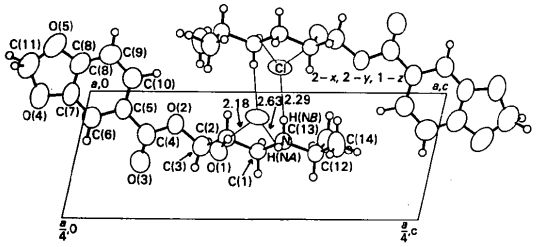


Fig. 3. Packing view down *b*; cation–chloride contact distances (Å).

A previous survey (Ammon *et al.*, 1975), which showed a clear relationship between the Ar–CH(OH) (I) and Ar–O–CH_2–CH(OH) (II) moieties, found that the angle between the aromatic ring and the C(3)–C(2)–C(1)–N plane in class (I) drugs and the angle between the C(3)–O(2)–C(4)–C(5) and C(3)–C(2)–C(1)–N planes in class (II) drugs both fell in the *narrow* range of 56·6–87·0° for nine adrenergic drugs (adrenaline tartrate was the exception at 2·8°). We have made a more recent survey of sixteen class (II) compounds and found a range of 6·3–87·8° for the angle between the C(3)–O(2)–C(4)–C(5) and C(3)–C(2)–C(1)–N planes. In (IV), the corresponding angle, between C(3)–O(2)–C(4)–O(3) and C(3)–C(2)–C(1)–N, is 44·1 (3)°.

A packing diagram is given in Fig. 3. The molecules are elongated approximately parallel to [001]. The only intermolecular contact less than van der Waals distances between the organic cations is N–O(1) (at $1-x, 2-y, 1-z$) of 3·070 (2) Å. The principal cation···chloride interactions involve strong O–H···Cl^- (at $2-x, 2-y, 1-z$) and N–H···Cl^- (at x, y, z) contacts of 2·18 (3) and 2·29 (2) Å respectively, and a weaker N–H···Cl^- (at $2-x, 2-y, 1-z$) contact of 2·63 (2) Å. These distances change to 2·08 (3) and 2·14 (2) Å respectively for 'corrected' O–H and N–H hydrogen-atom positions (O–H = 0·97, N–H = 1·03 Å).

This work was supported in part through the facilities of the University of Maryland Computer Science Center and through a grant from the Progetto finalizzato del CNR Chimica Fine e Secondaria.

References

AMMON, H. L., BALSAMO, A., MACCHIA, B., MACCHIA, F., HOWE, D.-B. & KEEFE, W. E. (1975). *Experienta*, **31**, 644–646.

AMMON, H. L., HOWE, D.-B., ERHARDT, W. D., BALSAMO, A., MACCHIA, B., MACCHIA, F. & KEEFE, W. E. (1977). *Acta Cryst.* B**33**, 21–29.

ARIENS, E. J. (1967). *Ann. NY Acad. Sci.* **139**, 606–631.

BARRETT, A. M. (1972). *Drug Design*, edited by E. J. ARIENS, Vol. 3, p. 205. New York: Academic Press.

CROMER, D. T. & MANN, J. B. (1968). *Acta Cryst.* A**24**, 321–324.

CROMER, W. T. (1970). *Am. Chem. Soc. 160th National Meeting Abstracts*, p. 14a. Washington: American Chemical Society.

DANGOUMAU, J., BARRANS, Y. & COTRAIT, M. (1973). *J. Pharmacol.* **4**, 5.

JEN, T. & KAISER, C. (1977). *J. Med. Chem.* **20**, 693–698.

JOHNSON, C. K. (1971). *ORTEPII*. Report ORNL-3794, revised. Oak Ridge National Laboratory, Tennessee.

KAISER, C., JEN, T., GARVEY, E., BOWEN, W. D., COLELLA, D. F. & WARDELL, J. R. JR (1977). *J. Med. Chem.* **20**, 687–692.

LÖVGREN, K., HEDBERG, A. & NILSSON, J. L. G. (1980). *J. Med. Chem.* **23**, 624–627.

MACCHIA, B., MACCHIA, F. & MARTINELLI, A. (1980). *Eur. J. Med. Chem.* **15**, 515–520.

MACCHIA, B., MACCHIA, F. & MARTINELLI, A. (1983). *Eur. J. Med. Chem. Chim. Ther.* **18**, 85–90.

MAIN, P., FISKE, S. J., HULL, S. E., LESSINGER, L., GERMAIN, G., DECLERCQ, J.-P. & WOOLFSON, M. M. (1980). *MULTAN80. A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data.* Univs. of York, England, and Louvain, Belgium.

PETRONGOLO, C., MACCHIA, B., MACCHIA, F. & MARTINELLI, A. (1977). *J. Med. Chem.* **20**, 1645–1653.

STEWART, J. M., MACHIN, P. A., DICKINSON, C. W., AMMON, H. L., HECK, H. & FLACK, H. (1976). The *XRAY* system. Tech. Rep. TR-446. Computer Science Center, Univ. of Maryland, College Park, Maryland.

STEWART, R. F., DAVIDSON, E. R. & SIMPSON, W. T. (1965). *J. Chem. Phys.* **42**, 3175–3187.

TATSUNO, H., GOTO, K., SHIGENOBU, K., KASUYA, Y., OBASE, H., YAMADA, Y. & KUDO, S. (1977). *J. Med. Chem.* **20**, 394–397.

ZAAGSMA, J. (1979). *J. Med. Chem.* **22**, 441–449.

Acta Cryst. (1986). C**42**, 449–451

Nonsteroidal Antiinflammatory Drugs. II. Structure of (2-Ethoxy-5-indanyl)acetic Acid

BY TADASHI HATA, SADAO SATO AND CHIHIRO TAMURA

Analytical and Metabolic Research Laboratoires, Sankyo Co. Ltd, 1-2-58 *Hiromachi, Shinagawa-ku, Tokyo* 140, *Japan*

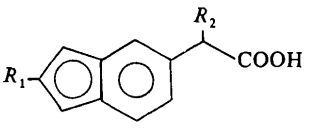
(*Received* 12 *September* 1985; *accepted* 12 *November* 1985)

Abstract. $C_{13}H_{16}O_3$, $M_r = 220·3$, triclinic, $P\bar{1}$, $a = 10·950$ (3), $b = 11·699$ (3), $c = 4·721$ (1) Å, $\alpha = 83·39$ (2), $\beta = 104·14$ (3), $\gamma = 88·53$ (3)°, $V = 581·6$ (3) Å^3, $Z = 2$, $D_x = 1·26$ g cm^{-3}, graphite-monochromated Cu $K\alpha$, $\lambda = 1·5418$ Å, $\mu = 7·3$ cm^{-1}, $F(000) = 236$, $T = 298$ K, final $R = 0·095$ for 1032

0108-2701/86/040449-03$01.50

reflections. The torsion angle of the carboxyl group with respect to the benzene ring in phenylacetic acids shows that the orientation of the carboxylic acids is less restricted than in 2-phenylpropionic acids. The five-membered ring of the indan moiety takes an envelope conformation with an axial ethoxy group.

Introduction. In the course of a series of studies into non-steroidal antiinflammatory drugs, several indanylpropionic and acetic acid derivatives were synthesized, among which 2-(2-isopropyl-5-indanyl)propionic acid (I*a*) exhibited particularly potent activity (Yoshida *et al.*, 1980). In the crystalline state of this compound, the five-membered-ring system of indan adopts an envelope conformation with the isopropyl group in an equatorial position (Hata, Sato & Tamura, 1986). Since the ethoxy and methoxy derivatives (I*b*)–(I*d*) have shown rather poor activities, the crystal structure determination of the title compound (I*b*) was undertaken to compare its structural characteristics with those of the related active compounds.



(I)

(*a*) $R_1 = CH(CH_3)_2$ $R_2 = Me$
(*b*) $R_1 = OEt$ $R_2 = H$
(*c*) $R_1 = OMe$ $R_2 = Me$
(*d*) $R_1 = OMe$ $R_2 = H$

Experimental. Colorless prisms grown from hexane solution by slow evaporation of a solution in a mixture of diethyl ether and hexane at room temperature; approximate crystal dimensions 0·1 × 0·1 × 0·9 mm. Crystal twinned on (001) plane but ratio of twinned fragments is 1:0·26. *hk*0 reflections multiplied by 0·79. Rigaku-Denki AFC-5 automated diffractometer, graphite-monochromated Cu $K\alpha$. Seventeen reflections with $17 < 2\theta < 30°$ used to determine cell parameters. No absorption correction. $2\theta_{max} = 120°$, ω–2θ scan, range of *hkl*: −11–11, −12–13, 0–5. No significant variation in intensities of three standard reflections. 1737 reflections measured; 1032 unique with $F \geq 3\sigma(F)$ used for structure solution and refinement.Structure solved by direct methods using *MULTAN*78 (Main, Hull, Lessinger, Germain, Declercq & Woolfson, 1978). Full-matrix least-squares refinement based on F for non-H atoms with anisotropic thermal parameters. H-atom positions determined from difference Fourier syntheses and refined with isotropic thermal parameters. Thermal parameters of H atoms fixed ($B = 13·0$ Å^2). Final refinement converged at $R = 0·095$, $wR = 0·065$, $S = 0·71$; $w = 1/\sigma^2(F)$; $(\Delta/\sigma)_{max}$ 0·01 for non-H atoms, 0·17 for H atoms. Further improvement of the discrepancy factor by another weighting scheme failed owing to crystal twinning and to some disorder of the ethoxy group. Max. peak height on final $\Delta\rho$ map 0·2 e Å^{-3}. Atomic scattering factors from *International Tables for X-ray Crystallography* (1974). Calculations performed with the *DIRECT-SEARCH* program system described by Koyama & Okada (1975).

Discussion. Fractional atomic coordinates and equivalent isotropic thermal parameters are given in Table 1.* The atom labelling and the anisotropic thermal ellipsoids are shown in Fig. 1. Bond lengths and angles are given in Table 2. They are all normal within the limits of experimental error.

The torsional angles C(2)–C(1)–C(7)–C(8) and C(1)–C(7)–C(8)–O(9) in the acetic acid side chain are 101·5 (10) and 25·7 (15)°, respectively. As shown in Table 3, these angles in some phenylacetic acids have been reported to be 38·2–112·6 and −98·4–25·7°, respectively. In contrast, the corresponding angles of 2-phenylpropionic acid side chains of the antiinflammatory drugs are 96·4–117·7 and 77·3–90·2°, respectively. Therefore, the side chains of acetic acids may rotate more freely than those of propionic acids.

The five-membered ring system of the indan moiety adopts an envelope-shaped conformation wherein the C(12) atom, to which the ethoxy group is connected in the axial position, is displaced by 0·40 (2) Å from the plane through the other four atoms of the ring, whereas the five-membered ring of the most active compound (I*a*) has been reported to take an envelope conformation with the isopropyl group in the equatorial position (Hata, Sato & Tamura, 1986). Therefore, the model compounds of 2-ethoxy- and 2-isopropylindan were of interest in performing the empirical force-field energy calculation using the program *MM2'* (Jaime & Ōsawa, 1983). This would provide data for substituent effects on the conformation in solution. For both cases of axial and equatorial conformations in the model compounds, various rotamers were generated by simultaneously varying the torsional angles, τ_1 and τ_2, at intervals of 10° and optimized. These angles correspond to C(11)–C(12)–O(14)–C(15) and C(12)–O(14)–C(15)–C(16) of the title compound. The observed torsional angles of the title compound in the crystalline state were $\tau_1 = -76·8$ (10) and $\tau_2 = 164·8$ (8)°, close to those angles of the global minimum-energy conformation with the axial 2-ethoxy group ($\tau_1 = -85$ and $\tau_2 = 175°$), which is only 1·34 kJ mol^{-1} higher in energy than that of the

* Lists of structure factors, anisotropic thermal parameters and H-atom coordinates have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 42639 (10 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

equatorial conformation. In contrast, similar calculations for 2-isopropylindan indicated that the global-minimum conformation with an equatorial isopropyl group was more stable than that with an axial substituent by 10·3 kJ mol^{-1}. The potently active compound (*Ia*) exhibits a strong preference for an equatorial-substituent conformation, while less-active compounds seem to adopt this only to a small degree. Therefore, we suppose that this equatorial conformation may influence the antiinflammatory activity.

The molecules form centrosymmetric dimers *via* hydrogen bonds between the carbonyl groups. The O(9)···O(10) hydrogen-bond length is 2·651 (9) Å.

We thank Professor E. Ōsawa of Hokkaido University for kindly supplying the program *MM2'* and Dr A. Terada of The Chemical Research Laboratories of our company for providing samples.

Table 1. *Fractional atomic coordinates* (×10^4) *and equivalent isotropic thermal parameters, with e.s.d.s in parentheses*

$B_{eq} = \frac{1}{3}\sum_i\sum_j B_{ij}a_i^*a_j^*\mathbf{a}_i.\mathbf{a}_j$.

	x	y	z	B_{eq}(Å^2)
C(1)	1633 (7)	3065 (7)	3225 (17)	2·9 (3)
C(2)	509 (8)	3566 (7)	3486 (18)	3·0 (3)
C(3)	−197 (7)	2950 (6)	5088 (16)	2·4 (2)
C(4)	205 (7)	1852 (7)	6520 (16)	2·6 (3)
C(5)	1318 (8)	1348 (8)	6257 (19)	3·3 (3)
C(6)	2041 (7)	1960 (8)	4559 (18)	3·4 (3)
C(7)	2386 (8)	3734 (8)	1323 (20)	3·5 (3)
C(8)	3486 (7)	4289 (7)	3056 (22)	3·4 (3)
O(9)	4043 (5)	3940 (5)	5645 (14)	4·6 (2)
O(10)	3897 (6)	5124 (6)	1567 (13)	5·0 (2)
C(11)	−1444 (8)	3304 (7)	5676 (22)	3·5 (3)
C(12)	−1907 (8)	2164 (7)	6826 (19)	3·3 (3)
C(13)	−749 (8)	1383 (8)	8130 (21)	3·4 (3)
O(14)	−2668 (5)	1625 (4)	4439 (13)	4·2 (2)
C(15)	−3891 (10)	2102 (12)	3320 (30)	6·8 (5)
C(16)	−4662 (11)	1292 (12)	1497 (32)	7·5 (5)

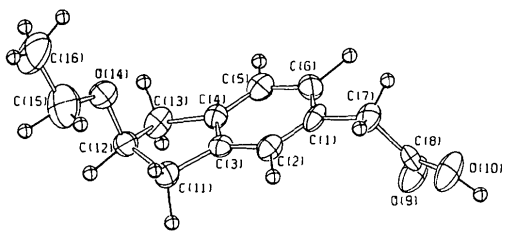


Fig. 1. *ORTEP* plot (Johnson 1965) of the title compound with thermal ellipsoids at the 50% probability level.

Table 2. *Bond lengths* (Å) *and bond angles* (°) *with e.s.d.'s in parentheses*

C(1)–C(2)	1·389 (12)	C(7)–C(8)	1·491 (12)
C(1)–C(6)	1·383 (11)	C(8)–O(9)	1·242 (11)
C(1)–C(7)	1·527 (13)	C(8)–O(10)	1·293 (11)
C(2)–C(3)	1·371 (12)	C(11)–C(12)	1·527 (12)
C(3)–C(4)	1·389 (10)	C(12)–C(13)	1·500 (11)
C(3)–C(11)	1·515 (12)	C(12)–O(14)	1·447 (10)
C(4)–C(5)	1·379 (12)	O(14)–C(15)	1·389 (12)
C(4)–C(13)	1·514 (13)	C(15)–C(16)	1·492 (19)
C(5)–C(6)	1·410 (13)		
C(2)–C(1)–C(6)	120·8 (8)	C(1)–C(7)–C(8)	113·6 (8)
C(2)–C(1)–C(7)	118·8 (7)	C(7)–C(8)–O(9)	124·1 (8)
C(6)–C(1)–C(7)	120·3 (8)	C(7)–C(8)–O(10)	114·4 (8)
C(1)–C(2)–C(3)	119·1 (7)	O(9)–C(8)–O(10)	121·2 (7)
C(2)–C(3)–C(4)	121·4 (7)	C(3)–C(11)–C(12)	103·3 (6)
C(2)–C(3)–C(11)	128·9 (7)	C(11)–C(12)–C(13)	106·1 (7)
C(4)–C(3)–C(11)	109·7 (7)	C(11)–C(12)–O(14)	111·0 (7)
C(3)–C(4)–C(5)	119·7 (8)	C(13)–C(12)–O(14)	106·8 (7)
C(3)–C(4)–C(13)	110·0 (7)	C(4)–C(13)–C(12)	104·0 (7)
C(5)–C(4)–C(13)	130·2 (7)	C(12)–O(14)–C(15)	115·3 (8)
C(4)–C(5)–C(6)	119·6 (8)	O(14)–C(15)–C(16)	109·5 (11)
C(1)–C(6)–C(5)	119·4 (8)		

Table 3. *Torsional angles* (°) *of the carboxyl groups in some phenylacetic and 2-phenylpropionic acids*

Compound	Torsional angles C(2)–C(1)–C(7)–C(8)	Torsional angles C(1)–C(7)–C(8)–O(9)
Phenylacetic acids	38·2–112·6	−98·4–25·7
present compound	101·5	25·7
4-(benzyloxy)phenylacetic acid[a]	85·8, 38·2	−98·4, −90·7
4-(phenoxymethyl)phenylacetic acid[b]	112·6	7·7
2-Phenylpropionic acids	96·4–111·7	77·3–90·2
ibuprofen[c]	96·4	89·3
flurbiprofen[d]	107·7	77·3
naproxen[e]	111·7	90·2

References: (*a*) Bats & Canenbley (1984*a*); (*b*) Bats & Canenbley (1984*b*); (*c*) McConnell (1974); (*d*) Flippen & Gilardi (1975); (*e*) Ravikumar, Rajan, Pattabhi & Gabe (1985).

References

BATS, J. W. & CANENBLEY, R. (1984*a*). *Acta Cryst.* C**40**, 993–995.

BATS, J. W. & CANENBLEY, R. (1984*b*). *Acta Cryst.* C**40**, 995–997.

FLIPPEN, J. L. & GILARDI, R. D. (1975). *Acta Cryst.* B**31**, 926–928.

HATA, T., SATO, S. & TAMURA, C. (1986). *Acta Cryst.* C**42**, 96–98.

International Tables for X-ray Crystallography (1974). Vol. IV. Birmingham: Kynoch Press. (Present distributor D. Reidel, Dordrecht.)

JAIME, C. & ŌSAWA, E. (1983). *Tetrahedron*, **39**, 2769–2778.

JOHNSON, C. K. (1965). *ORTEP*. Report ORNL-3794. Oak Ridge National Laboratory, Tennessee.

KOYAMA, Y. & OKADA, K. (1975). *Acta Cryst.* A**31**, S18.

MCCONNELL, J. F. (1974). *Cryst. Struct. Commun.* **3**, 73–75.

MAIN, P., HULL, S. E., LESSINGER, L., GERMAIN, G., DECLERCQ, J.-P. & WOOLFSON, M. M. (1978). *MULTAN*78. *A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data*. Univs. of York, England, and Louvain, Belgium.

RAVIKUMAR, K., RAJAN, S. S., PATTABHI, V. & GABE, E. J. (1985). *Acta Cryst.* C**41**, 280–282.

YOSHIDA, N., TERADA, A., TOMITA, K., WACHI, K., NARUTO, S., TANAKA, S., MIYAZAWA, H., TANAKA, K., MISAKA, E., IIZUKA, Y., UMEMURO, Y., KOJIMA, T. & TACHIKAWA, R. (1980). *Ann. Rep. Sankyo Res. Lab.* **32**, 65–72.