745. *Reserpine Analogues: Synthesis of β-Carboline Derivatives.*

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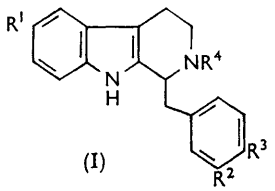
Some 2-(hydroxyalkyl)-1,2,3,4-tetrahydro-β-carboline derivatives have been prepared and subsequently esterified so as to provide analogues of reserpine.

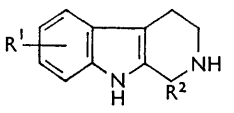
Chloroalkyl methyl ketones used in the syntheses were reduced, by an improved procedure (sodium borohydride), to the respective alcohols.

It was established that the reaction of propylene oxide with secondary amines can be extended to 1,2,3,4-tetrahydro-β-carboline.

As the β-carboline nucleus forms part of the structure of reserpine and occurs, as well as in the *Rauwolfia* alkaloids, also in a number of physiologically active natural bases, *e.g.*, the *Harmala* alkaloids, β-carboline derivatives, mainly substituted at position 1, became of interest as analogues of reserpine. Logemann *et al.*[1] prepared a series of 1-benzyltetrahydro-β-carbolines (I), where R^1, R^2, and R^3 are hydrogen, methoxyl, or acyloxy-groups and R^4 is an acyl group, the compounds showing no pharmacological activity. Their 2-substituted compounds were all amides. Similar compounds were also synthesised



(I)



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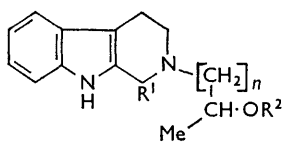

(III)

by Onda and Kawanishi.[2] Protiva *et al.* prepared 1-cyclohexylmethyl-1,2,3,4-tetrahydro-β-carboline, its 4-methoxycyclohexylmethyl analogue,[3] and several 1-(arylalkyl)tetrahydro-β-carbolines [4] (II), where R^1 is hydrogen or methoxyl and R^2 is phenyl, benzyl, cyclohexyl, etc.; the methanesulphonates of these were reported to have reserpine-like properties and, in particular, 1-benzyl-1,2,3,4-tetrahydronorharman was a potent sedative that has found clinical application. On the other hand, only two 2-substituted β-carboline derivatives have been prepared. Onda and Sasamoto [5] reported 2-benzyl-1,2,3,4-tetrahydro-β-carboline and the 1,3-dioxo-derivative, the latter being claimed as a useful hypotensive agent. 2-Substituted β-carbolines thus merited further investigation.

The compounds prepared by us have the general formula (III) where R^1 is hydrogen or methyl, R^2 is hydrogen or 3,4,5-trimethoxybenzoyl, and n is 1, 2, or 3. The simple amide 2-(3,4,5-tetramethoxybenzoyl)-1,2,3,4-tetrahydro-β-carboline was also prepared.

Of the different methods used for introduction of the substituent in the 2-position, by far the best (yield 76%) was the reaction of the tetrahydro-β-carboline derivative with propylene oxide in the cold.

The chloroalkyl acetate intermediates used were prepared from chloroalkyl methyl ketones by the improved procedure with sodium borohydride as the reducing agent, the reaction proceeding easily and in good yield.

Experimental

1,2,3,4-Tetrahydro-2-(4'-hydroxypentyl)-β-carboline.—1,2,3,4-Tetrahydro-β-carboline (500 mg.) (obtained by the reduction of norharman with sodium and alcohol [6]) and 4-chloro-1-methylbutyl acetate (462 mg.) (obtained by reduction and acetylation of 5-chloropentan-2-one [7]

[1] Logemann, Almirante, Caprio, and Meli, *Chem. Ber.*, 1955, **88**, 1952.
[2] Onda and Kawanishi, *J. Pharm. Soc. Japan*, 1956, **76**, 966.
[3] Protiva, Jilek, Hach, Adlerova, and Mychajlyszyn, *Chem. listy*, 1957, **51**, 2109.
[4] Protiva, Jilek, Hachova, Novak, Vejdelek, and Adlerova, *Chem. listy*, 1957, **51**, 1915.
[5] Onda and Sasamoto, *Pharm. Bull. (Japan)*, 1957, **5**, 305.
[6] Snyder, Parmerter, and Katz, *J. Amer. Chem. Soc.*, 1948, **70**, 222.
[7] Williamson and Schinz, *Helv. Chim. Acta*, 1952, **35**, 2403; Schreiber, *Org. Synth.*, 1951, **31**, 74.

with sodium borohydride and acetyl chloride) were refluxed in dry ethanol (90 ml.) for 72 hr. The solvent was removed *in vacuo*, and the residue dissolved in chloroform and extracted with 3% aqueous hydrochloric acid. The aqueous extract was basified with aqueous sodium hydroxide and extracted with chloroform, this extract being then dried ($MgSO_4$) and chromatographed on a column (33 × 1 cm.) of alumina (35 g.). The first fraction (15 ml.) contained 51 mg. of a dark-brown gum and the second (40 ml.) yielded crystals (255 mg.), m. p. 150°. The remainder was mainly tetrahydro-β-carboline. In all, 600 mg. were obtained from 674 mg. used. The crystals were sparingly soluble in ether, and moderately so in ethyl acetate. Recrystallisation from ethyl acetate gave the required *compound*, m. p. 150—151° (Found: C, 74·6; H, 8·6; N, 10·5; O, 6·45. $C_{16}H_{12}N_2O$ requires C, 74·4; H, 8·5; N, 10·8; O, 6·2%.

1,2,3,4-*Tetrahydro*-2-4′-*hydroxypentyl*-1-*methyl*-β-*carboline*.—1-Methyl-β-carboline (1·75 g.) (obtained from DL-tryptophan and acetaldehyde [6,8,9]) and 4-chloro-1-methylbutyl acetate [10] (1·9 g.) were heated in dry benzyl alcohol under nitrogen for 15 hr. at 120—130°. After cooling, addition of dry ether (200 ml.) precipitated a dark-brown gum which solidified and was then washed with ether and twice with acetone, giving an almost colourless solid (2·45 g., ~80%), m. p. 195—200°. This material was dissolved in methanol (100 ml.), and sodium borohydride [11] (6 g.) was added in small portions with stirring and cooling so that the temperature did not rise above 30°. The mixture was stirred for a further 1½ hr. and left overnight. The solvent was removed *in vacuo* and the residue treated with water; a brown gum separated which was extracted with chloroform; the extracts were washed with saturated brine and dried (K_2CO_3). On removal of the solvent the product appeared as a light-brown gum. This material (2·16 g.) was refluxed for 1½ hr. with methanolic sodium hydroxide. On removal of the solvent *in vacuo* and treatment with water a brown gum separated which solidified. Recrystallisation from dry methanol gave the required *compound*, m. p. 171—173° (Found: C, 74·8; H, 9·1; N, 10·3. $C_{17}H_{24}N_2O$ requires C, 75·0; H, 8·8; N, 10·3%).

In the same way 1,2,3,4-tetrahydro-2-3′-hydroxybutyl-β-carboline, m. p. 176—179°, and 1,2,3,4-tetrahydro-2-2′-hydroxypropyl-β-carboline, m. p. 147°, were obtained.

1,2,3,4-*Tetrahydro*-2-2′-*hydroxypropyl*-β-*carboline* (*Alternative Synthesis*).—1,2,3,4-Tetrahydro-β-carboline (500 mg.) and propylene oxide (185 mg.) were dissolved in dry methanol (3·2 ml.) and left overnight. Crystals (360 mg.), m. p. 147—148°, separated. A further crop of the 2,2′-*hydroxypropyl compound* was obtained on concentration of the mother-liquor (total yield 76%) (Found: C, 73·3; H, 7·8; N, 12·15. $C_{14}H_{18}N_2O$ requires C, 73·05; H, 7·8; N, 12·2%). No m. p. depression was observed on admixture with the compound mentioned above.

1,2,3,4-*Tetrahydro*-2-[4-(3,4,5-*trimethoxybenzoyloxypentyl*)]-β-*carboline Hydrochloride*.—1,2,3,4-Tetrahydro-2-4′-hydroxypentyl-β-carboline (1·35 g.) was added to dry pyridine (13 ml.), and the mixture was cooled. 3,4,5-Trimethoxybenzoyl chloride (2·34 g.) was added in small portions. The mixture became red and the base dissolved. After 4 days at room temperature the solution was added to ice–water (750 ml.) containing aqueous ammonia (*d* 0·88; 6·5 ml.), a cream-coloured precipitate appearing. This was dissolved in chloroform, washed with dilute hydrochloric acid, then with aqueous sodium hydrogen carbonate, dried (Na_2CO_3), and recovered. It was then extracted with dry ether and the extract was filtered and treated with dry hydrogen chloride, the cream-coloured product separating. After purification it was obtained as a cream-coloured semicrystalline powder which acquired ability to flow on exposure to air for 24 hr. Dried over phosphorus pentoxide the *product* sintered at 95° and softened at 108—110° [Found: C, 62·7; H, 6·6; Cl, 7·15; N, 5·9; O, 17·4. $(C_{26}H_{32}N_2O_5,HCl)_2,H_2O$ requires C, 62·7; H, 6·8; Cl, 7·1; N, 5·6; O, 17·7%].

The *picrate*, prepared in dry ethanol and recrystallised from ethanol–ether, had m. p. 168° (decomp.) (Found: C, 56·6; H, 5·0; N, 10·4. $C_{32}H_{35}N_5O_{12}$ requires C, 56·4; H, 5·1; N, 10·3%).

1,2,3,4-*Tetrahydro*-1-*methyl*-2-[4-(3,4,5-*trimethoxybenzoyloxypentyl*)]-β-*carboline Hydrochloride*.—Similarly 1,2,3,4-tetrahydro-2-4′-hydroxypentyl-1-methyl-β-carboline (0·91 g.) gave a corresponding *hydrochloride monohydrate*, sintering at 108° and softening at 118° (decomp.) (Found: C, 62·2; H, 7·5; N, 5·3. $C_{27}H_{34}N_2O_5,HCl,H_2O$ requires C, 61·9; H, 7·1; N, 5·4%).

[8] Harvey and Robson, *J.*, 1938, 97.
[9] Gray, Spinner, and Cavallito, *J. Amer. Chem. Soc.*, 1954, **76**, 2792.
[10] Dewael, *Bull. Soc. chim. belges*, 1930, **39**, 87.
[11] Elderfield, Gensler, Brody, Head, Dickermann, Wiederhold III, Kremer, Hageman, Kreysa, Griffing, Kupchan, Newman, and Maynard, *J. Amer. Chem. Soc.*, 1946, **68**, 1579.

1,2,3,4-*Tetrahydro*-2-[2-(3,4,5-*trimethoxybenzoyloxypropyl*)]-β-*carboline Hydrochloride*.—Likewise 1,2,3,4-tetrahydro-2-2′-hydroxypropyl-β-carboline (1·14 g.) gave the *ester hydrochloride hemihydrate*, softening at 130° (decomp.) (Found: C, 61·4; H, 6·4; N, 5·8. $C_{24}H_{28}N_2O_5,HCl,\frac{1}{2}H_2O$ requires C, 61·2; H, 6·4; N, 6·0%).

1,2,3,4-*Tetrahydro*-2-(3,4,5-*trimethoxybenzoyl*-β-*carboline*.—1,2,3,4-Tetrahydro-β-carboline (crude, m. p. 196—202°) (4 g.) was dissolved in hot dry benzene (400 ml.), and 3,4,5-trimethoxybenzoyl chloride (2·7 g.) in dry benzene (35 ml.) was added gradually. Precipitation of tetrahydro-β-carboline hydrochloride began almost immediately. After 3 hr. this was filtered off and the benzene solution was extracted successively with 1% hydrochloric acid, 1% sodium hydrogen carbonate solution, and water. The organic layer was dried ($MgSO_4$) and the solvent removed. Recrystallisation of the residue from dry ethanol gave the *amide* as prisms, m. p. 185·5—186·5° (Found: C, 68·8; H, 6·1; N, 7·6; OMe, 25·1. $C_{21}H_{22}N_2O_4$ requires C, 68·8; H, 6·0; N, 7·8; OMe, 25·4%).

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