1262. *The Stereochemistry of the Tropane Alkaloids. Part XVII.* Correlation of Valeroidine with* S(−)-*Methoxysuccinic Acid and of Mono- and Di-tigloyltropane-*3,6-*diol with its* R(+)-*Antimer*

By Gábor Fodor and Ferenc Sóti

The configuration of (−)-valeroidine (I) has been correlated with (+)-6-methoxytropinone (II), which has been degraded to *S*(−)-methoxysuccinic acid (IV). Consequently, the alkamine of valeroidine has the 3*S* : 6*S* absolute configuration, the opposite 3*R* : 6*R* being true for the alkamine of natural mono- and di-tigloytropanediols.

Valeroidine (I) [1] is derived from (−)-tropane-3α,6β-diol (VIII) while its antimer is the alkamine of 6β-tigloyloxy-3α-hydroxytropane [2] and of 3α,6β-ditigloyloxytropane.[3]

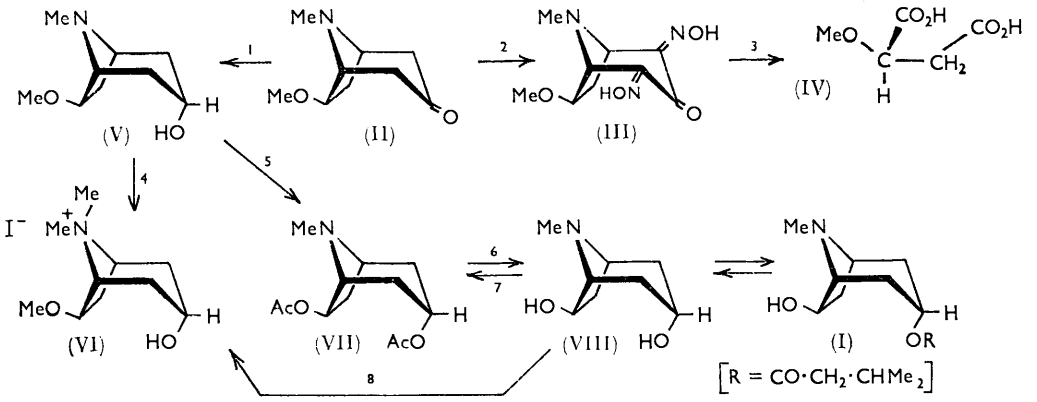
The relative configurations of the hydroxyl groups in valeroidine were established by chemical methods; [4-6] the absolute configuration was deduced tentatively on the basis of Hudson's lactone rule [7,8] during cyclisation of *N*(−)-ethoxycarbonylmethyl-3α,6β-dihydroxytropanium iodide to the (+)-lactone; in consequence, the 3*R* : 6*R* configuration was ascribed [9] to the (−)-diol and hence the 3*S* : 6*S* structure to the (+)-enantiomer. More rigorous proof of configuration, here described, calls for reversal of these assignments, and shows Hudson's empirical lactone rule to have been inapplicable in this series, as for γ-allonolactone.[10]

Stepwise degradation of 6-methoxytropinone, *e.g.*, to 4-oxoproline [11] failed. Therefore 6-methoxytropan-3-one (II) [12] was nitrosated in an analogous way to tropinone [13] into the 2,4-dioximino-derivative and this was refluxed with 65% nitric acid. Methoxysuccinic acid contaminated with some oxalic acid was obtained in 20% yield, m. p. 104—106° alone and mixed with a specimen prepared by methylation from (±)-malic acid with subsequent hydrolysis of the ester. Based upon this success, 6-methoxytropan-3-one was resolved by (+)-tartaric acid, and the dextrorotatory derivative (II) converted into the dioximino-ketone hydrochloride (III) [better yields have been achieved when nitrosating the tartrate of the (+)-ketone] and this, in turn, was oxidised by nitric acid to give *S*(−)-methoxysuccinic acid (IV) obtained also from *S*(−)-malic acid by methylation.[14] As the next step the (+)-ketone (II) was hydrogenated catalytically to (−)-6-methoxytropine (V). Correlation of this with (−)-tropane-3α,6β-diol (VIII) was achieved in two steps: (i) Acetobromolysis of this methoxy-compound gave methyl bromide and (−)-3α,6β-diacetoxytropane (VII) without affecting the C–O bond at the asymmetric centre at C-6. This (−)-3,6-diacetoxytropane proved to be identical in every respect with the product

* Part XVI, C. H. MacGillavry and G. Fodor, *J.*, 1964, 597. A preliminary account of this work has been given in *Tetrahedron Letters*, 1964, 1917.

[1] G. Barger, W. F. Martin, and W. Mitchell, *J.*, 1937, 1820; W. Mitchell and E. M. Trautner, *J.*, 1947, 1330.
[2] W. C. Evans and W. J. Griffin, *J.*, 1963, 4348.
[3] W. C. Evans and M. Wellendorf, *J.*, 1958, 1991; 1959, 1406.
[4] G. Fodor, Ö. Kovács, and L. Mészáros, *Research* (*London*), 1952, 534; *J.*, 1953, 2341.
[5] G. Fodor, J. Tóth, and I. Vinze, *Helv. Chim. Acta*, 1954, **37**, 907.
[6] G. Fodor, J. Tóth, I. Koczor, and I. Vincze, *Chem. and Ind.*, 1955, 1260; P. Dobó, G. Fodor, G. Janzsó, I. Koczor, J. Tóth, and I. Vinze, *J.*, 1959, 3461.
[7] C. S. Hudson, *J. Amer. Chem. Soc.*, 1909, **31**, 66; 1910, **32**, 338.
[8] B. Witkop *Experientia*, 1956, **12**, 372.
[9] G. Fodor, I. Vincze, and J. Tóth, *Experientia*, 1957, **13**, 183; *J.*, 1961, 3219.
[10] W. W. Pigman, R. M. Goepp, jun., "Chemistry of the Carbohydrates," Academic Press, New York, 1948, p. 296.
[11] A. A. Patchett and B. Witkop, *J. Amer. Chem. Soc.*, 1957, **79**, 185.
[12] R. Willstätter, *Ber.*, 1897, **30**, 2679.
[13] A. Stoll, E. Jucker, and A. Lindenmann, *Helv. Chim. Acta*, 1954, **37**, 495.
[14] T. Purdie and W. Marshall, *J.*, 1893, **63**, 217.

we obtained by acetylation from the alkamine of natural valeroidine. (ii) Deacetylation of the diacetate gave pure (−)-3α,6β-tropanediol. Furthermore, (−)-tropane-3α,6β-diol (VIII) was methylated with methyl sulphate on O-6 and N and the methosulphate, in turn, converted into the methiodide (VI) of (−)-6-methoxytropan-3α-ol, identical with a specimen obtained on quaternising (−)-6-methoxytropan-3α-ol (V).



This provides unequivocal evidence for the relative configuration of the methoxy-group as β in (+)-6-methoxytropan-3-one and it has the absolute configuration *S*. Consequently, (−)-tropane-3,6-diol (VIII) from Javanese Coca leaves and also from valeroidine has the *S* configuration at C-6. Hence, all these compounds possess 3*S* : 6*S* configuration, quite opposite to those deduced in previous investigations [9] by adopting Hudson's lactone rule. Thus, the 3*R* : 6*R* configuration is valid for the dextrorotatory alkamine both of 6β-tigloyloxytropan-3α-ol from leaves of *Datura cornigera* and of 3α,6β-ditigloyloxytropane from *Datura ferox*, *D. innoxia*, and *D. stramonium*.

Experimental

Resolution of 6-Methoxytropan-3-one.—6-Methoxytropan-3-one (31·13 g.; 0·184 mole), prepared on the lines of Stoll, Jucker, and Lindenmann,[12] and D-tartaric acid (27·6 g.; 0·184 mole) were dissolved in 98 ml. of 90% ethanol by warming gently. After 4 days at 25° the first crop (10·25 g.) had m. p. 126—129°; $[\alpha]_D^{25}$ +23·05° (*c* 2, in H_2O) and then recrystallised from 96% ethanol (51 ml.) giving a pure tartrate of the (+)-base (8·96 g.), m. p. 128·5—131·5°; $[\alpha]_D^{30}$ +23·93° (*c* 2, in H_2O) (Found: C, 48·95, 48·8; H, 6·7, 6·65; N, 4·65. $C_{13}H_{21}NO_8$ requires C, 48·9; H, 6·6; N, 4·4%).

(+)-6β-*Methoxytropan-3-one* (II).—The *tartrate* (7·98 g.; 0·025 mole) dissolved in water (40 ml.) was alkalised by sodium hydroxide (8 g.) in water (40 ml.) then saturated with potassium carbonate (20 g.) and the whole extracted continuously for 6 hr. with ether.

The oily residue of the ethereal extract (4·01 g.) was distilled in a vacuum, b. p. 66—68°/0·2 mm. (3·47 g.; 82%), giving the colourless *keto-base* which solidified on standing; m. p. 43—45°; $[\alpha]_D^{22·5}$ +23·09° (*c* 2, in H_2O) (Found: C, 65·0, 65·1; H, 8·6, 9·5; N, 8·7, 8·6. $C_9H_{15}NO_2$ requires C, 63·9; H, 8·9; N, 8·3%).

(+)-6β-*Methoxy*-2,4-*dioximinotropan*-3-*one* (III) *Hydrochloride.*—(i) *From the* (+)-*ketone.* (+)-6-Methoxytropan-3-one (1·71 g.; 0·01 mole) was mixed with freshly distilled n-butyl nitrite (2·27 ml.; 0·02 mole) and glacial acetic acid (2 ml.) and the whole was then added drop by drop during 5 min. with stirring and cooling with ice to glacial acetic acid (made completely anhydrous with acetic anhydride) (8 ml.) saturated previously with HCl at 0°. Stirring was stopped after 4 hr. and the mixture left overnight. The pale yellow solid which separated was filtered off, washed with a few drops of acetic acid and then with cold dry ethanol, and dried to give the *hydrochloride* (1·55 g.; 59%; $[\alpha]_D^{20}$ +0·66° (*c* 2, in H_2O).

(ii) *From the tartrate.* The *dextrorotatory* tartrate (10·88 g.; 0·0341 mole) and n-butyl

nitrite (7·74 ml.; 0·0682 mole) were dissolved in glacial acetic acid (30 ml.) and added during 10 min. at 0°c to glacial acetic acid (30 ml.) which had been previously saturated with HCl. Stirring was continued for further 3½ hr., then the reaction mixture was kept overnight at 25°. The oximino-ketone hydrochloride (7·04 g.; 78·5%) was washed with acetic acid and dried in a desiccator; $[\alpha]_D^{20}$ +0·86° (*c* 2, H_2O). For microanalysis a sample was washed three times with a total of a tenfold volume of hot anhydrous ethanol and dried (Found: N, 15·2, 15·2; Cl^-, 13·1, 13·1. $C_9H_{14}ClN_3O_4$ requires N, 15·9; Cl^-, 13·45%).

Degradation of (+)-6β-*Methoxy*-2,4-*dioximinotropan*-3-*one* (III) *to* S(−)-*Methoxysuccinic Acid* (IV).—(+)-2,4-Dioximino-6β-methoxytropan-3-one hydrochloride (1·056 g.; 0·004 mole) was dissolved in 65% nitric acid (13·84 ml.; 0·2 mole). The solution became brown and its temperature rose to 50° while gas was evolved. During 1½ hr. the mixture was heated gradually 127—129° and kept thereat for 1½ hr. It was then colourless. After cooling to 20°, K_2CO_3 (10 g.) was added with sufficient water to keep the solution just homogeneous. The solution was then extracted for 24 hr. continuously with ether. The yellow oily residue (0·341 g.) was then refluxed with dichloroethane (17 ml.), that extract cooled down, filtered, and evaporated. The residual gum (0·197 g.) was taken up in hot dry benzene (100 ml.); the solution when kept at +10° for 2 days deposited crystals (0·074 g.), m. p. 73—85°, containing some oxalic acid. The latter was removed by sublimation at 50—60°/1 mm. and identified as benzylamine oxalate.[15] The non-sublimed part (0·067 g.; 11%) melted at 85—90° alone and in admixture with authentic *S*(−)-methoxysuccinic acid; $[\alpha]_D^{29}$ −30·73° (*c* 2, H_2O).

Methyl S(−)-*Methoxysuccinate*.—*S*(−)-Malic acid (13·54 g.; 0·101 mole) {m. p. 99·5—102·5°; $[\alpha]_D$ −2·46° (*c* 2, in H_2O)} was dissolved in water (100 ml.), then concentrated ammonium hydroxide (23·4 ml.; 0·2 mole) and a solution of silver nitrate (33·98 g.; 0·2 mole) in water (50 ml.) were added.

Silver malate (28·95 g.; 0·0832 mole) which precipitated was filtered off, washed with water, and dried at 90° in a vacuum. It was methylated by refluxing with excess (100 ml.) of methyl iodide for 4 hr. with stirring. Then silver oxide (38·6 g.; 0·1664 mole) was added with continued stirring and refluxing for further 5 hr. The excess of methyl iodide was distilled off, and the residue extracted several times with dry ether in the cold, the combined extracts were dried (Na_2SO_4) and evaporated to give an oily residue (14·14 g.). Distillation (10 mm.) gave methyl *S*(−)-methoxysuccinate (6·53 g.; 37%), b. p. 102—103°/10 mm. $[\alpha]_D^{28}$ −50·09° (*c* 3·27, in acetone). Lardon and Reichstein [16] reported b. p. 108—112°/11 mm. and $[\alpha]_D^{16}$ −47·8° (*c* 3, in acetone).

S(−)-*Methoxysuccinic Acid* (IV).—The *methyl ester* (4·40 g.; 0·025 mole) was heated with 1·25N-NaOH (80 ml.) for 1 hr. in a thermostat at 100° ± 1°. After cooling the solution was acidified with orthophosphoric acid (12·5 ml.) and then extracted continuously with ether for 24 hr. The residue of the extraction consisted of colourless crystals (3·22 g.), which were recrystallised from 1,2-dichloroethane (160 ml.), to give pure (2·47; 67%) methoxysuccinic acid, m. p. 87—90°; $[\alpha]_D^{28}$ −33·84° (*c* 2, in H_2O). Purdie and Marshall [14] reported m. p. 89° and $[\alpha]_D^{18}$ −32·94° (*c* 10·4700, in H_2O) (Found: C, 40·9, 41·0; H, 5·55, 5·6. Calc. for $C_5H_8O_5$: C, 40·5; H, 5·4%).

(−)-6β-*Methoxytropin* (V).—The (+)-*ketone tartrate* (III) (6·386 g.; 0·02 mole) was dissolved in a mixture of 96% ethanol (200 ml.) and water (100 ml.) and the solution hydrogenated over 4 g. of Raney nickel in a rotary autoclave at 58—60°/70—75 atm. The filtered solution was concentrated in a vacuum to 30 ml. and NaOH (4 g.) and K_2CO_3 (20 g.) added. It was extracted continuously with ether for 70 hr. The residue of the extract, a colourless oil (3·125 g.), was distilled to give a hygroscopic solid (2·82 g.; 82·5%), b. p. 93—94°/0·5 mm.; $[\alpha]_D^{20}$ −10·38° (*c* 1·95, in H_2O). The *racemate* of (V) was described [13] as a viscous oil.

Methiodide (VI).—Prepared from the base with CH_3I in acetone and recrystallised from anhydrous ethanol, it had m. p. 208—209°; $[\alpha]_D^{28}$ +6·52° (*c* 2, in H_2O) (Found: N, 4·7, 4·6; I, 40·8, 40·9. $C_{10}H_{20}INO_2$ requires N, 4·5; I, 40·5%).

Acetobromolysis of (V) *to* 3,6-*Diacetoxytropane* (VII).—(−)-6β-Methoxytropane (0·615 g.; 0·0036 mole) was dissolved in anhydrous ethanol (2 ml.) and converted into the *hydrobromide* by adding 4·274% HBr in dry ethanol (6·82 ml.; 0·0036 mole) and then evaporating. The crystalline residue was dissolved in acetyl bromide (2·7 ml.; 0·036 mole) and heated to a sealed

[15] R. Boudet, *Bull. Soc. chim. France*, 1948, 392.
[16] A. Lardon and T. Reichstein, *Helv. Chim. Acta*, 1949, **32**, 2003.

glass tube to 110—120° for 4 hr. After cooling the whole was poured on ice (30 g.) the K_2CO_3 (23 g.) added, and the whole extracted with ether continuously for 18 hr. The ethereal extract after drying (Na_2SO_4) and evaporating was an oil (0·683 g.) which, distilled *in vacuo*, gave (−)-3α,6β-diacetoxytropane (0·601 g.; 69%), b. p. 80—83°/0·07 mm.; $[\alpha]_D^{24}$ −16·06° (*c* 2·06, in EtOH); n_D^{20} 1·4772. Its infrared spectrum (Perkin-Elmer Infracord) was identical with that of an authentic (−)-3α,6β-diacetoxytropane prepared by acetylation from (−)-tropan-3α-6β-diol [4,9,17] (see below) (Found: C, 60·3, 60·1; H, 8·2, 8·4. Calc. for $C_{12}H_{19}NO_4$: C, 59·7; H, 7·9%).

Hydrolysis of (VII) *to the Diol* (VIII).—The *diacetate* (0·180 g.; 0·75 mmole) was refluxed with N-HBr (2 ml.; 0·002 mole) for 1 hr. then evaporated to dryness. The foamy residue, *i.e.*, the hydrobromide, was converted into the *base* as follows. First K_2CO_3 (0·3 g.) and water (0·2 ml.) were mixed and the paste added to the hydrobromide. Then dry alcohol was driven off twice to get the base anhydrous. The latter was extracted 8 times with a total of 40 ml. of hot dichloroethane. On cooling, colourless crystals of (−)-3α,6β-tropanediol separated (0·068 g.; 58%), m. p. 211° alone and in admixture with an authentic specimen.[17] The infrared spectra were also identical; $[\alpha]_D^{27}$ −17·41° (*c* 1·11, in EtOH).

Acetylation of (−)-*Tropane*-3α,6β-*diol* (VIII) *to* (VII).—The (−)-tropanediol (0·706 g.; 4·5 mmole) of $[\alpha]_D^{23}$ −20·5° (*c* 1·09, in ethanol) was refluxed with acetic anhydride (10 ml.) for 3·5 hr. After cooling, water (2 ml.) was added to decompose excess of anhydride and the solution evaporated to dryness. The amorphous residue was dissolved in the minimum of water, alkalised with K_2CO_3 (7 g.) then extracted continuously with ether for 20 hr. and the extract evaporated. The solvent was removed to give an oil (VII) (1·049 g.), b. p. 109—114°/0·5 mm., yield 0·74 g. (68%); $[\alpha]_D^{23}$ −16·82° (*c* 1·97, in EtOH); n_D^{20} 1·4739 (Found: N, 6·2. Calc. for $C_{12}H_{19}NO_4$: N, 5·8%).

Selective Methylation of (−)-3α,6β-*Tropanediol* (VIII).—The (−)-tropanediol (0·471 g.; 0·003 mole) of $[\alpha]_D^{17}$ −20·9° (*c* 2, in EtOH), was dissolved in water (60 ml.). First barium hydroxide octahydrate (11·42 g.; 0·035 mole) was added and to the slurry methyl sulphate (2·85 ml.; 0·03 mole) was added drop by drop during 5 min. with stirring and cooling to +2°. The mixture was stirred for a further 2 hr. at 25° and kept overnight. Afterwards barium ions were precipitated by N-H_2SO_4 (80 ml.; 0·04 mole) and the barium sulphate was separated in the centrifuge. The sulphate and methosulphate ions were then removed completely by an IRA 400 anion-exchange resin (100 g.) column. The alkaline solution leaving the column was neutralised by 57% hydriodic acid (0·003 mole) and was evaporated below 65° in a vacuum to give the crystalline *methiodide*. This was washed with dry ethanol and recrystallised twice from the same solvent to give 0·037 g. (4%) of the 6β-methoxytropan-3α-ol methoidide (VI), m. p. 207—209° undepressed by the methiodide of the methoxytropanol obtained from (+)-6-methoxytropan-3-one. The infrared spectra were identical; $[\alpha]_D^{23}$ +4·60° (*c* 1·93, in H_2O).

This work was supported by the Hungarian Academy of Sciences and the United Pharmaceutical Works Ltd. The authors thank Mrs. M. Boross, I. Sarkady, and E. Tatár for microanalyses and to Mr. Iván Pál for technical assistance.

Stereochemical Research Laboratory,
Hungarian Academy of Sciences, Budapest, Hungary.

[Present address (G. F.): Department de Chimie,
Université Laval, Quebec, Canada.]

[*Received, May 10th*, 1965.]

[17] A. Stoll, A. Lindenmann, and E. Jucker, *Helv. Chim. Acta*, 1953, **36**, 1506.