Absolute Configuration of a Dissymmetric Spiran

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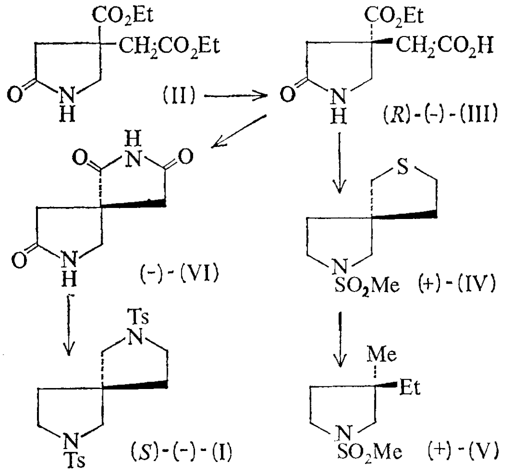
IN the assignment of absolute configuration to optically active compounds, axially dissymmetric molecules pose a special problem, since in the absence of asymmetrically substituted atoms direct correlation with centrodissymmetric reference standards is not usually possible.[1] Nevertheless ingenious solutions have enabled elucidation of absolute configuration of representative members of most families in this symmetry group, especially hindered biphenyls,[2] allenes,[3] alkylidenecyclohexanes,[4] and related compounds possessing molecular asymmetry.[5] The largest group of axially dissymmetric molecules for which no configurational assignments have yet been made are spirans. We now report the first unambiguous proof of the absolute configuration of an axially dissymmetric spiran, the 2,7-diazaspiro[4,4]nonane derivative (I).



Our approach to the determination of configuration was to synthesize (I) from a centrodissymmetric intermediate (III) whose configuration could then be established by straightforward correlations. Dialkylation of ethyl cyanoacetate with ethyl bromoacetate gave diethyl 3-cyano-3-ethoxycarbonylglutarate,† m.p. 40—41°, which was hydrogenated‡ over Raney nickel to the lactam (II), m.p. 65—66·5°. Hydrolysis with one equivalent of alkali led to a mono-acid, m.p. 127—129°, which was partially resolved with quinine. The laevorotatory acid (III), m.p. 153—156°, $[\alpha]_D^{24}$ $-22{\cdot}3°$ (H_2O), was converted by successive reaction with diazomethane, lithium aluminium hydride, and methanesulphonyl chloride into an *NOO*-trimethylsulphonate, which on treatment with refluxing ethanolic sodium

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† Satisfactory analyses were obtained for all new crystalline compounds.

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sulphide afforded the thioether (IV), m.p. 60—62°, $[\alpha]_D^{23}$ +0·61° ($CHCl_3$).

Raney nickel desulphurization of (IV) gave the sulphonamide (V), m.p. 26·5—27·5°, $[\alpha]_D^{24}$ +3·1° ($CHCl_3$). The enantiomer of (V), $[\alpha]_D^{23}$ −5·4° ($CHCl_3$), was synthesized from (*S*)-(−)-2-ethyl-2-methylsuccinic acid, $[\alpha]_D^{24}$ −5·0° (c = 16·5 in $CHCl_3$)[8] by conversion to the imide, lithium aluminium hydride reduction, and reaction with methanesulphonyl chloride. Since the absolute configuration of (*S*)-(−)-2-ethyl-2-methylsuccinic acid has been determined both by the quasi-racemate method[9] and by unequivocal chemical correlations,[10] these reactions establish the configuration of (−)-(III) as (*R*).

Pyrolysis of the ammonium salt of (*R*)-(−)-(III) at 200—250° led to the imide (VI), m.p. 205—208°, $[\alpha]_D^{23}$ −0·55° (H_2O). Lithium aluminium hydride reduction followed by treatment with toluene-*p*-sulphonyl chloride gave (*S*)-(−)-(I), m.p. 133—133·5°, $[\alpha]_D^{24}$ −11·6° ($CHCl_3$). Compound (I) shows a plain negative o.r.d, curve.

Assignment of the (*S*)-configuration to the laevorotatory spiran (I) thus rests on a direct correlation with (*S*)-(−)-2- ethyl-2-methylsuccinic acid. It is of interest that the empirical rule of Lowe[11] relating absolute configuration of allenes to the screw pattern of polarizability fails to predict correctly the absolute configuration of (I). Work is continuing in our laboratory toward the synthesis of additional optically active spirans to test the extension of Lowe's rule to spirans.

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[6] We have observed that the rotation of this diacid in chloroform is strikingly dependent on concentration; illustrative values of $[\alpha]_D^{24}$ for acid of 85% optical purity are −5·0° at c 16·5, −0·6° at c 10·6, +1·7° at c 8·5, +9·4° at c 4·3, and +18·9° at c 2·2. For configurational correlations the sign of the acid should be checked by conversion to its mono- and di-methyl esters; *cf.* S. Ställberg-Stenhagen, *Arkiv. Kemi*, 1951, **3**, 273.

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