standing at room temperature and smelled strongly of dimethylamine.

Degradation of Scopinone Methobromide with Sodium Bicarbonate.—Scopinone methobromide[10] (62 mg., 0.25 mmole) and sodium bicarbonate (21 mg., 0.25 mmole) dissolved in 50 ml. of distilled water were heated on the steam-bath. Periodically 1-ml. samples were withdrawn, diluted 1:100 with distilled water (concentration = 5×10^{-5} *M*) and the ultraviolet spectrum taken. The yield of *m*-hydroxybenzaldehyde was estimated on the basis of the intensity of the 253 mμ absorption maximum. Heating was stopped after 9 hours, and the solution was concentrated to a volume of approximately 10 ml. by evaporation in a stream of dry air at room temperature. This solution was acidified (*p*H 3, hydrion paper) with 7 drops of 1 *N* sulfuric acid. The acidic solution was extracted four times with ether, and the ethereal extract was dried over anhydrous magnesium sulfate. Evaporation of the ether *in vacuo* gave a white solid (25 mg., 82%), m.p. 100–102° (authentic *m*-hydroxybenzaldehyde recrystallized from water, m.p. 102–103°). A mixture melting point with authentic *m*-hydroxybenzaldehyde was undepressed (100–102°). The infrared spectra of the product and authentic *m*-hydroxybenzaldehyde in chloroform solution were identical. The product was recovered from the chloroforom solution and converted to the 2,4-dinitrophenylhydrazone, m.p. 261–262° (*m*-hydroxybenzaldehyde, 2,4-DNP, m.p. 259°), mixture m.p. 257–260°.

Degradation of Scopinone Methobromide without Base.—Scopinone methobromide (62 mg., 0.25 mmole) was dissolved in distilled water and heated on the steam-bath. Periodically 1-ml. samples were withdrawn and analyzed as above. Heating was stopped after 14 hours, and the solution was evaporated to dryness at room temperature in a stream of dry air. *m*-Hydroxybenzaldehyde (15 mg., 49%) was isolated from the residual product.

Stability of γ-Tropolone in Base.—An aqueous solution of γ-tropolone was prepared as described previously[1,4] by dissolving teloidinone methobromide (66.5 mg.) and barium hydroxide (5.0 g.) in 50 ml. of distilled water. The solution was heated on the steam-bath until the yield of γ-tropolone was constant. The solution was then heated for 12 additional hours with no significant change in the intensity or location of the γ-tropolone absorption maxima.

ITHACA, N. Y.

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

The Absolute Configuration of the C_8-Atom in the Pyrrolizidine Moieties of the Senecio Alkaloids

BY ROGER ADAMS AND D. FLEŠ[1,2]

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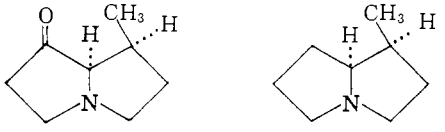
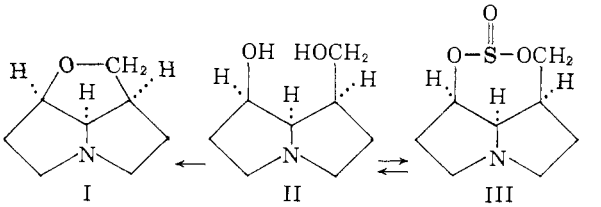
(−)-Methyl 2-acetyl-1-pyrrolidineacetate, a degradation product of monocrotaline, was condensed with methylmagnesium iodide to yield (−)-1-(2-hydroxy-2-methylpropyl)-2-(1-hydroxy-1-methylethyl)-pyrrolidine. The same carbinol was prepared from (S)(−)-proline by converting it first to the methyl ester, condensing this ester with methyl bromoacetate, and finally treating the methyl (−)-2-carbomethoxy-1-pyrrolidineacetate with methylmagnesium iodide. The configuration of the C_8-atom in the pyrrolizidine moiety of monocrotaline was thus related to (S)(−)-proline.

In a recent paper[3] a proof of the absolute configuration of the C_1 atom of retronecanone was established as S[4]. This was effected by correlating the configuration of (−)-3-methyl-5-aminovaleric acid, which had previously been converted into retronecanone,[5] with that of (S)(−)-methylsuccinic acid. The results were in agreement with the findings deduced by Warren and Klemperer[6] on the basis of the degradation of (−)-heliotridane to (S)(+)-3-methylheptane.



(−)-retronecanone[7] (−)-heliotridane

The absolute configuration of the C_8-atom in desoxyretronecine (V) has now been undertaken. From a consideration of the scale molecular models of anhydroplatynecine[8] (I), Leonard and Felley[9] concluded that the methyl group in heliotridane must be *trans* to the hydrogen attached to the C_8-atom. Dry, Koekemoer and Warren[10] performed experiments that led them to the same conclusion. Adams and Van Duuren[11] converted platynecine (II) into a tricyclic product, platynecine sulfite (III), by treatment with thionyl chloride. Hydrolysis of compound III with cold dilute alkali regenerated platynecine. They deduced also a *trans* relationship of the C_1-methyl group and the C_8-hydrogen atom in heliotridane.



I II III

Since the absolute configuration of the C_1-atom of the pyrrolizidine moiety of the necine alkaloids has been experimentally proved,[3,6] the absolute configuration of the C_8-atom can be deduced on the basis of the relationships established

(1) "Pliva" Pharmaceutical and Chemical Works, Zagreb, Yugoslavia.

(2) The authors are grateful for a grant from the Alfred P. Sloan Foundation which made this investigation possible.

(3) R. Adams and D. Fleš, THIS JOURNAL, **81**, 4946 (1959).

(4) The symbolism presented by R. S. Cahn, C. K. Ingold and V. Prelog, *Experientia*, **12**, 81 (1956).

(5) R. Adams and N. J. Leonard, THIS JOURNAL, **66**, 257 (1944).

(6) F. L. Warren and M. E. von Klemperer, *J. Chem. Soc.*, 4574 (1958).

(7) The structural formulas of the pyrrolizidine bases are drawn in such a way that the  bond is in the plane of the paper, while the two rings are inclined on the carbon–nitrogen axis toward each other above the plane of the paper.

(8) A. Orekhov, R. A. Konovalova and W. Tiedebel, *Ber.*, **68**, 1886 (1935); R. A. Konovalova and A. Orekhov, *ibid.*, **69**, 1908 (1936).

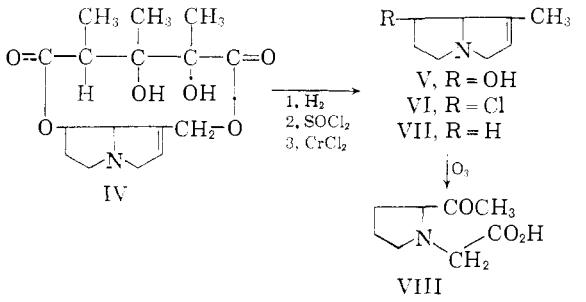
(9) N. J. Leonard and D. L. Felley, THIS JOURNAL, **72**, 2537 (1950).

(10) L. J. Dry, M. J. Koekemoer and F. L. Warren, *J. Chem. Soc.*, 59 (1955).

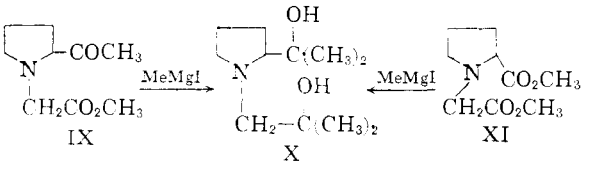
(11) R. Adams and B. L. Van Duuren, THIS JOURNAL, **76**, 6379 (1954).

previously,[9,10,11] assuming that during the dehydration of platynecine to anhydroplatynecine, the inversion of groups on the asymmetric carbon atoms does not occur. These conclusions, however, have not been confirmed by appropriate chemical correlation of the C_8-atom with a compound of known absolute configuration. With this objective in view the configuration of the C_8-atom of desoxyretronecine, a degradation product of monocrotaline, was correlated with that of (S)(−)-proline.

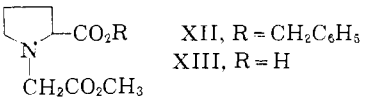
Monocrotaline (IV) was selectively hydrogenolyzed to desoxyretronecine (V) with hydrogen in the presence of palladium-on-strontium carbonate catalyst, as described by Adams, Shafer and Braun.[12] It was, however, observed, that the catalyst was much more selective when poisoned with quinoline. Desoxyretronecine was then converted to the hydrochloride of (−)-2-acetyl-1-pyrrolidineacetic acid (VIII) following the procedure of Adams and Mahan[13]: desoxyretronecine (V) was treated with thionyl chloride to replace the hydroxyl with chlorine; the resulting chloroisoheliotridene (VI) was reduced with chromous chloride to isoheliotridene (VII); ozonolysis of compound VII resulted in the ketonic acid VIII.



The ketonic acid VIII was next converted to its methyl ester IX which gave (−)-1-(2-hydroxy-2-methylpropyl)-2-(1-hydroxy-1-methylethyl)-pyrrolidine (X) upon condensation with methylmagnesium iodide. The same carbinol (X) was prepared from methyl (−)-2-carbomethoxy-1-pyrrolidineacetate (XI) by condensation with methylmagnesium iodide.

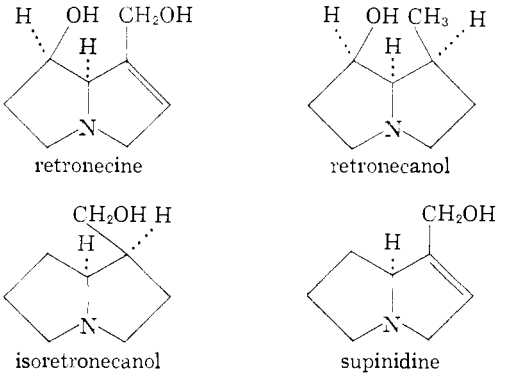


The dimethyl ester XI was synthesized from the methyl ester of (S)(−)-proline by condensation with methyl bromoacetate. It was also prepared indirectly from the benzyl ester of (−)-proline by condensation with methyl bromoacetate followed by hydrogenolysis of the methyl (−)-2-carbobenzyloxy-1-pyrrolidineacetate (XII) to methyl (−)-2-carboxy-1-pyrrolidineacetate (XIII). The latter was esterified to compound XI with methanolic hydrochloric acid.



In view of the fact that the absolute configuration of (−)-proline has been established[14] as S and that the preparation of the carbinol X from desoxyretronecine and from (S)(−)-proline proceeds through reactions not involving the C_8-atom of (−)-desoxyretronecine or the C_2-atom of (S)(−)-proline, the configuration of the C_8-atom of desoxyretronecine and therefore of the corresponding atom in monocrotaline has been proved unequivocally to be R.

The previously proved relationship of many natural-occurring pyrrolizidine derivatives to each other[15] permits the deduction of the absolute configuration of the C_8-atom in chloroisoheliotridene (VI), retronecine, retronecanol and platynecine (II) as R and in isoheliotridene (VII), heliotridane, isoretronecanol and supinidine as S.



Acknowledgment.—The authors are indebted to Mr. J. Nemeth, Miss C. Higham and Miss Jane Liu for the microanalysis and to Mr. P. E. McMahon and Mr. B. A. Shoulders for the determination of the infrared and nuclear magnetic resonance spectra.

Experimental

Desoxyretronecine (V).—A solution of 10 g. of monocrotaline in 300 ml. of absolute ethanol was hydrogenolyzed at atmospheric pressure in the presence of 200 mg. of 5% palladium-on-strontium carbonate catalyst[12] poisoned with 20 mg. of quinoline. The theoretical amount of hydrogen (690 ml., S.T.P.) was consumed in 2.5 hours, and the uptake of hydrogen stopped completely after that time. The reaction mixture was refluxed until the precipitated desoxyretronecine monocrotalate dissolved, the catalyst was separated by filtration, the ethanol evaporated *in vacuo*, and the residue suspended in 50 ml. of acetone. The crystalline salt was collected by suction and washed with acetone to give 10 g. of desoxyretronecine monocrotalate, m.p. 171–172° (lit.[12] m.p. 172.5–172.8°). Desoxyretronecine was prepared from the salt in the manner previously described,[12] m.p. 77–78°, yield 3.5 g. (82%).

Benzyl (−)-Prolinate Hydrochloride.—A suspension of 6 g. of (S) (−)-proline in 30 ml. of acetyl chloride was cooled to 0° and treated with 13.2 g. of phosphorus pentachloride under vigorous shaking as described by Fischer and Reif.[16]

(12) R. Adams, P. R. Shafer and B. H. Braun, THIS JOURNAL, **74**, 5612 (1952).

(13) R. Adams and J. E. Mahan, *ibid.*, **65**, 2009 (1943).

(14) P. Karrer and P. Portmann, *Helv. Chim. Acta*, **31**, 2088 (1948).

(15) R. Adams and M. Gianturco, *Angew. Chem.*, **69**, 5 (1957); F. L. Warren in "Progress in the Chemistry of Organic Natural Products," Vol. XII, Springer, Wien, 1955, p. 198.

(16) E. Fischer and G. Reif, *Ann.*, **363**, 118 (1908).

After about 15 minutes the phosphorus pentachloride was in solution and the reaction mixture was held in ice for an additional hour. Addition of 45 ml. of cold petroleum ether (b.p. 40–60°) caused a heavy precipitate of acid chloride hydrochloride to separate. It was removed by filtration on a sintered glass funnel protected from moisture, washed with two 25-ml. portions of petroleum ether (b.p. 40–60°) and dried *in vacuo*. The acid chloride was dissolved with cooling in 15 ml. of benzyl alcohol and to the solution 100 ml. of ether was added. The supernatant liquor was decanted from the oily precipitate which was three times triturated with 50 ml. of ether. The residue finally crystallized. It was dissolved in 30 ml. of isopropyl alcohol and precipitated by the addition of 50 ml. of ether; yield 7.8 g.(62%). After two crystallizations from isopropyl alcohol it was pure, m.p. 197–198°; rotation: 0.0629 g. made up to 5 ml. with water at 25° gave α_D −1.25°, *l* 2; $[\alpha]^{25}D$ −49.7 ± 0.2°.

Anal. Calcd. for $C_{12}H_{16}ClNO_2$: C, 59.63; H, 6.67; N, 5.79. Found: C, 59.79; H, 6.79; N, 6.02.

Methyl (−)-2-Carbobenzyloxy-1-pyrrolidineacetate (XII).—A suspension of 7.8 g. of benzyl (−)-prolinate hydrochloride, 9.8 g. of finely pulverized anhydrous potassium carbonate and 5.2 g. of methyl bromoacetate in 15 ml. of benzene was refluxed for 6 hours with vigorous stirring. After cooling, the reaction mixture was treated with a solution of 1.5 g. of potassium carbonate in 20 ml. of water, extracted with three 30-ml. portions of ether, and the combined ethereal layers were treated with three 10-ml. portions of 10% hydrochloric acid. The aqueous layer was made strongly alkaline with solid potassium carbonate and the alkaline solution was extracted with three 30-ml. portions of ether. Evaporation of the ether yielded 8.14 g. (91%) of colorless oil. A sample was twice distilled for analysis, b.p. 130–135° (bath temperature) at 0.025 mm., $n^{21}D$ 1.5144; rotation: 0.0726 g. made up to 5 ml. with absolute ethanol at 25° gave α_D −1.96°, *l* 2; $[\alpha]^{25}D$ −67.5 ± 1°.

Anal. Calcd. for $C_{15}H_{19}NO_4$: C, 64.96; H, 6.91; N, 5.05. Found: C, 65.29; H, 7.02; N, 5.18.

Methyl (−)-2-Carboxy-1-pyrrolidineacetate Hydrochloride (XIII).—A solution of 8.1 g. of the methyl benzyl ester XII in 30 ml. of absolute ethanol was treated with hydrogen in the presence of 133 mg. of 5% palladium-on-charcoal catalyst at room temperature and atmospheric pressure. The theoretical amount of hydrogen (650 ml., S.T.P.) was consumed in one hour. The catalyst was removed by filtration, the solvent evaporated under reduced pressure, the oily residue dissolved in a mixture of 30 ml. of benzene–ether (1:1) and the solution saturated with hydrogen chloride with cooling. The oily precipitate which crystallized on scratching was separated by filtration and weighed 6.5 g. After two recrystallizations from methanol and ether (1:3) the product was pure, m.p. 190–191° dec., yield 5.4 g. (82%); rotation: 0.0400 g. made up to 5 ml. with methanol at 25° gave α_D −0.80°, *l* 2; $[\alpha]^{25}D$ −50 ± 0.4°.

Anal. Calcd. for $C_8H_{19}ClNO_4$: C, 42.96; H, 6.31; N, 6.26. Found: C, 43.14; H, 6.30; N, 6.19.

Methyl (−)-2-Carbomethoxy-1-pyrrolidineacetate (XI). A.—A solution of 1.86 g. of the hydrochloride of methyl 2-carboxy-1-pyrrolidineacetate (XIII) in 50 ml. of methanol saturated with hydrochloric acid was kept for 48 hours at room temperature, the solvent evaporated *in vacuo* and the oily residue dissolved in 7 ml. of water, alkalinized with solid potassium carbonate, and extracted with three 50-ml. portions of ether. After removal of solvent *in vacuo* 1.52 g. (92%) of colorless oil resulted. A sample was purified for analysis by distillation, b.p. 65–70° (bath temperature) at 0.025 mm., $n^{16}D$ 1.4608; rotation: 0.0969 g. made up to 5 ml. with methanol at 24° gave αD −3.22°, *l* 2; $[\alpha]^{24}D$ −83 ± 0.8°.

Anal. Calcd. for $C_9H_{15}NO_4$: C, 53.72; H, 7.51; N, 6.96. Found: C, 53.61; H, 7.40; N, 7.14.

B.—From 9.4 g. of methyl (−)-prolinate hydrochloride,[17] 17.6 g. of potassium carbonate and 9 g. of methyl bromoacetate, following the procedure for preparing the benzyl ester XII, a yield of 4.6 g. (40%) of methyl (−)-2-carbomethoxy-1-pyrrolidineacetate was obtained, $n^{16}D$ 1.4609. On redistillation the boiling point was 80° (bath temperature) at 0.04 mm.; rotation: 0.0826 g. made up to 5 ml. with methanol at 26° gave αD −2.69°, *l* 2; $[\alpha]^{26}D$ −81.4 ± 0.7°.

Anal. Found: C, 53.62; H, 7.48; N, 7.14.

Methyl (−)-2-Acetyl-1-pyrrolidineacetate (IX).—A solution of 0.47 g. of (−)-2-acetyl-1-pyrrolidineacetic acid hydrochloride (VIII) in 20 ml. of methanol saturated with hydrogen chloride was allowed to stand overnight at room temperature. The solvent was evaporated *in vacuo*, the oily residue suspended in 10 ml. of chloroform and treated with 5% aqueous sodium bicarbonate until all the acid was neutralized. The chloroform layer was separated and dried over potassium carbonate. Upon evaporation of the solvent *in vacuo*, a yield of 0.41 g. (98%) of yellow oil resulted. Redistillation of 155 mg. gave a colorless oil which turned yellow after several days at room temperature, b.p. 80° (bath temperature) at 0.03 mm.; rotation: 0.0434 g. made up to 5 ml. with chloroform at 26° gave αD −1.11°, *l* 2; $[\alpha]^{26}D$ −63.6 ± 0.5°.

Anal. Calcd. for $C_8H_{15}NO_3$: C, 58.36; H, 8.16; N, 7.56. Found: C, 58.60; H. 8.20; N, 7.68.

1-(2-Hydroxy-2-methylpropyl)-2-(2-hydroxy-2-methylethyl)-pyrrolidine (X). A. From Methyl (−)-2-Carbomethoxy-1-pyrrolidineacetate (XI).—To 50 ml. of a Grignard solution prepared from 3.6 g. of magnesium was added with stirring a solution of 4.15 g. of the dimethyl ester XI in 150 ml. of ether. The precipitate which formed in the beginning went into solution, but after refluxing for 2 hours a second precipitate separated. The reaction mixture was then cooled and hydrolyzed with a solution of 15.6 g. of ammonium chloride in 45 ml. of water. The aqueous layer was separated, extracted with three 20-ml. portions of ether, the combined ethereal solutions dried over potassium carbonate and the solvent evaporated *in vacuo* to give 3.5 g. (84%) of white crystalline product. The product was readily purified in the form of large prisms after one crystallization from petroleum ether (b.p. 40–60°), m.p. 60–61°; rotation: 0.0763 g. made up to 5 ml. with benzene at 26° gave αD −0.26°, *l* 2; $[\alpha]^{26}D$ −8.5 ± 0.7°.

Anal. Calcd. for $C_{11}H_{23}NO_2$: C, 65.63; H, 11.52; N, 6.96. Found: C, 65.69; H, 11.44; N, 6.79.

B. From Methyl (−)-2-Acetyl-1-pyrrolidineacetate (IX).—A solution of 0.370 g. of the ketonic ester IX in 30 ml. of ether was added dropwise with stirring into an ethereal solution of methylmagnesium iodide prepared from 288 mg. of magnesium. The reaction mixture was refluxed for 20 hours, hydrolyzed with 20 ml. of water, the ether layer separated and the residue thoroughly extracted with ether. The extract was dried over potassium carbonate and ether evaporated to yield 0.316 g. of colorless oil which crystallized on standing a short time. It was twice recrystallized from petroleum ether (b.p. 40–60°), m.p. 59–61°, yield 0.1 g. (25%). The melting point was undepressed in admixture with the product prepared under A. Both carbinols were identical as indicated by superimposable infrared spectra in carbon tetrachloride solution; rotation: 0.0252 g. made up to 3 ml. with benzene at 25° gave αD −0.15°, *l* 2; $[\alpha]^{25}D$ −9 ± 1°.

Anal. Found: C, 65.53; H, 11.31; N, 6.99.

The mother liquor from which 0.1 g. of crystalline carbinol was removed gave on evaporation of the petroleum ether 0.18 g. of colorless oil which was distilled *in vacuo*, b.p. 110–115° (bath temperature) at 0.03 mm. It proved to be the partially racemized carbinol as indicated by identical infrared and nuclear magnetic resonance spectra; rotation: 0.0481 g. made up to 3 ml. with benzene at 26° gave αD −0.16°, *l* 2; $[\alpha]^{26}D$ −5 ± 0.7°.

Anal. Found: C, 65.46; H, 11.04; N, 7.34.

URBANA, ILL.

(17) B. F. Erlanger, H. Sachs and E. Brand, THIS JOURNAL, **76**, 1806 (1954).