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SYNTHESIS OF OPTICALLY ACTIVE SPIROSULFURANES

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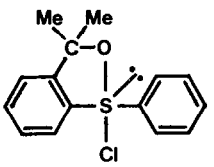
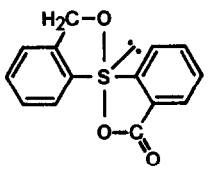
The synthesis of optically active sulfuranes is of both practical and theoretical interest.[1] The first optically active sulfurane, the (+)-enantiomer of the monocyclic chlorosulfurane (1), has been prepared recently by Martin and Balthazor.[2] Now we report on the synthesis of the enantiomers of the first optically active spirosulfurane, both (+)- and (-)-1,1'-spirobi-[3H-2,1-benzoxathiol]-3'-one (2), close analogues of the spirosulfurane (3) described by us in an earlier paper.[3] Based on variable temperature ^{1}H NMR observations, estimates are given on the configurational stability of the optically inactive spirosulfurane oxide (4), an oxidation product of the two enantiomers of the spirosulfurane (2).



(1)



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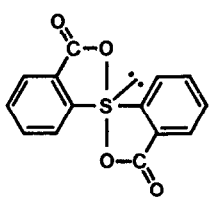

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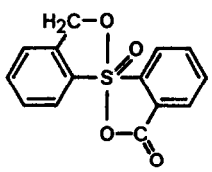


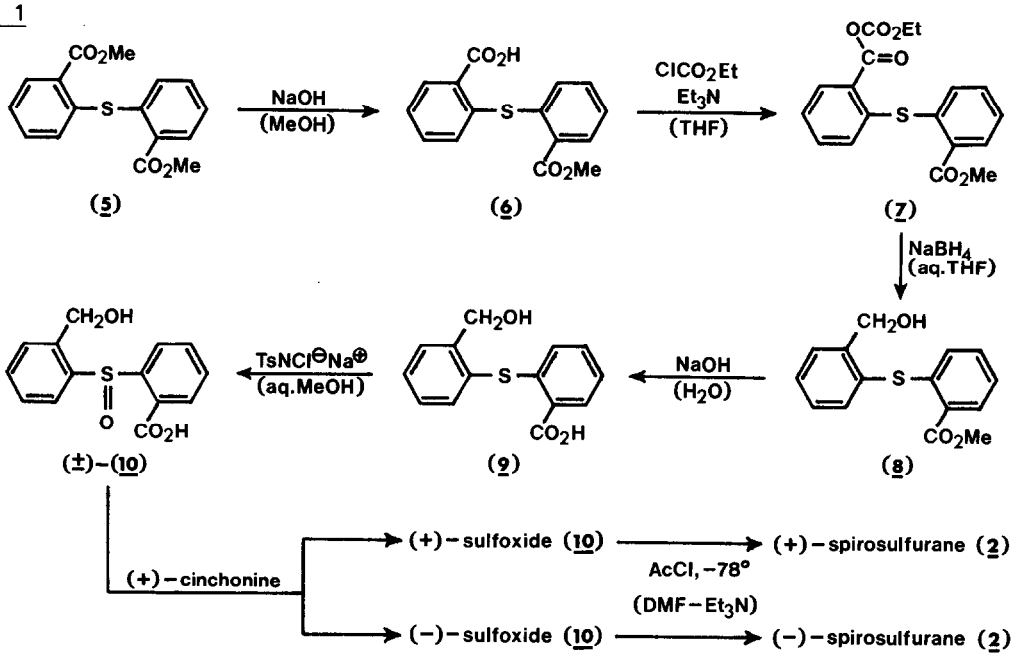
(4)

The synthesis followed the route outlined in Scheme 1. Its first objective was the preparation of the optically active sulfoxides (+)- and (-)-(10) which were subsequently converted into the spirosulfuranes (+)- and (-)-(2) without loss of enantiomeric purity.

The diester (5)[4] (1 mol) was hydrolysed with sodium hydroxide (1 mol) in methanol to give, after acidification and repeated crystallizations, the monoester (6) (mp 186-187°C, yield 60%). The treatment of the compound (6) (0.2 mol) with ethyl chloroformate (0.2 mol) in the presence of triethylamine (0.2 mol) in tetrahydrofurane at -10°C produced the mixed anhydride (7) which was without isolation reduced into the hydroxymethyl compound (8) with sodium borohydride[5] (0.8 mol). The subsequent hydrolysis of the crude product (8) with sodium hydroxide (0.4 mol) in methanol gave, after acidification, the hydroxy acid (9) (mp 139-140°C, yield 85%). The reaction of the compound (9) (0.1 mol) with chloramine-T (0.11 mol) in aqueous methanol produced

the (±)-sulfoxide (10) [mp 212°C, yield 95%; IR ν_{max} (KBr) 3238s (alcohol OH), 3100-2300br (carboxyl OH), 1700s (carboxyl C=O), 1012s (sulfoxide S=O) cm^{-1}; ^1H NMR $\delta(CDCl_3)$ 4.72 (1H, d, 12 Hz), 5.67 (1H, d, 12 Hz), 7 - 8.7 (8H, m) ppm].[6] The racemic sulfoxide (10) was treated with an equimolar amount of (+)-cinchonine in ethanol and the resulting mixture of diastereomeric salts, after three recrystallizations from ethanol - benzene - ethyl acetate solvent systems, afforded one of the diastereomers {$[\alpha]_{546}^{20}$ +195.1° (c=1.4 in DMF), mp 192-193°C} from which the (+)-sulfoxide (10) {$[\alpha]_{546}^{20}$ +163.3° (c=1.4 in DMF), mp 179-181°C} was liberated with diluted sulfuric acid at 0°C (yield 29%). The (-)-sulfoxide (10) {$[\alpha]_{546}^{20}$ -159.6° (c=1.6 in DMF), mp 180-182°C} was obtained from the mother liquor of the first crystallization of the diastereomeric mixture in a similar manner (yield 33%).

Scheme 1

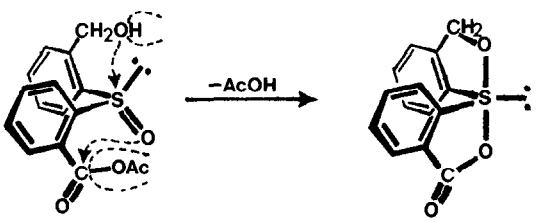


The enantiomers of the spirosulfurane (2) were prepared by treating the corresponding (+)- and (-)-sulfoxides (10) (0.01 mol) with acetyl chloride (0.012 mol) at -70°C in the presence of triethylamine (0.025 mol) in dimethylformamide (yield 74%).[7] With the exception of optical activity[8] {$[\alpha]_{546}^{20}$ +113.4° (c=1.2 in $CHCl_3$) and $[\alpha]_{546}^{20}$ -114.5° (c=1.7 in $CHCl_3$)} their physical properties proved identical [mp 187-189°C; IR lack of characteristic absorptions of sulfoxides and carboxylic acids, ν_{max} (KBr) 1740s ("lactone" C=O) cm^{-1}]. The ^1H NMR spectrum [$\delta(CDCl_3)$ 5.38 (1H, d, 13 Hz), 5.84 (1H, d, 13 Hz), 7.15 - 8.3 (8H, m) ppm] shows diastereotopic methylene protons at 5.38 and 5.84 ppm with J_{AB} 13 Hz. In accord with their different steric dispositions relative to the adjacent benzene ring, the two methylene protons exhibit different, stereospecific long range couplings with the aromatic protons. Mirroring the configurational stability of these molecules, the NMR spectra recorded at elevated temperatures (up to 200°C) attests the absence of any sizeable ligand exchange process, a fact noted also for other spiro-

sulfuranes.[1] The configurational stability of the enantiomers of the spirosulfurane (2) follows also from their resistance against heating: thermal treatment in "diglyme" in a sealed tube at 210°C for one hour caused no detectable decrease in the optical rotatory power. Refluxing in aceton-water (9:1) (10 h) left the enantiomers of the compound (2) unchanged; the hydrolysis of the spirosulfurane (2) could be achieved by treatment with sodium hydroxide (1.5 equiv.) in aqueous methanol at 0°C (30 min), giving the corresponding sulfoxide (10) with unchanged optical purity (see Scheme 3).

In the presence of only one molar equivalent of triethylamine, the reaction between the sulfoxide (10) and acetyl chloride yielded the mixed anhydride (11)[9] [identified by its IR spectrum, ν_{max} (KBr) 3345s (alcohol OH), 1808s and 1700s (anhydride C=O), 1004s and 995s (sulfoxide S=O) cm^{-1}]. The compound (11), which is stable in the solid state, can readily be converted into the corresponding spirosulfurane (2) by dissolution in dimethylformamide and subsequent addition of triethylamine. This suggests that a mixed anhydride of type (11) is a possible intermediate of acyloxysulfurane formation as shown in Scheme 2 for one of the enantiomers of the compound (11).[10]

Scheme 2



(S)-(11) (S)-(2)

The oxidation of both the (+)- and the (-)-spirosulfurane (2) with ozone at -15°C or with acetyl nitrate (2.0 mol excess) in dichloromethane gave the optically inactive sulfurane oxide (4) (mp 198-200°C, yield 70 and 50%, resp. Scheme 3). The ^1H NMR spectrum of the spirosulfurane oxide (4) in $CDCl_3$ at room temperature shows a sharp singlet resonance at δ 5.37 ppm for the methylene protons. On lowering the temperature, however, this resonance undergoes changes characteristic of exchanging AB spin systems with decreasing exchange rate and gives, at -70°C, an AB resonance pattern with δ_A 5.30, δ_B 5.44 ppm and J_{AB} 14.5 Hz. The coalescence of the two separate resonances occurs at -49°C. By using the approximations for an exchanging AB system,[11] the activation free energy of the rate process is found to be 11 kcal/mol. This process, resulting in the interchange of the environments of the methylene protons, is obviously attribu-

Scheme 3

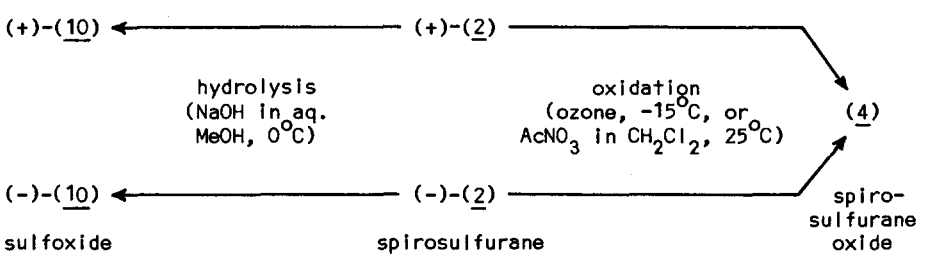


table to the intramolecular ligand permutation leading to a fast racemization at ambient temperature. The considerable decrease of the configurational stability of the spirosulfurane oxide (4) as compared with that of the parent spirosulfurane (2) can be understood in terms of the assumptions of the Nyholm-Gillespie Theory,[12] stating that bonded-pair - bonded-pair repulsions are less than lone-pair - bonded-pair repulsions. In other words, the replacement of the lone electron pair by an oxygen ligand eliminates the occurrence in the transition state of the extremely high repulsion effect of the apical lone pair which is generally believed to be the major factor of the configurational stability of sulfuranes.[2] The above findings provide experimental evidence for the validity of these assumptions in sulfurane chemistry.

Acknowledgements. The authors are grateful to Dr. F. Ruff for many helpful discussions and to Mr. P. Sándor for his skilful assistance in the measurements of NMR spectra.

REFERENCES AND NOTES

1. For a review see: J.C. Martin and E.F. Perozzi, Science, 191, 154 (1976) and references cited therein.
2. a) J.C. Martin and T.M. Balthazor, J. Amer. Chem. Soc., 97, 5634 (1975); b) ibid. 99, 152 (1977) and references cited therein.
3. a) I. Kapovits and A. Kálmán, J.C.S. Chem. Comm., 1971, 649; b) The X-ray analysis of the spirosulfurane (3) demonstrated the presence of enantiomeric pairs in the crystal lattice, see: A. Kálmán, I. Sasvári and I. Kapovits, Acta Cryst., B29, 355 (1973).
4. O. Hinsberg, Ber. Dtsch. Chem. Ges., 43, 1874 (1910).
5. cf. K. Ishizumi, K. Koga and S. Yamada, Chem. Pharm. Bull. Tokyo, 16, 492 (1968).
6. All the new compounds reported here have satisfactory analytical and t.l.c. data. The ^1H NMR spectra were recorded on a 100.1 MHz Varian XL-100-FT instrument at 25°C. Chemical shifts are quoted in ppm from Me_4Si.
7. In the course of our preliminary experiments the racemic spirosulfurane (2) was prepared by this procedure. The ^1H and ^{13}C NMR experiments performed in the presence of a chiral shift reagent have shown that solutions of the racemic spirosulfurane (2) contains the (+)- and (-)-enantiomers in equal amounts and that the barrier to interconversion is sufficiently high (>25 kcal/mol) to permit the synthesis of the optically active forms.
8. The optical purity of the enantiomers of both the spirosulfurane (2) and the sulfoxide (10) was evaluated from the respective ^1H NMR spectra recorded with added amounts of an Eu-optishift reagent. In each case the enantiomeric purity proved to be higher than 95%.
9. cf. a) S. Oae and T. Numata, Tetrahedron, 32, 2699 (1976) and references cited therein; b) I. Kapovits, J. Rábai, F. Ruff and Á. Kucsman, to be published.
10. The convention proposed in Ref. 2b was used in designating the configuration of the spirosulfurane (2).
11. R.J. Kurland, M.B. Rubin and W.B. Wyse, J. Chem. Phys., 40, 2426 (1964).
12. a) R.J. Gillespie and R.S. Nyholm, Quart. Rev. Chem. Soc., 11, 339 (1957); b) R.J. Gillespie, "Molecular Geometry", van Nostrand Reinhold, Princeton, 1972.