The reduction[7] of 2,3-dimethylindole with tin and hydrochloric acid yielded a colorless, acid-soluble oil, b.p. 234–236°, $n^{25}D$ 1.556, d^{25} 0.994, which a vapor phase chromatogram showed to contain *ca.* 60% *cis*- and *ca.* 40% *trans*-2,3-dimethylindoline. The benzenesulfonamide[1b] of the *cis* isomer isolated from this mixture melts at 70–71°.

The acid-soluble product of the reaction of aniline with crotyl bromide was fractionated. As shown by vapor phase chromatogram, the fraction b.p. 230–240°, $n^{25}D$ 1.554, d^{25} 0.990, contained besides three other compounds, *ca.* 55% *trans*-2,3-dimethylindoline and *ca.* 19% *cis*-2,3-dimethylindoline.

Acknowledgment.—We wish to thank Professor Martin G. Ettlinger for valuable advice.

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS, URBANA, ILL.]

Synthesis of Substituted Pyrrolidines and Pyrrolizidines

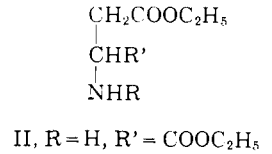
BY ROGER ADAMS, SEIJI MIYANO AND M. D. NAIR

RECEIVED FEBRUARY 17, 1961

Condensation of N-substituted β-aminopropionitriles with diethyl oxalate yields N-substituted 4-cyano-2,3-dioxopyrrolidines. Application of this reaction to the synthesis of pyrrolizidine and octahydropyrrocoline ring systems is described. The relationship of synthetic *dl*-1-hydroxymethyl-2-hydroxypyrrolizidine to the Senecio bases macronecine, hastanecine or turneforcidine is discussed.

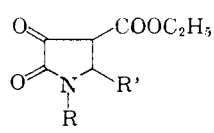
The synthesis of 2,3-dioxopyrrolidines (I) and derivatives by means of the condensation of esters of oxalic acid with β-aminopropionic esters was first reported by Southwick and co-workers.[1,2] This reaction now has been applied to the synthesis of pyrrolizidine derivatives, some of which represent the basic moieties of certain Senecio alkaloids.

Condensation of ethyl aspartate (II) and ethyl β-aminoglutaconate (III) with dimethyl oxalate yielded the expected 4,5-dicarbethoxy-2,3-dioxopyrrolidine (IV) and 4-carbethoxy-5-carbethoxymethylene-2,3-dioxopyrrolidine (V), respectively. Diazomethane converted these dioxo compounds into their enol ethers IVa and Va.



II, R = H, R' = $COOC_2H_5$

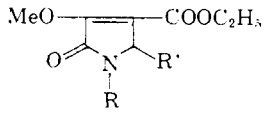
III, R = H, R' = $=CHCOOC_2H_5$



I, R = H, R' = H

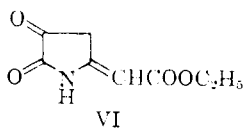
IV, R = H, R' = $COOC_2H_5$

V, R = H, R' = $=CHCOOC_2H_5$

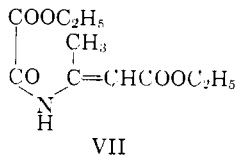


IVa, R = H, R' = $COOC_2H_5$

Va, R = H, R' = $=CHCOOC_2H_5$



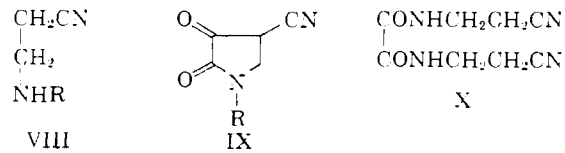
VI



VII

On the other hand, condensation of diethyl oxalate with ethyl β-aminocrotonate in the presence of potassium ethoxide did not yield the cyclization product VI but instead a compound of molecular formula $C_{10}H_{15}NO_5$, presumably ethyl β-oxalylaminocrotonate (VII). This structure is supported by its infrared spectrum which shows the presence of a secondary non-cyclic amide band[3] at 1507 cm.$^{-1}$.

A reaction of similar character is the condensation of β-aminopropionitriles (VIII) with diethyl oxalate to give 2,3-dioxo-4-cyanopyrrolidines (IX). N-Methyl-, N-ethyl-, N-β-cyanoethyl-, N-benzyl- and N-cyclohexyl-β-aminopropionitriles (VIII) condensed smoothly with diethyl oxalate in the presence of sodium alkoxides to give the corresponding N-substituted 4-cyano-2,3-dioxopyrrolidines (IX). Reaction of N - β - cyanoethyl - 4 - cyano - 2,3 - dioxopyrrolidine with diazomethane yielded the enol ether. As these β-aminopropionitriles are conveniently prepared by cyanoethylation of amines, the oxalate condensation provides a very convenient route to substituted pyrrolidines. The parent compound, β-aminopropionitrile, reacted otherwise, however, and gave with diethyl oxalate only β-cyanoethyloxamide (X), characterized by analysis and infrared spectrum.



VIII IX X

R = CH_3, C_2H_5, CH_2CH_2CN, $CH_2C_6H_5$, C_6H_{11}

The extension of this reaction to the synthesis of pyrrolizidine derivatives involved the condensation of ethyl 2-pyrrolidylacetate (XI) with diethyl oxalate in the presence of sodium ethoxide. A single product, 1 - carbethoxy - 2,3 - dioxo - pyrrolizidine (XII), resulted in good yield. Diazomethane converted this product to its enol ether, 1-carbethoxy-2-methoxy-3-oxopyrrolizid-1,3-ene.

The required ethyl pyrrolidylacetate (XI) could be prepared conveniently by reduction of ethyl pyrrolylacetate with 5% rhodium-on-alumina[4,5] catalyst at ordinary pressure, a method superior to

(1) P. L. Southwick and L. L. Seivard, *J. Am. Chem. Soc.*, **71**, 2532 (1949).

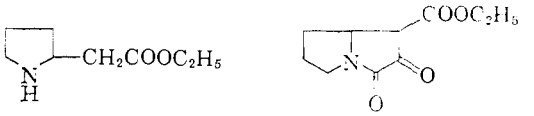
(2) P. L. Southwick and R. T. Crouch, *ibid.*, **75**, 3414 (1953).

(3) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1959, p. 205.

(4) C. G. Overberger, L. C. Palmer, B. S. Marks and N. R. Byrd, *J. Am. Chem. Soc.*, **77**, 4100 (1955).

(5) R. Adams, S. Miyano and D. Fleš, *ibid.*, **82**, 1466 (19601.

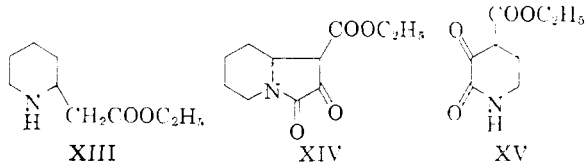
the reduction with platinum oxide at high pressure as described by Clemo and Melrose.[6]



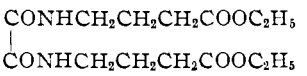
XI XII

Fused five- and six-membered ring compounds also can be prepared by similar procedures. Ethyl 2-piperidylacetate (XIII), formed by the hydrogenation of ethyl 2-pyridylacetate over rhodium-on-alumina catalyst, condenses with diethyl oxalate to 1 - carbethoxy - 2,3 - dioxoöctahydropyrrocoline (XIV) in good yield.

When the primary amine, ethyl γ-aminobutyrate, was condensed with ethyl oxalate, a single product was formed, N,N′-γ-carbethoxy-propyloxamide (XVI); no cyclizing occurred to compound XV and this ester thus resembles β-aminopropionitrile in its reaction with ethyl oxalate.

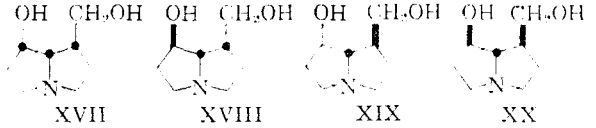


XIII XIV XV



XVI

The initial objective in this research was to obtain 1 - hydroxymethyl - 2 - hydroxypyrrolizidine by the lithium aluminum hydride reduction of 1-carbethoxy-2,3-dioxopyrrolizidine (XII). This compound is of particular interest because of its possible relationship to the basic moieties, macronecine, hastanecine or turneforcidine. All three have the molecular formula $C_8H_{15}NO_2$ but are different from platynecine (XVII) and dihydroxyheliotridane (XVIII), as judged by their reported physical properties. There are only two remaining isomers (XIX and XX and their mirror images) of 7-hydroxy-1-hydroxymethylpyrrolizidine and consequently all three of these necines cannot be accommodated with the hydroxyls in the same positions.



XVII XVIII XIX XX

If hastanecine and turneforcidine are different from each other, one must be a position isomer of platynecine. All of the known necines possess a 1-hydroxymethyl group and the only other position of hydroxylation encountered in the natural necines in addition to position 7 of the pyrrolizidine nucleus is position 2. Thus, rosmarinecine, the basic moiety of the alkaloid Rosmarinine, is 1-hydroxymethyl-2,7-dihydroxypyrrolizidine. On this basis, Leonard[7] has suggested that one or more of the $C_8H_{15}NO_2$ necines of undetermined structure might be a 1-hydroxymethyl-2-hydroxypyrrolizidine.

Culvenor[8] has questioned the published observations on hastanecine and turneforcidine and suggests the possibility that these two bases are either identical with or enantiomers of each other. Considering the molecular rotational differences, he has suggested that macronecine and hastanecine or turneforcidine are the unknown stereoisomers of platynecine. The opinions of Warren[9] and Culvenor are at variance. Warren notes that since hastanecine and turneforcidine were isolated in the same laboratories, their reported non-identity is hardly open to question. The base from the alkaloid retusine,[8] isomeric with platynecine, has not yet been sufficiently characterized to warrant consideration.

Recently the structure of macronecine, the basic portion of the alkaloid macrophylline, has been studied by Danilova and Utkin.[10] These authors degraded their base by elimination of the secondary hydroxyl group to the known 1-hydroxymethylpyrrolizidine, trachelanthamidine. They assumed that the hydroxyl group eliminated was in position 7 but provided no proof for this. The possibility is not excluded that the secondary hydroxyl group might be in another position, presumably 2, of the pyrrolizidine nucleus.

In the light of this discussion the synthesis of 1-hydroxymethyl-2-hydroxypyrrolizidine was undertaken to determine whether it is identical with any of the natural necines. Reduction of 1-carbethoxy-2,3-dioxopyrrolizidine with lithium aluminum hydride yielded an oil, the analysis for which demonstrated that dehydration had taken place during the reduction, as might have been anticipated from the study of the reduction of 2-cyclohexanone carboxylate.[11] Paper chromatography indicated the presence of a mixture of two or three of the possible olefinic alcohols. A pure crystalline picrate, but not perchlorate, could be isolated from the mixture. The mixture absorbed one mole of hydrogen over platinum oxide catalyst, and from the resulting saturated material a pure crystalline picrate was isolated. Analysis indicated the base to be $C_8H_{15}NO$. This picrate was not identical with either (+)-trachelanthamidine picrate or (±)-isoretronecanol picrate.

A facile conversion of the 2-keto group of compound XII to a secondary alcohol was accomplished by reduction with 5% rhodium-on-alumina catalyst and hydrogen at initial pressure of 20 p.s.i. and room temperature. The resulting compound crystallized readily and was identified as 1-carbethoxy-2-hydroxy-3-oxopyrrolizidine (XXI). Subsequent treatment with lithium aluminum hydride in tetrahydrofuran yielded 1-hydroxymethyl-2-hydroxypyrrolizidine (XXII) as a crystalline solid.

(6) G. R. Clemo and T. A. Melrose, *J. Chem. Soc.*, 424 (1942).

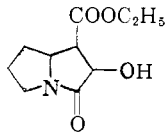
(7) N. J. Leonard in R. H. F. Manske, "The Alkaloids," Vol. VI, Academic Press, Inc., New York, N. Y., 1959.

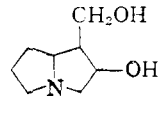
(8) C. C. J. Culvenor and L. W. Smith, *Austral. J. Chem.*, **10**, 464 (1957).

(9) F. L. Warren in "Progress in the Chemistry of Organic Natural Products," Vol. 12, p. 198, Springer, Wien, 1955.

(10) A. V. Danilova and L. M. Utkin, *Zhur. Obshchei Khim.*, **30**, 345 (1960).

(11) A. S. Dreiding and J. A. Hartman, *J. Am. Chem. Soc.*, **75**, 939 (1953); V. M. Mićović and M. Lj. Mihailović, *Bull. soc. chim. Belgrade*, **19**, 329 (1954).


XXI


XXII

1-Hydroxymethyl-2-hydroxypyrrolizidine failed to react with thionyl chloride at 0° and the starting material was recovered unchanged. Under these conditions *cis*-1,2- and 1,3-diols usually form cyclic sulfite esters. Thus the absence of any reaction could indicate that the hydroxymethyl and hydroxy groups are *trans* oriented. Heating under reflux with thionyl chloride, however, yielded 1-chloromethyl-2-chloropyrrolizidine, characterized as its picrate.

Synthetic *dl*-1-hydroxymethyl-2-hydroxypyrrolizidine (m.p. 123–124°) was different from macronecine,[12] m.p. 127–128.5°, as indicated by comparison of the infrared spectra. Whether this compound is the racemic form of hastanecine (m.p. 113–114°) or turneforcidine (m.p. 118.5–120°) cannot be determined without direct comparison with samples of these latter products.

Acknowledgments.—The authors are indebted to A. P. Sloan Foundation for financial support which made this investigation possible. They thank Mr. P. E. McMahon for the infrared spectra and Mr. Josef Nemeth, Mrs. A. S. Bay and Miss Jane Liu for the microanalyses.

Experimental

4,5-Dicarbethoxy-2,3-dioxopyrrolidine (IV).—An ethanol solution of sodium ethoxide was prepared from 0.77 g. of sodium and 30 ml. of absolute ethanol. To this was added a mixture of 6.3 g. of ethyl aspartate and 4.9 g. of diethyl oxalate and the resulting mixture was refluxed for 1 hour. Removal of solvent, followed by acidification of the residue with 10% hydrochloric acid, precipitated 8.6 g. (94.1%) of crystals, which were purified by recrystallization from benzene–petroleum ether (b.p. 40–60°); m.p. 127–128°.

Anal. Calcd. for $C_{10}H_{13}NO_6$: C, 49.38; H, 5.39; N, 5.76. Found: C, 49.38; H, 5.49; N, 5.34.

4,5-Dicarbethoxy-2-oxo-3-methoxy-3-pyrroline (IVa).—A suspension of 4 g. of 4,5-dicarbethoxy-2,3-dioxopyrrolidine in ether was added to an ethereal solution of 2 g. of diazomethane. The resulting mixture became homogeneous in several minutes. After standing for 20 min. the ether was distilled off. Vacuum distillation of the residual oil gave 4.1 g. (97%) of the product boiling at 171–174° (0.7 mm.) which solidified on standing in an ice-box. It was purified by recrystallization from benzene–petroleum ether (b.p. 40–60°); m.p. 67.5–68.5°.

Anal. Calcd. for $C_{11}H_{15}NO_6$: C, 51.36; H, 5.88; N, 5.45. Found: C, 51.91; H, 5.78; N, 5.20.

4-Carbethoxy-5-carbethoxymethylene-2,3-dioxopyrrolidine (V).—To a solution of 0.56 g. of sodium in 20 ml. of absolute ethanol was added 3.7 g. of diethyl oxalate and the mixture was shaken for 10 min. Then 5 g. of ethyl β-aminoglutaconate[13] was dropped in rapidly with stirring. The sodium salt of the product precipitated as a yellow solid; no heating was required. After standing 1 hour the mixture was filtered and washed with ether. Acidification of the sodium salt with 10% hydrochloric acid gave 5.5 g. (91.7%) of colorless crystals. They were purified by recrystallization from ethanol; m.p. 210–211°.

Anal. Calcd. for $C_{11}H_{13}NO_6$: C, 51.76; H, 5.13; N, 5.49. Found: C, 52.03; H, 5.14; N, 5.27.

(12) The authors desire to thank Professor Danilova for a sample of macronecine.

(13) W. O. Emery, *Ber.*, **23**, 3761 (1890).

4-Carbethoxy-5-carbethoxymethylene-2-oxo-3-methoxy-3-pyrroline (Va).—A solution of 2 g. of diazomethane in ether was dropped into a suspension of 2.5 g. of 4-carbethoxy-5-carbethoxymethylene-2,3-dioxopyrrolidine in ether. Reaction started with effervescence and after several minutes the methoxy compound separated. The product was purified by recrystallization from ethanol, m.p. 105–106°. The yield was 1.9 g. (73%).

Anal. Calcd. for $C_{12}H_{15}NO_6$: C, 53.53; H, 5.62; N, 5.20. Found: C, 53.88; H, 5.77; N, 5.38.

Ethyl β-Oxalylaminocrotonate (VII).—To an ethereal solution of potassium ethoxide which was prepared from 1.3 g. of potassium and 9 ml. of absolute ethanol in 50 ml. of absolute ether was added 4.9 g. of ethyl oxalate and the mixture was shaken for 5 min. Then 4.3 g. of ethyl β-aminocrotonate was dropped in with frequent shaking. In less than 5 min. the potassium salt of the condensation product started to deposit as a dense yellow solid which was collected by filtration, washed with absolute ether and dried. The yield of potassium salt was 6.1 g. It was acidified with 10% hydrochloric acid to yield a light yellow oil which on standing crystallized; yield 3.5 g. (45.8%). It was purified by recrystallization from 50% ethanol; m.p. 57–58°.

Anal. Calcd. for $C_{10}H_{15}NO_5$: C, 52.39; H, 6.60; N, 6.11. Found: C, 52.80; H, 6.56; N, 6.44.

An attempt to cyclize the compound to 2,3-dioxopyrrolidine by use of potassium ethoxide failed.

Preparation of 4-Cyano-2,3-dioxopyrrolidines.—Two different procedures are illustrated below. The constants of the products are given in Table I.

Procedure A.—To a suspension of 5.4 g. of sodium methoxide in 50 ml. of anhydrous ether was added 11.8 g. of methyl oxalate and the mixture shaken for a few minutes. Into this solution 8.4 g. of β-methylaminopropionitrile[14] in 30 ml. of anhydrous ether was added dropwise. An exothermic reaction started at once and the sodium salt of the product soon separated. Addition was controlled at such a rate that a continuous reflux of ether was maintained. After the addition was complete the mixture was heated under reflux for 30 min. and the salt removed by filtration and treated with 10% hydrochloric acid. The crude product was filtered off and recrystallized from ethanol to give 11.2 g. (81.2%) of 4-cyano-2,3-dioxo-1-methylpyrrolidine in the form of white prisms, m.p. 189–190°.

Procedure B.—To a solution of 1.2 g. of sodium in 50 ml. of absolute ethanol was added 7.3 g. of diethyl oxalate and the mixture was shaken for a few minutes. To this was added 8 g. of β-benzylaminopropionitrile[15] and the mixture was heated gently under reflux for 2 hr. After removal of ethanol the residual liquid was acidified with 10% hydrochloric acid to give colorless crystals which were purified by recrystallization from ethanol. The yield of 4-cyano-2,3-dioxo-1-benzylaminopyrrolidine was 7.5 g. (70%), m.p. 186–187°.

4-Cyano-3-methoxy-2-oxo-N-β-cyanoethyl-3-pyrroline.—A suspension of 2.0 g. of 4-cyano-2,3-dioxo-N-β-cyanoethylpyrrolidine in 30 ml. of ether was added to an ethereal solution of diazomethane. After allowing to stand at room temperature for 4 hr. the solvent was removed under reduced pressure. The residue was crystallized from 95% ethanol for purification; m.p. 158–159°.

Anal. Calcd. for $C_9H_9N_3O_2$: C, 56.52; H, 4.74; N, 21.98. Found: C, 56.56; H, 4.63; N, 21.32.

N,N′-γ-Dicarbethoxypropyloxamide (XVI).—To 1 g. of ethyl γ-aminobutyrate and a solution of 0.2 g. of sodium in 10 ml. of absolute ethanol, was added dropwise 1.1 g. of diethyl oxalate. A crystalline mass precipitated. After heating under reflux for 30 min. and standing overnight, the crystals were separated by filtration. The product was purified by recrystallization from water; colorless needles, m.p. 107–108°, yield 0.5 g. (41%).

Anal. Calcd. for $C_{14}H_{24}N_2O_6$: C, 53.15; H, 7.65; N, 8.86. Found: C, 53.08; H, 7.63; N, 8.64.

N,N′-β-Cyanoethyl Oxamide (X).—To a stirred suspension of 10.8 g. of sodium methoxide in 100 ml. of absolute ether was added 23.6 g. of dimethyl oxalate followed by 14 g. of β-aminopropionitrile. An exothermic reaction started

(14) A. H. Cook and K. J. Reed, *J. Chem. Soc.*, 399 (1945).

(15) J. King and F. McMillan, *J. Am. Chem. Soc.*, **68**, 1468 (1946).

TABLE I

4-CYANO-2,3-DIOXOPYRROLIDINES

R	Yield,[a] %	M.p.,[b] °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
CH_3	81.2(A) 75.0(B)	189–190	$C_6H_6N_2O_2$	52.17	51.99	4.38	4.38	20.28	20.22
C_2H_5	67.2(A)	200–201	$C_7H_8N_2O_2$	55.25	55.61	5.30	5.08	18.41	18.49
CH_2CH_2CN	41.3(A) 58.5(B)	175–176	$C_8H_7N_3O_2$	54.23	54.62	3.98	4.10	23.72	23.90
$CH_2C_6H_5$	70.0(B)	186–187	$C_{12}H_{10}N_2O_2$	67.28	67.25	4.71	4.66	13.07	13.27
C_6H_{11}	66.0(B)	169	$C_{11}H_{14}N_2O_2$	64.06	63.87	6.84	6.95	13.58	13.20

[a] The letters A and B indicate the procedure used in the preparation (see Experimental section). [b] All the products were purified by recrystallization from ethanol.

and refluxing was continued for 10 min. The precipitated solid was treated with 10% hydrochloric acid and the product was collected by filtration and recrystallized from water; m.p. 244–245°, yield 15.5 g. (79%).

Anal. Calcd. for $C_8H_{10}N_4O_2$: C, 49.48; N, 5.19; N, 28.85. Found: C, 49.23; H, 4.90; N, 28.54.

Ethyl 2-Piperidylacetate (XIII).—Reduction of 5 g. of ethyl 2-pyridylacetate in 30 ml. of acetic acid with 0.5 g. of 5% rhodium-on-alumina catalyst was complete in 3 hr. (650 ml. of hydrogen absorbed). After removal of catalyst and the solvent under reduced pressure, the residual liquid was distilled; colorless viscous liquid, b.p. 119–123° (33 mm.) (lit.[16] b.p. 105° (14 mm.)), yield 4.8 g. (92.6%).

1-Carbethoxy-2,3-dioxoöctahydropyrrocoline (XIV).—A mixture of 1.1 g. of ethyl 2-piperidylacetate and 1.0 g. of diethyl oxalate was added to a solution of 0.18 g. of sodium in 15 ml. of absolute ethanol. The mixture was heated under reflux for 3 hr. during which time the sodium salt of the product separated from the reddish solution. This salt was filtered off, washed with ether and poured into ice-cold 10% hydrochloric acid. The colorless crystals that separated were recrystallized from water; m.p. 113–114°, yield 1.0 g. (70%).

Anal. Calcd. for $C_{11}H_{15}NO_4$: C, 58.65; H, 6.71; N, 6.22. Found: C, 58.60; H, 6.91; N, 6.67.

Ethyl 2-Pyrrolidylacetate (XI).—A solution of 11.5 g. of ethyl 2-pyrrolylacetate[6] in 40 ml. of glacial acetic acid was hydrogenated in the presence of 2.0 g. of 5% rhodium-on-alumina and an initial pressure of 30 p.s.i. The theoretical amount of hydrogen was absorbed in 1.5 hr. The catalyst was removed and the acetic acid solution poured into 30 ml. of 20% hydrochloric acid. After two extractions with ether, the aqueous phase was basified carefully with solid potassium carbonate and extracted repeatedly with chloroform. The combined extract was dried (Na_2SO_4), the solvent removed, and the residual brown oil distilled in vacuum to give 7.2 g. (62%) of pure colorless oil, b.p. 50–51° (0.2 mm.), $n^{25}D$ 1.4485.

The picrolonate was prepared in and recrystallized from ethanol; m.p. 150–151.5°.

Anal. Calcd. for $C_8H_{15}NO_2 \cdot C_{10}H_8N_4O_5$: C, 51.31; H, 5.47; N, 16.52. Found: C, 51.49; H, 5.50; N, 16.36.

1-Carbethoxy-2,3-dioxopyrrolizidine (XII).—To a cooled solution of 1.4 g. of freshly cut sodium in 40 ml. of absolute ethanol was added with stirring a mixture of 6.8 g. of ethyl 2-pyrrolidylacetate and 7.0 g. of dry diethyl oxalate. The reaction mixture warmed up. It was heated under reflux for 4 hr. during which time the color changed to dark red. The ethanol was removed under reduced pressure, the gummy residue cooled and scratched with 30 ml. of 20% hydrochloric acid. The white crystals that separated were removed by filtration, washed with ice-cold water, dried and recrystallized from benzene–petroleum ether (b.p. 40–60°) to give colorless needles, m.p. 119–120°. Extraction of the aqueous mother liquor with chloroform yielded an additional 0.9 g. of product. The total yield was 7.5 g. (82%).

Anal. Calcd. for $C_{11}H_{13}NO_4$: C, 56.86; H, 6.20; N, 6.63. Found: C, 56.53; H, 6.29; N, 6.60.

The 1-Carbethoxy-2-methoxy-3-oxopyrrolizid-1,2-ene.—To an ethereal suspension of 3 g. of 1-carbethoxy-2,3-dioxopyrrolizidine was added an ethereal solution of 3 g. of diazomethane. In a few minutes most of the solid dissolved with effervescence. The solution was filtered, the ether removed, and the residual oil distilled under reduced pressure; colorless oil, b.p. 185–187° (0.7 mm.), yield 2.8 g. (77.8%).

Anal. Calcd. for $C_{11}H_{15}NO_4$: N, 6.22. Found: N, 6.31.

Reduction of 1-Carbethoxy-2,3-dioxopyrrolizidine with Lithium Aluminum Hydride.—To a stirred solution of 1.6 g. of lithium aluminum hydride in 50 ml. of anhydrous tetrahydrofuran was added dropwise a solution of 3.0 g. of 1-carbethoxy-2,3-dioxopyrrolizidine in 20 ml. of anhydrous tetrahydrofuran. After the addition was complete, the reaction mixture was heated under reflux for 3 hr. A mixture of water and tetrahydrofuran then was added carefully to decompose the unreacted hydride. The mixture was filtered through Super-cel, the filtrate dried over anhydrous sodium sulfate, and the solvent removed under reduced pressure. The residual oil was distilled under reduced pressure to give 0.9 g. (45.7%) of colorless liquid, b.p. 93–95° (1.7 mm.), which turned yellow on standing for a few hours.

The picrate was prepared in ether and crystallized from absolute ethanol; m.p. 166–168°.

Anal. Calcd. for $C_8H_{13}NO \cdot C_6H_3N_3O_7$: C, 45.65; H, 4.25; N, 15.22. Found: C, 45.36; H, 4.67; N, 15.03.

Paper chromatography of the base using butanol–acetic acid as the solvent system indicated the presence of more than one compound. No attempt was made to separate the components.

1-Carbethoxy-2,3-dioxopyrrolizidine was unattacked by sodium borohydride. Lithium borohydride reduction yielded a mixture of products.

Catalytic Reduction of the Lithium Aluminum Hydride Reduction Product.—A solution of 0.4 g. of the base in 25 ml. of absolute ethanol was shaken with 0.1 g. of platinum oxide catalyst and hydrogen at room temperature and atmospheric pressure. The absorption of 58 ml. of hydrogen (calcd. for 1 mole, 64 ml.) required 30 min. and the absorption then ceased. The catalyst was removed and the solvent distilled off under reduced pressure. The residual oil was converted into its picrate in ether and crystallized from ethanol–ether; m.p. 184–185°.

Anal. Calcd. for $C_8H_{15}NO \cdot C_6H_3N_3O_7$: C, 45.41; H, 4.86; N, 15.14. Found: C, 45.32; H, 5.16; N, 15.16.

1-Carbethoxy-2-hydroxy-3-oxopyrrolizidine (XXI).—A solution of 5.0 g. of 2,3-dioxo-1-carbethoxypyrrolizidine in 40 ml. of glacial acetic acid was hydrogenated in the presence of 1.5 g. of 5% rhodium-on-alumina and at an initial pressure of 20 p.s.i. Absorption of the theoretical amount (1 mole) of hydrogen was complete in 30 min. The catalyst was filtered off and the solvent removed under reduced pressure. The residue crystallized on cooling. It was purified by recrystallization from benzene–petroleum ether (b.p. 40–60°) to give 4.2 g. (82%) of shining platelets, m.p. 137.5°.

Anal. Calcd. for $C_{10}H_{15}NO_4$: C, 56.32; H, 7.08; N, 6.57. Found: C, 56.56; H, 7.31; N, 6.72.

1-Hydroxymethyl-2-hydroxypyrrolizidine (XXII).—To a stirred slurry of 3.0 g. of powdered lithium aluminum hydride in 75 ml. of freshly purified tetrahydrofuran was added dropwise a solution of 5.0 g. of 1-carbethoxy-2-hydroxy-3-oxopyrrolizidine in 75 ml. of tetrahydrofuran. After the addition was over, the slurry was heated under reflux with stirring for 4 hr., cooled, excess of hydride decomposed

(16) G. R. Clemo, W. McG. Morgan and R. Raper, *J. Chem. Soc.*, 1743 (1935).

by addition of wet tetrahydrofuran, and the precipitate separated by filtration through Super-cel. The filtrate was dried and evaporated to leave a gum which crystallized on trituration with acetone. Recrystallization from acetone yielded 2.8 g. (75.5%) of white prisms, m.p. 123–124°.

Anal. Calcd. for $C_8H_{15}NO_2$: C, 61.11; H, 9.61; N, 8.91. Found: C, 61.10; H, 9.76; N, 8.76.

The hydrochloride was prepared in ethanol and crystallized from ethanol–ether; m.p. 111–112.5°.

Anal. Calcd. for $C_8H_{15}NO_2 \cdot HCl$: C, 49.60; H, 8.33. Found: C, 49.63; H, 8.62.

The picrate prepared in ethanol and crystallized from ethanol–ether gave shining yellow prisms, m.p. 166–167°.

Anal. Calcd. for $C_8H_{15}NO_2 \cdot C_6H_3N_3O_7$: C, 43.52; H, 4.69; N, 14.50. Found: C, 43.50; H, 5.19; N, 13.98.

1-Chloromethyl-2-chloropyrrolizidine.—A mixture of 1.3 g. of 1-hydroxymethyl-2-hydroxypyrrolizidine in 5 ml. of chloroform and 3 ml. of thionyl chloride was heated under reflux for 4 hr. at the end of which time most of the solvent and excess of thionyl chloride were removed under diminished pressure, the residue taken up in chloroform, washed with 10% aqueous sodium hydroxide, the organic layer dried and the solvent evaporated. The resulting oil was converted into its picrate in ethanol, and recrystallized from ethanol; m.p. 168–169°.

Anal. Calcd. for $C_8H_{13}Cl_2N \cdot C_6H_3N_3O_7$: C, 39.72; H, 3.81; N, 13.24. Found: C, 39.62; H, 3.77; N, 13.56.

1-Hydroxymethyl-2-hydroxypyrrolizidine failed to react with thionyl chloride at 0°. At the end of 30 min. the starting material was recovered as the hydrochloride.

[CONTRIBUTION FROM THE DANIEL SIEFF RESEARCH INSTITUTE, THE WEIZMANN INSTITUTE OF SCIENCE, REHOVOTH, ISRAEL]

Synthetic Studies on Sphingolipids. VI. The Total Syntheses of Cerasine and Phrenosine

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The galactocerebrosides cerasine (VIIIa) and phrenosine (VIIIb) and the Gaucher spleen glucocerebroside have been synthesized and found identical with the natural products. The N-acyl-3-O-benzoylsphingosine bases (VI) were condensed with the corresponding aceto-bromo sugars in the presence of mercuric cyanide, and the resulting acylated glycosides (VII) were saponified to the glycosides VIII. The β-configuration has been assigned to the natural cerebrosides.

The cerebrosides, first isolated from brain tissue in 1874,[1] were found to be composed of sphingosine, D-galactose and a long-chain fatty acid. The amide linkage of the acidic component and the glycosidic nature involving one of the two hydroxylic groups have long been recognized by early investigators.[2–5] However, it was not until 1952 that structure II was established for the two cerebrosides by Carter and co-workers,[6] who showed that the galactosyl group is attached to C-1 of the sphingosine molecule. The structure of sphingosine as *trans*-D-*erythro*-1,3-dihydroxy-2-amino-4-octadecene (I) was proven both by degradation[7–8] and by synthesis.[9]

The term cerasine has been applied to the cerebroside IIa in which the acidic component is lignoceric acid, while phrenosine (IIb) contains cerebronic acid. Although these lipids certainly exist in nature as individual compounds, the fatty acids could not be obtained in a pure form by hydrolysis. Lignoceric (*n*-tetracosanoic) acid was found to contain small amounts of homologous acids.[10] The identity and purity of natural cerebronic acid has been the subject of considerable discussion. Klenk's assumption[11–12] that it is pure α-hydroxy-*n*-tetracosanoic acid was not substantiated by later investigators.[13–15] Indeed, Chibnall, *et al.*,[10] were able to show that the purified acid contained up to 15% of the C-26 homolog. Various melting-points and specific rotations have been reported for cerebronic acid. The optically active α-hydroxytetracosanoic acid synthesized in the present investigation closely corresponded to the physical data which characterize the purest cerebronic acid obtained from natural sources.[10]

In a preliminary communication[16] we reported a synthesis of dihydrocerebrosides which involved the Koenigs–Knorr reaction[17] of a DL-ceramide[18] of type VI with 2,3,4,6-tetra-O-acetyl-α-D-galactopyranosyl bromide in the presence of silver carbonate. The reaction proceeded sluggishly over a period of 48 hr., even with a large excess of the bromo-sugar. The products showed the expected infrared absorption spectra and gave good analytical values, including the percentage of galactose. The relatively low melting points of 125–130° were attributed to the presence of a conglomerate of D-galactosides instead of a racemic compound. Surprisingly, we later found that this reaction, when applied to the benzoyl-ceramides of D-sphingosine and D-dihydrosphingosine (VIa and

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