537. *Constitution of Carpaine.*

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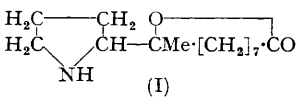
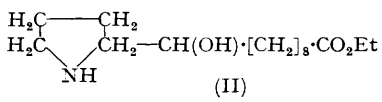
Dehydrogenation of ethyl 10-hydroxy-10-2′-pyrrolidinyldecanoate with palladium–charcoal yielded a pyrrole and not a pyridine derivative. Dehydrogenation of ethyl carpamate yielded ethyl carpyrinate, proved to be a 3- or 5-hydroxypyridine derivative. Carpaine is therefore a piperidine alkaloid and the hydroxyl group involved in lactone formation should therefore be at position 3 or 5 of the piperidine ring.

BARGER, ROBINSON, and WORK (*J.*, 1937, 711) assigned structure (I) to the alkaloid carpaine from *Carica papaya* L. Rapaport and Baldridge (*J. Amer. Chem. Soc.*, 1951, **73**, 343) obtained myristic acid by a two-stage Hofmann degradation of carpaine, proving conclusively that this structure was untenable. The formulation of carpaine as a pyrrolidine derivative was based on the observation (Barger, Girardet, and Robinson,



(I)



(II)

Helv. Chim. Acta, 1933, **16**, 90) that carpyrine and *apo*carpyrine obtained by dehydrogenation of carpaine with selenium gave colour tests with *p*-dimethylaminobenzaldehyde normally given by pyrrole compounds. Recently, Rapaport and Baldridge (*J. Amer. Chem. Soc.*, 1952, **74**, 5365) showed that deoxycarpyrinic acid obtained by dehydrogenation of carpaine with palladium–charcoal was a pyridine derivative which could be oxidized to pyridine-2 : 6-dicarboxylic acid and that the *p*-dimethylaminobenzaldehyde test is not specific to pyrrole derivatives, being also given by 2 : 6-lutidine (and deoxycarpyrinic acid). They also sought to prove that expansion of a five-membered to a six-membered ring could not have taken place by showing that methyl 9-(5-methyl-2-pyrrolidinyl)nonanoate yielded only the corresponding pyrrole derivative under the same conditions of dehydrogenation.

Ring expansion would, however, be more likely if an α-amino-alcohol system were present in the pyrrolidine derivative. We find, however, that 10-hydroxy-10-2′-pyrrolidinyldecanoate (II), an α-amino-alcohol, gives on dehydrogenation with palladium–charcoal only a pyrrole derivative. Carpaine is therefore unlikely to be a pyrrolidine derivative.

Dehydrogenation of carpaine by palladium–charcoal leads to loss of 2 mols. of hydrogen and elimination of the hydroxylic oxygen atom involved in lactone formation, as reported by Rapaport and Baldridge (*loc. cit.*). The location of this oxygen atom is therefore left uncertain.

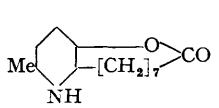
We find that ethyl carpamate on similar dehydrogenation yields three mols. of hydrogen and a product to which the name ethyl carpyrinate is assigned. Ethyl carpyrinate was soluble in dilute acids and in dilute sodium hydroxide solution, but insoluble in sodium carbonate solution. It gave a cherry-red colour with ferric chloride solution and a blue colour with the Folin–Denis reagent for phenols. Its absorption spectrum (see Figure) closely resembles that of 3-hydroxypyridine (Specker and Gawrasch, *Ber.*, 1942, **75**, 1338), and the shifts in absorption maxima in acidic and basic media are in the same direction and

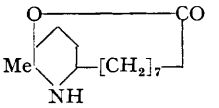
of the same order with both compounds (see Table). Ethyl carpyrinate is therefore an ethyl 8-(6-methyl-2-pyridyl)octanoate with a hydroxyl group in either the 3- or the 5-

Ethyl carpyrinate					3-Hydroxypyridine *				
In EtOH :	$\lambda_{max.}$	223	247	287	In MeOH :	$\lambda_{max.}$	243	278	—
	log ε	3·91	2·75	3·78		log ε	2·68	3·60	—
In 0·1N-HCl–EtOH :	$\lambda_{max.}$	234	251	302	In 0·1N-HCl–MeOH :	$\lambda_{max.}$	245	284	—
	log ε	3·80	2·15	3·97		log ε	2·22	3·81	—
In 0·01N-KOH–EtOH :	$\lambda_{max.}$	247	272	310	In 0·1N-NaOMe–MeOH :	$\lambda_{max.}$	238	265	304
	log ε	4·00	2·78	3·79		log ε	4·00	2·80	3·63

* Values from Specker and Gawrasch (*loc. cit.*).

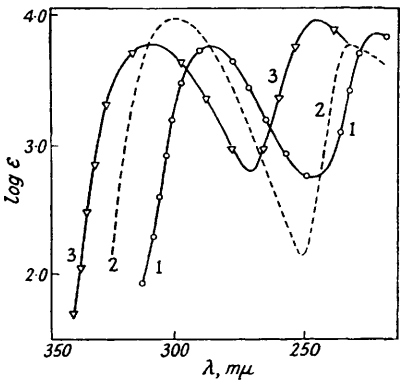
position of the ring. In carpaine, the point of attachment of the lactone ring to the piperidine nucleus should correspond, leading to structure (III) or (IV) for the alkaloid. Further experiments are in progress to distinguish between these possibilities.

(III) 



(IV)

On the basis of the above observations, carpamic acid would have a secondary hydroxyl group. We find that the diol obtained by reduction of carpaine with lithium aluminium hydride yielded a tribenzoyl derivative. Only a dibenzoate would be expected if the hydroxylic oxygen involved in lactone formation were tertiary as in (I).



Ethyl carpyrinate :
1, *in* EtOH,
2, *in* 0·1N-HCl–EtOH,
3, *in* 0·01N-KOH–EtOH.

Experimental

Ultra-violet absorption spectra were determined in a Beckman Model DUV Spectrophotometer.

2-ω-*Carbethoxynonanoylpyrrole*.—This was prepared by the method of Barger, Robinson, and Short (*J.*, 1937, 715), except that the pyrrylmagnesium bromide was run straight from the flask in which it was prepared by a tap provided at the bottom into the solution of the 9-carbethoxynonanoyl chloride in ether. The yield of the product distilling at 180—210°/0·5 mm. varied between 40 and 50%. Recrystallized from light petroleum (b. p. 50—52°), it had m. p. 28°.

Ethyl 10-*Hydroxy*-10-2′-*pyrrolidinyldecanoate*.—A solution of the foregoing ester (0·2 g.) in acetic acid (10 ml.) was reduced at a hydrogen pressure of 60 lb./sq. in. in the presence of Adams catalyst (0·1 g.). After 2 hr., the solution was filtered. The total filtrate from several batches of ester (total 1·3 g.) was diluted with distilled water (150 ml.). The non-basic material was extracted with ether (2 × 75 ml.). The combined ethereal extracts were shaken with 30-ml. portions of water until free from basic material. The combined aqueous solutions were rendered distinctly basic with solid sodium carbonate and after saturation with potassium chloride extracted with ether (5 × 75 ml.). The ethereal extract was dried (Na_2SO_4) and evaporated. The semi-solid residue (0·8 g.) was recrystallised from light petroleum (b. p. 50—52°), giving the *hydroxy-ester* (0·42 g.), m. p. 69·5—70·5° (Found : C, 67·9; H, 10·8; N, 4·9. $C_{16}H_{31}O_3N$ requires C, 67·4; H, 10·9; N, 4·9%). Evaporation of the light petroleum mother-liquors yielded a basic oil, apparently stereoisomeric with the above compound.

Hydrolysis with alcoholic 0·5N-potassium hydroxide gave the corresponding amino-acid, isolated as the *hydrochloride*, m. p. 124·5—126·5° (Found : C, 57·3; H, 9·65; N, 4·5. $C_{14}H_{28}O_3NCl$ requires C, 57·5; H, 9·5; N, 4·8%).

10-*Hydroxy*-10-2′-*pyrryldecanoic Acid*.—A solution of ethyl 10-hydroxy-10-2′-pyrrolidinyldecanoate (0·5 g.) in *p*-cymene (25 ml.) was heated under reflux with 5% palladised charcoal (0·2 g.), in a slow stream of carbon dioxide. During 6·5 hr. 75 ml. (N.T.P.) of hydrogen were evolved (calc. for 2 mols., 78·6 ml.), after which evolution ceased. The solution was cooled and filtered, and the residue washed with benzene (50 ml.). The filtrate was extracted with N-acetic acid (3 × 50 ml.). Evaporation of the acid extract gave, however, no residue, showing absence of basic material in the dehydrogenation product. The benzene–*p*-cymene solution was concentrated *in vacuo* to 25 ml. and refluxed for 9 hr. after addition of alcoholic N-potassium hydroxide (50 ml.). The solvent was then removed *in vacuo* and the residue was treated with water (100 ml.). After being shaken with ether (2 × 75 ml.), the aqueous extract was rendered just acidic to Congo-red and extracted with ether (3 × 75 ml.). Removal of ether after drying (Na_2SO_4) yielded a brownish semi-solid mass (0·3 g.). This was purified by sublimation at 165—175°/0·5 mm., giving a colourless material, m. p. 70—74°, excessively soluble in all solvents and becoming pink rapidly. Two recrystallisations from 60% alcohol yielded a product, m. p. 76—78°, but it was not obtained analytically pure owing to the extreme ease of decomposition.

Ethyl Carpyrinate.—A solution of ethyl carpamate (1·0 g.) in *p*-cymene (50 ml.) was heated under reflux with 5% palladised charcoal (0·5 g.) in a current of carbon dioxide. In about 3 hr. 240 ml. (N.T.P.) of hydrogen was evolved (calc. for 3 mols., 235·8 ml.), after which evolution ceased. The solution was cooled, filtered, and washed with benzene (50 ml.). The combined filtrate and washings were thrice extracted with 2N-acetic acid (3 × 50 ml.). The acid extract was concentrated to 20 ml. and made slightly basic with solid sodium carbonate, saturated with potassium chloride, and extracted with ether repeatedly. The combined ethereal extracts were dried (Na_2SO_4) and evaporated, yielding a colourless crystalline solid (0·9 g.), m. p. 77—78°. Recrystallisation from absolute ether gave crystals of *ethyl carpyrinate*, m. p. 78—80° (Found : C, 68·9; H, 8·8; N, 4·9. $C_{16}H_{25}O_3N$ requires C, 68·8; H, 9·0; N, 5·0%).

Carpyrinic acid was obtained in quantitative yield by the hydrolysis of its ester with alcoholic 0·5N-potassium hydroxide and was isolated as the *hydrochloride* which, recrystallised from anhydrous acetone, had m. p. 85—86·5° after drying for 24 hr. at 80° (Found : C, 58·7; H, 7·8; N, 5·05%; *C*-Me, 0·88 group. $C_{14}H_{22}O_3NCl$ requires C, 58·4; H, 7·65; N, 4·9%). Unlike deoxycarpyrinic acid hydrochloride this is insoluble in chloroform.

Reduction of Carpaine with Lithium Aluminium Hydride.—A solution of carpaine (1 g.) in dry ether (50 ml.) was added dropwise to lithium aluminium hydride (2·0 g.) in ether (50 ml.). The mixture was stirred and refluxed for 4 hr. Next morning sufficient water was added to decompose the excess of hydride. The ether was decanted and the residue repeatedly extracted with ether. The combined ethereal extracts were dried (Na_2SO_4) and evaporated. The residue (0·97 g.; m. p. 48—52°) was dissolved in cold absolute ether, and the solution filtered and left in the ice-box overnight. The *product* separated as colourless needles, m. p. 49—52° (Found : C, 69·2; H, 11·9; N, 5·85. $C_{14}H_{29}O_2N$ requires C, 69·1; H, 11·9; N, 5·7%). Benzoylation in pyridine gave a *tribenzoyl* derivative, m. p. 76—78° (from dilute alcohol) (Found : C, 75·3; H, 7·8; N, 2·7. $C_{35}H_{41}O_5N$ requires C, 75·7; H, 7·4; N, 2·5%).

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