

The Absolute Configuration of 2- and 3-Isopropyl- γ -butyrolactone

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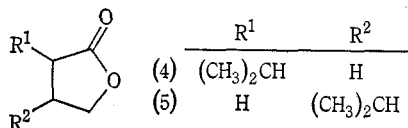
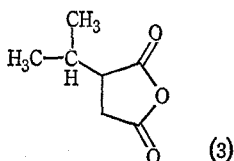
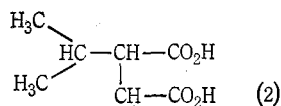
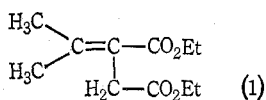
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Abstract

The absolute configuration of 2- and 3-isopropyl- γ -butyrolactone has been determined to be (*S*)-(-).

As part of a project to determine the absolute configuration of scabequinone, it became necessary to know the absolute configuration of 3-isopropyl- γ -butyrolactone (5) so that it could be compared with an ozonolysis product of the natural compound.¹ The present paper reports the absolute configuration of this lactone together with that of the isomeric 2-isopropyl- γ -butyrolactone (4) as both compounds appear to be possible degradation products of other naturally occurring compounds.



Diethyl isopropylidenesuccinate (1) was prepared from acetone and diethyl succinate, sodium hydride being used as the base in the Stobbe condensation,^{2,3} and (\pm)-isopropylsuccinic acid (2) was prepared from (1) by hydrogenation of the double bond and hydrolysis of the ester groups utilizing the dissolution of Raney nickel alloy in aqueous sodium hydroxide.⁴ Resolution of the (\pm)-carboxylic acid (2) with strychnine yielded (*S*)-(+)-isopropylsuccinic acid (2)⁵ which was converted into

¹ Allan, R. D., Dunlop, R. W., Kendall, M., Wells, R. J., and Macleod, J. K., *Tetrahedron Lett.*, 1973, 3.

² Plešek, J., and Hermánek, S., in 'Sodium Hydride; Its Use in the Laboratory and in Technology' (Ed. G. Jones) p. 105 (Iliffe Books: London 1968).

³ Adkins, H., and Wojcik, B., *J. Amer. Chem. Soc.*, 1934, **56**, 2424.

⁴ Cook, P. L., *J. Org. Chem.*, 1962, **27**, 3873.

⁵ Fredga, A., and Leskinen, E., *Ark. Kemi, Mineral. Geol. B*, 1944, **19**, 6 (*Chem. Abstr.*, 1947, **41**, 1616).

(S)-isopropylsuccinic anhydride (3) with acetic anhydride. The product obtained by reduction of the anhydride (3) with sodium borohydride was shown to be a mixture of isomeric lactones (4) and (5) (2:1) by gas chromatographic analysis and the isomers were separated using preparative gas chromatography.

The major isomer, which eluted first, was shown to be 2-isopropyl- γ -butyrolactone (4) and the other product proved to be 3-isopropyl- γ -butyrolactone (5). In the p.m.r. spectra the signals due to the methyl group protons in (4) appeared as a pair of doublets at δ 0.92 (*J* 7 Hz) and δ 1.03 (*J* 8 Hz) and those in (5) appeared as a pair of doublets at δ 0.91 (*J* 7 Hz) and δ 0.95 (*J* 6 Hz). The chemical shift difference between the magnetically non-equivalent methyl groups is greater in (4) than (5) because in the former case these methyl groups are situated closer to the magnetically anisotropic carbonyl group.⁶ Correspondingly the chemical shift of the methine proton of the isopropyl group in (4) (δ 1.9) was much higher than that for the same proton in (5) (δ 1.6). The rest of the two p.m.r. spectra was as expected for a five-membered ring lactone except for the signals due to the protons bonded to C 4 in (5).⁷ In this case the proton *cis* to the isopropyl group was shielded by this group (δ 3.73) when compared to the other C 4 proton (δ 4.26).

The mass spectra confirmed the structures of the two lactones. Thus the M-CO peak (*m/e* 100) was much more intense in the mass spectrum of (4) (10%) than in (5) (1%) because the loss of CO generates a secondary ion radical from (4) and a primary ion radical from (5). Fragmentation of the isopropyl group as either $C_3H_7^+$ (*m/e* 85) or $C_3H_6^+$ (*m/e* 86) yielded much more intense peaks in the mass spectrum of (4) (15%, 100%) than (5) (4%, 20%) because a conjugated ion radical is produced from (4) and a non-conjugated ion radical is produced from (5). The remainder of the two mass spectra were as expected for a five-membered lactone.⁸

The reduction of the anhydride (3) produced somewhat unexpected results as it is the first example of a metal hydride reduction in which the major part of the reduction took place at the least sterically hindered carbonyl group.⁹⁻¹¹

Thus the absolute configurations have been deduced as (S)-(-)-2-isopropyl- γ -butyrolactone (4) and (S)-(-)-3-isopropyl- γ -butyrolactone (5).

Experimental

All melting points are uncorrected. The infrared spectra were measured with a Perkin-Elmer 237 spectrometer. The p.m.r. spectra were recorded on a Jeol JNM-MH-100 spectrometer with chemical shifts quoted in p.p.m. from tetramethylsilane as internal standard. Mass spectra were recorded on a MS-902 mass spectrometer. Gas chromatographic analysis was conducted on an Aerograph Hy-Fi using a 6 ft by 1/8 in. stainless steel column packed with HMDS-treated Chromosorb W coated with Carbowax 20M (15%). Preparative gas chromatography was carried out on an Aerograph Autoprep 705 using a 15 ft by 3/8 in. stainless steel column packed with HMDS-treated Chromosorb W coated with Carbowax 20M (10%). Optical rotations were measured with a Perkin-Elmer 141 polarimeter.

⁶ Siddall, T. H., and Stewart, W. E., in 'Progress in Nuclear Magnetic Resonance Spectroscopy' (Eds J. W. Emsley, J. Feeney and L. H. Sutcliffe) Vol. 5, Ch. 2 (Pergamon: Oxford 1969).

⁷ Lowry, J. B., and Riggs, N. V., *Tetrahedron Lett.*, 1964, 2911.

⁸ Porter, Q. N., and Baldas, J., 'Mass Spectrometry of Heterocyclic Compounds' p. 182 (John Wiley: New York 1972).

⁹ Bailey, D. M., and Johnson, R. E., *J. Org. Chem.*, 1970, **35**, 3574.

¹⁰ Bloomfield, J. J., and Lee, S. L., *J. Org. Chem.*, 1967, **32**, 3919.

¹¹ Johnson, R. N., and Riggs, N. V., *Aust. J. Chem.*, 1971, **24**, 1643.

(S)-(+)-Isopropylsuccinic Acid

Diethyl isopropylidenesuccinate (47%) was prepared by a Stobbe condensation using sodium hydride as the base, b.p. 147–149°/30 mm (lit.³ 115–122°/7 mm); ν_{\max} (neat) 1745s, 1720s and 1640m cm^{-1} . The unsaturated diester was hydrogenated and hydrolysed in the one step, utilizing the dissolution of nickel–aluminium alloy (1 : 1) in aqueous sodium hydroxide (10%), to yield (\pm)-isopropylsuccinic acid (34%), m.p. 108–110° (lit.¹² 118–120°); ν_{\max} (Nujol) 1700s cm^{-1} . The (\pm)-dicarboxylic acid was resolved through the strychnine salt, m.p. 120–125° (lit.¹² 124–131°), and gave (*S*)-(+)-isopropylsuccinic acid, m.p. 85–86° (lit.⁵ 88–89°); ν_{\max} (Nujol) 1700 cm^{-1} ; $[\alpha]_{\text{D}}^{23} + 22.5^\circ$ (H_2O) (lit.⁵ + 22.9 (H_2O)).

(S)-Isopropylsuccinic Anhydride

A solution of the (*S*)-(+)-dicarboxylic acid (5 g) in acetic anhydride (15 ml) was boiled (5 h) and then concentrated to dryness. Distillation of the residue yielded *S*-isopropylsuccinic anhydride (3.6 g, 81%), b.p. 151–152°/32 mm (lit.¹² 164°/45); ν_{\max} (neat) 1870s and 1800m cm^{-1} .

Reduction of (S)-Isopropylsuccinic Anhydride

A solution of the (*S*)-anhydride (2.2 g) in dry tetrahydrofuran (10 ml) was added (0.5 h) to a mixture of sodium borohydride (0.75 g) and dry tetrahydrofuran (20 ml) stirred at 0°. The mixture was stirred (7.5 h), diluted with hydrochloric acid (10 ml, 2M) and extracted with ether. The ether extracts were dried (MgSO_4), the solvent distilled at reduced pressure and the residue distilled to yield a mixture of lactones (1.38 g, 70%), b.p. 125–129°/30 mm. Gas chromatographic analysis (150°, 25 ml/min) indicated that there were two lactones present (6.5 min and 9 min, 2 : 1 respectively) and these were separated by preparative gas chromatography (175°, 200 ml/min). The major component was (*S*)-(-)-2-isopropyl- γ -butyrolactone, M^+ 128.0831 (expected M^+ for $\text{C}_7\text{H}_{12}\text{O}_2$, 128.0837); ν_{\max} (neat) 1775s cm^{-1} . P.m.r. (CCl_4): signals centred at δ 0.92 (d, *J* 7 Hz, 3, CH_3), 1.03 (d, *J* 8 Hz, 3, CH_3), 2.20 (m, 4, propyl methine and CH_2CHCO) and 4.20 (m, 2, CH_2O). Mass spectrum (75 eV): *m/e* (rel. int.) 128 (1), 113 (4), 100 (10), 87 (15), 86 (100), 85 (32), 83 (2), 82 (3), 81 (3), 70 (10), 69 (37), 68 (4), 67 (3), 58 (18), 57 (3), 56 (15), 55 (25), 54 (3), 53 (6), 44 (10), 43 (41), 42 (25), 41 (74), 40 (6); metastable peaks at 99.5, 77.8, 58.0. $[\alpha]_{\text{D}}^{23} - 14.2^\circ$ (CCl_4). Gas chromatographic analysis (150°, 25 ml/min) indicated that the lactone was pure (6.5 min).

The minor component was (*S*)-(-)-3-isopropyl- γ -butyrolactone, M^+ 128.0832; ν_{\max} (neat) 1780s cm^{-1} . P.m.r. (Cl_4): signals centred at δ 0.91 (d, *J* 7 Hz, 3, CH_3), 0.95 (d, *J* 6 Hz, 3, CH_3), 1.60 (m, 1, propyl methine), 2.25 (m, 3, CH_2CHCO), 3.73 (m, 1, CHO) and 4.26 (m, 1, CHO). Mass spectrum (75 eV): *m/e* (rel. int.) 128 (29), 113 (6), 98 (4), 97 (7), 87 (4), 86 (20), 85 (6), 84 (4), 83 (4), 81 (2), 80 (2), 71 (6), 70 (80), 69 (64), 68 (4), 67 (6), 58 (15), 57 (7), 56 (76), 55 (100), 54 (6), 53 (6), 51 (2), 50 (2), 45 (2), 44 (11), 43 (93), 42 (58), 41 (69), 40 (6); metastable peaks at 99.8, 78.0, 73.5, 56.8. $[\alpha]_{\text{D}}^{23} - 12.3^\circ$ (CCl_4). Gas chromatographic analysis (150°, 25 ml/min) indicated that this lactone was pure (9 min).

Acknowledgment

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¹² 'Dictionary of Organic Compounds' 4th Edn, p. 1963 (Eyre–Spottiswoode: London 1965).