The Configurations of Dimethylmyleran (2,5-Bismethanesulphonyloxyhexane)

By A. R. JONES

(*Pharmacology Department, The University, Manchester* M13 9PL)

Summary Reaction of the two isomeric forms of dimethylmyleran with sulphide or hydroxide ions gives cyclic products from which the *meso*- and (±)-configurations can be deduced.

DIMETHYLMYLERAN (2,5-bismethanesulphonyloxyhexane) (I) was introduced clinically in 1957 for the treatment of chronic granulocytic leukemia.[1] Whereas its synthesis produces a mixture of *meso*- and (±)-forms, only one, as yet unidentified, isomer[2] has been isolated.[3]

Fractional recrystallisation† from benzene and methanol of the product from mesylation of a mixture of *meso*- and (±)-hexane-2,5-diols separated the isomers:‡ m.p. 104—105° and m.p. 38—39°. Refluxing ethanolic sodium sulphide converted the high-m.p. isomer into *cis*-2,5-dimethyltetrahydrothiophen (II) and the low-m.p. isomer

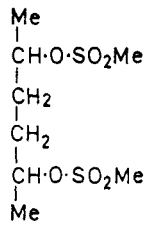
† A similar separation has been achieved by Professor W. C. J. Ross, Chester Beatty Research Institute, London.
‡ Satisfactory analytical and spectral data were obtained for all compounds.

into *trans*-2,5-dimethyltetrahydrothiophen (III), isolated as the respective bis-$HgCl_2$ (m.p. 177—179°; 67%) and mono-$HgCl_2$ (m.p. 114°; 60%) complexes. Steam distillation of these complexes from 4N-HCl liberated the sulphides (b.p. 138—139°)[4] which, with dilute hydrogen peroxide in acetone gave, respectively, *cis*- and *trans*-2,5-dimethyltetrahydrothiophen *S*-oxide (VI). The 100 MHz n.m.r. spectra (D_2O) of the sulphoxides agreed with the assigned configurations; 2- and 5-H give two superimposed quartets (δ 3·18 p.p.m.) in the *cis*-isomer whereas in the *trans*-isomer they are non-equivalent (δ 3·03 and 3·08 p.p.m.). This sequence indicates that as the displacement reaction proceeds with full inversion of configuration,[5] the high-m.p. isomer of dimethylmyleran is *meso* and the low-m.p. isomer the (±) form.

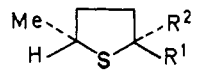
Base hydrolysis (2N aqueous NaOH) of the *meso*- and (±)-isomers gives, respectively, *cis*- and *trans*-2,5-dimethyltetrahydrofuran (IV) and (V) in quantitative yield, their n.m.r. spectra ($CDCl_3$) being in agreement with those previously established.[6] Identical products are obtained by hydrolysis in refluxing 50% aqueous acetone[7] and in water at 38°.

Each cyclisation produces one isomeric product, determined by g.l.c. (silicone XL-60 on acid-washed DMCS Chromosorb W), showing that the reactions of dimethylmyleran follow an S_N2 mechanism and not S_N1 as has been generally accepted.[7,8]

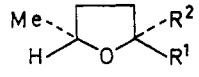
Initial anti-fertility examination in male mice of both isomers at equivalent dose levels indicates the *meso*- as



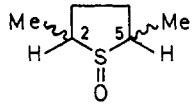
(I)



(II) R^1 = H R^2 = Me
(III) R^1 = Me R^2 = H



(IV) R^1 = H R^2 = Me
(V) R^1 = Me R^2 = H



(VI)

being more active than the (±)-isomer in inhibiting spermatogonial development.[9]

(*Received, June* 21*st*, 1971; *Com.* 1010)

[1] H. R. Bierman, A. G. Knudson, K. H. Kelly, and G. M. Timmis, *Proc. Amer. Ass. Cancer Res.*, 1957, **2**, 188.
[2] (a) G. M. Timmis, R. F. Hudson, R. D. Marshall, and H. R. Bierman, *U.S.P.* 3,041,241/1962 (*Chem. Abs.*, 1962, **57**, 13898c) give m.p. 97.5°; (b) R D. Marshall, Ph.D. Thesis, London, 1955, 51 gives m.p. 97·5°; (c) G. Ferrari and E. Marcon, *Boll. chim. farm.*, 1957, **96**, 429 give m.p. 98—100°.
[3] The low-m.p. isomer is mentioned (S. S. Brown, J. L. Everett, and G. M. Timmis, B.P. 861,818/1961 (*Chem. Abs.*, 1961,**55**, 23, 347d) give m.p. 44—45°) though no details are given.
[4] E. V. Whitehead, R. A. Dean, and F. A. Fidler, *J. Amer. Chem. Soc.*, 1951, **73**, 3632.
[5] R. M. Dodson and V. C. Nelson, *J. Org. Chem.*, 1968, **33**, 3966.
[6] D. Gagnaire and P. Monzeglio, *Bull. Soc. chim. France*, 1965, 474.
[7] G. M. Timmis and R. F. Hudson, *Ann. New York Acad. Sci.*, 1958, **68**, 727.
[8] Ref. 2b; W. C. J. Ross, "Biological Alkylating Agents", Butterworths, London, 1962, p. 187, G. P. Warwick, *Cancer Res.*, 1963, **23**, 1315.
[9] H. Jackson, B. W. Fox, and A. W. Craig, *J. Reprod. Fertil.*, 1961, **2**, 447.