Table IV. Distances (Å) between Ring Centroids and Oxygen Atoms and Angles (Degrees) between the Normals to the Phenyl Rings of Each Molecule

| Compd | Ring A center to ring C center | Ring A center to oxygen | Ring C center to oxygen | Angle between normals |
|---|---|---|---|---|
| 1[a] | 4.84 | 5.68 | 5.51 | 90 |
| 2 | 5.06 | 5.34 | 6.68 | 125.3 |
| 3 | 5.06 | 4.99 | 6.46 | 118.4 |
| 3[b] | 5.02 | 4.95 | 6.52 | 112.2 |
| 4 | 4.93 | 4.92 | 6.48 | 114.2 |

[a]References 1 and 2. [b]Values obtained for crystallographically independent molecule.

1. The separation of the ring centroids in 3 is the same as in 2 and only slightly greater than that found in 4; yet, the biological activity of 2 is much greater than that of 3 or 4.

2. The ring C to oxygen distances in 3 and 4 are about the same as those in 2, whereas the corresponding distance in 1 is about 1 Å shorter. On the other hand, the ring A to oxygen distances in 3 and 4 are both within 0.4 Å of that in 2.

3. Next consider the angles between the normals to the aromatic rings in these molecules. The angles in 2, 3, and 4 are approximately 120° whereas the angle in 1 is near 90°. Thus, there is no correlation between the anticonvulsant activity and this parameter (at least as observed in the crystalline state).

Figure 3 shows 3 superimposed upon 2 in such a manner as to have the rings coincident. It can be seen that the conformations of the two molecules are remarkably similar. There is only a small difference in the orientation of the C rings which is probably due to crystal packing forces. The only chemical difference between 2 and 3 is the 4′ substituent. It has been generally observed that 4′-substituted benzodiazepines show minimal pharmacological activity.[8,‡]

Although a separate figure showing 4 superimposed on 2 is not presented here, it is apparent from Figures 2 and 3 that the conformation of 4 is almost identical with that of 2 and 3.

For contrast, Figure 4 shows 1 superimposed on 2 so as to achieve the "best" overlap of the phenyl rings and corresponding oxygen atoms. It can be seen that there is a certain similarity in the conformation of these two active compounds, but the conformational similarity is by far not as pronounced as that found between 2 and 3.

## Conclusion

Compounds 3 and 4 are more closely related, structurally and conformationally, to diazepam than diphenylhydantoin. Nonetheless, the three benzodiazepines exhibit marked differences in their anticonvulsant properties.

These findings show that conformational similarities of molecules do not necessarily indicate similar biological properties. Many other factors, many still unknown, play an important role in the biological activity of chemical entities.

**Supplementary Material Available.** Tables of the atomic parameters, observed and calculated structure factors, bond lengths, and angles will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JMED-74-374.

‡ For a description of the tests, see ref 9.

## References


(1) E. A. Swinyard and L. S. Goodman in "Antiepileptic Drugs," D. M. Woodbury, J. K. Penry, and R. P. Schmidt, Ed., Raven Press, New York, N. Y., 1972.
(2) A. Camerman and N. Camerman, *Science*, **168**, 1457 (1970).
(3) A. Camerman and N. Camerman, *J. Amer. Chem. Soc.*, **94**, 268 (1972).
(4) A. Camerman and N. Camerman, *Acta Crystallogr., Sect. B*, **27**, 2205 (1971).
(5) (a) A. Camerman and N. Camerman, *Mol. Pharmacol.*, **7**, 406 (1971); (b) *J. Amer. Chem. Soc.*, **94**, 8553 (1972).
(6) L. H. Sternbach, R. Ian Fryer, W. Metlesics, E. Reeder, G. Sach, G. Saucy, and A. Stempel, *J. Org. Chem.*, **27**, 3788 (1962).
(7) G. Germain, P. Main, and M. M. Woolfson, *Acta Crystallogr., Sect. B*, **26**, 274 (1970).
(8) L. H. Sternbach, L. O. Randall, R. Banziger, and H. Lehr in "Drugs Affecting the Central Nervous System," Vol. 2, A. Burger, Ed., Marcel Dekker, New York, N. Y., 1968, Chapter 6.
(9) L. H. Sternbach, G. A. Archer, J. V. Early, R. I. Fryer, E. Reeder, N. Wasyliw, L. O. Randall, and R. Banziger, *J. Med. Chem.*, **8**, 815 (1965).


## Determination of the Absolute Configuration of (+)-2-(6-Methoxy-2-naphthyl)propionic Acid†


J. Riegl, M. L. Maddox, and I. T. Harrison*

*Syntex Research, Stanford Industrial Park, Palo Alto, California 94304.*

*Received September 12, 1973*

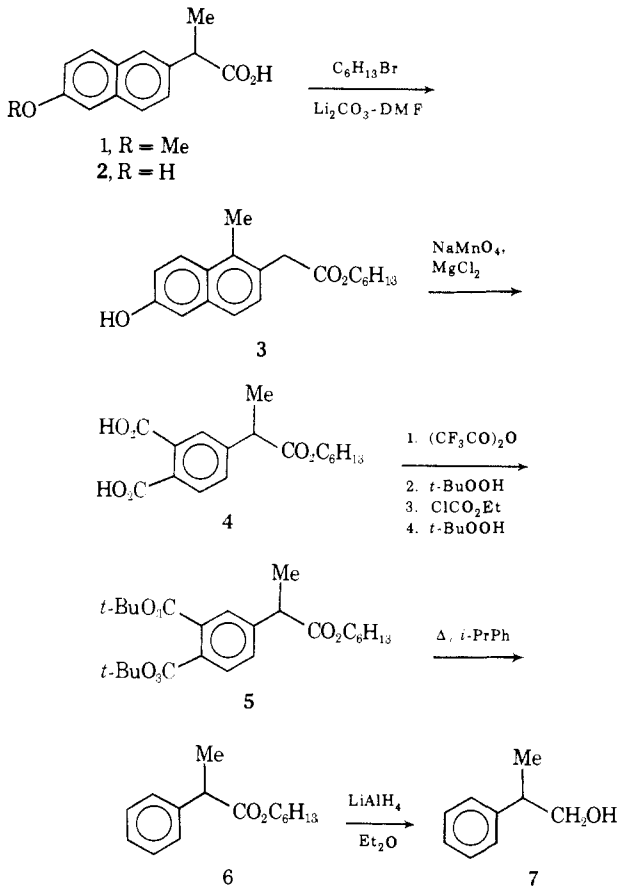
We have determined the absolute stereochemistry of the antiinflammatory agent (+)-2-(6-methoxy-2-naphthyl)propionic acid (naproxen,[1] 1) by degradation to (−)-2-phenyl-1-propanol (7), a substance of known[2] *S* chirality.

Reaction of (+)-2-(6-methoxy-2-naphthyl)propionic acid (1) with hydrogen bromide in acetic acid cleaved the methyl ether forming the phenolic acid 2, which was converted to the hexyl ester 3. Oxidation of 3 with sodium permanganate under buffered conditions gave the phthalic acid derivative 4, which was decarboxylated[3] by pyrolysis of the bis-*tert*-butyl peroxy ester 5 forming hexyl 2-phenylpropionate (6). Reduction of 6 with lithium aluminum hydride gave 2-phenyl-1-propanol (7) (Scheme I). Identification of 7 as the (−) antipode by measurement of the optical rotation was not considered conclusive on account of the small angles (7°) involved. However, identification was readily made by comparison with authentic samples of (−)- and (±)-7 by nmr in the presence of the chiral shift reagent tris[3-(trifluoromethylhydroxymethylene)-*d*-camphorato]europium.[4] In the presence of 0.52 equiv of the shift reagent, a pair of doublets at 10.28 and 10.43 ppm was observed for the ortho protons of the phenyl group of (±)-7. The low-field doublet was shown to be due to the (−) antipode by addition of small amounts of authentic (−)-7. In the presence of 0.67 equiv of the shift reagent, only one doublet at 10.48 ppm was observed for 7 derived from naproxen. This was unambiguously identified as the (−) antipode by addition of authentic (−)-7.

Interconversions have been made[5-9] between optically resolved adjacent members of the series: tartaric acid, D-glyceraldehyde, serine, alanine, 2-phenylpropionic acid, and 2-phenyl-1-propanol, and the absolute configuration

†Publication No. 408 from the Syntex Institute of Organic Chemistry.

**Scheme I**




of tartaric acid has been determined[10] by a modified X-ray diffraction technique. It has thereby been shown[2] that (−)-2-phenylpropanol has the *S* configuration. Naproxen must also have the *S* configuration. The more active antipodes of antiinflammatory indan-1-carboxylic acids have previously been assigned the *S* configuration by ORD methods.[11] The ORD curve of naproxen was more complex than anticipated, precluding the use of this method.

## Experimental Section

Melting points were taken on a Mel-Temp apparatus and are corrected. A Perkin-Elmer 137 spectrophotometer was used to record the ir spectra. Nmr spectra were determined on a Varian Associates HA-100 spectrometer using $Me_4Si$ as internal standard. Optical rotations were measured with a Perkin-Elmer 141 polarimeter. Cyclohexanedimethanol succinate was used as stationary phase for gas chromatography. Satisfactory ir and nmr spectra were obtained for compounds **2**–**7**. Analyses indicated only by symbols of the elements were within ±0.4% of the theoretical values.

**(+)-2-(6-Hydroxy-2-naphthyl)propionic Acid (2).** A mixture of naproxen (**1**, 100 g, 0.43 mol), 48% HBr (250 ml), and AcOH (250 ml) was heated under reflux for 1.5 hr. Dilution of the cooled mixture with water followed by filtration gave **2** (81 g, 86%), mp 188–191°, $[\alpha]^{25}D$ +94° (Pyr), after recrystallization from EtOH. *Anal.* ($C_{13}H_{12}O_3$) C, H.

**(+)-Hexyl 2-(6-Hydroxy-2-naphthyl)propionate (3).** A mixture of **2** (14 g, 0.065 mol), $Li_2CO_3$ (14 g, 0.19 mol), hexyl bromide (20 g, 0.12 mol), and DMF (200 ml) was heated to 90° for 4 hr. After the addition of hexane and water, insoluble material was removed by filtration. The hexane layer was separated and washed with sodium bicarbonate solution and with water. Evaporation of solvent and excess hexyl bromide *in vacuo* gave **3** (18 g, 93%), mp 74–76°, $[\alpha]^{25}D$ +32° ($CHCl_3$), after recrystallization from hexane. *Anal.* ($C_{19}H_{24}O_3$) C, H.

**(+)-Hexyl 2-(3,4-Dicarboxyphenyl)propionate (4).** To a solution of the ester **3** (24 g, 0.08 mol) in acetone (400 ml) was added during 0.5 hr a solution of $NaMnO_4$ (20 g, 0.14 mol) and $MgCl_2$ (20 g, 0.21 mol) in water (75 ml) and the solution stirred for a further 3 hr. The precipitated $MnO_2$ was removed by filtration and washed with acetone and with water. The filtrate was acidified and extracted with ether. The acidic product was then extracted into sodium bicarbonate solution which was separated, acidified, and extracted with ether giving the acid **4** (2.1 g, 8%), $[\alpha]^{25}D$ +15° ($CHCl_3$).

**Hexyl 2-(3,4-Di-*tert*-butylperoxycarbonylphenyl)propionate (5).** A solution of **4** (410 mg, 1.27 mmol) in trifluoroacetic anhydride (5 ml) was kept at 20° for 30 min. Evaporation of the reagent and chromatography of the residue in $CH_2Cl_2$ on silica gel gave the anhydride (290 mg, 75%): ir (film) 1852, 1779 (anhydride) and 1730 $cm^{-1}$. *Anal.* ($C_{17}H_{20}O_5$) C, H. A solution of the anhydride (810 mg, 2.66 mmol) in dry benzene (6 ml) at 0° was treated with *tert*-butyl hydroperoxide (0.6 ml) and $Et_3N$ (0.6 ml, 4.38 mmol). After 1 hr the solution was evaporated *in vacuo;* dry THF (8 ml) and $Et_3N$ (0.37 ml, 2.7 mmol) were added and cooled to −25°. To this solution was added ethyl chloroformate (0.3 ml, 3.14 mmol) followed, after 30 min, by *tert*-butyl hydroperoxide (0.3 ml). After a further 30 min, the mixture was warmed up to −5° and a further quantity of $Et_3N$ (0.37 ml, 2.7 mmol) was added. After an additional 1 hr, the mixture was poured into dilute HCl and ether. The ether layer was separated and washed with sodium bicarbonate solution and with water, and the solvent was removed giving **5** (420 mg, 71%).

**Hexyl 2-Phenylpropionate (6) and 2-Phenylpropanol (7).** A solution of the perester **5** (250 mg, 0.54 mmol) in isopropylbenzene (10 ml) was heated under reflux for 3 hr and the solvent fractionated off through a Vigreux column. The residue was distilled at 130° (bath temperature) and 3 mm of pressure giving **6** (64.5 mg, 51%). *Anal.* ($C_{15}H_{22}O_2$) H; C: calcd, 76.88; found, 77.38. A solution of **6** (64 mg, 0.27 mmol) in ether (10 ml) at 0° was treated with lithium aluminum hydride (150 mg, 3.9 mmol). After 1 hr excess reagent was decomposed by addition of acetone and water (1 ml). The mixture was filtered and the ether distilled from the filtrate giving **7** (35 mg, 94%), which was purified by gas chromatography. Pure material had the same retention time on 200-ft capillary columns as authentic samples: *m/e* 136 ($M^+$). The nmr spectrum ($CCl_4$) in the presence of tris[3-(trifluoromethylhydroxymethylene)-*d*-camphorato]europium was identical with that of authentic samples of (−)-**7**.

## References

(1) I. T. Harrison, B. Lewis, P. Nelson, W. Rooks, A. Roszkowski, A. Tomolonis, and J. H. Fried, *J. Med. Chem.*, **13**, 203 (1970).
(2) M. B. Watson and G. W. Youngson, *J. Chem. Soc., Perkin Trans. 1*, 1597 (1972).
(3) K. B. Wiberg, B. R. Lowry, and T. H. Colby, *J. Amer. Chem. Soc.*, **83**, 3998 (1961).
(4) H. L. Goering, J. N. Eikenberry, and G. S. Koermer, *J. Amer. Chem. Soc.*, **93**, 5913 (1971).
(5) A. Wohl and F. Momber, *Ber.*, **47**, 3346 (1914); **50**, 455 (1917).
(6) P. Brewster, E. D. Hughes, C. K. Ingold, and P. A. D. S. Rao, *Nature (London)*, **166**, 178 (1950).
(7) E. Fischer and K. Raske, *Ber.*, **40**, 3717 (1907).
(8) H. I. Bernstein and F. C. Whitmore, *J. Amer. Chem. Soc.*, **61**, 1324 (1939).
(9) G. Fodor and G. Csepreghy, *J. Chem. Soc.*, 3222 (1961).
(10) J. M. Bijvoet, A. F. Peerdeman, and A. J. van Bommel, *Nature (London)*, **168**, 271 (1951).
(11) P. F. Juby, W. R. Goodwin, T. W. Hudyma, and R. A. Partyka, *J. Med. Chem.*, **15**, 1297 (1972).

## Anticonvulsant Activity of Substituted Indolealkylamines†

V. K. Agarwal, A. K. Chaturvedi, T. K. Gupta, Surendra S. Parmar,* and Benjamin De Boer

*Department of Pharmacology and Therapeutics, King George's Medical College, Lucknow University, Lucknow 3, India, and Department of Physiology and Pharmacology, University of North Dakota School of Medicine, Grand Forks, North Dakota 58201.*
*Received August 6, 1973*

Administration of 5-hydroxytryptamine, an indolealkylamine, for several days has been shown to develop an an-