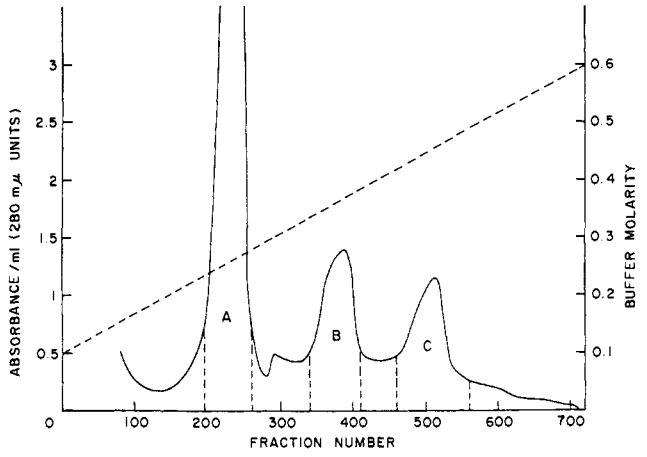

Figure 4. Chromatography of the reaction mixture in the preparation of the tridecanucleotide d-EtSpTpTpA^{Bz}pA^{Bz}pTpC^{An}pC^{An}-pA^{Bz}pTpA^{Bz}pTpG^{i-Bu}pC^{An}. For explanation of the peaks, see text.

plied to a DEAE-cellulose column (65 × 2 cm) which was eluted with a gradient of 6 l. of 0.1 *M* bicarbonate buffer in the mixing vessel and 6 l. of 0.6 *M* buffer in the reservoir. The chromatographic pattern is shown in Figure 4. Paper chromatographic examination of hydrolyzed aliquots in system C for 3 days showed that peak A contained d-pA^{Bz}-pTpG^{i-Bu}pC^{As}, peak B contained the starting nonamer, and C the required tridecamer. Peak C was evaporated to dryness to give 5.3 μmol (23%) of **2**.

Preparation of *S*-Ethyl Tridecamer 3. A sample of **2** (100 OD_{280} units) was hydrolyzed using concentrated ammonium hydroxide (3 ml) for 18 hr at room temperature, and then evaporated to dryness. The residue was dissolved in 75 ml of a solution containing 0.05 *M* sodium chloride, 7 *M* urea, and 0.2 *M* Tris, pH 7.4, and applied to a DEAE column (52 × 2 cm, chloride form) which had been preequilibrated with the same buffer. A linear gradient was immediately applied, consisting of 1 l. of the original buffer in the mixing vessel and 1 l. of a solution containing 0.3 *M* sodium chloride, 7 *M* urea, and 0.2 *M* Tris, pH 7.4 in the reservoir. The column was run at room temperature and 6-ml fractions were collected. Tubes 301–329 contained the only nucleotidic peak to be eluted from the column (57 OD_{260} units). Aliquots (60 ml) of this solution were freed from salts and urea by passage through a column of Bio-Gel P-2 (130 × 2 cm, 100–200 mesh, Bio-Rad Labs) which was eluted with water. In this way, 40 OD_{260} units of *S*-ethyl tridecamer **3** were obtained. Molecular weight[18] was 4200 (calculated 4036).

Unprotected Tridecamer 1. A sample (100 OD_{280} units) of **2** was treated with concentrated ammonium hydroxide (3 ml) overnight at room temperature, and evaporated to dryness. Aqueous pyridine (50%, 1 ml) was added, followed by a solution of iodine (10 mg) in acetone (1 ml). After storage overnight, the solution was diluted to 25 ml with a buffer solution containing 0.05 *M* sodium chloride, 7 *M* urea, and 0.2 *M* Tris, pH 7.4, and applied to a DEAE-cellulose column (52 × 2 cm, chloride form). A gradient was applied, consisting of 1.5 l. of the original buffer in the mixing vessel, and 1.5 l. of a solution containing 0.5 *M* sodium chloride, 7 *M* urea, and 0.2 *M* Tris, pH 7.4, in the reservoir. The nucleotidic material was obtained in fractions 250–270. Salts and urea were removed using a Bio-Gel P-2 column as described in the preparation of **3**. Fourteen OD_{260} units of the unprotected tridecamer **1** were obtained. Molecular weight[18] was 4180 (calculated 3992).

Acknowledgments. We are indebted to Mr. T. F. Gabriel for analytical data, to Dr. C. L. Harvey for enzymological experiments, and to Dr. P. Bartl and Mr. D. Luk for molecular weight determinations.

Crystal and Molecular Structure of an Antiinflammatory Agent, Indomethacin, 1-(*p*-Chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic Acid[1]

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Abstract: The crystal and molecular structure of the antiinflammatory agent indomethacin has been determined by single-crystal X-ray diffraction methods. Crystals of indomethacin, 1-(*p*-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid, were grown from anhydrous acetonitrile. The crystals are triclinic, space group $P\bar{1}$, with cell constants: $a = 9.295$ (2) Å, $b = 10.969$ (1) Å, $c = 9.742$ (1), Å, $\alpha = 69.38$ (1)°, $\beta = 110.79$ (1)°, $\gamma = 92.78$ (1)°, and $Z = 2$. The calculated density is 1.37 g/cm^3; the observed value is 1.38 (1) g/cm^3. The structural solution was obtained by a routine application of the symbolic-addition method of direct sign determination. Full-matrix least-squares refinement based on 3678 counter-collected X-ray intensities gave a final *R* index of 0.059. The indole, *p*-chlorophenyl, and carboxylic acid groups are each nearly planar. The relative orientation of the *p*-chlorophenyl and indole groups is unusual and may play an important role in the chemistry of indomethacin. The crystal structure exhibits the expected hydrogen bonding of the carboxylic acid groups about centers of inversion to form molecular dimers.

The role of nonsteroidal aryl acids in antiinflammatory chemotherapy is well known. Whitehouse[3] has given a general review of the biochemical and pharmacological properties of antiinflammatory drugs. In particular, Shen[4] has recently summarized these properties for the antiinflammatory agent in-

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(3) M. W. Whitehouse, *Fortschr. Arzneimittelforsch.*, 8, 321 (1965).

(4) T. Y. Shen, private communication (1971).

domethacein (Figure 1), 1-(*p*-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid. He has noted that the biochemical profile of indomethacin may be broadly described in two parts: (1) inhibition of enzymes, notably the proteolytic enzymes, and mediators; (2) effects on cellular membranes. The broad spectrum of activity of indomethacin is probably the basis of its mode of action in the complex antiinflammatory process, its relatively nonspecific clinical efficiency, and its potential side effects.[4]

Our interest in the structural properties of indomethacin is twofold: (1) it was brought to our attention[5] that a structural study of indomethacin might aid in the elucidation of its mechanistic action; (2) there is, somewhat surprisingly, relatively little known about the crystal chemistry of nonsteroidal indole-based derivatives. In respect to the second point, preliminary crystal data on tryptophan hydrobromide,[6] L-tryptophan,[7,8] DL-tryptophan,[9] indole,[10] and several substituted tryptamines[11] have been reported, but complete structures have been reported only for 3-indolylacetic acid,[12] glycyl-L-tryptophan,[13] and the molecular complexes of skatole and indole with *s*-trinitrobenzene.[14]

As an aid in understanding the above mentioned mechanistic studies and to provide further structural data on substituted indoles, we have investigated the solid state structure of indomethacin by X-ray diffraction methods and give a full report of the results here.

Experimental Section

A sample of indomethacin was supplied to us by Dr. Karst Hoogsteen of the Merck Institute of Therapeutic Research, Rahway, N. J. Crystals suitable for X-ray analysis were grown from an acetonitrile solution by slow evaporation of the solvent. Optical and X-ray examination indicated that the crystal system is triclinic. Preliminary cell constants were determined from Weissenberg photographs.

A rectangular prism, 0.15 × 0.17 × 0.22 mm, was mounted with the *a* axis roughly coincident with the ϕ axis of a highly modified General Electric XRD-5 Datex-automated diffractometer. Cell constants were calculated from a least-squares fit to the $(\sin^2\theta)/\lambda^2$ values for 25 high-angle reflections and are tabulated in Table I.

Table I. Crystal Data for Indomethacin

$a = 9.295 \pm 0.002$ A	$C_{19}NO_4ClH_{16}$
$b = 10.969 \pm 0.001$ Å	Mol wt 357.8
$c = 9.742 \pm 0.001$ Å	Space group $P\bar{1}$
$\alpha = 69.38 \pm 0.01°$	$Z = 2$
$\beta = 110.79 \pm 0.01°$	$F(000) = 372$
$\gamma = 92.78 \pm 0.01°$	$D_m = 1.38 \pm 0.01$ g cm^{-3}
$V = 869.8$ Å^3	$D_x = 1.37$
$\lambda(\text{Cu K}\alpha_1) = 1.5405$ Å	

The density was measured by flotation in a mixture of carbon tetrachloride and methylene chloride. One hemisphere of data was collected by the θ–2θ scan technique using Ni-filtered Cu Kα radiation to a 2θ limit of 155°. A total of 3678 reflections was collected under the following experimental conditions: (1) a scan speed of 1°/min; (2) background counts for 20 sec at the beginning and end of the scan range; (3) a scan range that varied from 1.8° at $2\theta = 10°$ to 3.6° at $2\theta = 155°$. Three standard reflections were monitored periodically during the data collection and showed only small, random variations over the period of the experiment. Each reflection was assigned a variance, $\sigma^2(I)$, based on counting statistics plus a term $(0.02S)^2$ where S is the scan count. The 300 reflections with net intensities less than zero were treated in the following way: (1) their contributions to the unweighted residual, R, were taken to be zero; (2) their contributions to the weighted residual, $\Sigma w \cdot (F_o^2 - F_c^2)^2$, were calculated in the normal way. The intensities were corrected for Lorentz and polarization effects. The calculated linear absorption coefficient for copper radiation is 21.66 cm^{-1}; the maximum error due to neglect of absorption effects was estimated to be 8% in the intensities, which we considered sufficiently small to be ignored.

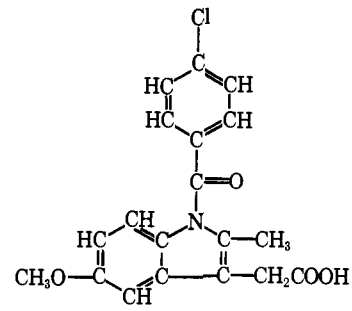

Figure 1. Chemical formula of indomethacin. See Figure 2 for the numbering system used in this analysis.

Solution and Refinement of the Structure. The observed structure amplitudes were placed on an approximately absolute scale by means of a Wilson plot.[15] Normalized structure amplitudes, $|E|$, were calculated in the normal fashion,[16] and a set of Σ_2 interactions[16,17] was tabulated. Consideration of the magnitudes of the $|E|$ values and the number of high probability Σ_2 interactions for each reflection led to an initial set of origin-determining and symbolic[18] signs, Table II. This starting set of signs was input to Long's program[19] and expanded to the 200 E's with magnitudes above 1.78. The most consistent set of signs was that with $A = B = C = D = (-)$. An E map was calculated based on these 200 signed E's and 24 of the 25 nonhydrogen atoms were positioned. The methyl carbon, C(17), on the indole ring was clearly revealed on a subsequent difference Fourier map. The R_1 value, $\Sigma||F_o| - |F_c||/\Sigma|F_o|$, at this stage was 0.33.

Table II. Initial Phasing Data

hkl	$\|E\|$	Sign	Parity
122	3.45	+	oee
276	3.59	+	eoe
$\bar{5}61$	3.77	+	oeo
022	3.06	A	eee
$\bar{6}63$	3.27	B	eeo
$1\bar{4}0$	3.07	C	oee
$39\bar{2}$	3.04	D	ooe

Refinement of the structure was by least-squares, the quantity minimized being $\Sigma w(F_o^2 - S^2F_c^2)^2$, where $1/S$ is the scale factor for F_o. Atomic scattering factors for Cl, C, N, and O were taken from "International Tables for X-ray Crystallography"[20] while the

(5) K. Hoogsteen, private communication (1970).
(6) R. R. Ayyar, R. Chandrasekharan, and R. Srinivasan, reported as a private communication (1966) by R. E. Marsh and J. Donohue, *Advan. Protein Chem.*, **22**, 235 (1967).
(7) B. Khawas and G. S. R. K. Murti, *Indian J. Phys.*, **42**, 175 (1968).
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(9) B. Khawas and G. S. R. K. Murti, *ibid., Sect. B*, **25**, 2663 (1969).
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(19) R. E. Long, Ph.D. Thesis, University of California at Los Angeles, Los Angeles, Calif., 1965.
(20) "International Tables for X-Ray Crystallography," Vol. III, Kynoch Press, Birmingham, 1962, pp 202–203.

Table III. Final Nonhydrogen Atom Parameters ($\times 10^4$)[a]

	x	y	z	B_{11}[b]	B_{22}	B_{33}	B_{12}	B_{13}	B_{23}
Cl(1)	−3036 (1)	10702 (1)	509 (1)	123 (1)	153 (1)	223 (1)	77 (1)	102 (2)	1 (2)
N(1)	4331 (2)	7923 (1)	4599 (2)	94 (2)	62 (2)	91 (2)	11 (3)	53 (4)	−17 (3)
O(1)	4637 (2)	10045 (1)	3303 (3)	148 (3)	75 (2)	170 (3)	−50 (3)	100 (4)	−25 (3)
O(2)	2773 (2)	4081 (1)	9189 (2)	158 (3)	104 (2)	169 (3)	3 (3)	178 (4)	33 (3)
O(3)	9178 (2)	3908 (1)	8933 (2)	190 (3)	67 (1)	169 (3)	32 (3)	−138 (4)	−77 (3)
O(4)	8843 (2)	6038 (1)	8332 (2)	128 (2)	67 (1)	129 (2)	7 (3)	−26 (4)	−73 (3)
C(2)	5732 (2)	7309 (2)	4793 (2)	92 (3)	83 (3)	88 (3)	−12 (4)	50 (4)	−64 (4)
C(3)	5972 (2)	6103 (2)	5918 (2)	80 (2)	74 (2)	79 (2)	0 (3)	23 (4)	−57 (3)
C(4)	4746 (2)	5926 (2)	6520 (2)	81 (2)	64 (2)	80 (2)	−2 (3)	21 (4)	−49 (3)
C(5)	4478 (2)	4881 (2)	7711 (2)	100 (3)	64 (2)	97 (3)	3 (3)	40 (4)	−37 (3)
C(6)	3193 (3)	5011 (2)	8052 (2)	125 (3)	79 (2)	114 (3)	−21 (4)	96 (4)	−24 (4)
C(7)	2200 (2)	6166 (2)	7244 (3)	115 (3)	100 (2)	161 (4)	10 (4)	146 (5)	−40 (5)
C(8)	2461 (2)	7202 (2)	6077 (2)	113 (3)	81 (2)	132 (3)	42 (4)	90 (5)	−26 (4)
C(9)	3729 (2)	7063 (2)	5694 (2)	94 (3)	63 (2)	87 (2)	−2 (3)	50 (4)	−33 (3)
C(10)	3766 (2)	9234 (2)	3622 (2)	133 (3)	62 (2)	92 (3)	−3 (4)	53 (5)	−33 (4)
C(11)	2063 (2)	9530 (2)	2948 (2)	121 (3)	57 (2)	91 (3)	6 (3)	55 (4)	−28 (3)
C(12)	1454 (3)	10734 (2)	2775 (2)	157 (3)	63 (2)	132 (3)	−4 (4)	91 (5)	−55 (4)
C(13)	−116 (3)	11072 (2)	2064 (3)	176 (4)	65 (2)	170 (4)	39 (4)	147 (6)	−37 (4)
C(14)	−1073 (2)	10235 (2)	1483 (2)	118 (3)	90 (2)	124 (3)	38 (4)	81 (5)	2 (4)
C(15)	−492 (3)	9044 (2)	1624 (2)	133 (3)	87 (2)	136 (3)	−7 (4)	53 (5)	−63 (4)
C(16)	1069 (2)	8693 (2)	2369 (2)	128 (3)	63 (2)	125 (3)	16 (4)	38 (5)	−53 (4)
C(17)	6647 (3)	7923 (2)	3796 (3)	146 (4)	110 (3)	138 (3)	−33 (5)	142 (6)	−64 (5)
C(18)	7281 (2)	5094 (2)	6493 (2)	90 (3)	83 (2)	106 (3)	19 (4)	31 (4)	−78 (4)
C(19)	8499 (2)	5064 (2)	8012 (2)	80 (2)	66 (2)	106 (3)	−1 (3)	35 (4)	−51 (4)
C(20)	3806 (2)	2948 (2)	10183 (3)	183 (4)	82 (2)	129 (3)	−33 (5)	111 (6)	−26 (4)

[a] The final value of the extinction parameter g^{23} was 15.9 (8) $\times 10^{-6}$. [b] The form of the anisotropic ellipsoid is $\exp[-(B_{11}h^2 + B_{22}k^2 + B_{33}l^2 + B_{12}hk + B_{13}hl + B_{23}kl)]$. [c] Numbers in parentheses here and in succeeding tables are estimated standard deviations.

atomic scattering factor for H was that of Stewart, *et al.*[21] Weights were set equal to $1/\sigma^2(F^2)$. All calculations were done under the CRYM system on an IBM 360/75 computer. Six cycles of full-matrix least-squares refinement including positional and isotropic temperature parameters for the Cl, C, N, and O atoms gave R_1 = 0.11 and $R_2 = \Sigma w(F_o^2 - F_c^2)^2/\Sigma w F_o^4$ = 0.063. A difference Fourier map was then calculated using the data with $(\sin^2\theta)/\lambda^2$ less than 0.25; it indicated the positions of all 16 hydrogen atoms. Including the contributions of the hydrogen atoms in the calculated structure factors reduced R_1 to 0.10 and R_2 to 0.047.

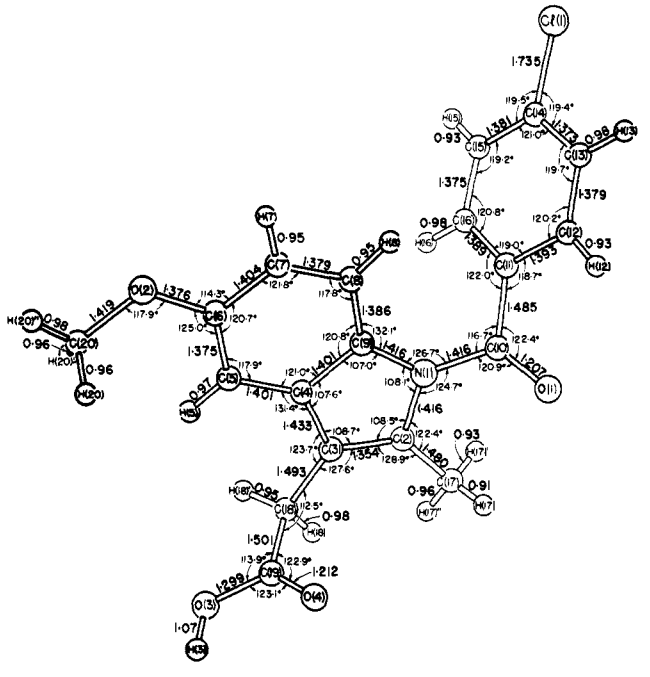

Figure 2. An illustration of the molecular geometry, numbering system and bonding distances and angles for indomethacin.

In the remaining cycles of refinement, anisotropic temperature parameters were assigned to the Cl, C, N, and O atoms. Due to limitations in core storage, the matrix was broken up into two parts: (1) the scale factor, an extinction parameter[22,23] and the anisotropic temperature parameters for the Cl, C, N, and O atoms; (2) the positional parameters for both the hydrogen and nonhydrogen atoms. The isotropic temperature parameters for the hydrogen atoms were fixed at 4.0 Å. Eight cycles of least-squares gave as final residuals R_1 = 0.059, R_2 = 0.009, and an estimated standard deviation of an observation of unit weight of 1.7.[24] No shift in the final cycle of least-squares was greater than 0.3 times its standard deviation. A final difference Fourier map had an average background of ±0.2 e/Å^3. The only significant area on this map was in the vicinity of the Cl atom, where the background ranged from −0.5 to 0.6 e/Å^3. The final nonhydrogen positional and thermal parameters are collected in Table III. The final hydrogen positional parameters are given in Table IV.

Discussion of the Structural Results

The bonding distances and angles are shown in Figure 2. On the basis of the formal standard errors derived from the least-squares refinement and the internal consistencies of chemically equivalent bond distances, we estimate the standard deviations in the distances and angles involving heavy atoms to be 0.005 Å and 0.2–0.4°. The corresponding estimated standard deviations in distances and angles involving hydrogen atoms are 0.03 Å and 1°.

The molecular conformation and thermal ellipsoids for indomethacin are illustrated by a stereoview[25] in Figure 3. Interest in the molecular structure of in-

(21) R. F. Stewart, F. R. Davidson, and W. T. Simpson, *J. Chem. Phys.*, 42, 3175 (1965).

(22) W. H. Zachariasen, *Acta Crystallogr.*, 16, 1139 (1963).

(23) A. C. Larson, *ibid.*, 23, 664 (1967).

(24) A complete list of observed and calculated structure factors will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Business Operations Office, Books and Journals Division, American Chemical Society, 1155 Sixteenth St., N.W., Washington, D. C. 20036, by referring to author, title of article, volume, and page number. Remit check or money order tor $3.00 for photocopy or $2.00 for microfiche.

(25) C. K. Johnson, "ORTEP, a Fortran Thermal Ellipsoid Plot Program for Crystal Structure Illustrations," U. S. Atomic Energy Commission Report ORNL-3794, Oak Ridge National Laboratory, Oak Ridge, Tenn., 1965.

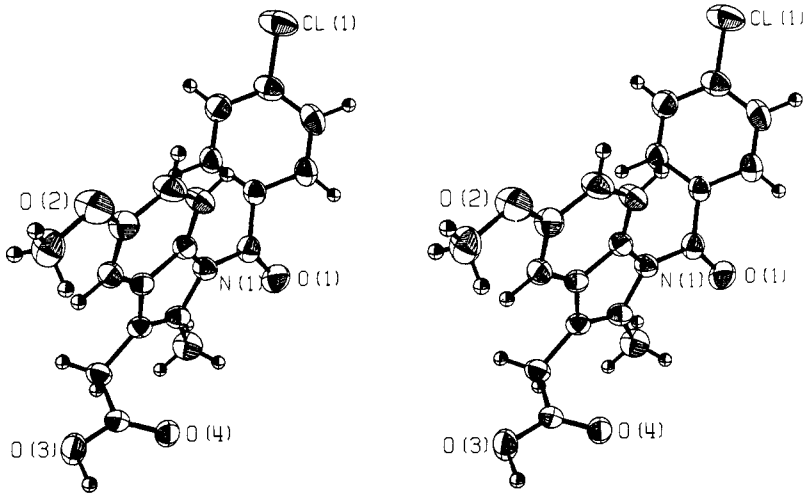

Figure 3. A stereoview of the molecular configuration of indomethacin. The thermal ellipsoids are drawn at the 50% probability level.

domethacin probably centers on the geometry of the linkage between the *p*-chlorophenyl group and the indole ring. The methyl substituent at C(2) of the indole ring prevents the carbonyl group C(10)–O(1) from being coplanar with the indole ring, thus reducing the double-bond character in the N(1)–C(10) bond; the signed[26] torsion angle O(1)–C(10)–N(1)–C(2) is −25.5 (3)°, while the C(10)–N(1) distance of 1.416 Å is considerably longer than the normal value for an amide linkage, about 1.32 Å.[27] Further indication of the strain in this portion of the molecule is the nonplanarity of the bonding about N(1), which lies 0.06 Å from the plane of its three adjacent carbon atoms. Even with these distortions, the O(1)···C(17) distance is only 2.853 Å—surely near the lower limit of a carbon–oxygen third-nearest-neighbor distance.

A similar steric strain, involving H(8) of the indole ring, prevents the benzene ring from being coplanar with the carbonyl group; the torsion angle C(12)–C(11)–C(10)–O(1) is −39.3 (3)°. An alternative conformation, with the carbonyl group coplanar with the benzene ring but approximately perpendicular to the indole ring, would seem to be possible; however, the increased twist about the N(1)–C(10) bond would further reduce the double-bond character in this bond. The relative orientations of the benzene ring, the carbonyl group, and the indole ring under reaction conditions may very well play an important role in the chemistry of indomethacin.

Few structural results for the indole ring in nonsteroidal indole-based derivatives have been reported. Table V compares the bonding distances found for the indole ring in indomethacin and in 3-indolylacetic acid,[12] together with the results of a Pople-type SCF–LCAO–MO description of indole.[28] The agreement between the distances found in indomethacin and 3-indolylacetic acid is acceptable while the agreement with the molecular orbital values for indole is surprisingly good. The indole ring is very nearly planar (Table VI). The methoxy group C(20)–O(2) is nearly

Table IV. Final Hydrogen Atom Parameters (× 10³)[a]

	x	*y*	*z*
H(3)	1001 (3)	395 (2)	999 (3)
H(5)	519 (3)	410 (2)	824 (3)
H(7)	131 (3)	621 (2)	749 (3)
H(8)	172 (3)	794 (2)	551 (3)
H(12)	217 (3)	1125 (2)	320 (3)
H(13)	−53 (3)	1192 (2)	197 (3)
H(15)	−117 (3)	850 (2)	122 (3)
H(16)	150 (3)	786 (2)	247 (3)
H(17)	715 (3)	857 (2)	408 (3)
H(17)′	604 (3)	825 (2)	273 (3)
H(17)″	738 (3)	729 (2)	386 (3)
H(18)	781 (3)	527 (3)	575 (3)
H(18)′	691 (3)	425 (2)	664 (3)
H(20)	481 (3)	316 (2)	1072 (3)
H(20)′	396 (3)	245 (2)	960 (3)
H(20)″	341 (3)	249 (2)	1102 (3)

[a] All hydrogen atoms were assigned the same fixed isotropic temperature factor of 4.0 Å².

Table V. A Comparison of the Bonding Distances in Indomethacin, 3-Indolylacetic Acid, and Indole[a]

	Indomethacin, Å	3-Indolylacetic acid, Å	Indole, Å
N(1)–C(2)	1.416	1.401	1.40
C(2)–C(3)	1.354	1.342	1.35
C(3)–C(4)	1.433	1.470	1.46
C(4)–C(5)	1.401	1.434	1.41
C(4)–C(9)	1.401	1.407	1.40
C(5)–C(6)	1.375	1.409	1.39
C(6)–C(7)	1.404	1.396	1.40
C(7)–C(8)	1.379	1.409	1.39
C(8)–C(9)	1.386	1.422	1.40
C(9)–N(1)	1.416	1.385	1.41
C(3)–C(18)	1.493	1.514	
C(18)–C(19)	1.501	1.495	
C(19)–O(3)	1.299	1.298	
C(19)–O(4)	1.212	1.223	

[a] The numbering system is that used in this study for indomethacin. The values for 3-indolylacetic acid were taken from the X-ray study of Karle, *et al.*,[12] and the values for indole from the molecular orbital calculations of Dewar and Gleicher.[28]

(26) G. M. Brown and H. A. Levy, *Science*, **141**, 921 (1963).
(27) R. E. Marsh and J. Donohue, *Advan. Protein Chem.*, **22**, 235 (1967).
(28) M. J. S. Dewar and G. J. Gleicher, *J. Chem. Phys.*, **44**, 759 (1966).

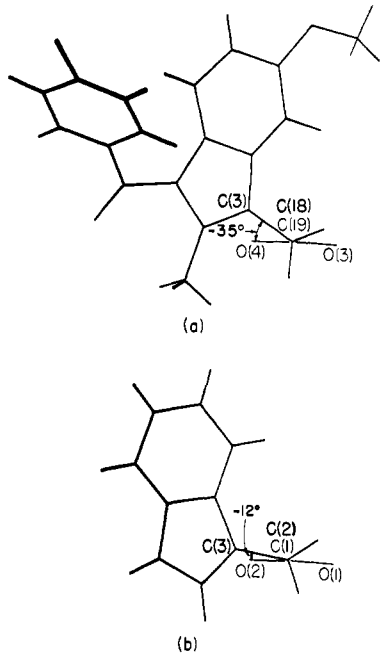

Figure 4. A comparison of the molecular geometries of indomethacin and 3-indolylacetic acid. The view direction is the C_α–C bond of the carboxylic acid function. The indicated torsion angle is C_α–C_β–C–O.

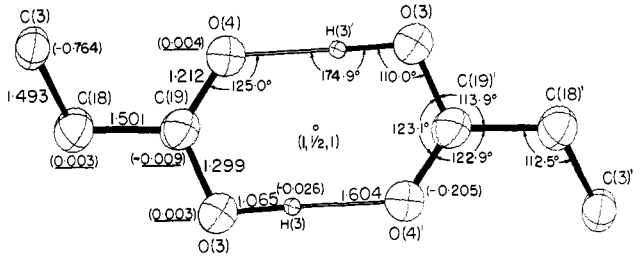

Figure 5. The geometry and dimensions of the carboxylic acid hydrogen bond dimer in indomethacin. The numbers in parentheses adjacent to the atoms are their respective deviations from the least-squares plane of the carboxylic acid group. Underlined deviations indicate that the atom was included in the calculation of the least-squares plane.

parallel to this mean indole plane. In this orientation O(2) is presumably sp^2-hybridized, with the remaining p orbital overlapping with the π system of the indole ring. The distances O(2)–C(6), 1.376 Å, and O(2)–C(20), 1.419 Å, are consistent with averages, 1.362 (4) Å and 1.431 (4) Å, calculated from recent examples[29-31] of the methoxy group parallel to a π system. As a consequence of the close C(20)–C(5) interatomic contact, 2.833 Å, the methoxy hydrogens are ordered and staggered about C(5).

The dimensions of the acetic acid residue are normal and agree with the values found in 3-indolylacetic acid[12] and in other X-ray determinations.[32] Figure 4 is a conformational comparison of indomethacin and 3-indolylacetic acid viewed down the C_α–C bond of the carboxylic acid group. The relatively large difference

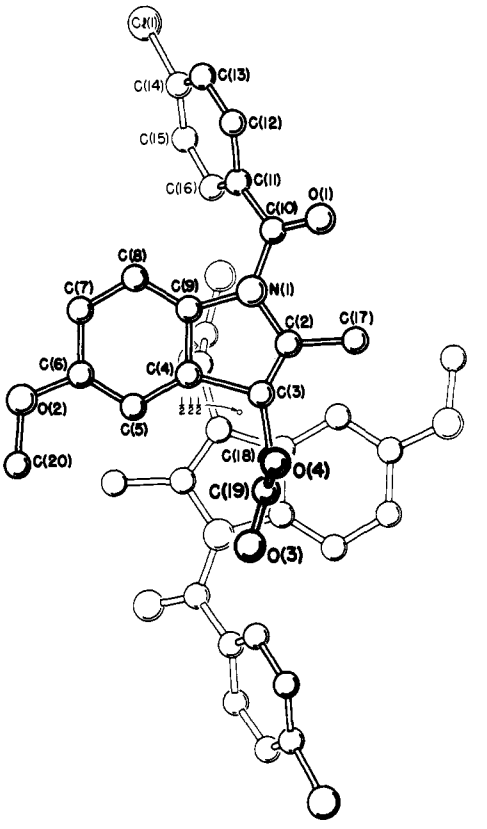

Figure 6. The molecular overlap viewed normal to the least-squares plane of the indole ring.

in the torsion angle about the C_α–C bond is indicative of the rotational freedom about this bond. The angle between the plane normals of the indole ring and the carboxylic acid group is 92.9 (3)° in indomethacin and 90.0 (6)°[33] in 3-indolylacetic acid.

Table VI. Least-Squares Planes and the Deviations of Individual Atoms from These Planes[a]

Atom	Distance, A	Atom	Distance, Å
	p-Chlorophenyl Ring and Substituents[b,c]		
C(11)	0.001	C(16)	0.008
C(12)	−0.010	Cl(1)	−0.055*
C(13)	0.010	C(10)	−0.113*
C(14)	−0.002	O(1)	−0.844*
C(15)	−0.007		
	Indole Ring and Substituents[b,d]		
N(1)	−0.019	C(9)	−0.030
C(2)	0.031	O(1)	0.692*
C(3)	0.006	C(10)	0.102*
C(4)	−0.014	C(17)	0.011*
C(5)	−0.005	C(18)	0.012*
C(6)	−0.000	O(2)	0.015*
C(7)	0.016	C(20)	0.155*
C(8)	0.016		

[a] Direction cosines q are relative to the unit-cell axes; D is the origin-to-plane distance. [b] Atoms marked with an asterisk were given zero weight in the calculation of the least-squares planes. [c] $q(a) = -0.461$, $q(b) = -0.092$, $q(c) = 0.893$; $D = 0.718$ Å. [d] $q(a) = 0.277$, $q(b) = 0.664$, $q(c) = 0.723$; $D = 10.146$ Å.

Two features dominate the crystal packing. The first is the expected hydrogen bonding of the carboxylic

(29) H. Hope and A. T. Christensen, *Acta Crystallogr., Sect. B*, **24**, 375 (1968).
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(31) I. L. Karle and J. Karle, *ibid., Sect. B*, **26**, 1276 (1970).
(32) M. Nardelli, G. Fava, and G. Giraldi, *ibid.*, **15**, 737 (1962).
(33) This angle was originally given incorrectly by Karle, *et al.*,[12] as 60.8°.

Table VII. Intermolecular Contacts Less than 3.6 Å

Atom 1	Atom 2	Symmetry[a]	Distance, Å
C(3)	C(3)	$-x+1, -y+1, -z+1$	3.557
C(4)	C(18)	$-x+1, -y+1, -z+1$	3.406
C(9)	C(18)	$-x+1, -y+1, -z+1$	3.596
C(14)	C(16)	$-x, -y+2, -z$	3.516
C(15)	C(15)	$-x, -y+2, -z$	3.527
O(1)	C(20)	$x, y-1, z+1$	3.425
O(1)	O(1)	$-x+1, -y+2, -z+1$	3.096
O(1)	N(1)	$-x+1, -y+2, -z+1$	3.417
O(1)	C(10)	$-x+1, -y+2, -z+1$	3.194
O(2)	O(3)	$x+1, y, z$	3.262
O(2)	O(4)	$-x+1, -y+1, -z+2$	3.231
O(3)	C(13)	$x-1, y+1, z-1$	3.392
O(3)	C(16)	$-x+1, -y+1, -z+1$	3.474
O(3)	O(4)	$-x+2, -y+1, -z+2$	2.667
O(3)	C(19)	$-x+2, -y+1, -z+2$	3.515
O(4)	C(12)	$-x+1, -y+2, -z+1$	3.313
O(4)	C(13)	$-x+1, -y+2, -z+1$	3.271
O(4)	O(4)	$-x+2, -y+1, -z+2$	3.267
O(4)	C(19)	$-x+2, -y+1, -z+2$	3.356

[a] Transformation to be applied to the coordinates of atom 1 as listed in Table III. Only contacts between heavy atoms are tabulated here.

acid group about centers of inversion to form molecular dimers. The dimensions of the hydrogen bond dimer are given in Figure 5. Although it has been pointed out by Donohue[34] that the β-carbon atom of the carboxylic acid hydrogen bond dimer is usually coplanar with the carboxylate group, the β-carbon in indomethacin, C(3), is 0.76 Å out of the carboxylate plane (Figure 5). The second important feature of the crystal packing is the overlapping of the indole ring with the acetic acid group of another molecule. A view of the crystal packing normal to the indole ring is given in Figure 6, and the overall crystal packing is illustrated in Figure 7. Intermolecular distances between heavy atoms closer than 3.6 Å are collected in Table VII.

(34) J. Donohue, *Acta Crystallogr., Sect. B*, 24, 1558 (1968).

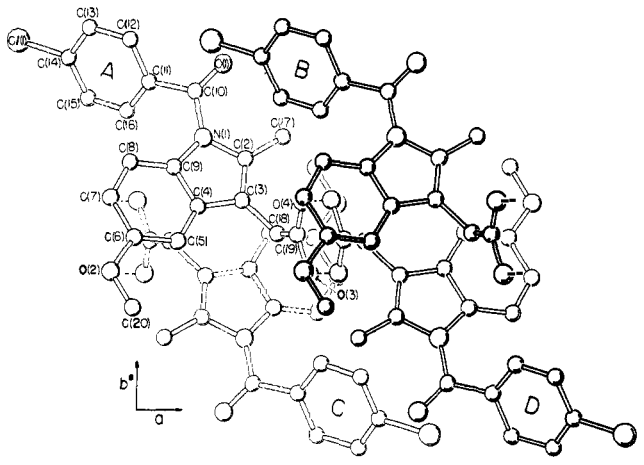


Figure 7. A view normal to the *ab** plane of the crystal packing in indomethacin. The labeled molecules and their symmetry transforms relative to the coordinates in Table III are: A: x, y, z; B: $1+x, y, 1+z$; C: $1-x, 1-y, 1-z$; D: $2-x, 1-y, 2-z$.

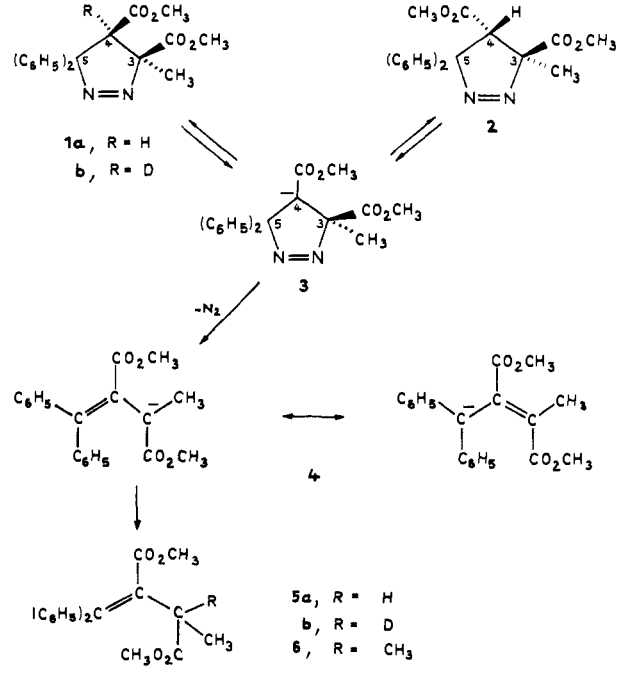
Communications to the Editor

Formation of an Allyl Anion from 1-Pyrazolin-4-yl Anion by Cycloreversion. Electronic Prototype of 1,3-Dipolar Cycloaddition

Sir:

1,3-Dipoles are heteroallyl anions[1] and their cycloadditions are symmetry-allowed concerted processes of the type $_\pi 2_s + _\pi 4_s$.[2,3] The combination of an allyl anion with ethylene to form a cyclopentyl anion[3] may be regarded as the still unknown electronic prototype of a 1,3-dipolar cycloaddition. The addition of cyclopentadienylmagnesium bromide to benzyne[4] comes perhaps closest to this prototype; however, there is no evidence about the concertedness of this reaction. We wish to report on the formation of an allyl anion by a 1,3-cycloreversion reaction, the fast rate of which suggests the absence of high-energy intermediates.

On treatment of dimethyl *cis*- or *trans*-3-methyl-5,5-diphenyl-1-pyrazoline-3,4-dicarboxylate[5] (**1a** or **2**) with



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(3) A. Eckell, R. Huisgen, R. Sustmann, G. Wallbillich, D. Grashey, and E. Spindler, *Chem. Ber.*, 100, 2192, 2212 (1967).
(4) W. T. Ford, R. Radue, and J. A. Walker, *Chem. Commun.*, 966 (1970).
(5) W. M. Jones and W.-T. Tai, *J. Org. Chem.*, 27, 1030 (1962).