ACKNOWLEDGMENTS AND ADDRESSES

Received May 11, 1970, from the *Bionucleonics Department, School of Pharmacy and Pharmacal Sciences, Purdue University, Lafayette, IN 47907*

Accepted for publication December 10, 1970.

This investigation was supported in part by the National Institute of Environmental Health Sciences, U. S. Public Health Service, and was conducted under the auspices of the Institute for Environmental Health.

* Present address: Department of Biology, South Campus of Allegheny County Community College, West Mifflin, PA 15122

Crystal Structure of a 1:1 Aminopyrine–Barbital Complex

SETSUO KIRYU

Abstract □ The crystal structure of a 1:1 complex of aminopyrine and barbital was determined from three-dimensional X-ray diffraction data. The unit cell dimensions are $a = 11.915$, $b = 26.922$, $c = 7.199$ Å, and $\beta = 97° 17'$. The space group is $P2_1/c$; $Z = 4$. The intensity data were collected photographically, and the structure was solved directly by the symbolic addition method. Molecules in the crystal are arranged in the series of aminopyrine–barbital–barbital–aminopyrine linked by hydrogen bondings. The ethyl groups and phenyl groups are in contact with the same groups of other molecules, with normal van der Waals' interactions.

Keyphrases □ Aminopyrine–barbital complex—crystal structure □ Crystal structure—1:1 aminopyrine–barbital complex □ Molecular structure—aminopyrine, barbital □ X-ray diffractometry—analysis

Since aminopyrine diethylbarbiturate appeared as a potent analgetic about half a century ago, numerous physicochemical as well as pharmacological investigations of this well-known system have been reported.

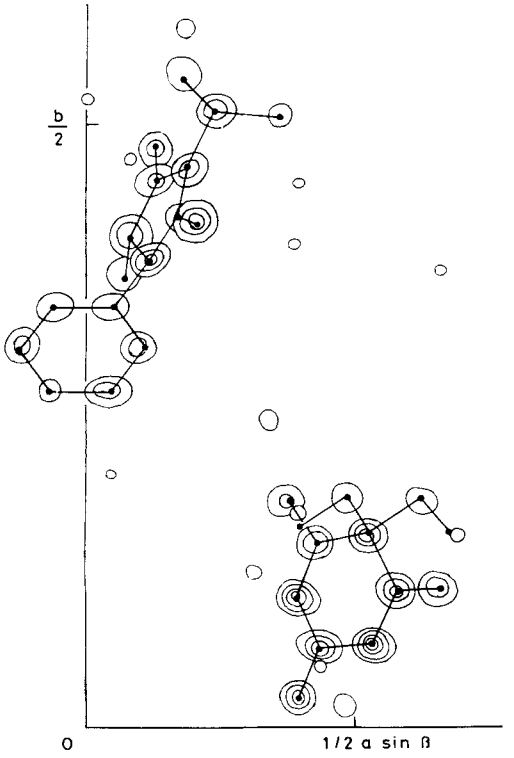


Figure 1—*Sections from a three-dimensional E-map projected along the c-axis. The contours are at equal intervals on an arbitrary scale.*

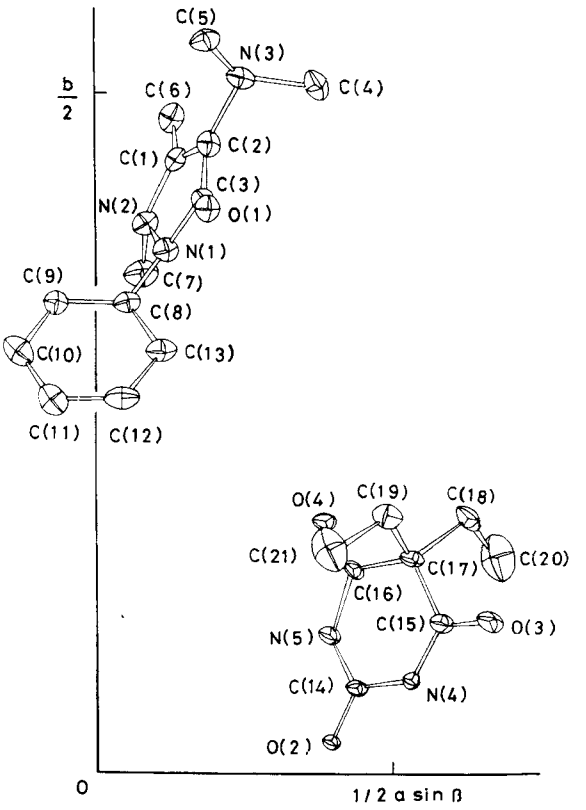


Figure 2—*Ellipsoidal representations of atomic thermal parameters and the atomic numbering scheme.*

Today a variety of information on this compound, such as its thermal or spectroscopic properties, is available; but the only study on its crystal structure was reported by Hertel in 1931 (1), and it does not offer sufficient information. Therefore, structure analysis by the X-ray diffraction method was undertaken to determine the exact crystal structure of this compound.

Table I—Initial Phase Assignments

h	*k*	*l*	|*Fo*|	|*E*|	Sign
5	10	5	35.2	4.34	+
−2	1	1	148.5	2.59	−
8	2	5	23.0	3.75	+
1	22	0	40.2	3.56	a
8	11	2	35.2	3.53	b
6	1	5	28.5	3.27	c

Table II—Positional Parameters and Their Estimated Standard Deviations (Fractional Coordinate × 10^4)

	x	y	z
	Aminopyrine		
C (1)	1322 (4)	4522 (2)	0884 (7)
C (2)	1871 (4)	4638 (2)	2586 (7)
C (3)	1764 (4)	4227 (2)	3806 (7)
C (4)	3599 (6)	5055 (3)	3699 (11)
C (5)	1809 (7)	5374 (3)	4482 (11)
C (6)	1257 (5)	4818 (3)	−0893 (7)
C (7)	0726 (7)	3708 (3)	−0639 (8)
C (8)	0524 (5)	3495 (2)	3466 (7)
C (9)	−0653 (5)	3491 (2)	3058 (8)
C (10)	−1292 (7)	3136 (3)	3848 (9)
C (11)	−0727 (7)	2778 (3)	5079 (10)
C (12)	0434 (7)	2794 (3)	5478 (9)
C (13)	1092 (6)	3148 (2)	4668 (8)
N (1)	1169 (4)	3865 (2)	2721 (5)
N (2)	0819 (4)	4066 (2)	0934 (6)
N (3)	2385 (4)	5104 (2)	3077 (6)
O (1)	2070 (3)	4171 (1)	5520 (5)
	Barbital		
C (14)	4360 (4)	0651 (2)	3912 (7)
C (15)	5788 (5)	1146 (2)	5774 (8)
C (16)	4294 (5)	1539 (2)	3415 (8)
C (17)	5280 (5)	1619 (2)	4925 (8)
C (18)	6226 (7)	1912 (3)	4122 (11)
C (19)	4864 (7)	1931 (3)	6501 (11)
C (20)	6713 (11)	1617 (6)	2561 (16)
C (21)	3922 (10)	1675 (6)	7405 (16)
N (4)	5293 (4)	0705 (2)	5236 (6)
N (5)	3915 (4)	1069 (1)	3052 (6)
O (2)	3956 (3)	0243 (1)	3522 (5)
O (3)	6613 (5)	1152 (2)	6968 (7)
O (4)	3851 (5)	1886 (2)	2537 (8)

Table IV—Least-Squares Planes

1. Equations of Planes[a]

Plane[b]	A	B	C	D
1	0.87750	−0.38927	−0.38909	−3.6277
2	−0.17236	0.61039	0.78873	7.6042
3	−0.70524	0.08008	0.78816	−1.3226

2. Displacements from the Plane (Å × 10^3)

Plane	Displacement
1	C(1) 25, C(2) 0, C(3) −24, N(1) 38, N(2) −39; atoms not forming the plane C(6) 145, C(7) 680, C(8) −457, N(3) −88, O(1) −125
2	C(8) −1, C(9) 4, C(10) 0, C(11) −6, C(12) 9, C(13) −5
3	C(14) 17, C(15) −19, C(16) −17, C(17) 28, N(4) −3, N(5) −6; atoms not forming the plane O(2) 48, O(3) −34, O(4) −69

[a] The equations are in the form $AX + BY + CZ = D$, referred to the crystallographic axes, with X, Y, and Z in Å units. [b] Plane number: 1, pyrazolone ring of aminopyrine; 2, benzene ring of aminopyrine; and 3, pyrimidine ring of barbital.

EXPERIMENTAL

Single crystals were prepared by slow evaporation of an ether solution, containing 0.7 g. of aminopyrine and 1.0 g. of barbital, in a refrigerator, whereupon colorless thin needles extending along the *c*-axis were obtained. The lattice constants of the monoclinic unit cell were determined from Weissenberg and precission photographs with Cu$K\alpha$ radiation (λ = 1.5418 Å); a = 11.915 ± 0.007, b = 26.922 ± 0.005, c = 7.199 ± 0.011 Å, and β = 97° 17′ ±12′.

The cell contains four aminopyrine ($C_{13}H_{17}N_3O$) and four barbital ($C_8H_{12}N_2O_3$) molecules; the observed density is 1.26 g.·cm.$^{-3}$, calculated 1.20 g.·cm.$^{-3}$. Systematic absences of $0k0$ for k odd and $h0l$ for l odd indicate the space group to be $P2_1/c$. Linear absorption coefficient for Cu$K\alpha$ radiation is μ = 8.1 cm.$^{-1}$. The total number of electrons per unit cell is $F(000)$ = 888.

The dimensions of the specimen used for collecting the intensity data were 0.3 × 0.2 × 2.0 mm. Equi-inclination Weissenberg photographs, $hk0$-$hk6$ and $h0l$-$h2l$, were taken with Cu$K\alpha$ radiation, using the multiple-film technique. The intensities were estimated with a microphotometer and also visually by comparison with

Table III—Thermal Parameters and Their Estimated Standard Deviations (× 10^4)[a]

	B11	B22	B33	B12	B13	B23
			Aminopyrine			
C(1)	73 (4)	16 (1)	122 (11)	14 (3)	32 (10)	7 (4)
C(2)	78 (4)	15 (1)	102 (10)	0 (3)	−1 (9)	0 (4)
C(3)	72 (4)	14 (1)	110 (10)	4 (3)	−17 (9)	−3 (4)
C(4)	92 (6)	28 (2)	350 (21)	−30 (5)	50 (17)	28 (9)
C(5)	136 (8)	22 (1)	340 (21)	−2 (5)	94 (19)	−69 (8)
C(6)	104 (6)	25 (1)	96 (12)	20 (4)	20 (11)	28 (5)
C(7)	161 (8)	20 (1)	114 (13)	3 (5)	0 (14)	−34 (6)
C(8)	95 (5)	14 (1)	105 (11)	5 (3)	23 (10)	−5 (4)
C(9)	92 (5)	20 (1)	179 (13)	1 (4)	18 (12)	−10 (6)
C(10)	133 (7)	25 (1)	186 (15)	−15 (5)	74 (16)	2 (7)
C(11)	126 (7)	26 (1)	229 (16)	−19 (5)	70 (16)	−10 (7)
C(12)	185 (9)	16 (1)	180 (15)	4 (5)	64 (17)	20 (6)
C(13)	126 (6)	13 (1)	149 (12)	3 (4)	−3 (13)	3 (5)
N(1)	95 (4)	16 (1)	84 (8)	5 (3)	−18 (8)	2 (3)
N(2)	95 (4)	18 (1)	85 (9)	6 (3)	−9 (8)	−6 (4)
N(3)	111 (5)	16 (1)	139 (10)	−7 (3)	15 (10)	1 (4)
O(1)	95 (3)	17 (1)	103 (7)	1 (2)	−53 (7)	6 (3)
			Barbital			
C(14)	72 (4)	9 (1)	148 (11)	−1 (3)	−9 (9)	3 (4)
C(15)	98 (5)	11 (1)	224 (13)	−8 (3)	−47 (12)	6 (5)
C(16)	98 (5)	9 (1)	226 (14)	0 (3)	−26 (12)	10 (5)
C(17)	92 (5)	9 (1)	196 (13)	−13 (3)	−29 (11)	−2 (4)
C(18)	130 (8)	22 (1)	369 (21)	−45 (5)	0 (19)	57 (8)
C(19)	136 (8)	22 (1)	329 (20)	−2 (5)	10 (19)	−89 (8)
C(20)	195 (14)	65 (4)	445 (32)	−30 (12)	331 (35)	1 (19)
C(21)	179 (12)	57 (3)	432 (30)	−46 (10)	257 (30)	−145 (16)
N(4)	77 (4)	11 (1)	221 (11)	−4 (2)	−69 (9)	13 (4)
N(5)	89 (4)	10 (1)	161 (10)	1 (2)	−59 (9)	6 (3)
O(2)	78 (3)	9 (1)	235 (9)	−9 (2)	−69 (8)	2 (3)
O(3)	150 (5)	17 (1)	372 (14)	−23 (3)	−283 (14)	21 (5)
O(4)	160 (6)	10 (1)	426 (15)	−2 (3)	−237 (15)	42 (5)

[a] Thermal parameters are given according to the expression: $T = \exp[-(h^2B11 + k^2B22 + l^2B33 + hkB12 + hlB13 + klB23)]$.

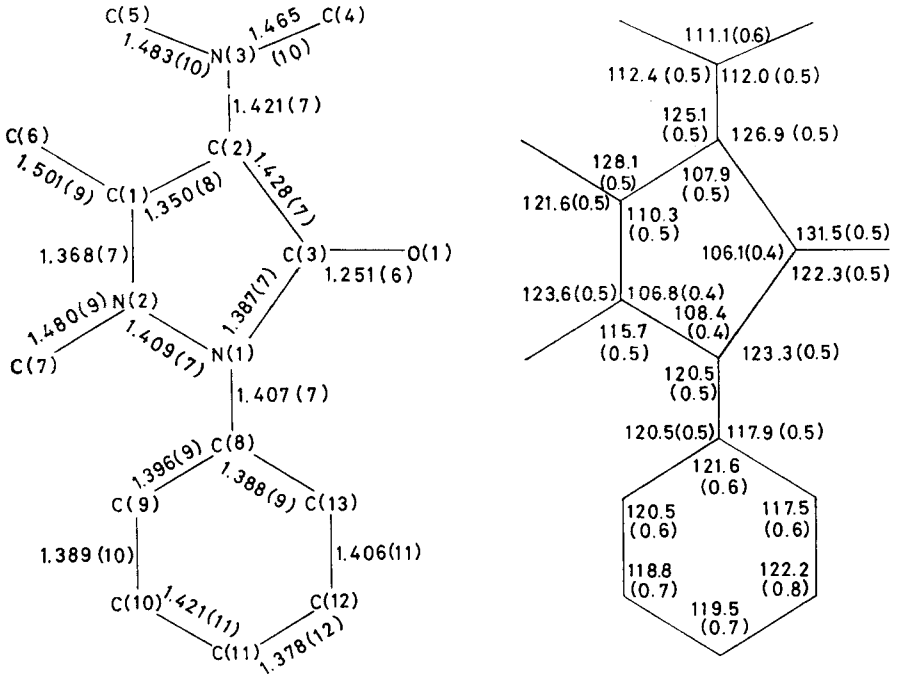


Figure 3—*Bond lengths (Å) and bond angles with their estimated standard deviations for aminopyrine.*

a calibrated scale. The number of unique reflections examined was 3669, among which were 1176 reflections of zero intensity. Corrections were applied for Lorentz and polarization factors but not for absorption.

STRUCTURE DETERMINATION

The structure was solved directly by the symbolic addition procedure for centrosymmetric crystals (2). Three reflections used to specify the origin and three additional reflections, each phase of which was designated by a symbol, are listed in Table I.

In the course of the phase determination, it became apparent that $a = b = +$ and $a = -c$. Phases were finally determined for 394 reflections of 477 with $|E| \geqq 1.5$, and 382 of them were found to be correct after refinement. The positions of the atoms were readily found in the E-map computed with these 394 reflections (Fig. 1). Six cycles of block diagonal least-squares refinement applied to the positional parameters and the isotropic temperature and overall scale factors reduced the R-index from 0.50 to 0.27. Further refinement was carried out, introducing anisotropic temperature factors; after eight cycles of refinement the R-value was reduced to 0.177 (0.108 for observed reflections). The weighting scheme was $\sqrt{w} = 0.2$ for $Fo = 0$, $\sqrt{w} = 1.0$ for $0 < Fo < 11$, and $\sqrt{w} = 11/Fo$ for $Fo \geqq 11$, and the function minimized was $\Sigma w(Fo - KFc)^2$.

The three-dimensional difference Fourier map, as well as the values of the positional and thermal parameters, showed no inconsistency with the structure obtained from the initial E-map, but few peaks of hydrogen atoms were clearly distinguishable in the difference Fourier map. Therefore, no further refinement, including the hydrogen atoms, was carried out. Maximum shifts of the positional and thermal parameters during the final cycle did not exceed a third of their standard deviations. The final positional and thermal parameters with their standard deviations are listed in Tables II and III, and the ellipsoidal representation of the thermal parameters is shown in Fig. 2.

The atomic scattering factors used for carbon, nitrogen, and oxygen were those of Berghuis *et al.* (3). Computations were carried out on the FACOM 230-60 of the Computer Center of Kyushu University with the programs UNICS (4), except for the computations of Fourier synthesis which were computed with a program written by the author.

DESCRIPTION OF THE STRUCTURE

The interatomic distances and the bond angles calculated on the basis of the parameters obtained are shown in Figs. 3 and 4.

Molecular Structure of Aminopyrine—In the five-membered pyrazolone ring, all the bond lengths lie between the corresponding

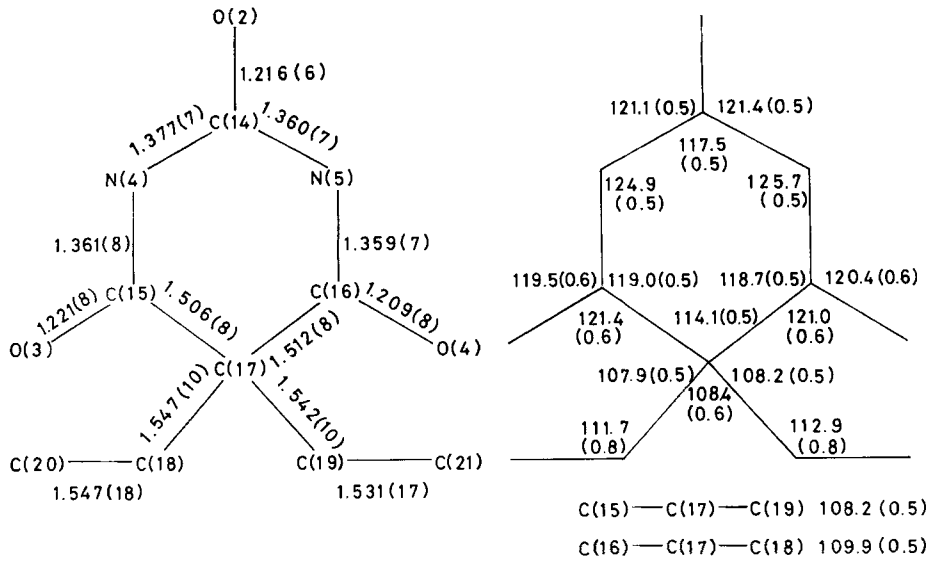


Figure 4—*Bond lengths (Å) and bond angles with their estimated standard deviations for barbital.*

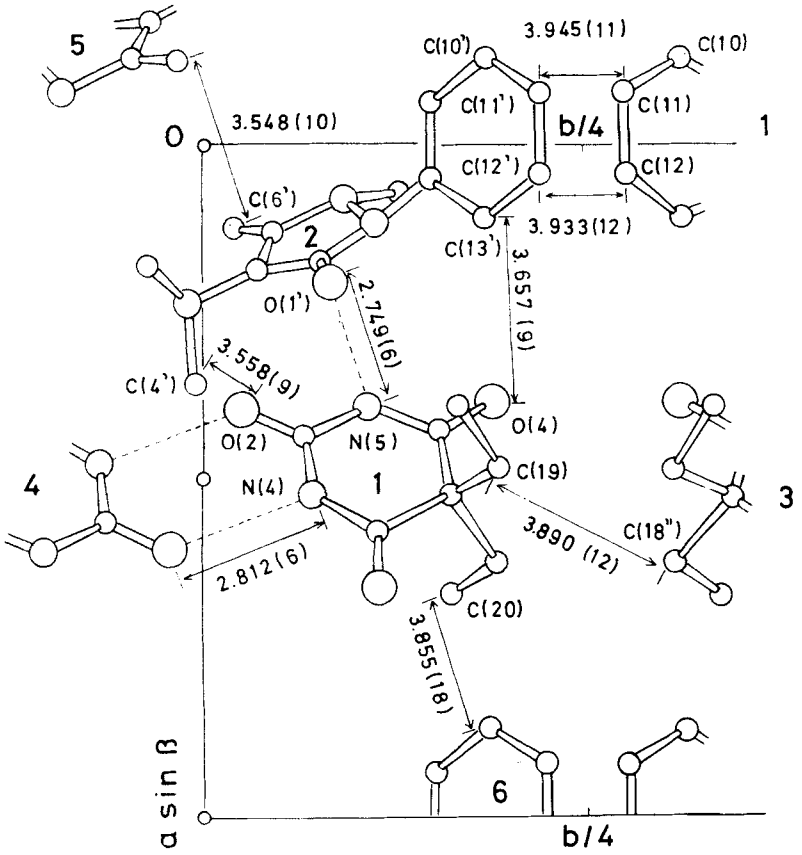


Figure 5—*Intermolecular atomic distances (Å) with their estimated standard deviations. The hydrogen bondings are shown by broken lines. The numbers on the molecules show following symmetry operations: (1)* x, y, z; *(2)* x, $^1/_2-$y, $-^1/_2+$ z; *(3)* x, $^1/_2-$y, $^1/_2+$ z; *(4) 1*−x, −y, *1*−z; *(5)*−x, $-^1/_2+$ y, $-^1/_2-$z; *and (6) 1* + x, $^1/_2-$y, $-^1/_2+$ z.

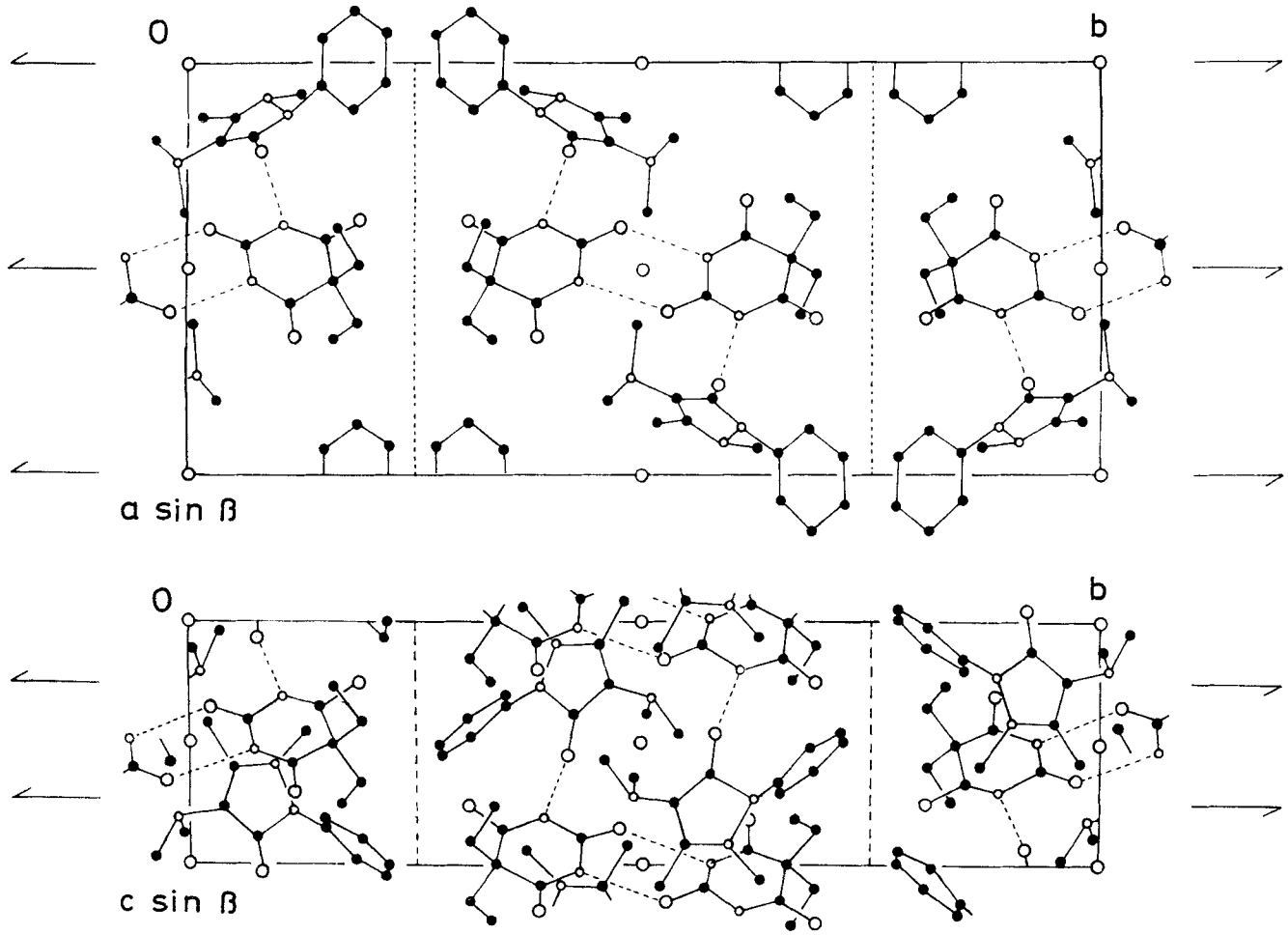


Figure 6—*The molecular arrangement viewed along the* c- *and* a-*axes. The hydrogen bondings are shown by broken lines.*

single- and double-bond values. The C(1)—N(2) bond length of 1.350 Å, however, shows an isolated double-bond character and the N(1)—N(2) distance 1.409 Å approximates a single-bond length.

Significant out-of-plane distortions occur in the ring (Table IV). The coordinations around the nitrogen atoms are not planar but pyramidal, and the substituents on N(1) and N(2), the phenyl and methyl groups, deviate from one another in a *trans*-configuration from the least-squares plane of the ring. The phenyl ring is completely planar (Table IV), and the C—C bond lengths (1.378–1.421 Å) and the bond angles (117.5–122.2°) are those of the typical benzenoid structure. The ring is inclined by 39° with respect to the plane of the pyrazolone ring. The dimethylamino group on C(2) is also of a pyramid configuration; the C(2)—N(3) bond length of 1.421 Å is a little shorter than that of a pure single bond at 1.47 Å (5) and is perhaps affected by the conjugated system of the pyrazolone ring.

Molecular Structure of Barbital—The values of bond lengths and angles are in reasonable agreement with the corresponding values for the same molecule in the barbital crystal (Form I) reported by Craven *et al.* (6). The C—N bond lengths of 1.359–1.377 Å in the pyrimidine ring show about 20–30% of double-bond characters, and there are no significant differences among the three C—O pure double-bond lengths. The C—C bond lengths of 1.506 and 1.512 Å in the pyrimidine ring approximate that of the single bond, while the steric requirement of the ring formation leads to a slight broadening of the angle at the tetrahedrally bonded atom C(17) from the tetrahedral angle of 109.4–114.1°. In the ethyl groups, the C—C—C angles and the C—C bond lengths agree quite well with those of normal paraffin. For an isolated barbital molecule, the ring atoms should be coplanar and the hydrocarbon chain of the ethyl groups should be normal to the ring plane. Some significant deviations of the ring atoms from the plane, however, were observed in this crystal (Table IV). The pyrimidine ring is slightly folded along the C(15)—C(16) line at an angle of about 4°. Similar distortions were also found in the pyrimidine rings in barbital I (6) and in other dialkylbarbiturate crystals (7, 8), in which the foldings of the planes were observed along the N(4)—C(16) diagonals.

Crystal Structure—The intermolecular atomic distances are shown in Fig. 5, and the arrangement of the molecules in the crystals is shown in Fig. 6. The short distances between the carbonyl and the imino groups, O(1)—N(5) 2.749 Å and O(2)—N(4) 2.812 Å, suggest hydrogen bondings. The interaction between two barbital molecules with hydrogen bonds is quite similar to that in barbital crystal I, in which the molecules are arranged in infinite planar ribbons with two kinds of hydrogen bonding (6). There are no infinite chains of molecules linked by hydrogen bonds in this compound; only two aminopyrine and two barbital molecules are linked in the series of aminopyrine–barbital–barbital–aminopyrine. The hydrocarbon groups, *i.e.*, the ethyl and phenyl groups, are in contact with one another in normal van der Waals' interactions. No other unusually close contacts or overlappings of molecules, which are found in some charge-transfer complexes, were observed.

REFERENCES

(1) E. Hertel, *Z. Phys. Chem.*, **1931**, 267.

(2) J. Karle and I. L. Karle, *Acta Crystallogr.*, **21**, 849(1966).

(3) J. Berghuis, I. J. M. Haanappel, M. Potters, B. O. Loopstra, C. H. MacGillavry, and A. L. Veenendaal, *ibid.*, **8**, 478(1955).

(4) "UNICS, The Universal Crystallographic Computation Program System," Crystallographic Society of Japan, 1967.

(5) W. J. Orville-Thomas, *Chem. Rev.*, **57**, 1179(1957).

(6) B. M. Craven, E. A. Vizzini, and M. M. Rodrigues, *Acta Crystallogr., Sect. B*, **25**, 1978(1969).

(7) B. M. Craven and E. A. Vizzini, *ibid.*, **25**, 1993(1969).

(8) B. M. Craven and C. Cusatis, *ibid.*, **25**, 2291(1969).

ACKNOWLEDGMENTS AND ADDRESSES

Received September 8, 1970, from the *Faculty of Pharmaceutical Science, Kyushu University, Katakasu, Fukuoka, Japan.*

Accepted for publication December 8, 1970.

The author expresses his thanks to Professor I. Ueda and Dr. A. Okazaki for facilities for X-ray diffraction measurement, and to Professor S. Iguchi for his continued guidance and encouragement.

Synthesis and Selected Pharmacology of Anthranilamides

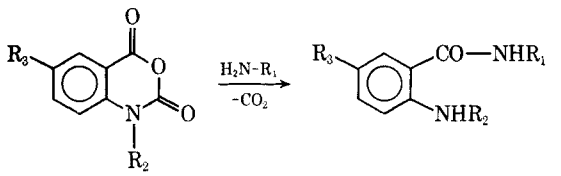
NED D. HEINDEL*, WILLIAM P. FIVES*, THOMAS F. LEMKE*, and RICHARD A. CARRANO†

Abstract □ A series of anthranilamides of diverse structure were prepared by the nucleophilic ring opening of isatoic anhydrides. Sixteen analogs, 10 of them previously unknown in the literature, were submitted to general pharmacologic screening. Several of the compounds displayed CNS depression, anti-inflammatory–analgesic, and antitremor activities.

Keyphrases □ Anthranilamides—synthesis from isatoic anhydrides □ CNS depressant activity—anthranilamides □ Anti-inflammatory, analgesic potential—anthranilamides □ Antitremor activity—anthranilamides

Literature reports regarding the general pharmacology of anthranilamides are sparse. In recent years, however, numerous studies appeared on the analgesic, antipyretic, and anti-inflammatory activities of anthranilamides (*o*-aminobenzamides) (1–5). One claim was made that their physiological activity rests, at least in part, on their metabolic conversion to salicylate analogs (6).

Synthetically, these compounds are obtained by nucleophilic ring opening of substituted isatoic anhydrides with amines (Scheme I). Although procedures



Scheme I

were suggested for these transformations (7, 8), an improved modification has been developed which simplifies the experimental method and enhances the yield by the use of *N*,*N*-dimethylformamide as a solvent when