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Synthetic Experiments in the Group of Hypotensive Alkaloids—XXI.* Chemistry of 1,2,3,4-Tetrahydronorharmane-1-carboxylic Acid and Derivatives†

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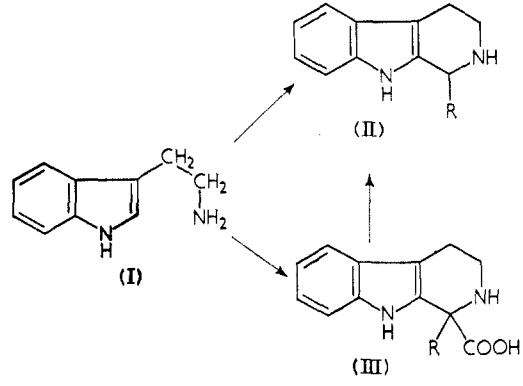
From the work of Hahn *et al.*,[1] it has been known for a long time that by condensation with aldehydes and α-keto acids 'under physiological conditions', tryptamine (I) gives 1-substituted 1,2,3,4-tetrahydronorharmanes (II) and the appropriate 1-substituted 1-carboxylic acids (III) respectively, which decarboxylate very easily. Thus, for example, the reaction of tryptamine (I) with pyruvic acid,[1] recently re-studied by Spenser,[2] yields 85 per cent of 1-methyl-1,2,3,4-tetrahydronorharmane-1-carboxylic acid (III; R = CH_3).

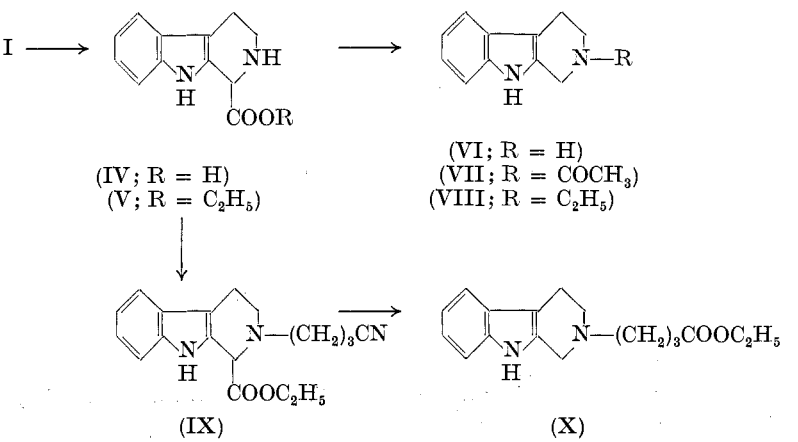


* Part XX: *Coll. Trav. chim. Tchécosl.* In press.

† Preliminary Communication: *Argumenta Lectionum Congr. Pharm., Karlovy Vary*, Sept. 7–10, 1959, 26, 115, 212.

In the course of our attempts to synthesize tricyclic and tetracyclic models of the alkaloid reserpine,[3–5] it was necessary to study the condensation of tryptamine (I) with the next lower homologue of pyruvic acid, glyoxylic acid. As far as we were able to ascertain, this reaction has not been studied before. Janot *et al.*[6] described the reaction of tryptamine with ethyl glyoxylate under physiological conditions, but were able to isolate as the only product 1,2,3,4-tetrahydronorharmane (II; R = H) in a yield of 26 per cent, i.e. the product of cyclization, hydrolysis and decarboxylation. For further synthetic use, it was important to find conditions for the reaction of tryptamine (I) with glyoxylic acid under which decarboxylation would not take place. This was achieved, and the carboxylic acid, $C_{12}H_{12}N_2O_2$, was prepared in a high yield and identified as 1,2,3,4-tetrahydronorharmane-1-carboxylic acid (IV) by its infrared spectrum, and by further transformations to known 1,2,3,4-tetrahydronorharmane derivatives.

By esterification of the acid IV with absolute ethanol and dry hydrogen chloride, we obtained the hydrochloride of the required ethyl ester (V) together with a smaller quantity of 1,2,3,4-tetrahydronorharmane hydrochloride (VI). This decarboxylation product (VI) is also obtained from the acid IV or the ester V by refluxing with aqueous ethanolic hydrochloric acid. In alkaline solution the salt of acid IV is stable; it is obtained in good yield by saponification of the ethyl ester V with a solution of sodium hydroxide in aqueous ethanol.



(IX) (X)

The action of boiling acetic anhydride also causes decarboxylation of acid IV; *N*-acetylation takes place at the same time, yielding the amide VII. The same compound was also obtained directly by acetylation of 1,2,3,4-tetrahydronorharmane (VI). Reduction of the amide VII with lithium aluminium hydride gave a new base of this group—2-ethyl-1,2,3,4-tetrahydronorharmane (VIII).

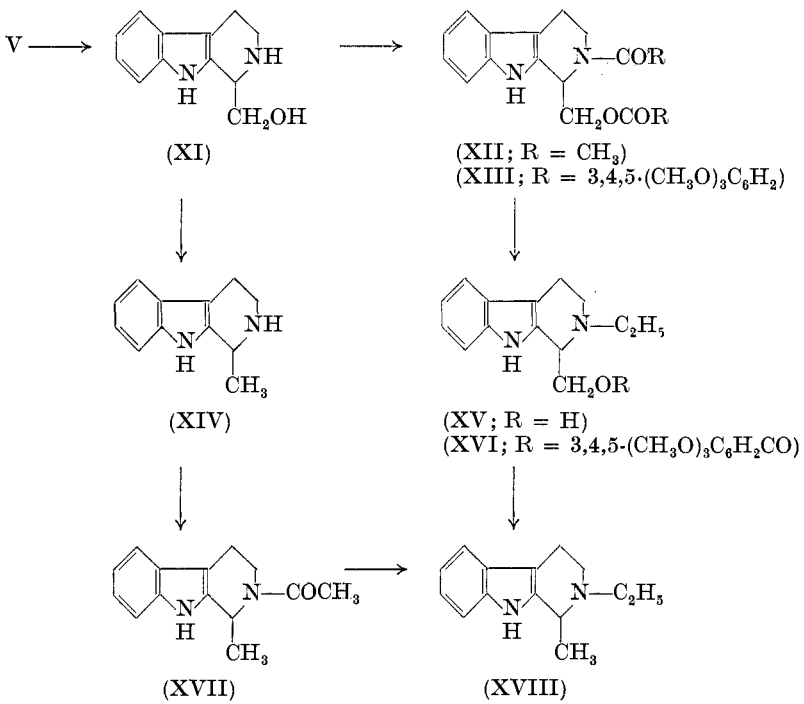
In an attempt to construct the fourth ring of the yohimbane skeleton, we performed the alkylation of ethyl ester V with γ-bromobutyronitrile. The nitrile ester IX thus obtained could not, however, be cyclized under the conditions of the Dieckmann cyclization; in an attempt to transform it into the diester by the action of ethanolic hydrogen chloride, the carboxyl function in position 1 was lost and 2-(3-carbethoxypropyl)-1,2,3,4-tetrahydronorharmane (X) was obtained.

Lithium aluminium hydride reduction of the ester V gave 1-hydroxymethyl-1,2,3,4-tetrahydronorharmane (XI). The preparation of this substance was first described by Dúbravková *et al.*[7, 8] and recently also by Spenser.[2] The Slovak authors[7, 8] used the Bischler–Napieralski cyclization of benzyloxyacetotryptamide followed by catalytic hydrogenation with simultaneous debenzylation; Spenser[2] condensed tryptamine with glycolaldehyde. However, our products greatly differ in the melting points of the base and the hydrochloride from that of the previous authors.[2, 7, 8] There is still no explanation of these discrepancies (see Experimental).

Acetic anhydride transformed our amino alcohol XI into the respective *O*,*N*-diacetyl derivative (XII). Similarly, the reaction of the amino alcohol XI with 3,4,5-trimethoxybenzoyl chloride in pyridine gave the *O*,*N*-bis(3,4,5-trimethoxybenzoyl) derivative (XIII) as the only product. Hydride reduction of compound XII gave 1-hydroxymethyl-2-ethyl-1,2,3,4-tetrahydronorharmane (XV), which was transformed by the action of 3,4,5-trimethoxybenzoyl chloride into the trimethoxybenzoate XVI.

The amorphous tosylate, obtained by the action of *p*-toluenesulphonyl chloride on the amino alcohol XI in pyridine, gave on lithium aluminium hydride reduction a base, identified in the form of a picrate (by comparing with the picrate of the authentic product[9, 10]) as 1,2,3,4-tetrahydroharmane (XIV). The *N*-acetyl

derivative (XVII) of this base yielded by a further hydride reduction 2-ethyl-1,2,3,4-tetrahydroharmane (XVIII). The same compound was obtained from the hydride reduction of the amorphous tosylate of the amino alcohol XV.



Pharmacology

The hydrochlorides of the amino alcohols XI and XV and of the trimethoxybenzoate XVI were tested for central depressant and hypotensive activities and compared with reserpine.

The central depressant effect was tested on the rotating-rod and evaluated in terms of the dose causing all mice in a group of 10 to fall down at one interval at least (the records were carried out at intervals of 30–60 min). Furthermore, potentiation of thiopental anaesthesia (40 mg/kg of thiopental i.v.) was tested in mice in terms of the dose which doubled the thiopental sleeping time.

The hypotensive effect was studied in dogs under chloralose-phenobarbital anaesthesia. Doses were determined which caused a fall of 20–30 per cent in the blood pressure. All compounds were administered intravenously in a solvent containing propylene glycol, benzyl alcohol and water. The results are summarized in Table I.

All three compounds in lower doses either did not influence the blood pressure at all or increased it moderately. The fall in blood pressure is only transitory (15–30 min). The results suggest that some inhibitory activity is caused by the compounds in the potentiation of thiopental anaesthesia, but inhibition of motor coordination, as studied by the rotating-rod test, is effected only by toxic doses; whereas the effects of reserpine in both tests appear on administration of approximately equal doses.

Table I. Pharmacological properties

Substance	LD_{50}, mg/kg	Rotating-rod, mg/kg	Potentiation of thiopental anaesthesia, mg/kg	Hypotensive effect, mg/kg
XI·HCl	25·0	>10	2·5	25·0
XV·HCl	30–40	>10	2·5	5·0[a]
XVI·HCl	25–30	>15	25·0	10·0
Reserpine	15–20	0·5–1·0	0·5	0·5–1·0

[a]The transitory fall was followed by a lasting rise of blood pressure.

Experimental*

1,2,3,4-Tetrahydronorharmane-1-carboxylic acid (IV). Method A—Reaction of tryptamine (I) with glyoxylic acid. A solution of tryptamine hydrochloride[11] (254 g) in water (2 l.) was cooled to 15° and added slowly to 6·5 l. of a stirred aqueous solution of

* Melting points are uncorrected. Analytical samples were dried for 5 h *in vacuo* (0·2 mm) at a suitable temperature (according to the melting point of the substance). Analyses are by Mrs. J. Komancová, Mrs. J. Schmidtová, Mrs. E. Dvořáková, Mrs. V. Šmídová, Miss M. Aixnerová and Mrs. E. Vaníčková of our Analytical Chemistry Laboratory. Infrared spectra are by Dr. B. Kakáč of our Department of Physical Chemistry and were measured with a Zeiss UR-10 spectrophotometer.

glyoxylic acid (96 g). Stirring and cooling was continued and the mixture was treated with a 50 per cent solution of sodium hydroxide until pH 4 was reached, which was optimal for the separation of the product. After standing overnight at room temperature, the product was filtered off, washed with water and dried; yield 247 g (89 per cent); m.p. 207–208° (d.). Infrared spectrum (Nujol): 1200, 1263, 1375–95, 1576, 1661, 3320 cm^{-1}.

Anal. Calcd. for $C_{12}H_{12}N_2O_2$: C, 66·65; H, 5·59; N, 12·96. Found: C, 66·50; H, 5·83; N, 12·94.

Method B—Alkaline saponification of the ethyl ester V. A solution of sodium hydroxide (1·5 g) in water (3 ml) and ethanol (15 ml) was refluxed for 6 h with the ethyl ester hydrochloride V (1·0 g). After evaporating to dryness, the residue was dissolved in water (25 ml), the solution was filtered with charcoal and the filtrate neutralized with 50 per cent acetic acid. The product which separated (0·45 g) was filtered off and purified by precipitation from an ammonia–water–ethanolic solution with acetic acid; m.p. 207–208° (d.). The spectrum is identical with that of the sample obtained by method A.

Anal. Calcd. for $C_{12}H_{12}N_2O_2$: C, 66·65; H, 4·59; N, 12·96. Found: C, 67·32; H, 5·75; N, 13·32.

Ethyl 1,2,3,4-tetrahydronorharmane-1-carboxylate (V). A suspension of the dried and well powdered acid IV (30 g) in absolute ethanol (600 ml) was saturated with stirring with dry hydrogen chloride and then refluxed for 2 h. From the clear solution thus obtained, 400 ml of ethanol was distilled off under reduced pressure and the product which separated was filtered off (10·05 g) and identified as 1,2,3,4-tetrahydronorharmane hydrochloride (VI), m.p. 282–284°. Further evaporation and cooling of the filtrate gave 22·0 g (57 per cent) of the ester *hydrochloride*, m.p. 164–165° (d.). For analysis it was recrystallized from ethanol acidified with a small quantity of hydrochloric acid.

Anal. Calcd. for $C_{14}H_{17}ClN_2O_2$: C, 59·90; H, 6·10; Cl, 12·62; N, 9·98. Found: C, 59·28; H, 6·57; Cl, 12·72; N, 9·92.

A solution of this hydrochloride and sodium picrate gave the *picrate*, yellow-orange needles, m.p. 164° (d.) (from 60 per cent ethanol).

Anal. Calcd. for $C_{20}H_{19}N_5O_5$: C, 50·74; H, 4·05; N, 14·80. Found: C, 50·93; H, 4·29; N, 14·92.

The free *base* was obtained from a solution of the hydrochloride and sodium hydroxide, by extraction with chloroform and evaporation of the solvent; yellowish needles from 60 per cent ethanol; m.p. 110–111°. Infrared spectrum ($CHCl_3$): 1032, 1185, 1253, 1744, 3475 cm^{-1}.

Anal. Calcd. for $C_{14}H_{16}N_2O_2$: C, 68·83; H, 6·60; N, 11·46. Found: C, 69·00; H, 6·79; N, 11·41.

1,2,3,4-Tetrahydronorharmane (VI).[5] *Method A*—From acid IV. A mixture of acid IV (1·5 g), ethanol (10 ml) and conc. hydrochloric acid (3 ml) was refluxed for 1 h. Partial evaporation of the dark solution thus obtained gave 0·72 g of a *hydrochloride*, m.p. 287–288° (Kofler block; crystallized from ethanol). Infrared spectrum (Nujol): 1060, 1160, 1205, 1246, 1578, 3185 cm^{-1}.

Anal. Calcd. for $C_{11}H_{13}ClN_2$: C, 63·31; H, 6·28; Cl, 17·00; N, 13·42. Found: C, 63·50; H, 6·20; Cl, 16·83; N, 13·29.

The filtrate gave by the action of sodium hydroxide 0·22 g free *base*;[5] long needles from ethanol, m.p. 202–203°.

Anal. Calcd. for $C_{11}H_{12}N_2$: C, 76·71; H, 7·02; N, 16·27. Found: C, 76·71; H, 7·23; N, 16·32.

Method B—From the ester V. A mixture of the hydrochloride of V (1·0 g), ethanol (20 ml) and 19 per cent hydrochloric acid (5 ml) was refluxed for 2 h. The residue (0·85 g), obtained by evaporation under reduced pressure, was dissolved in boiling ethanol (40 ml), the solution was decolorized with charcoal and partially evaporated. The hydrochloride of VI (0·30 g) separated, m.p. 287–289°, after crystallization from ethanol. Evaporation of the filtrate gave 0·50 g of the hydrochloride of the starting base V, m.p. 167–168° (d.).

2-Acetyl-1,2,3,4-tetrahydronorharmane (VII). Method A—from 1,2,3,4-tetrahydronorharmane (VI). A mixture of the base VI (4·0 g) and acetic anhydride (50 ml) was refluxed for 2 h and then evaporated *in vacuo* to dryness. The residue was stirred for 20 min with 5 per cent acetic acid (50 ml), filtered, washed with water and dried; yield 4·3 g, m.p. 237–238° (prisms from 70 per cent ethanol).

Anal. Calcd. for $C_{13}H_{14}N_2O$: C, 72·87; H, 6·59; N, 13·08. Found: C, 72·90; H, 6·84; N, 12·94.

Method B—from the acid IV. A mixture of acid IV (1·08 g)

and acetic anhydride (15 ml) was refluxed for 1 h and then evaporated to dryness under reduced pressure. The residue was dissolved in a small quantity of warm acetic acid and the solution precipitated with water; yield 650 mg, m.p. 236·5–238° (after crystallization from 70 per cent ethanol). A mixture with the substance obtained by method A showed the same melting point.

2-Ethyl-1,2,3,4-tetrahydronorharmane (VIII). A solution of VII (2·8 g) in tetrahydrofuran (250 ml) was dropped into a stirred suspension of lithium aluminium hydride (1·0 g) in the same solvent (20 ml) and the mixture was refluxed 2 h with stirring. After standing overnight it was decomposed by treatment with 20 per cent sodium hydroxide solution (5 ml), and the precipitate was filtered off and washed thoroughly with ether. The filtrates gave, on evaporation, 1·8 g of the new base, m.p. 137–138° after recrystallization from ethanol.

Anal. Calcd. for $C_{13}H_{16}N_2$: C, 77·96; H, 8·05; N, 13·99. Found: C, 77·68; H, 8·32; N, 14·00.

Hydrochloride, m.p. 227–229°, after recrystallization from ethanol.

Anal. Calcd. for $C_{13}H_{17}ClN_2$: C, 65·95; H, 7·24; Cl, 14·98; N, 11·83. Found: C, 66·07; H, 7·32; Cl, 14·82; N, 11·70.

Picrate, needles of m.p. 171–172°, after recrystallization from ethanol.

Anal. Calcd. for $C_{19}H_{19}N_5O_7$: C, 53·14; H, 4·46; N, 16·31. Found: C, 53·46; H, 4·67; N, 16·60.

Ethyl 2-(3-cyanopropyl)-1,2,3,4-tetrahydronorharmane-1-carboxylate (IX). A mixture of the ester V (7·0 g), methyl propyl ketone (15 ml), γ-bromobutyronitrile (4·7 g)[12, 13] and anhydrous potassium carbonate (4·0 g) was heated with stirring for 8 h on a water bath to 90–95°. After cooling, a mixture of ice and water (100 g) was added, the product extracted with ether, transferred into dilute hydrochloric acid and the solution of the hydrochloride purified by filtration with the aid of charcoal. The base was liberated with a 20 per cent solution of sodium carbonate, extracted with ether, the ethereal solution dried with potassium carbonate and evaporated; yield 5·72 g of crude base.

A sample of the base was transformed in the usual manner into the *picrate*, m.p. 152–153° (d.) (fine needles from 70 per cent ethanol).

Anal. Calcd. for $C_{24}H_{24}N_6O_9$: C, 53·33; H, 4·48; N, 15·55. Found: C, 53·06; H, 4·73; N, 15·61.

Hydrochloride, m.p. 78° (hygroscopic crystals from ethanol–ether).

Anal. Calcd. for $C_{18}H_{22}ClN_3O_2$: Cl, 10·19; N, 12·08. Found: Cl, 9·88; N, 12·06.

2-(3-Carbethoxypropyl)-1,2,3,4-tetrahydronorharmane (*X*). A solution of the esternitrile IX (5·18 g) in absolute ethanol (35 ml) was saturated with dry hydrogen chloride with external cooling and then refluxed for 7 h. It was then evaporated under reduced pressure and the ammonium chloride (0·78 g) which separated during the evaporation was filtered off. The dark residue was dissolved in water (50 ml), the base was liberated with a 20 per cent solution of sodium bicarbonate (20 ml) and extracted with ether. The solution was dried with potassium carbonate and evaporated. The residue (4·5 g) crystallized after trituration with a mixture of ether and petroleum ether; yield 1·42 g, m.p. 122·5–123° (recrystallized from 60 per cent ethanol).

Anal. Calcd. for $C_{17}H_{22}N_2O_2$: C, 71·30; H, 7·74; N, 9·78. Found: C, 71·61; H, 7·61; N, 10·03.

1-Hydroxymethyl-1,2,3,4-tetrahydronorharmane (*XI*). A solution of the ester V (20 g) in tetrahydrofuran (120 ml) was dropped into a suspension of lithium aluminium hydride (10 g) in tetrahydrofuran (200 ml) and absolute ether (200 ml), with stirring, and the mixture was refluxed for 3 h. After standing overnight, it was decomposed by means of a 20 per cent solution of sodium hydroxide (35 ml) and worked up in the usual manner. The crude product (19·6 g) was warmed with ethanol (15 ml) and filtered after cooling; yield 16·0 g, m.p. 152°, after recrystallization from ethanol.

Anal. Calcd. for $C_{12}H_{14}N_2O$: C, 71·26; H, 6·98; N, 13·85. Found: C, 71·24; H, 7·00; N, 13·84.

Dúbravková[7] and Ježo[8] gave for the base (not analyzed) the m.p. 213–215°; Spenser[2] described his product as a trihydrate and gave m.p. 138–139°, and 144–145° after distillation (still as a trihydrate!).

Picrate, yellow-brown short needles, m.p. 202° (d.) (from aqueous ethanol).

Anal. Calcd. for $C_{18}H_{17}N_5O_8$: C, 50·11; H, 3·97; N, 16·24. Found: C, 50·25; H, 4·25; N, 16·22.

Hydrochloride, m.p. 221–222° (d.) (from ethanol–ether); crystallized according to the analytical result with one-half mole of ethanol.

Anal. Calcd. for $C_{26}H_{36}Cl_2N_4O_3$: C, 59·65; H, 6·93; Cl, 13·55; N, 10·70. Found: C, 59·61; H, 6·72; Cl, 13·56; N, 10·62.

Dúbravková[7] and Ježo[8] gave for their hydrochloride (crystallized from ethanol, not analyzed) m.p. 216–218°; Spenser's hydrochloride[2] (described as a monohydrate), m.p. 215–216°, was also crystallized from ethanol.

1-Acetoxymethyl-2-acetyl-1,2,3,4-tetrahydronorharmane (*XII*). A mixture of the amino alcohol XI (1·0 g) and acetic anhydride (6 ml) was refluxed in an oil bath for 90 min and then evaporated to dryness *in vacuo*. The crystalline residue was mixed with warm water (10 ml), filtered off and washed with water; yield 1·20 g, m.p. 164–165° (needles from 80 per cent ethanol).

Anal. Calcd. for $C_{16}H_{18}N_2O_3$: C, 67·11; H, 6·34; N, 9·78; CH_3CO, 30·06. Found: C, 67·23; H, 6·60; N, 10·06; CH_3CO, 29·12.

1-(3,4,5-Trimethoxybenzoyloxymethyl)-2-(3,4,5-trimethoxybenzoyl)-1,2,3,4-tetrahydronorharmane (*XIII*). A solution of the amino alcohol XI (4·04 g) in absolute pyridine (40 ml) was treated with 3,4,5-trimethoxybenzoyl chloride (7·0 g), the mixture stirred and after dissolution left for 48 h at room temperature. After evaporating to dryness under reduced pressure, the residue was dissolved in chloroform, and the solution washed with dilute hydrochloric acid and then with a 10 per cent solution of sodium carbonate. After drying with sodium sulphate, the solution was evaporated, the residue dissolved in benzene and chromatographed on 120 g of neutral alumina. By means of benzene, 0·80 g of an oily product was eluted, which crystallized; m.p. 127–129° (from 90 per cent ethanol). The analysis indicates a sesquihydrate.

Anal. Calcd. for $C_{32}H_{34}N_2O_9 . 1·5\ H_2O$: C, 62·23; H, 6·04; OCH_3, 30·15. Found: C, 62·46; H, 5·95; OCH_3, 28·98.

1-Hydroxymethyl-2-ethyl-1,2,3,4-tetrahydronorharmane (*XV*). The diacetyl compound XII (12·0 g) was reduced with lithium aluminium hydride (9·0 g) in tetrahydrofuran (150 ml) and absolute ether (250 ml) by 4 h refluxing. After standing overnight, the mixture was decomposed with external cooling by a 20 per cent solution of sodium hydroxide (45 ml) and worked up similarly as in the foregoing examples. The crude product was obtained in a

yield of 9·5 g; the analytical sample was recrystallized from ethanol, m.p. 130–132°.

Anal. Calcd. for $C_{14}H_{18}N_2O$: C, 73·01; H, 7·88; N, 12·17. Found: C, 73·28; H, 8·14; N, 12·33.

Hydrochloride, m.p. 203–204° (from ethanol–ether).

Anal. Calcd. for $C_{14}H_{19}ClN_2O$: C, 63·03; H, 7·18; Cl, 13·29; N, 10·50. Found: C, 63·32; H, 7·18; Cl, 13·41; N, 10·52.

1-(3,4,5-Trimethoxybenzoyloxymethyl)-2-ethyl-1,2,3,4-tetrahydronorharmane (XVI). 3,4,5-Trimethoxybenzoyl chloride (3·7 g) was dissolved in a solution of the amino alcohol XV (3·5 g) in absolute pyridine (30 ml) and the solution was left at room temperature for 48 h. The *hydrochloride* which separated (5·1 g) was filtered off, washed with pyridine and water and the analytical sample recrystallized from ethanol; m.p. 216–218°.

Anal. Calcd. for $C_{24}H_{29}ClN_2O_5$: Cl, 7·69; N, 6·08; OCH_3, 20·20. Found: Cl, 7·52; N, 5·88; OCH_3, 20·23.

The base was set free from the hydrochloride in the usual manner; m.p. 136°, after recrystallization from 70 per cent acetone.

Anal. Calcd. for $C_{24}H_{28}N_2O_5$: C, 67·90; H, 6·65; N, 6·60; OCH_3, 21·93. Found: C, 68·16; H, 6·94; N, 6·50; OCH_3, 22·20.

1,2,3,4-Tetrahydroharmane (XIV). A solution of the amino alcohol XI (2·02 g) in absolute pyridine (10 ml) was treated with a solution of *p*-toluenesulphonyl chloride (3·8 g) in pyridine (8 ml) and the mixture stirred at room temperature for 4 h. It was then decomposed with absolute ethanol (10 ml) and chloroform (10 ml) and evaporated to dryness under reduced pressure. The residue was dissolved in a small volume of ethanol and the solution poured into water. The oil which separated was extracted with ether, the solution washed with N hydrochloric acid, then with a 5 per cent solution of sodium carbonate and water, dried with sodium sulphate and evaporated. The residue was dissolved in benzene and chromatographed on 50 g of alumina (act. II). The product (1·8 g) was eluted with benzene and 10 per cent methanol and without further purification used for further work.

A solution of this crude *p*-toluenesulphonyl derivative (1·4 g) in absolute tetrahydrofuran (50 ml) was dropped with stirring into a suspension of lithium aluminium hydride (1·5 g) in tetrahydrofuran (120 ml) and the mixture refluxed for 3 h. After

standing overnight, it was decomposed with a 20 per cent solution of sodium hydroxide (8 ml) and worked up as above. The crude base (240 mg) was transformed into the *picrate*, m.p. 223–224° (from ethanol).

Anal. Calcd. for $C_{18}H_{17}N_5O_7$: C, 52·05; H, 4·13; N, 16·86. Found: C, 52·24; H, 4·31; N, 16·80.

The base XIV was also prepared by a previously described procedure[9] from tryptamine and acetaldehyde and transformed in the usual manner into the picrate, m.p. 223–224° (d.) (from ethanol). In admixture with a sample obtained by the hydride reduction, it melted without depression.

Anal. Calcd. for $C_{18}H_{17}N_5O_7$: C, 52·05; H, 4·13; N, 16·86. Found: C, 52·30; H, 4·21; N, 16·33.

2-Acetyl-1,2,3,4-tetrahydroharmane (*XVII*). A mixture of 1,2,3,4-tetrahydroharmane (3·20 g) and acetic anhydride (20 ml) was refluxed for 90 min and after cooling evaporated to dryness *in vacuo*. The residue was dissolved in boiling ethanol (50 ml), and the solution was filtered, evaporated and brought to crystallization by cooling; yield 2·0 g, m.p. 205–206° (from ethanol).

Anal. Calcd. for $C_{14}H_{16}N_2O$: C, 73·65; H, 7·06; N, 12·27. Found: C, 73·55; H, 7·24; N, 12·24.

The same compound was obtained by a different method by Tatsui,[14] who did not mention its properties.

2-Ethyl-1,2,3,4-tetrahydroharmane (*XVIII*). *Method A*—From the acetyl derivative XVII. 2-Acetyl-1,2,3,4-tetrahydroharmane (XVII) (1·30 g) was reduced with lithium aluminium hydride (1·0 g) in tetrahydrofuran (75 ml) by refluxing for 2 h. After decomposition of the mixture with a 20 per cent solution of sodium hydroxide and the usual working up, 1·2 g of the crude base was obtained, transformed by treatment with an ethereal solution of hydrogen chloride to the *hydrochloride* (hemihydrate), m.p. unsharp 110–120° (from ethanol–ether).

Anal. Calcd. for $C_{14}H_{19}ClN_2.0{\cdot}5\ H_2O$: C, 64·73; H, 7·76; N, 10·78. Found: C, 64·53; H, 7·97; N, 10·40.

From the solution of the hydrochloride the *base* was set free by treatment with aqueous ammonia, m.p. 96–98° (needles from aqueous ethanol).

Anal. Calcd. for $C_{14}H_{18}N_2.0{\cdot}5\ C_2H_5OH$: C, 75·91; H, 8·92. Found: C, 76·38; H, 8·67.

Picrate, m.p. 203·5° (from aqueous ethanol). In a mixture with the picrate obtained by method B it melted without depression.

Method B—From the *p*-toluenesulphonate of the amino alcohol XV. A solution of XV (2·30 g) in absolute pyridine (10 ml) was treated with *p*-toluenesulphonyl chloride (2·0 g) in pyridine (5 ml) and the coloured mixture left overnight at room temperature. Ethanol (15 ml) and chloroform (15 ml) were then added and the mixture was evaporated to dryness. The residue was dissolved in aqueous ethanol and the solution treated with a 5 per cent solution of sodium hydroxide. The product (2·5 g) separated, was filtered off and used without identification for further work.

A solution of the crude *p*-toluenesulphonate (2·0 g) in absolute tetrahydrofuran (70 ml) was reduced with lithium aluminium hydride (1·0 g) by refluxing for 3 h. The mixture was then worked up as in the foregoing cases, giving 0·48 g of the amorphous base, transformed to the *picrate*, m.p. 202–203° (from ethanol).

Anal. Calcd. for $C_{20}H_{21}N_5O_7 . 0{\cdot}5\ H_2O$: C, 53·09; H, 4·90; N, 15·48. Found: C, 52·60; H, 4·94; N, 14·94.

Summary. By reaction of tryptamine with glyoxylic acid, 1,2,3,4-tetrahydronorharmane-1-carboxylic acid (IV) was obtained, which was used as a starting material for the preparation of a series of 1,2,3,4-tetrahydronorharmane derivatives. The chemistry of 1-hydroxymethyl-1,2,3,4-tetrahydronorharmane (XI) and its *N*-ethyl derivative (XV) was especially studied. These two amino alcohols and the 3,4,5-trimethoxybenzoate of the latter were tested for central depressant and hypotensive activities.

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