Stereochemistry of Carpamic Acid.

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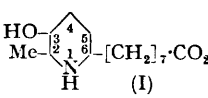
Carpamic acid is shown to have the substituents at $C_{(2)}$ and $C_{(6)}$ *cis* to each other. On the basis of negative evidence the 3-hydroxyl group is assigned the equatorial conformation.

Carpamic acid (I), obtained by hydrolysis of the alkaloid carpaine, has three asymmetric centres. It was desired in the first instance to convert carpamic acid into deoxycarpamic acid under conditions which would preserve the configuration at $C_{(2)}$ and $C_{(6)}$. Although ethyl carpamate was recovered unchanged after treatment with thionyl chloride, ethyl *N*-methylcarpamate was converted by this reagent into ethyl chlorodeoxy-*N*-methylcarpamate which could be reduced catalytically to ethyl deoxy-*N*-methylcarpamate. Crystalline derivatives of the last compound suitable for characterisation could not be prepared, the salts being highly hygroscopic. However, treatment with cyanogen bromide effected smooth demethylation yielding ethyl (—)-deoxycarpamate, characterised as hydrochloride.



(I)

Deoxycarpyrinic acid [ω-(6-methyl-2-pyridyl)octanoic acid], obtained by dehydrogenation of carpaine (Rapaport and Baldridge, *J. Amer. Chem. Soc.*, 1952, **74**, 5365), was reduced catalytically in an acid medium to racemic deoxycarpamic acid, the product being isolated as the ethyl ester hydrochloride. A single product was obtained in quantitative yield. Since catalytic reduction of 2 : 6-disubstituted pyridines in acid medium leads only to the *cis*-isomers (Scheuing and Winterhalder, *Annalen*, 1929, **473**, 126), the substituents in racemic ethyl deoxycarpamate obtained by this method should have a *cis*-relation to each other. This was confirmed by reducing deoxycarpyrinic acid with sodium and alcohol: fractional crystallisation of the product, isolated as the ester hydrochloride, yielded a hydrochloride, m. p. 127—128°, identical with the catalytic reduction product, and a second hydrochloride, m. p. 83—85°. Since the melting-point behaviour of *cis-trans* pairs is reversed in the case of 1 : 3-disubstituted *cyclo*hexanes and 2 : 6-disubstituted piperidines, the higher-melting hydrochloride should be that of the 2 : 6-*cis*-isomer.

The infrared spectrum of racemic ethyl *cis*-deoxycarpamate hydrochloride was identical with that of the (—)-isomer prepared as indicated above. This is clear proof that in carpamic acid, the 2- and the 6-substituent have a *cis*-relationship and both may be said to be equatorial.

The resistance to dehydration exhibited by carpamic acid (Barger, Robinson, and Work, *J.*, 1937, 711), the ready replacement of the hydroxyl group in ethyl *N*-methylcarpamate by chlorine, and the failure of ethyl carpamate to undergo epimerisation on prolonged heating with sodium pentyloxide all suggest that the hydroxyl group in carpamic acid is equatorial. Attempts to oxidise carpamic acid or its derivatives to the corresponding $C_{(3)}$ ketone have so far proved unfruitful and positive evidence for assigning the equatorial position to the hydroxyl group could not therefore be obtained.

Experimental

N-Methylcarpaine.—A mixture of carpaine (2 g.), formaldehyde (2·3 ml.), formic acid (2·3 ml.), and toluene (2 ml.) was refluxed (oil-bath) for 4 hr., after which it was cooled and poured into water (50 ml.). The mixture was rendered alkaline with sodium carbonate and extracted with benzene. The benzene extracted was washed once with water and, after drying (Na_2SO_4) and removal of the solvent, gave an oil which solidified. One crystallisation from acetone–water yielded *N*-methylcarpaine (2·05 g.), m. p. 84° (Found: C, 70·9; H, 10·4. Calc. for $C_{15}H_{27}O_2N$: C, 71·2; H, 10·7%) (m. p. 71° is given in "The Alkaloids, Chemistry and Physiology," Manske and Holmes, Academic Press, Inc., New York, 1950, Vol. I, p. 99).

N-Methylcarpamic Acid.—A solution of *N*-methylcarpaine (3·8 g.) in concentrated

hydrochloric acid (60 ml.) was refluxed for 3 hr., after which it was evaporated to dryness *in vacuo*. *N*-Methylcarpamic acid hydrochloride (3·8 g.) was thus obtained crystalline but extremely hygroscopic, and was converted directly into the ethyl ester.

Ethyl N-*Methylcarpamate*.—A solution of *N*-methylcarpamic acid hydrochloride (3·8 g.) in absolute alcohol (75 ml.) was saturated with dry hydrogen chloride at 0°. After 48 hr., the alcohol was distilled off. The residue was dissolved in water and, after basification with sodium carbonate, the base was extracted with benzene. On evaporation, drying (Na_2SO_4), and distillation, *ethyl* N-*methylcarpamate* (3·8 g.), b. p. 146—150°/0·3 mm., was obtained (Found: C, 68·0; H, 11·0. $C_{17}H_{33}O_3N$ requires C, 68·2; H, 11·0%).

Ethyl Chlorodeoxy-N-*methylcarpamate*.—Ethyl *N*-methylcarpamate (3·8 g.) in chloroform (5 ml.) was cooled in ice and treated with thionyl chloride (1·2 ml.) drop by drop with shaking. Next morning the mixture was poured into ice-water (25 ml.) and extracted with ether. The acid extract was rendered alkaline with sodium carbonate and extracted with ether. Drying (Na_2SO_4) and evaporation of the ether extract gave a dark brown oil (3 g.) which on fractionation yielded ethyl *N*-methylcarpamate (500 mg.), b. p. 148°/0·3 mm., and then the crude chloro-compound (2 g.), b. p. 170—200°/0·3 mm. Refractionation yielded *ethyl chlorodeoxy*-N-*methylcarpamate* (1·6 g.), b. p. 190—200°/0·3 mm. (Found: C, 64·0; H, 11·3. $C_{17}H_{32}O_2NCl$ requires C, 64·3; H, 10·1%).

Ethyl Deoxy-N-*methylcarpamate*.—Crude chloro-compound (2 g.) in absolute alcohol (30 ml.) was shaken with Adams catalyst (0·3 g.) in hydrogen at 60 lb. for 6 hr. The solution was filtered and evaporated on a water-bath. The residue was suspended in a little water, rendered alkaline with sodium carbonate, and extracted with benzene. On evaporation of the benzene extract after drying (Na_2SO_4), a colourless oil (1·6 g.) was obtained. This on fractionation yielded fractions (i) (1·3 g.), b. p. 120—140°/0·3 mm., and (ii) (200 mg.), b. p. 148°/0·3 mm. The former yielded *ethyl deoxy*-N-*methylcarpamate* (800 mg.), b. p. 130°/0·3 mm., $[\eta]^{28}$ 1·448 (Found: C, 71·7; H, 11·8. $C_{17}H_{33}O_2N$ requires C, 72·1; H, 11·7%). The second fraction was ethyl *N*-methylcarpamate.

Ethyl (−)-*Deoxycarpamate*.—To a solution of cyanogen bromide (400 mg.) in absolute benzene (3 ml.) was added ethyl deoxy-*N*-methylcarpamate (800 mg.) in benzene (3 ml.) drop by drop with stirring. The mixture was kept overnight. On removal of the solvent an amber-coloured, non-basic liquid (800 mg.) was obtained, which did not contain bromine. This (800 mg.) was hydrolysed by boiling 20% sulphuric acid (10 ml.). The solution was cooled and, after dilution with water and extraction of the non-basic material with ether, was treated with a slight excess of barium chloride solution. The precipitated barium sulphate was filtered off, and the filtrate evaporated to dryness *in vacuo* The residue was esterified by the Fischer procedure, giving an oil (300 mg.) which was converted into the hydrochloride by the usual procedure. One crystallisation yielded pure *ethyl* (−)-*deoxycarpamate hydrochloride*, m. p. 130—131°, $[\alpha]_D^{28}$ −10·3° (*c*, 2·6 in EtOH) (Found: C, 62·6; H, 10·7. $C_{16}H_{32}O_2NCl$ requires C, 62·9; H, 10·5%).

Ethyl cis-(±)-*Deoxycarpamate*,—A solution of deoxycarpyrinic acid hydrochloride (1 g.) in absolute alcohol (35 ml.) containing 5 drops of concentrated hydrochloric acid was hydrogenated over Adams catalyst (200 mg.) at 60 lb. On filtration and evaporation racemic *ethyl* cis-*deoxycarpamate hydrochloride*, m. p. 123—126°, was obtained in quantitative yield. One crystallisation from alcohol–ether gave the pure compound, m. p. 127—128° (Found: C, 62·7; H, 10·1. $C_{16}H_{32}O_2NCl$ requires C, 62·9; H, 10·5%).

Reduction of Deoxycarpyrinic Acid with Sodium and Alcohol.—A solution of deoxycarpyrinic acid (1 g.) in alcohol was reduced by sodium (10 g.) in the usual way. The product isolated as the hydrochloride (800 mg.) was esterified by the Fischer procedure. Fractional crystallisation of the ester hydrochloride from alcohol–ether gave ethyl *cis*-deoxycarpamate hydrochloride (400 mg.), m. p. 128°, as the first fraction. This did not depress the m. p. of the compound obtained as above. From the mother-liquor *ethyl* trans-*deoxycarpamate hydrochloride* (300 mg.), m. p. 80—85°, was obtained. Two crystallisations from alcohol–ether raised the m. p. to 83—85° (Found: C, 63·1; H, 10·4%).

Action of Sodium Pentyloxide on Ethyl Carpamate.—A solution of sodium (2·5 g.) in pentanol (60 ml.) containing ethyl carpamate (700 mg.) was refluxed for 4 hr. Fractional crystallisation of the product gave a single compound, isolated as the hydrochloride, which was identical with the starting material (m. p. and mixed m. p.).

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