

29. *Synthetical Experiments in the Paraberine Group. Part II.*
Synthesis of 17-Keto-3 : 12-dimethoxy-6 : 15 : 16 : 17-tetrahydroparaberine.

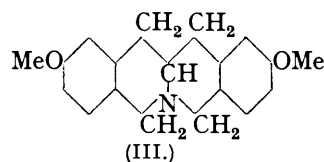
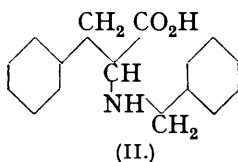
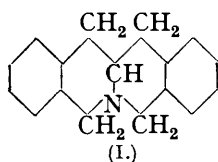
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To throw light on the preferential selection of angular structures by Nature, attempts were made to synthesise compounds of the type of paraberine having linear structures. The synthesis of tetrahydroparaberine (i) from dibenzylmethylamine by the action of formaldehyde or through its formyl derivative and (ii) from dl- β -phenyl-N-benzylalanine could not be achieved. Attempts were next made to prepare suitable dimethoxytetrahydroparaberines, which might be more amenable to synthesis owing to the presence of activating *p*-methoxy-groups.

β -3-Methoxyphenylalanine was synthesised, and its formyl derivative converted into N-formyl- β -3-methoxyphenyl-N-3'-methoxybenzylalanine by the action of 3-methoxybenzyl chloride. The formyl compound after hydrolysis was converted into 6-methoxy-2-3'-methoxybenzyl-1 : 2 : 3 : 4-tetrahydroisoquinoline-3-carboxylic acid by the action of formaldehyde. This acid, which was also synthesised by another method, on cyclisation with 70% sulphuric acid gave 17-keto-3 : 12-dimethoxy-6 : 15 : 16 : 17-tetrahydroparaberine in about 15% yield.

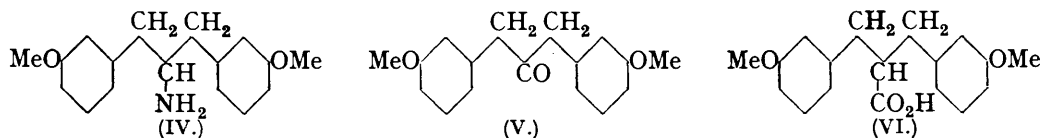
IN Part I (*J. Annamalai Univ.*, 1934, 3, 208), the synthesis of 8 : 17-diketo-6 : 17-dihydroparaberine was described. During the final ring closure, an unexpectedly high yield of about 60% was obtained, which was not quite in conformity with the ideas expressed by Campbell, Haworth, and Perkin (*J.*, 1926, 32) and was probably due to stereochemical differences introduced by the presence of a double bond. To throw further light on the problem of ease of formation of compounds having linear structures, the synthesis of tetrahydroparaberine (I) and its 2 : 12-(III) and 3 : 12-dimethoxy-derivatives was attempted.

The synthesis of (I) from dl- β -phenyl-N-benzylalanine (II) could not be achieved. The synthesis of 2 : 12-dimethoxytetrahydroparaberine (III) was next attempted because it might be facilitated by the presence of the activating *p*-methoxy-groups. The requisite

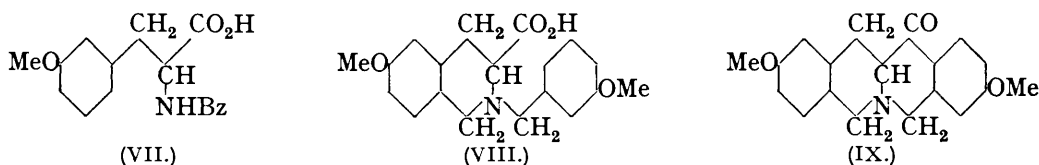


$\alpha\gamma$ -di-3-methoxyphenylisopropylamine (IV), however, was only obtained in poor yield : it was prepared by electrolytic reduction of the oxime of the ketone (V) and also by means

of the Hofmann reaction from the *amide* of the acid (VI). The main product of the latter reaction was a neutral nitrogenous substance, m. p. 135—136°, which is being further investigated by one of us (S. N. C.).



N-Benzoyl- β -3-methoxyphenylalanine (VII), required for the synthesis of 17-keto-3:12-dimethoxy-6:15:16:17-tetrahydroparaberine (IX), was prepared by hydrolysing the azlactone obtained from 3-methoxybenzaldehyde with dilute sodium hydroxide solution and reducing the product with sodium amalgam. Hydrolysis of (VII) with 10% hydrochloric acid gave β -3-methoxyphenylalanine, which was converted into 6-methoxy-2:3'-methoxybenzyl-1:2:3:4-tetrahydroisoquinoline-3-carboxylic acid (VIII) by two routes: (a) its formyl derivative was condensed with 3-methoxybenzyl chloride and the product, after the removal of the formyl group, was converted into (VIII) by means of formaldehyde; (b) it was converted into the isoquinoline derivative by means of formaldehyde and the 3-methoxybenzyl group then introduced.



The acid (VIII) was cyclised by means of sulphuric acid to 17-keto-3:12-dimethoxy-6:15:16:17-tetrahydroparaberine (IX), which was isolated as the *semicarbazone* in a yield of about 15%.

The more difficult formation of (IX) compared with the ease of formation of the corresponding dimethoxytetrahydroprotoberberine (compare Chakravarti, Haworth, and Perkin, J., 1927, 2278; 1929, 196) points to the correctness of the conclusion of Campbell, Haworth, and Perkin (*loc. cit.*), although the types of final cyclisation involved are different and not strictly comparable.

The synthesis of 2:12-dimethoxytetrahydroparaberine is reserved for a future communication.

EXPERIMENTAL.

dl-*N*-Formyl- β -phenyl-*N*-benzylalanine.—Benzyl chloride (4 g.) was added to a solution of *dl*-*N*-formyl- β -phenylalanine (5 g.) (Fischer and Schoeller, *Annalen*, 1907, 357, 2) in methyl alcohol (20 c.c.), and the mixture refluxed for 4 hours on the water-bath. The alcohol was then removed, and the residue stirred with a little benzene. The *dl*-*N*-formyl- β -phenyl-*N*-benzylalanine obtained, after crystallising twice from methyl alcohol-ethyl acetate, formed clusters of colourless prisms (4.2 g.), m. p. 233° (Found: C, 72.1; H, 6.3. $C_{17}H_{17}O_3N$ requires C, 72.1; H, 6.0%), easily soluble in water and alcohol, sparingly soluble in hot benzene and ethyl acetate, and almost insoluble in cold benzene and light petroleum.

dl- β -Phenyl-*N*-benzylalanine.—The preceding formyl derivative (3 g.) and 10% hydrochloric acid (100 c.c.) were heated together under reflux for 4 hours and then evaporated to dryness on a steam-bath. A solution of the residue in the minimum amount of water was neutralised with ammonia and concentrated; *dl*- β -phenyl-*N*-benzylalanine, m. p. 222—225° (decomp.), separated (Found: N, 5.4. $C_{16}H_{17}O_2N$ requires N, 5.5%). It was readily soluble in water, but only very sparingly in the other usual organic solvents, and could be recrystallised from dilute alcohol. Attempts to convert it, by the action of (1) methylal and hydrochloric acid and (2) 40% formaldehyde in barium hydroxide solution, into the corresponding isoquinoline derivative in good yield were unsuccessful.

3-Methoxyphenylacetone nitrile.—An alcoholic solution of 3-methoxybenzyl bromide (20.1 g.), prepared from hydrogen bromide and a benzene solution of the alcohol, and potassium cyanide (6.9 g.) were boiled together for 6 hours, the nitrile (15.2 g.), b. p. 160—165°/40 mm., being formed.

3:3'-Dimethoxydibenzyl Ketone (V).—(i) The reaction between 3-methoxybenzyl bromide

(20.1 g.) and magnesium (2.43 g.) in dry ether (60 c.c.) was started by addition of a little methyl iodide or iodine, and the mixture finally heated for 20 minutes on the water-bath with vigorous shaking. 3-Methoxyphenylacetonitrile (14.8 g.), dissolved in ether (50 c.c.), was gradually added, and the whole heated on the water-bath for 30 minutes and left overnight. The semi-solid mass was decomposed with dilute sulphuric acid and the products were isolated with ether and distilled under 10 mm., the following fractions being obtained: (a) Below 120°, 4.3 g., containing mainly the unchanged nitrile; (b) at 120—150°, 11.9 g., containing mainly the ketone (V), b. p. 135—145°/10 mm. after repeated distillation; (c) at 150—170°, 4.5 g.; (d) above 170°, 6.2 g. From fractions (c) and (d), by trituration with alcohol, a substance, m. p. 61—62°, was obtained which appeared to be 3 : 3'-dimethoxydibenzyl and could be readily crystallised from alcohol (Found: C, 79.3; H, 7.5. $C_{16}H_{18}O_2$ requires C, 79.4; H, 7.4%).

(ii) 3-Methoxyphenylacetic acid (1.66 g.), prepared by the hydrolysis of 3-methoxyphenylacetonitrile with methyl-alcoholic potash, was dissolved in alcohol (5 c.c.) and neutralised with 20% sodium hydroxide solution, phenolphthalein being used as the indicator. Thorium nitrate (1.38 g.) in water (10 c.c.) was stirred in, and the thorium 3-methoxyphenylacetate collected, washed with a little alcohol, and dried at 150° for 1 hour. The salt (11 g.) on destructive distillation gave 2.5 g. of an oil, from which a small quantity of 3 : 3'-dimethoxydibenzyl, m. p. 61—62°, separated on trituration with alcohol. The alcoholic filtrate contained mainly the ketone (V) [*semicarbazone*, m. p. 133° (Found: N, 13.0. $C_{15}H_{21}O_3N_3$ requires N, 12.8%); oxime, an oil].

The oxime (4.5 g.), when reduced electrolytically (cf. Kaplansky, *Ber.*, 1927, 60, 1842), gave a very small amount of a base, which yielded a hydrochloride (0.15 g.), m. p. 169—170°, and formed an acetyl derivative, m. p. 94°, the analytical figures of which correspond to those of the *diacetyl* derivative of $\alpha\gamma$ -di-3-methoxyphenylisopropylamine (Found: C, 70.8; H, 7.3. $C_{21}H_{25}O_4N$ requires C, 71.0; H, 7.0%).

Di-3-methoxybenzylacetic Acid (VI).—Ethyl sodiomalonate (sodium 4.6 g., absolute alcohol 75 c.c., and ethyl malonate 33 g.) was heated on the water-bath with 3-methoxybenzyl bromide (41 g.) for 3 hours, the alcohol removed, water added, and the product isolated with ether, treated with sodium (4.6 g.) dissolved in alcohol (75 c.c.), and refluxed with 3-methoxybenzyl bromide (41 g.) for 3 hours. The alcohol was then removed, and the product isolated with ether and distilled. The fraction (35 g.), b. p. 190—192°/16 mm., on hydrolysis with aqueous alcoholic potassium hydroxide yielded *di-3-methoxybenzylmalonic acid*, which crystallised from alcohol or chloroform in prisms, m. p. 185—186° (Found: C, 65.9; H, 5.7. $C_{19}H_{20}O_6$ requires C, 66.3; H, 5.8%), readily soluble in alcohol and chloroform, sparingly soluble in water, benzene and ether, and almost insoluble in light petroleum. During the hydrolysis some *di-3-methoxybenzylacetic acid* (VI), m. p. 105°, was also formed, which was readily separated from the malonic acid by means of benzene, in which it was much more soluble.

The acid (VI), obtained in quantitative yield by heating the malonic acid at 210° for 15 minutes, crystallised from water in colourless prismatic needles, m. p. 105°. It formed a sparingly soluble *barium* salt (Found: Ba, 18.4. $C_9H_8O_4Ba$ requires Ba, 18.8%). Its ethyl ester had b. p. 150—153°/40 mm.

Di-3-methoxybenzylacetamide, prepared from the ester in the usual manner, crystallised from dilute methyl alcohol in long colourless needles, m. p. 102° (Found: N, 4.8. $C_{18}H_{21}O_3N$ requires N, 4.7%).

α -Benzamido-3-methoxycinnamic Acid.—The finely powdered azlactone (15 g., prepared from 3-methoxybenzaldehyde and hippuric acid) was heated with sodium hydroxide solution (3.3 g. in 1530 c.c. of water) on the steam-bath for 2—3 hours and the hot solution obtained was acidified. α -Benzamido-3-methoxycinnamic acid (14.2 g.), m. p. 178° (decomp.), separated in colourless crystals on cooling (Found: C, 68.6; H, 5.2; N, 4.4. $C_{17}H_{15}O_4N$ requires C, 68.7; H, 5.0; N, 4.7%). The acid was readily soluble in alcohol and chloroform, moderately soluble in hot benzene, and almost insoluble in light petroleum and cold water, and gave a sparingly soluble copper salt.

N-Benzoyl- β -3-methoxyphenylalanine (VII).—The above cinnamic acid (50 g.) was suspended in water (500 c.c.), and 2% sodium amalgam (520 g.) stirred in during 7 hours. When the solution was acidified, the *alanine* (VII), m. p. 144°, was precipitated; it was crystallised twice from methyl alcohol (Found: C, 68.0; H, 5.8; N, 4.7. $C_{17}H_{17}O_4N$ requires C, 68.2; H, 5.7; N, 4.7%).

β -3-Methoxyphenylalanine.—The alanine (VII) (10 g.) was heated under reflux with 10% hydrochloric acid (1250 c.c.) for 8 hours and the clear solution was concentrated to a small

volume, repeatedly extracted with benzene, and evaporated to dryness. The residue was dissolved in the minimum amount of water and neutralised with ammonia. β -3-Methoxyphenylalanine slowly separated; it crystallised from dilute alcohol in needles, m. p. 215° (decomp.) (Found: C, 61.4; H, 6.9; N, 7.0. $C_{10}H_{13}O_3N$ requires C, 61.5; H, 6.7; N, 7.2%). Yield, more than 90%.

N-Formyl- β -3-methoxyphenyl-N-3'-methoxybenzylalanine.— β -3-Methoxyphenylalanine (5 g.) and formic acid (3 c.c.) were warmed gently for 1 hour on the water-bath, and the excess of formic acid removed under diminished pressure. The residual semi-solid was heated for 2 hours on the steam-bath and crystallised from ethyl acetate, the formyl derivative being obtained in small prisms, m. p. 156°, readily soluble in hot water and alcohol and only sparingly in benzene. This (2 g.) and 3-methoxybenzyl chloride (2.5 g.) were refluxed together for 6 hours in methyl-alcoholic solution. The alcohol was removed, the residue stirred with benzene, and the solid which separated was crystallised from ethyl acetate, *N-formyl- β -3-methoxyphenyl-N-3'-methoxybenzylalanine* being obtained in plates, m. p. 186—188° (Found: C, 66.5; H, 6.2. $C_{19}H_{21}O_5N$ requires C, 66.5; H, 6.1%), very sparingly soluble in acetone and benzene, moderately soluble in ethyl acetate and water, and easily soluble in alcohol.

β -3-Methoxyphenyl-N-3'-methoxybenzylalanine.—The preceding formyl compound (1 g.) and 10% hydrochloric acid (100 c.c.) were heated under reflux for 4 hours, and the solution evaporated to dryness. The residue was dissolved in the minimum amount of water, and the solution made just alkaline with ammonia and concentrated on the water-bath; *β -3-methoxyphenyl-N-3'-methoxybenzylalanine*, m. p. 233°, which separated, was crystallised from hot water (Found: C, 68.5; H, 6.8. $C_{18}H_{21}O_4N$ requires C, 68.6; H, 6.7%).

6-Methoxy-2-3'-methoxybenzyl-1 : 2 : 3 : 4-tetrahydroisoquinoline-3-carboxylic Acid (VIII).—The above alanine (1 g.), dissolved in a slight excess of barium hydroxide solution, was treated with formaldehyde (5 c.c. of 40%) with vigorous shaking. The precipitate was dissolved in 25% hydrochloric acid (30 c.c.), and the solution evaporated to dryness on a steam-bath. The residue was made just alkaline with ammonia and boiled to remove the excess. The brown precipitate obtained was extracted several times with water, and the combined extracts concentrated to a small volume; the acid (VIII), m. p. 223—225°, then separated. Its barium salt was sparingly soluble and crystallised well (Found: Ba, 17.8. $C_{38}H_{40}O_8N_2Ba$ requires Ba, 17.5%).

6-Methoxy-1 : 2 : 3 : 4-tetrahydroisoquinoline-3-carboxylic Acid.— β -3-Methoxyphenylalanine (3 g.), dissolved in barium hydroxide solution, was shaken with 40% formaldehyde (8 c.c.) and the precipitate was collected, washed several times with methyl alcohol, and warmed with concentrated hydrochloric acid (40 c.c.) on the steam-bath for 25 minutes. The clear solution was evaporated almost to dryness, and the residue just neutralised with ammonia; *6-methoxy-1 : 2 : 3 : 4-tetrahydroisoquinoline-3-carboxylic acid* separated as a pale brown powder which, recrystallised from water, formed colourless plates, m. p. 263—264° (decomp.) (Found: N, 7.0. $C_{11}H_{13}O_3N$ requires N, 6.8%). When heated with 3-methoxybenzyl chloride and sodium acetate in alcoholic solution for 5 hours, it gave 6-methoxy-*N*-3'-methoxybenzyl-1 : 2 : 3 : 4-tetrahydroisoquinoline-3-carboxylic acid (VIII).

Semicarbazone of 17-Keto-3 : 12-dimethoxy-6 : 15 : 16 : 17-tetrahydroparaberine.—The acid (VIII) (2 g.) was warmed on the water-bath for 20 minutes with 70% sulphuric acid (7 c.c.), the product poured into cold water, and the filtered solution basified and extracted with chloroform (five times). Evaporation of the dried extract left a residue, which was converted into the *semicarbazone*; this separated from methyl alcohol as a colourless crystalline powder (0.31 g.), m. p. 250—252° (decomp.) (Found: N, 15.5. $C_{20}H_{22}O_3N_4$ requires N, 15.3%).