dimedon on the Condensation of Porphobilinogen in Neutral Solution.—In an attempt to trap the formaldehyde produced in a reaction such as 2 in Fig. 1, dimedon was added (11 moles per mole of porphobilinogen) to the usual neutral reaction mixture. The yield of uroporphyrin fell from 55 to 10%, but the isomer ratio was uncertain since only a small amount of material was available (Table II, expt. 12). In addition, there was some Ehrlich-positive material remaining after 21 hours at 60°. Had the dimedon attacked the porphobilinogen directly, removing the aminomethyl group, the resulting pyrrole would have been opsopyrroledicarboxylic acid. This pyrrole was shown to be stable under the reaction conditions: less than 3% decomposed in 20 hours. Although the Ehrlich color band was at the correct position (560 mμ) for this pyrrole, the absorption faded much too rapidly. Moreover, as this 560 mμ band faded, a band at 490 mμ appeared. This suggested that the unknown material was a dipyrrylmethane with an α-hydrogen which reacted normally with the Ehrlich reagent (*p*-dimethylaminobenzaldehyde), then underwent hydrogen transfer to the corresponding dipyrrylmethene. Similar observations have been made on known dipyrrylmethanes by Bogorad and Marks.[15] Paper chromatography also gave evidence of dipyrrylmethenes (oxidation) but not of opsopyrroledicarboxylic acid. This is direct evidence for an elimination reaction of type 2, Fig. 1.

Discussion.—The results presented here support the mechanism shown in Figs. 1 and 2, but further work is needed to provide detailed evidence. Treibs and Fritz[16] have used a similar mechanism to explain the acid-catalyzed "exchange" reactions of pyrroles and dipyrrylmethanes. This type of reaction has many analogies in the phenol–formaldehyde condensations,[17] and is mechanistically related to the Mannich reaction.[18]

(16) A. Treibs and G. Fritz, *Ann. Chem.*, **611**, 162 (1958).

Robinson[19] has proposed a scheme for the enzymatic condensation of porphobilinogen which allows the exclusive formation of isomer III uroporphyrin. Bullock, *et al.*,[20] have elaborated the aspect of intramolecular migration of the "formaldehyde" residue to explain the formation of a coproporphyrin which they claimed to be coproporphyrin III from a suitably substituted α-acetoxymethylpyrrole. The evidence presented in this paper does not strictly exclude this intramolecular migration. A real distinction awaits a method capable of differentiating isomer III from isomer IV.

When a sample of one of the coproporphyrin mixtures (expt. 18) was reduced to coproporphyrinogen and incubated with frozen-thawed *Euglena* cells, it gave a 35% yield of a labeled protoporphryin. Such a porphyrin would be useful in the study of bile pigment formation since labeled carbon monoxide would be evolved.[21] It is possible that the structural specificity of this enzymatic oxidation would allow the determination of the relative labeling of the methine carbons. This would lead to a more detailed understanding of both the chemical and the enzymatic condensation of porphobilinogen.

The high yields of uroporphyrinogen obtainable from porphobilinogen in neutral solution under anerobic conditions are of interest in connection with current views on the evolution of photosynthesis.[22]

Acknowledgment.—I wish to thank Dr. S. Granick for his continual interest and advice, and Mr. W. Cumming for able assistance.

(17) J. F. Walker, "Formaldehyde," second ed., A. C. S. Monograph No. 120, Reinhold Publ. Corp., New York, N. Y., 1953, Chapter 12.
(18) H. Hellmann and G. Opitz, *Angew. Chem.*, **68**, 265 (1956).
(19) R. Robinson, "The Structural Relations of Natural Products," Oxford University Press, New York, N. Y., 1955, p. 24.
(20) E. Bullock, A. W. Johnson, E. Markham and K. B. Shaw, *J. Chem. Soc.*, 1430 (1958).
(21) T. Sjostrand, *Nature*, **168**, 1118 (1951).
(22) S. Granick, *Ann. N. Y. Acad. Sci.*, **69**, 292 (1957).

[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

Conidine—Synthesis, Polymerization and Derivatives

BY EDWARD R. LAVAGNINO, ROBERT R. CHAUVETTE, WILLIAM N. CANNON AND EDMUND C. KORNFELD

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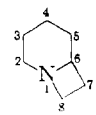
Conidine (IV) has been prepared in a three-step synthesis starting with 2-(β-hydroxyethyl)-pyridine. Treatment of IV with boron trifluoride-etherate or methyl iodide yields a polymer. Several derivatives of IV were prepared and studied. Octahydropyrrocoline was formed by the direct intramolecular cyclic alkylation of 2-(γ-hydroxypropyl)-piperidine at atmospheric pressure; however, attempts to cyclize 2-(β-hydroxyethyl)-piperidine to IV yielded only α-pipecoline.

As an extension of work in the field of polycyclic amines related to quinuclidine, the bicyclic base IV[1] was prepared and studied. This compound has not been reported previously, although substituted derivatives have been synthesized. The trivial name "conidine" was assigned to the ring system[2] when these derivatives were made.

Löffler and co-workers[3] prepared ε-coniceine, which has a methyl group at position 2. This was separated into two isomers termed 2-methyl-

(1) The numbering system is that used by the earlier workers and is used here to avoid confusion. The Ring Index suggested numbering is indicated at the right, and the systematic name is 1-azabicyclo[4.2.0]octane.



(2) K. Löffler and P. Plöcker, *Ber.*, **40**, 1310 (1907). G. R. Clemo and G. R. Ramage [*J. Chem. Soc.*, 2969 (1932)] have attempted without success to prepare conidine by cyclization of ethyl 2-carbethoxypiperidine-1-acetate.
(3) K. Löffler, *Ber.*, **42**, 948 (1909).

TABLE I

2-(β-HYDROXYALKYL)-PIPERIDINES

Piperidine	Yield, %	M.p., °C.	B.p., °C.	B.p., Mm.	Reference
2-(β-Hydroxyethyl)-	76	35–40	120–122	8	8–13
2-(β-Hydroxypropyl)-	74	41–43	83–85	2	3, 8, 9, 11, 12
2-(β-Hydroxyethyl)-5-ethyl-	83		123–125	6	14
2-(β-Hydroxyethyl)-6-methyl-	80	95–97			5, 15
2-(β-Hydroxyethyl)-4,6-dimethyl-	86	127–128			[a]

[a] New compound. *Anal.* Calcd. for $C_9H_{19}NO$: C, 68.74; H, 12.18; N, 8.91. Found: C, 68.72; H, 11.97; N, 8.69.

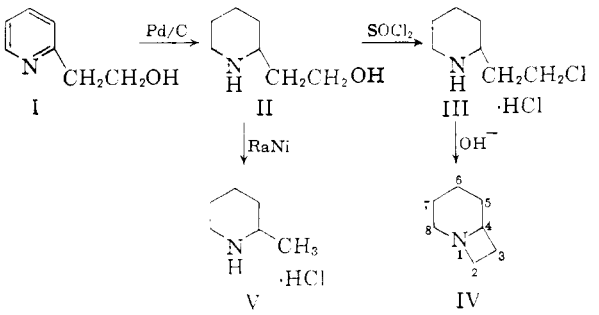
TABLE II

2-(β-CHLOROALKYL)-PIPERIDINE HYDROCHLORIDES

Piperidine hydrochloride	Yield, %[a]	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
2-(β-Chloroethyl)-[b]	90	163–165	$C_7H_{14}NCl\cdot HCl$					7.51	7.48
2-(β-Chloropropyl)-[c]	52	166–168	$C_8H_{16}NCl\cdot HCl$						
2-(β-Chloroethyl)-5-ethyl-[d]	66	106–108	$C_9H_{18}NCl\cdot HCl$	50.95	51.13	9.03	9.08	6.60	6.35
2-(β-Chloroethyl)-6-methyl-[d]	96	202–203	$C_8H_{16}NCl\cdot HCl$	48.49	48.48	8.65	8.62	7.07	6.79
2-(β-Chloroethyl)-4,6-dimethyl-[d]	93	216–217	$C_9H_{18}NCl\cdot HCl$	50.95	51.12	9.03	9.12	6.60	6.39

[a] Crude yield. [b] T. R. Norton, *et al.* (ref. 12), reports a m.p. 148–150°; K. Löffler, *Ber.*, **37**, 1879 (1904), reports a m.p. 149.5°. [c] T. R. Norton, *et al.* (ref. 12), reports a m.p. 168–170°. [d] Analytical samples were prepared by recrystallizing crude products from ethanol–ether.

conidine and iso-2-methylconidine. They also prepared 2-ethylconidine,[2] 3-methylconidine[4] (separated into two racemic modifications) and 8-methyl conidine.[5] Quaternary salts of conidine itself were obtained,[6] but apparently previous workers failed to isolate the parent free base.



Compound IV was synthesized in these laboratories by a scheme similar to that used by Löffler in making substituted conidines and by Brown and Eldred[7] for preparing quinuclidine. 2-(β-Hydroxyethyl)-pyridine (I) was hydrogenated to 2-(β-hydroxyethyl)-piperidine (II) using palladium-on-carbon catalyst in aqueous solution at 130–150°. Thionyl chloride converted this to 2-(β-chloroethyl)-piperidine hydrochloride (III), which when treated with base in dilute solution was cyclized to conidine (IV). Four substituted conidines were prepared in a similar manner (see Table III). The 2-(β-hydroxyalkyl)-piperidine and 2-(β-chloroalkyl)-piperidine hydrochloride precursors are listed in Tables I and II.

Conidine also was formed, but in lower yield, by cyclization of the chloride III using potassium hydroxide in diethylene glycol solution.

Conidine[16] is a colorless, water-soluble liquid with an amine-like odor. The pK_a in 66% dimethylformamide is 10.4. This may be compared with a value of 10.1 for quinuclidine in the same solvent. Perhaps of greatest interest was the observation that on standing at room temperature for an extended period of time, a sample of conidine was observed to thicken gradually and form a polymer. It was discovered subsequently that in the presence of a trace of boron trifluoride-etherate, thickening was noted within four hours, and a translucent, slightly soft polymer had formed in high yield in forty-eight hours. The polymer so formed is soluble in ethanol and in dilute hydrochloric acid from which it may be reprecipitated as an amorphous white solid upon addition of alkali. Tests have shown that polyconidine with an inherent viscosity[17] in the order of 0.9 to 1.0 can be obtained[18] by using a low catalyst concentration and a temperature of 25°. All of the substituted conidines listed in Table III, with the exception of ε-coniceine, readily formed polymers when treated with a trace amount of boron trifluoride-etherate.[19]

Since polyconidine can also be prepared from conidine using as catalyst a trace of methyl iodide, the production of the polymer may proceed by a

(4) K. Löffler and A. Grosse, *Ber.*, **40**, 1325 (1907).
(5) K. Löffler and H. Remmler, *ibid.*, **43**, 2048 (1910).
(6) K. Löffler and A. Grosse, *ibid.*, **40**, 1336 (1907).
(7) H. C. Brown and N. R. Eldred, THIS JOURNAL, **71**, 445 (1949).
(8) A. Ladenburg, *Ber.*, **22**, 2583 (1889).
(9) A. Ladenburg, *Ann.*, **301**, 117 (1898).
(10) C. S. Marvel and R. S. Shelton, THIS JOURNAL, **51**, 915 (1929).
(11) C. W. Tullock and S. M. McElvain, *ibid.*, **61**, 961 (1939).
(12) T. R. Norton, R. A. Seibert, A. A. Benson and F. W. Bergstrom, *ibid.*, **68**, 1572 (1946).
(13) R. R. Burtner and J. M. Brown, *ibid.*, **69**, 630 (1947).
(14) G. Prausnitz, *Ber.*, **25**, 2394 (1892).
(15) K. Hess, F. Merck and Cl. Vibrig, *ibid.*, **48**, 1886 (1915).
(16) Infrared spectra of conidine and several homologs have been recorded by Dr. H. E. Boaz of these laboratories.
(17) Schmidt and Marlies, "Principles of High Polymer Theory and Practice," McGraw-Hill Book Co., Inc., New York, N. Y., 1948, Chapter 6.
(18) These studies were carried out at the Battelle Memorial Institute, Columbus, Ohio.
(19) C. C. Price and M. Toy of the Univ. of Pennsylvania have prepared *d*- and *l*-conidine and are studying the preparation and properties of the optically active polymers. See THIS JOURNAL, **82**, 2613 (1960).

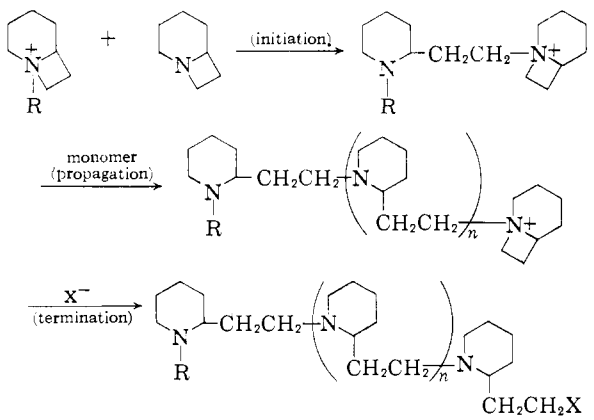
TABLE III

CONIDINE AND ALKYL CONIDINES

	B.p., °C.	$n^{25}D$	Yield, %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
Conidine	142–143	1.4663	73	$C_7H_{13}N$	75.61	75.71	11.79	11.91	12.60	12.61
ε-Coniceine[a]	146–153	1.4573	63	$C_8H_{15}N$	76.74	76.57	12.08	12.33	11.19	11.13
7-Ethylconidine	182–184	1.4655	40	$C_9H_{17}N$	77.63	77.55	12.31	12.49	10.06	9.86
8-Methylconidine[b]	154–158	1.4610	75	$C_8H_{15}N$						
6,8-Dimethylconidine[c]	170–172	1.4582	72	$C_9H_{17}N$	77.63	77.44	12.31	12.34	10.06	10.02

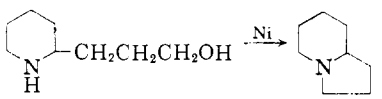
[a] K. Löffler, *Ber.*, **37**, 1879 (1904), reports a b.p. 151–152°. [b] Picrate m.p. 242–244°; Löffler and Remmler (ref. 5) report a b.p. 156°, picrate m.p. 237°. [c] Picrate m.p. 239–241° from ethanol. *Anal.* Calcd. for $C_{15}H_{20}N_4O_7$: C, 48.91; H, 5.47; N, 15.21. Found: C, 48.82; H, 5.44; N, 15.33.

scheme such as



This is essentially similar to the polymerization mechanism of ethyleneimine as proposed by Jones, *et al.*,[20] and Barb.[21]

Further exploration of methods for the synthesis of conidine led us to attempt the direct intramolecular cyclic alkylation of 2-(β-hydroxyethyl)-piperidine (II) in the presence of excess Raney nickel. Many alkylations of amines by alcohols using nickel catalysts under various conditions are known,[22–29] and in connection with another problem we have prepared octahydropyrrocoline (VII) in 72% yield by the direct cyclization of 2-(γ-hydroxypropyl)-piperidine (VI) in aqueous solution using Raney nickel.[30] However, when II



VI VII

was treated under identical conditions, cyclization did not occur. Rather dehydroxymethylation took place, and a 57% yield of α-pipecoline hydrochloride (V) was the only product isolated. Other workers[31–33] have shown that dehydroxymethylation of primary alcohols occurs with nickel catalysts at 100 atmospheres pressure and at a temperature of 150–200°. Zderic, Bonner and Greenlee,[34] however, have dehydroxymethylated several alcohols [among them 2-(β-hydroxyethyl)-pyridine] by refluxing them in ethanol at atmospheric pressure in the presence of large amounts of Raney nickel. These authors have proposed the structural requirements necessary for carbon–carbon bond cleavage.

To further our study of the chemistry of conidine five quaternary salts (Table IV) and three bis-quaternary salts (Table V) of the base were prepared. The bis-quaternary compounds were evaluated pharmacologically as hypotensive and ganglionic blocking agents. In hypertensive rats these compounds given orally or subcutaneously fail to induce any significant blood pressure response. Their toxicity in mice is marked and characterized by respiratory arrest.

Acknowledgments.—We gratefully acknowledge valuable assistance by Messrs. G. M. Maciak, W. L. Brown, H. L. Hunter and R. M. Hughes, elemental analyses; Messrs. P. W. Landis and L. G. Howard, physicochemical measurements; Mr. W. B. Scanlon, high pressure reductions; and Dr. R. C. Rathbun, pharmacological evaluation. We are especially indebted to Dr. H. E. Boaz for the infrared studies and interpretation thereof.

Experimental

All melting points and boiling points are uncorrected. The pyridine alcohols were with one exception obtained from Reilly Tar and Chemical Co. 2-(β-Hydroxypropyl)-pyridine was prepared by the method of Walter.[35]

2-(β-Hydroxyalkyl)-piperidines (Table I) were all prepared by the same general procedure. The preparation of 2-(β-hydroxyethyl)-piperidine is described below:

A solution of 370 g. (3.0 moles) of 2-(β-hydroxyethyl)-pyridine in distilled water was hydrogenated over 60 g. of 5% palladium-on-carbon at 3000 p.s.i. and 130–135°. Hydrogen uptake reached the theoretical after six hours. The water solution after cooling and removal of the catalyst by filtration was saturated with potassium carbonate. The organic layer that separated was distilled under vacuum to give 294 g. (76% yield) of 2-(β-hydroxyethyl)-piperidine, b.p. 120–122° (8 mm.). The liquid crystallized when

(20) G. D. Jones, A. Langsjoen, M. M. C. Newmann and J. Zomlefer, *J. Org. Chem.*, **19**, 125 (1944).

(21) (a) W. G. Barb, *J. Chem. Soc.*, 2564 (1955); (b) W. G. Barb, *ibid.*, 2577 (1955).

(22) C. Ainsworth, THIS JOURNAL, **78**, 1635 (1956).

(23) J. Baddiley, *J. Chem. Soc.*, 3693 (1950).

(24) G. N. Kao, B. D. Tilak and K. Venkataraman, *J. Sci. Ind. Research*, **14B**, No. 12, 624 (1955).

(25) R. G. Rice and E. J. Kohn, THIS JOURNAL, **77**, 4052 (1955).

(26) C. F. Winans and H. Adkins, *ibid.*, **54**, 306 (1932).

(27) L. J. Kitchen and C. B. Pollard, *ibid.*, **69**, 854 (1947).

(28) L. T. Plante, W. T. Lloyd, C. E. Schilling and L. B. Clapp, *J. Org. Chem.*, **21**, 82 (1956).

(29) L. T. Plante and L. B. Clapp, *ibid.*, **21**, 86 (1956).

(30) V. Boekelheide and S. Rothchild, THIS JOURNAL, **70**, 864 (1948), have prepared octahydropyrrocoline by the direct hydrogenation of 2-(γ-hydroxypropyl)-pyridine at 200° and 2500 p.s.i. with Raney nickel catalyst.

(31) V. N. Ipatieff, G. J. Czajkowski and H. Pines, *ibid.*, **73**, 4098 (1951).

(32) H. Pines, H. G. Rodenberg and V. N. Ipatieff, *ibid.*, **75**, 6065 (1953).

(33) H. Pines, H. G. Rodenberg and V. N. Ipatieff, *ibid.*, **76**, 771 (1954).

(34) J. A. Zderic, W. A. Bonner and T. W. Greenlee, *ibid.*, **79**, 1696 (1957).

(35) L. A. Walter, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 757.

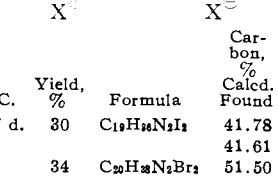
TABLE IV

QUATERNARY SALTS OF CONIDINE  $RX^{\ominus}$

R	X	M.p., °C.	Recrystn. solvent	Yield, %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
$-CH_2$	Br	214 d.	Ethanol–acetone	30	$C_8H_{16}NBr$	46.61	46.48	7.82	8.02	6.79	6.51
$-CH_3$	I	203–204 d.	Ethanol–ether	84	$C_8H_{16}NI$	37.96	38.19	6.37	6.50	5.53	5.74
$-C_2H_5$	Br	199–200 d.	Acetone	48	$C_9H_{18}NBr$	49.09	48.90	8.24	8.29	6.40	6.41
$-C_2H_5$	I	198–199 d.	Acetone–ethyl acetate	81	$C_9H_{18}NI$	40.46	40.23	6.78	6.96	5.24	5.14
$-(CH_2)_4\overset{\oplus}{N}(CH_3)_3I^{\ominus}$	I	255 d.	Ethanol–ethyl acetate	76	$C_{14}H_{30}N_2I_2$	35.01	34.34	6.30	6.54	5.84	5.33

TABLE V

BIS-QUATERNARY SALTS OF CONIDINE[a]



n	X	M.p., °C.	Yield, %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
5	I	145–177 d.	30	$C_{19}H_{36}N_2I_2$	41.78	41.61	6.66	6.74	5.14	4.89
6	Br	240 d.	34	$C_{20}H_{38}N_2Br_2$	51.50	51.62	8.21	8.62	6.00	5.92
10	Br	205–211 d.	30	$C_{24}H_{46}N_2Br_2$	55.17	55.10	8.87	8.97	5.36	5.59

[a] Recrystallized from acetone.

placed in the refrigerator and remained a solid at room temperature, with a melting range of 35–40°.

2-(β-Chloroalkyl)-piperidine hydrochlorides (Table II) were obtained by the reaction of thionyl chloride on the 2-(β-hydroxyalkyl)-piperidines. The preparation of 2-(β-chloroethyl)-piperidine hydrochloride is illustrative of this procedure.

One mole (129 g.) of 2-(β-hydroxyethyl)-piperidine dissolved in 225 ml. of chloroform was added dropwise with stirring to 260 g. (2.2 moles) of thionyl chloride maintained between 0–10° with an ice-bath. The ice-bath was removed after the addition, and the solution was stirred at room temperature for two hours. Absolute ethanol (150 ml.) was then added slowly, and the solution was refluxed for two hours and placed in the refrigerator overnight. The crystals which formed were collected on a filter and washed with a small volume of cold ethanol and then with ether. The addition of ether to the filtrate yielded an additional quantity of crystalline product. The total crude yield after drying *in vacuo* was 90%, m.p. 163–165°. The product was used without purification.

Conidine. (A) By Cyclization in Aqueous Solution.—A solution of 56 g. (0.3 mole) of 2-(β-chloroethyl)-piperidine hydrochloride and 25.6 g. (0.64 mole) of sodium hydroxide in six liters of water was stirred at 65–70° for two hours. Potassium hydroxide, 200 g., was added, and the mixture was steam distilled until the distillate was no longer basic (approximately 1500 ml. was collected). The distillate was covered with ether, and potassium hydroxide (1 g. for every milliliter of distillate collected) was added with cooling. This solution was then extracted five times with 200-ml. portions of ether, and after drying over potassium hydroxide pellets the ether was removed by fractionation through a 24-inch helix packed column. Distillation of the residue at atmospheric pressure through a Vigreux column yielded conidine boiling at 142–143°. A picrate was prepared in the usual manner and was recrystallized from absolute ethanol, m.p. 241–243°.

Anal. Calcd. for $C_{13}H_{16}N_4O_7$: C, 45.88; H, 4.74; N, 16.47. Found: C, 46.11; H, 5.02; N, 16.79.

The above general procedure was used in preparing the alkyl conidines listed in Table III from the appropriate 2-(β-chloroalkyl)-piperidine.

(B) **By Cyclization in Diethylene Glycol.**—A mixture of 250 ml. of diethylene glycol and 100 g. (1.78 moles) of potassium hydroxide pellets was heated with vigorous stirring to 190–200°. To this was added dropwise a solution of 56 g. (0.3 mole) of 2-(β-chloroethyl)-piperidine hydrochloride in 250 ml. of hot diethylene glycol. Conidine distilled during this process. After all the chloro compound had been added, the temperature was increased slowly to 225° and held at this point until no more material distilled. Twenty-five grams of potassium hydroxide pellets was added to the distillate mixture, and it was then extracted with two 150-ml. portions of ether. The combined ether extracts were dried over potassium hydroxide, and the ether was removed by distillation. The residue then was distilled yielding 12 g. (37%) of conidine.

Polymerization of Conidine (A).—One drop of boron trifluoride-etherate was added to 3 ml. of conidine in a test-tube at room temperature. Thickening was noted within four hours and definite polymer formation in 24 hours. After 48 hours a clear polymer had formed which could be cut with a knife. The fresh cut surface had no odor of monomeric conidine.

(B) On adding one drop of methyl iodide to 3 ml. of conidine an immediate vigorous reaction took place with the formation of some white, insoluble methiodide quaternary salt. No noticeable change occurred up to 48 hours, but on long standing (2 weeks) a clear polymer was formed.

The substituted conidines listed in Table III with the exception of ε-coniceine polymerized when treated as above with either boron trifluoride-etherate or methyl iodide.

Octahydropyrrocoline (VII).—A mixture of 15 g. of 2-(γ-hydroxypropyl)-piperidine (VI)[13,30] (prepared from the corresponding pyridine by the method described above for the preparation of 2-(β-hydroxyalkyl)-piperidines), one liter of water and 150 g. of moist Raney nickel[36] was stirred and heated to boiling. The heating was controlled so that distillate was collected slowly while water was added to keep the volume in the reaction flask constant. When the material distilling was no longer basic (after 750 ml. had been collected), the reaction was stopped, and the distillate was extracted three times with 200-ml. portions of ether. After drying the ether solution with anhydrous magnesium sulfate the ether was removed by distillation. The residue of octahydropyrrocoline distilled at 159–160° (743 mm.), $n^{25}D$ 1.4664, yield 9.5 g. (73%). The pK_a in 66% dimethylformamide was 9.1

Anal. Calcd. for $C_8H_{15}N$: N, 11.19. Found: N, 11.33.

A picrate prepared in the usual manner melted at 235–238°.[30]

2-β-Hydroxyethyl)-piperidine and Raney Nickel.—A mixture of 25 g. (0.19 mole) of 2-(β-hydroxyethyl)-piperidine and 225 g. of moist Raney nickel[36] in 1.5 liters of water was stirred in a reaction flask while distilling, keeping the volume constant by addition of water through a dropping funnel. The distillate was collected in a receiving flask containing dilute hydrochloric acid. When the material distilling was no longer basic (after 2 liters of distillate was collected), the distillation was stopped, and the distillate was evaporated *in vacuo* to yield a residual oil. The oil was crystallized by the addition of acetone yielding 14.8 g. (57%) of material, m.p. 206–206°, which was subsequently found to be α-pipecoline hydrochloride.

Anal. Calcd. for $C_6H_{13}N\cdot HCl$: C, 53.13; H, 10.40; N, 10.33. Found: C, 53.41; H, 10.21; N, 10.59.

(36) "Raney Catalyst in Water" supplied by the Raney Catalyst Co., Chattanooga, Tenn.

A mixture melting point with an authentic sample of α-pipecoline hydrochloride[37] showed no depression. One gram of the above product was converted to the free base, and a picrate was prepared in the usual manner. After recrystallization from acetone–ether the yellow crystalline picrate melted at 130–132°.

Anal. Calcd. for $C_{12}H_{16}N_4O_7$: C, 43.90; H, 4.91; N, 17.07. Found: C, 43.69; H, 5.13; N, 16.69.

The mixture melting point with the picrate of authentic α-pipecoline[37b] was 131–133°.

Quaternary Salts of Conidine (Table IV).—Conidine methyl bromide, ethyl bromide, methyl iodide and ethyl iodide were prepared by treating at room temperature ethereal solutions of conidine with a slight excess of the appropriate alkyl halide. The products did not crystallize easily. In each case it was necessary to remove the ether *in vacuo* and treat the oily residue with hot acetone or ethanol. The salts usually crystallized immediately on cooling to room temperature with or without the addition of ether or ethyl acetate. These quaternary salts were all hygroscopic.

4-Iodobutyltrimethylammonium Iodide.[38]—Trimethylamine was bubbled slowly through a solution of 80 g. (0.26 mole) of tetramethylene diiodide in 150 ml. of benzene at room temperature until 10 g. (0.17 mole) had been absorbed. The mixture was allowed to stand at room temperature for 48 hours, and then the crystalline precipitate was collected and recrystallized from isopropyl alcohol; m.p. 167–167.5° dec., yield 41 g. (42.8%).

Anal. Calcd. for $C_7H_{17}NI_2$: C, 22.78; H, 4.64; N, 3.80. Found: C, 22.95; H, 4.58; N, 4.00.

N-(4-Dimethylamino-*n*-butyl)-conidinium Iodide Methiodide (Table IV).—A solution of 4 g. (0.036 mole) of conidine and 14.8 g. (0.04 mole) of 4-iodobutyltrimethylammonium iodide in a mixture of 100 ml. of absolute ethanol and 120 ml. of ethyl acetate was heated under reflux overnight and then cooled. The crystalline precipitate which appeared was collected on a filter, washed with ethyl acetate and recrystallized from ethanol–ethyl acetate.

Pentamethylene Bis-(conidinium Iodide), Hexamethylene Bis-(conidinium Bromide) and Decamethylene Bis-(conidinium Bromide) (Table V).—These bis-quaternary salts of conidine were prepared by treating at room temperature a freshly distilled sample of conidine with one-half mole of the appropriate dihalide using ether or acetone as solvent. The products crystallized from the reaction mixtures and were collected by filtration after standing 24 hours. They were recrystallized from acetone. All three compounds were very hygroscopic.

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(37) (a) W. Marckwald, *Ber.*, **29**, 43 (1896); (b) A. Lipp, *Ann.*, **289**, 173 (1895).

(38) The procedure is essentially that used by A. P. Gray, D. C. Schlieper, E. E. Spinner and C. J. Cavallito, THIS JOURNAL, **77**, 3648 (1955), for preparing 3-bromopropyltrimethylammonium bromide.

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d- and *l*-Polyconidine

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2-(β-Hydroxyethyl)-piperidine has been resolved through recrystallization of the *d*-10-camphorsulfonate. By conversion to the β-chloroethyl compound and alkaline cyclization, *d*- and *l*-conidine were obtained. Polymerization with boron fluoride-etherate catalysis produced optically active, crystalline, isotactic *d*- and *l*-polyconidine, m.p. 94°, $[\alpha]_D$ ±140°.

Earlier efforts to prepare crystalline isotactic polyamines from propyleneimines[2] were disappointing in that conditions for obtaining polymers of high molecular weight were not available. We were therefore stimulated by the discovery that conidine could be polymerized to high molecular weight polymers[3] to investigate the preparation of this polymer in optically active, isotactic form. In addition to the interest in the difference in physical properties due to configurational changes at the asymmetric centers in each monomer unit, the preparation of optically active polymers with functional groups capable of catalytic activity might produce synthetic compounds analogous to the optically active protein catalyst systems.

For this purpose, we have resolved *dl*-2-(β-hydroxyethyl)-piperidine (I)[3] by careful recrystallization of the *d*-10-camphorsulfonate salt (II) from ethanol–ether. Since there was a strong tendency for the racemic salt (m.p. 124°) to separate, rather than the diastereoisomeric forms (m.p. 168 and 142°), the conditions for resolution are critical. A great deal of the active material was obtained by very slow crystallization so as to obtain large enough crystals of the diastereoisomeric salts to make hand separation effective.

Conversion of the alcohol to the chloride III[3] proceeded in much better yield when the amine was converted to the hydrochloride before addition of thionyl chloride.

When *d*-conidine (IV) was polymerized by bubbling gaseous boron fluoride into it, it was rapidly converted to a white polymeric powder. This low molecular weight benzene-soluble polymer, m.p. 75°, $[\alpha]_D$ +12.7°, proved to contain one boron fluoride molecule for each amine unit.

By use of boron fluoride-etherate catalyst in an ether solution of monomer, excellent conversion to moderately high molecular weight polymer was achieved within a week or two at room temperature. This polymer, with a strong optical rotation of opposite sign to that of the monomer from which it was formed, gave a sharply crystalline X-ray pattern. The principal diffraction bands are summarized in Table I.

Since *d*- or *l*-poly-(propylene oxide) chains are evidently interchangeable in the crystal lattice, as indicated by the identical X-ray patterns and melting points for *d*-polymer, *l*-polymer and mixtures of the two, it seemed of interest to examine mixtures of *d*- and *l*-polyconidine. Equal amounts of the two were dissolved in benzene and the solution was freeze-dried. The racemic isotactic polymer so produced had the same melting point but,

(1) This work was supported by a grant from the California Research Corporation.

(2) Y. Minoura, M. Takebayashi and C. C. Price, THIS JOURNAL, **81**, 4689 (1959).

(3) E. R. Lavagnino and E. C. Kornfeld, private communication; E. R. Lavagnino, R. R. Chauvette, W. N. Cannon and E. C. Kornfeld, THIS JOURNAL, **82**, 2609 (1960).