ACTA CHEMICA SCANDINAVICA 23 (1969) 967–970

The Stereochemistry of 1,2,3-Trihydroxy-3-methylbutane and 2,3-Dihydroxy-3-methylbutyric Acid

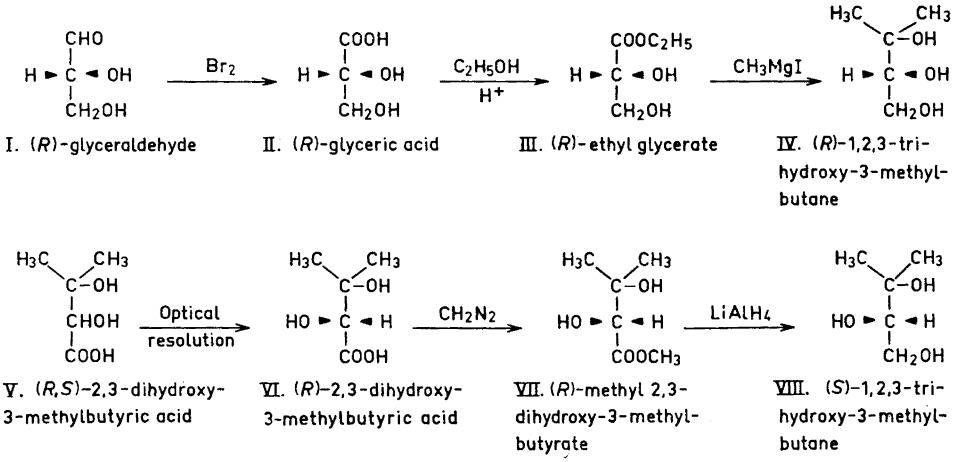
BENT EICHSTEDT NIELSEN,
POVL KROGSGAARD LARSEN and JOHN LEMMICH

The Royal Danish School of Pharmacy, Chemical Laboratory B, Copenhagen, Denmark

The configuration of (+)-1,2,3-trihydroxy-3-methylbutane (IV) is related to that of (+)-glyceraldehyde (I) and is shown to be 2(*R*). The configuration of (−)-2,3-dihydroxy-3-methylbutyric acid (VI) obtained by optical resolution of (±)-2,3-dihydroxy-3-methylbutyric acid is related to that of 2(*S*)-(−)-1,2,3-trihydroxy-3-methylbutane (VIII) and is shown to be 2(*R*).

During our investigations on the configuration of naturally occurring coumarins,[1] we were faced with the problem of determining the stereochemistry of 2,3-dihydroxy-3-methylbutyric acid.

(−)-2,3-Dihydroxy-3-methylbutyric acid (VI) was obtained by optical resolution of synthetic (±)-2,3-dihydroxy-3-methylbutyric acid (V) through formation of the quinine salt,[2] and was characterized as the *p*-phenylphenacyl-



I. (*R*)-glyceraldehyde
II. (*R*)-glyceric acid
III. (*R*)-ethyl glycerate
IV. (*R*)-1,2,3-trihydroxy-3-methylbutane
V. (*R,S*)-2,3-dihydroxy-3-methylbutyric acid
VI. (*R*)-2,3-dihydroxy-3-methylbutyric acid
VII. (*R*)-methyl 2,3-dihydroxy-3-methylbutyrate
VIII. (*S*)-1,2,3-trihydroxy-3-methylbutane

ester and the diacetate of the *p*-phenylphenacylester. Reduction of methyl 2,3-dihydroxy-3-methylbutyrate (VII) yielded (−)-1,2,3-trihydroxy-3-methylbutane (VIII). The optical antipode of (VIII) was obtained in the following manner: Bromine oxidation of (+)-glyceraldehyde (I) yielded (−)-glyceric acid (II). (+)-Ethyl glycerate (III) by Grignard synthesis gave (+)-1,2,3-trihydroxy-3-methylbutane (IV).

As the configuration of (+)-glyceraldehyde (I) is 2(*R*) it follows that the configuration of (+)-1,2,3-trihydroxy-3-methylbutane (IV) is 2(*R*).

As the configuration of (−)-2,3-dihydroxy-3-methylbutyric acid (VI) is related to that of 2(*S*)-(−)-1,2,3-trihydroxy-3-methylbutane (VIII) it follows that the configuration of (VI) is 2(*R*).*

The triols (IV) and (VIII) have been characterized as the tris-3,5-dinitrobenzoates.

EXPERIMENTAL

(±)-*2,3-Dihydroxy-3-methylbutyric acid (V).* 20.0 g of β,β-dimethylacrylic acid and 32.0 g of potassium hydroxide were dissolved in 800 ml of water. The temperature of the solution was kept at 2−5° by adding crushed ice. During 5 min and with mechanical stirring 32.0 g finely powdered potassium permanganate were added. The stirring was continued for 10 min after which a weak flow of sulfur dioxide was passed for ½ min through the suspension in order to stop the reaction. The mixture (pH 9) was filtered and the filtrate evaporated to 250 ml, adjusted to pH 2 with 4 N sulfuric acid and extracted with benzene. The aqueous phase was adjusted to pH 8 with sodium carbonate and evaporated to dryness. The residue was cooled in an ice bath, adjusted to pH 2 with 7 N sulfuric acid, and 70 g of a mixture of diatomaceous earth-anhydrous sodium sulfate (3:1) were added. The almost dry mixture was packed into a column. Benzene (100 ml) eluted the last trace of β,β-dimethylacrylic acid. Elution with diethyl ether (600 ml) and evaporation of the ether extract to constant weight yielded 12.90 g of (±)-2,3-dihydroxy-3-methylbutyric acid (V) as a colourless sirup.[2] A part of (V) was converted to the *p*-phenylphenacylester according to the method described by Stodola.[3] M.p. 121.5−122.0° (recrystallized from benzene). (Ref. 4, m.p. 182°). (Found: C 69.35; H 5.96; Calc. for $C_{19}H_{20}O_5$: C 69.50; H 6.14). IR- and PMR-spectra supported the structural assignments.

Resolution of (±)-2,3-dihydroxy-3-methylbutyric acid and isolation of (−)-2,3-dihydroxy-3-methylbutyric acid (VI). 12.80 g of (±)-2,3-dihydroxy-3-methylbutyric acid were resolved through formation of the quinine salt according to the method described by Sjölander and coworkers.[2] After 3 recrystallizations 11.63 g of the salt of (−)-2,3-dihydroxy-3-methylbutyric acid were obtained. M.p. 214−215° (decomp.), $[\alpha]_D^{22.9}$ −142° (*c* 1, methanol), (Ref. 2, m.p. 208−209°, 209−210°, $[\alpha]_D^{23}$ −142° (*c* 1, methanol)).

11.50 g of the above mentioned quinine salt were suspended in 200 ml of water, 27 ml of sodium carbonate (2 N) were added, and the mixture extracted with chloroform. The aqueous phase was filtered and the filtrate (pH *ca.* 8) was evaporated to dryness. (−)-2,3-dihydroxy-3-methylbutyric acid was isolated using the procedure described above for (±)-2,3-dihydroxy-3-methylbutyric acid, eluting only with diethyl ether (250 ml). Evaporation of the ether extract to constant weight gave 3.37 g of (−)-2,3-dihydroxy-3-methylbutyric acid (VI) as a colourless sirup. $[\alpha]_D^{23.1}$ −12.1° (*c* 2.1, 0.1 N hydrochloric acid), (Ref. 2, $[\alpha]_D^{23}$ −12.5°, −12.4° (*c* 2, 0.1 N hydrochloric acid)).

A part of (−)-2,3-dihydroxy-3-methylbutyric acid (VI) was converted to the *p*-phenylphenacyl ester according to the method described by Stodola,[3] m.p. 101.0−102.0°

* During the preparation of this manuscript the recent work of K. Hata and M. Kozawa, *J. Pharm. Soc. Japan* **88** (1968) 293, came to the authors' attention. Hata *et al.* have assigned the configuration 2(*R*) to the acid (VI) by comparison of the ORD-curve of (VI) with those of L-serine, L-alanine, and L-α-hydroxyisovaleric acid.

(recrystallized from cyclohexane, acetone-petroleum ether); $[\alpha]_D^{23.3}$ −12.0° (*c* 1.1, chloroform). (Found: C 69.69; H 6.07. Calc. for $C_{19}H_{20}O_5$: C 69.50; H 6.14). IR- and PMR-spectra supported the structural assignments.

(−)-*2,3-Diacetoxy-3-methylbutyric acid* p-*phenylphenacyl ester*. During 2 h and with magnetic stirring a mixture of 350 mg of (−)-2,3-dihydroxy-3-methylbutyric acid *p*-phenylphenacyl ester and 7 ml of acetic anhydride was heated on oil bath (Temp. 142–145°). After cooling the reaction mixture was shaken vigorously with water (50 ml), and extracted four times with methylene chloride. The combined, filtered, and dried methylene chloride phases were evaporated and the residue chromatographed on silica gel (Merck, 45 g). As eluent was used benzene, to which increasing amounts of ethyl acetate (0–4 %) were gradually added. 307 mg of a crystalline, thin layer chromatographically pure compound, m.p. 82.0–85.5°, were obtained. Several fractionated crystallizations, using petroleum ether, yielded 25 mg of long needles, m.p. 90.0–91.5°. $[\alpha]_{436}^{23.4}$ −12°, $[\alpha]_{365}^{23.4}$ −33° (*c* 0.6, chloroform).

IR- and PMR-spectra supported the structural assignments.

(−)-*Methyl 2,3-dihydroxy-3-methylbutyrate (VII)*. A solution of 1.80 g of (−)-2,3-dihydroxy-3-methylbutyric acid in 60 ml of anhydrous diethyl ether was treated with excess of diazomethane for 4 min and evaporated. A faint yellowish oil was obtained. Distillation gave 1.2 g of a colourless oil, b.p. 58–60°/0.3 mm Hg (Ref. 6, b.p. 58–60°/0.2 mm Hg). $[\alpha]_D^{20.3}$ −26.5° (*c* 1.8, methanol).

The structure was confirmed by PMR- and IR-spectroscopy.

(−)-*1,2,3-Trihydroxy-3-methylbutane (VIII)*. 386 mg of $LiAlH_4$ (0.010 mol) were stirred with 20 ml of anhydrous diethyl ether for 45 min. During 35 min and with vigorous stirring a solution of 1.00 g of (−)-methyl 2,3-dihydroxy-3-methylbutyrate (0.0067 mol) in 20 ml of anhydrous diethyl ether was added to the suspension. The reaction mixture was refluxed for 1½ h, cooled on an ice bath, and under vigorous stirring 25 ml of ice cooled sulfuric acid (1 N) were added drop by drop. After further stirring for 1 h at room temperature the ether layer was washed with 10 ml of water. The combined aqueous phases were adjusted to pH 8 with sodium carbonate and evaporated to dryness. The residue was mixed with 40 g of diatomaceous earth-anhydrous sodium sulfate (3:1). The powder was packed into a column and eluted with 300 ml of anhydrous ether. After evaporation to constant weight the residue was dried over phosphorus pentoxide at 10–15 mm Hg for 16 h, giving 500 mg of a sirupy liquid. After distillation of 350 mg of the sirup a colourless, highly hygroscopic and viscous liquid (125 mg) was obtained. B.p. 137–139°/11 mm Hg (Ref. 5, racemate, b.p. 145–147°/14 mm Hg); $[\alpha]_D^{20.1}$ −20.6° (*c* 1.3, methanol).

IR- and PMR-spectra supported the structural assignments.

(−)-*1,2,3-Tris-(3,5-dinitrobenzoyloxy)-3-methylbutane*. 120 mg of (−)-1,2,3-trihydroxy-3-methylbutane (VIII) (0.001 mol) and 780 mg of 3,5-dinitrobenzoylchloride (0.0035 mol) were dissolved in a mixture of anhydrous pyridine (0.8 ml) and chloroform (1.2 ml), and refluxed for 4½ h. After cooling the solution was mixed with 15 ml of methylene chloride, extracted with 10 ml of 1 N hydrochloric acid, 10 ml of water, and 10 ml of 1 N sodium carbonate, respectively. The dried methylene chloride solution was evaporated and the residue chromatographed on silica gel (Merck, 43 g). As eluent was used benzene to which ethyl acetate was added gradually, until a concentration of 6 % of ethyl acetate was reached. 240 mg of crystalline, partly racemized 1,2,3-tris-(3,5-dinitrobenzoyloxy)-3-methylbutane were obtained. After several fractionated crystallizations from acetone 203 mg of (−)-1,2,3-tris-(3,5-dinitrobenzoyloxy)-3-methylbutane were obtained, m.p. 179.5–180.5°; $[\alpha]_D^{23.0}$ −30.9° (*c* 2.2, acetone). (Found: C 44.61; H 2.71; N 12.09; Calc. for $C_{26}H_{18}O_{18}N_6$: C 44.46; H 2.58; N 11.96).

(+)-*Ethyl glycerate (III)*. 4.0 g of glyceraldehyde (I), as a light brown sirup, $n_D^{30.0}$ 1.4866; $[\alpha]_D^{24.9}$ +6.1° (*c* 2, water). (Ref. 7, $[\alpha]_D^{25}$ +8.7° ±0.5 (*c* 2, water, freshly prepared sample)) were oxidized to (−)-glyceric acid according to the method described by Baer and coworkers [8] using 9.70 g of bromine and 13.5 g of freshly prepared silver carbonate. From the resulting suspension silver bromide was removed by filtration and the filtrate adjusted to pH 10 with 32 ml of 2 N sodium hydroxide. The filtrate was passed through a column containing 100 ml of an ion exchange resin, acid form (Dowex 50 W × 8 100/200 mesh). The eluate when evaporated to constant weight yielded 4.60 g of (−)-glyceric acid as a light brown sirup.

The crude acid was dissolved in 150 ml of an anhydrous solution of hydrogen chloride in ethanol (15 w/w %) and refluxed for 3½ h. To the light brown solution finely powdered silver carbonate (11.5 g) was added. After stirring for 16 h the reaction mixture was filtered and the solvent evaporated. 4.77 g of the crude ester was obtained. Distillation gave 3.54 g of a colourless liquid. B.p. 114–116°/9.5–10 mm Hg; n_D^{20} 1.4429; $[\alpha]_D^{15.4}$ +9.41° (neat), (Ref. 10, $[\alpha]_D^{15.3}$ −9.54° (neat) for the optical antipode; Ref. 9, b.p. 120–121°/14 mm Hg).

(+)-1,2,3-Trihydroxy-3-methylbutane (IV). With mechanical stirring 3.0 g of (+)-ethyl glycerate (0.0224 mole) in 10 ml of anhydrous ether were added drop by drop to a methyl magnesium iodide solution prepared from 2.45 g of magnesium (0.1008 g atoms) and 15.1 g of methyl iodide (0.106 mole). The reaction mixture was refluxed on a water bath (50°) for further 1¾ h and then cooled in ice. With stirring, 80 ml of ice cooled sulfuric acid (2 N) were added dropwise, after which the stirring was continued for 1 h. The separated ether phase was washed with water (10 ml) and the combined water phases adjusted to pH *ca.* 11 with sodium hydroxide solution (2 N, 170 ml). The voluminous deposit was separated by centrifugation and washed with water (20 ml). The combined aqueous solutions were evaporated to dryness and (+)-1,2,3-trihydroxy-3-methylbutane was isolated as described above for the antipode. 3.5 l of anhydrous ether were used. The first eluate (75 ml) contained unreacted ester and was discharged. After evaporation and drying as previously described 1.62 g of crude product were obtained. Distillation gave 0.80 g of a colourless, highly hygroscopic, viscous liquid. B.p. 138–139°/10 mm Hg; (Ref. 5, racemate, b.p. 145–147°/14 mm Hg); $[\alpha]_D^{20.1}$ +22.1° (*c* 1.3, methanol).

(+)-1,2,3-Tris-(3,5-dinitrobenzoyloxy)-3-methylbutane. (+)-1,2,3-Tris-(3,5-dinitrobenzoyloxy)-3-methylbutane was prepared, using the method described above for (−)-1,2,3-tris-(3,5-dinitrobenzoyloxy)-3-methylbutane. 240 mg of (+)-1,2,3-trihydroxy-3-methylbutane yielded 770 mg of a partly racemized product, which after several fractionated crystallizations gave 397 mg of (+)-1,2,3-tris-(3,5-dinitrobenzoyloxy)-3-methylbutane, m.p. 179.5–181.0°; $[\alpha]_D^{23.0}$ +31.7° (*c* 2.2, acetone). (Found: C 44.61; H 2.69; N 12.06. Calc. for $C_{26}H_{18}O_{18}N_6$: C 44.46; H 2.58; N 11.96).

The IR-spectrum was identical with that of (−)-1,2,3-tris-(3,5-dinitrobenzoyloxy)-3-methylbutane.

IR-spectra were recorded on a Perkin-Elmer grating infrared spectrophotometer, Model 457. Spectra of solids were recorded as earlier described.[11] IR-spectra of liquids were recorded using the film technique.

Melting points and PMR-spectra were determined as in a previous paper.[11] Microanalyses were performed by Dr. A. Bernhardt, Mülheim.

REFERENCES

1. Nielsen, B. E. and Lemmich, J. *Acta Chem. Scand.* **23** (1969) 962.
2. Sjölander, K. F., Adelberg, E. A. and Tatum, E. L. *J. Am. Chem. Soc.* **76** (1954) 1085.
3. Stodola, F. H. *Microchem. J.* **7** (1963) 389.
4. Kögl, F., Duisberg, H. and Erxleben, H. *Ann.* **489** (1931) 191.
5. Colonge, J. and Cumet, J. *Compt. Rend.* **222** (1946) 1400.
6. Schindler, W. and Reichstein, T. *Helv. Chim. Acta* **25** (1942) 552.
7. Perlin, A. S. and Brice, C. *Can. J. Chem.* **34** (1956) 85.
8. Baer, E., Grosheints, J. M. and Fischer, H. O. L. *J. Am. Chem. Soc.* **61** (1939) 2607.
9. Frankland, P. and McGregor, J. *J. Chem. Soc.* **63** (1893) 511.
10. Frankland, P. and McGregor, J. *J. Chem. Soc.* **65** (1894) 760.
11. Nielsen, B. E. and Lemmich, J. *Acta Chem. Scand.* **18** (1964) 1379.

Received July 11, 1968.