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Crystal Structure of a 1:1 Aminopyrine-Cyclobarbital Complex

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The crystal structure of a 1:1 complex of aminopyrine and cyclobarbital was determined from X-ray diffraction data. The triclinic unit cell dimensions are $a=12.877$, $b=14.357$, $c=7.199$Å, $\alpha=91.49°$, $\beta=104.42°$, and $\gamma=100.05°$. The space group is $P\bar{1}$; $Z=2$. The intensity data were collected on a single crystal diffractometer and the structure was solved directly by the symbolic addition procedure. Molecules in the crystals were arranged in the series of aminopyrine-cyclobarbital-cyclobarbital-aminopyrine linked by hydrogen bonds. A partially disordered structure was observed of the cyclobarbital molecule.

As a part of a program for the pharmaceutical study on the molecular complex formation of drugs, the crystal structure of aminopyrine-barbital system was previously reported.[2] In this paper, the crystal structure determination of another molecular complex used as an analgetic, aminopyrine-cyclobarbital system, is reported.

Experimental and Structure Determination

Crystals were prepared by slow evaporation of ethanol solution including equimolar aminopyrine ($C_{13}H_{17}ON_3$) and cyclobarbital ($C_{12}H_{16}O_3N_2$) at room temperature. The lattice parameters and the reflection intensities were measured on Syntex $P\bar{1}$ automatic diffractometer using graphite monochromatized Cu$K\alpha$ radiation. The crystal data are: $C_{25}H_{33}O_4N_5$, triclinic system, $a=12.877\pm0.003$, $b=14.357\pm0.004$, $c=7.199\pm0.002$Å, $\alpha=91.49\pm0.02°$, $\beta=104.42\pm0.02°$, $\gamma=100.05\pm0.02°$, density observed 1.227, Calcd. 1.226 gcm^{-1}, $Z=2$, and space group $P\bar{1}$. Intensities for 3432 reflections were measured in the $\omega-2\theta$ scanning mode up to $2\theta=118°$, 797 reflections of which were considered to be unobserved ($I<3\sigma$ (I)). Dimensions of specimen were about 0.3 mm and absorption corrections were not applied.

The structure was solved by the symbolic addition procedure and the atomic parameters were refined by block-matrix least-squares method. The function minimized was $\sum w(Fo-KFc)^2$, where $\sqrt{w}=0$ for unobserved reflections, $\sqrt{w}=1$ for $Fo<10$, $\sqrt{w}=10/Fo$ for $Fo\geqq10$, and K is a scale factor. An E-map computed from 316 signed E's with absolute values greater than 1.5 gave the positions of all the expected nonhydrogen atoms. There were found, however, two peaks for C(23) atom in the cyclohexene ring of cyclobarbital molecule, and either of them was not satisfactorily refined, giving an unusually large thermal parameter or chemically unacceptable bond lengths. Then two other possible structures were examined. One was a structure of noncentrosymmetric space group $P1$ and the other was a disordered one. The refinement of the $P1$ structure, however, did not improve the bond lengths in cyclohexene ring. The structure was finally assumed to be a disordered one and the two positions were given to the C(23) atom. The occupancy ratio was not refined but fixed at C(231): C(232) = 0.6: 0.4 after several examinations (Fig. 1). The refinement of nonhydrogen atoms with the anisotropic temperature factors reduced R factor to 0.087. In the difference Fourier map at this stage, most hydrogen atom positions were readily found except those bonded to C(22), C(23), and C(24) located in the disordered region. Then 27 out of 33 hydrogen atoms were included in the final refinement with the isotropic temperature factors (R=0.056). The parameters determined are listed in Tables I and II.

Atomic scattering factors used for carbon, nitrogen, and oxygen were those of Berghuis, *et al.*[3] and that of McWeeny for hydrogen.[4] Computations were carried out in the Computer Center of Kyushu University with programs UNICS[5] and those written by one of authors (S.K).

1) Location: *1276, Katakasu Higashi-ku, Fukuoka.*
2) S. Kiryu, *J. Pharm. Sci.*, **60**, 699 (1971).
3) J. Berghuis, I.J. Haanappel, M. Potters, B.O. Loopstra, C.H. MacGillavry, and A.L. Veenendaal, *Acta Crystallogr.*, **8**, 478 (1955).
4) R. McWeeny, *Acta Crystallogr.*, **4**, 513 (1951).
5) "UNICS: The Universal Crystallographic Computation Program System," Crystallographic Society of Japan, Tokyo, 1967.

Description of the Structure

The interatomic distances and the bond angles calculated on the basis of the parameters obtained are shown in Fig. 2 and 3. C(22), C(23), and C(24) carbon atoms and all hydrogen atoms are excluded from the following discussion. The parameter values of the above three carbon atoms are less reliable due to the disorder, and some hydrogen atoms of the C(4) and C(5) methyl groups show unusually large thermal parameters and very diffused electron densities around the carbon atoms.

Molecular Structure of Aminopyrine

The values of bond lengths and angles are in good agreement with the corresponding values of the same molecule in the aminopyrine-barbital complex crystal.[2] In the five membered ring, the C(1)—C(2) bond length 1.352 Å shows an isolated double bond character and N(1)—N(2) distance 1.411 Å is approximately a single bond length. The coordinations around

Table I. Positional and Thermal Parameters with Their Standard Deviations ($\times 10^4$)

$T=\exp[-(h^2B_{11}+k^2B_{22}+l^2B_{33}+khB_{12}+hlB_{13}+klB_{23})]$

Atom	x	y	z	B_{11}	B_{22}	B_{33}	B_{12}	B_{13}	B_{23}
Aminopyrine									
C(1)	1465(2)	671(2)	5119(4)	71(2)	49(1)	181(6)	11(3)	56(5)	9(5)
C(2)	1985(2)	485(2)	6906(4)	76(2)	49(1)	193(6)	32(3)	60(5)	−1(5)
C(3)	1985(2)	1254(2)	8224(3)	57(2)	50(1)	169(5)	25(3)	42(5)	9(4)
C(4)	1853(3)	−925(2)	8625(6)	123(3)	58(2)	472(11)	56(4)	163(10)	101(7)
C(5)	3592(3)	−159(3)	8229(6)	88(3)	103(3)	469(12)	97(4)	130(9)	68(9)
C(6)	1286(3)	111(2)	3268(4)	105(3)	66(2)	194(6)	3(3)	85(7)	−31(5)
C(7)	1119(3)	2191(2)	3730(4)	102(3)	64(2)	193(6)	17(3)	29(6)	52(5)
C(8)	915(2)	2534(2)	7841(4)	69(2)	45(1)	205(6)	33(3)	68(5)	40(5)
C(9)	−196(2)	2479(2)	7124(5)	65(2)	62(2)	362(9)	33(3)	70(7)	51(6)
C(10)	−719(3)	3072(3)	7983(6)	83(3)	81(2)	545(13)	62(4)	203(9)	121(9)
C(11)	−120(3)	3717(2)	9506(5)	132(3)	72(2)	418(10)	83(4)	265(10)	68(8)
C(12)	978(3)	3780(2)	10160(4)	135(3)	61(2)	279(8)	60(4)	164(8)	23(6)
C(13)	1520(2)	3189(2)	9345(4)	95(2)	53(2)	197(6)	45(3)	74(6)	17(5)
N(1)	1469(2)	1894(1)	7107(3)	69(2)	50(1)	158(4)	34(2)	18(4)	1(4)
N(2)	1060(2)	1501(1)	5192(3)	80(2)	52(1)	149(4)	22(2)	17(4)	16(4)
N(3)	2413(2)	−357(2)	7391(3)	100(2)	60(1)	224(5)	66(3)	76(5)	12(4)
O(1)	2304(1)	1360(1)	10006(2)	77(1)	61(1)	157(4)	41(2)	3(4)	2(3)
Cyclobarbital									
C(14)	4465(2)	1190(2)	3935(4)	55(2)	51(1)	210(6)	25(3)	13(5)	25(5)
C(15)	5874(2)	2273(2)	6345(4)	57(2)	60(2)	219(6)	17(3)	17(5)	23(5)
C(16)	4470(2)	2892(2)	3754(4)	67(2)	54(2)	216(6)	29(3)	22(6)	7(5)
C(17)	5494(2)	3134(2)	5434(4)	62(2)	53(2)	200(6)	22(3)	21(5)	−14(5)
C(18)	5214(2)	3735(2)	7005(4)	80(2)	84(2)	225(7)	28(3)	64(6)	−41(6)
C(19)	6415(2)	3649(2)	4639(4)	70(2)	45(1)	192(6)	23(3)	31(5)	−2(5)
C(20)	4320(3)	3200(3)	7833(6)	89(3)	134(3)	349(10)	28(5)	138(9)	−7(9)
C(21)	6934(3)	4522(2)	5262(5)	109(3)	55(2)	323(8)	1(3)	147(8)	−38(6)
C(22)	7858(4)	5051(3)	4511(6)	160(4)	72(2)	447(12)	−37(5)	286(12)	−75(8)
C(231)[a]	8388(5)	4423(4)	3457(8)	116(5)	86(4)	332(15)	−22(7)	187(15)	−26(12)
C(232)	7729(9)	4565(6)	2445(14)	167(10)	74(6)	381(26)	11(12)	281(27)	68(19)
C(24)	7592(4)	3630(3)	2326(7)	184(5)	112(3)	569(15)	−101(6)	437(15)	−210(11)
C(25)	6710(3)	3103(2)	3111(5)	130(3)	68(2)	362(10)	−9(4)	208(9)	−77(7)
N(4)	5357(2)	1386(2)	5506(3)	62(2)	53(1)	237(5)	25(2)	−5(5)	40(4)
N(5)	4067(2)	1956(1)	3140(3)	61(2)	47(1)	218(5)	22(2)	−14(4)	14(4)
O(2)	4052(2)	386(1)	3305(3)	72(1)	48(1)	279(5)	18(2)	−32(4)	14(4)
O(3)	6626(2)	2340(1)	7787(3)	84(2)	76(1)	280(5)	6(2)	−101(5)	43(4)
O(4)	4018(2)	3502(1)	2967(3)	102(2)	55(1)	321(6)	60(2)	−70(5)	8(4)

a) C(231): C(232)=0.6: 0.4

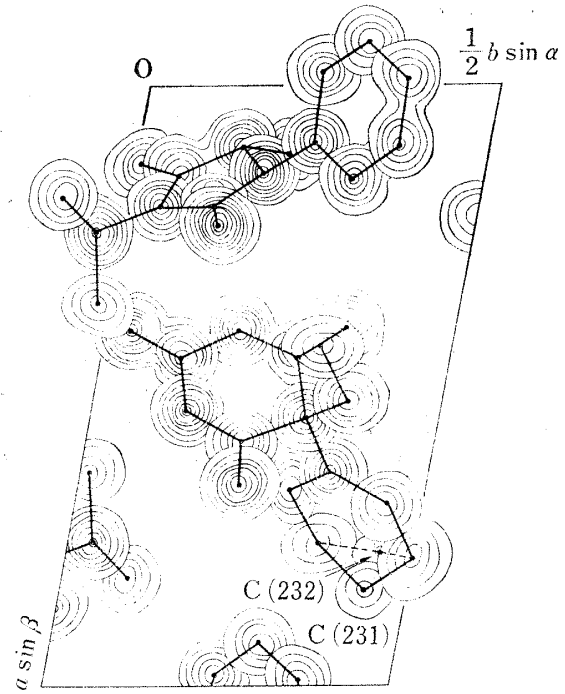

Fig. 1. Sections from the Final Electron Density Map projected along the *c*-Axis

Contours are at intervals of 1 eÅ^{-3} beginning with the 1 eÅ^{-3} contour.

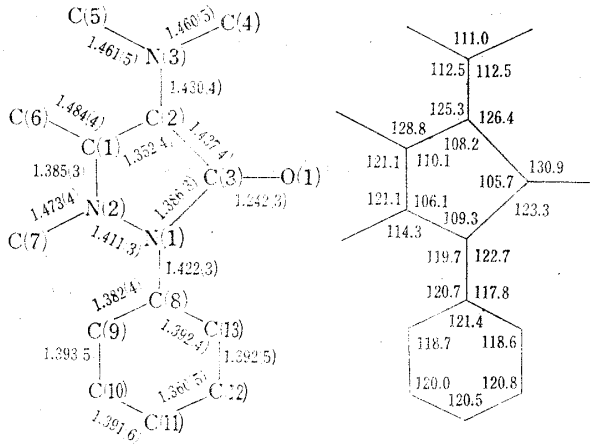

Fig. 2. Bond Lengths (Å) and Bond Angles with Their Estimated Standard Deviations for Aminopyrine

TABLE II. Hydrogen Atom Parameters with Their Standard Deviations

Atom	a)	$x \times 10^3$	$y \times 10^3$	$z \times 10^3$	B(Å^2)
H(1)	C(4)	197(3)	−55(3)	1004(6)	7.4(1.0)
H(2)		107(4)	−94(4)	809(8)	12.5(1.8)
H(3)		206(2)	−153(2)	869(4)	3.8(0.7)
H(4)	C(5)	393(4)	−80(3)	863(6)	8.0(1.1)
H(5)		374(5)	−5(5)	681(9)	14.3(2.0)
H(6)		374(4)	24(3)	952(7)	8.9(1.3)
H(7)	C(6)	169(3)	52(3)	242(5)	5.6(0.9)
H(8)		55(3)	−14(3)	279(5)	6.4(1.0)
H(9)		162(3)	−48(2)	355(5)	4.3(0.7)
H(10)	C(7)	188(3)	250(2)	399(5)	5.3(0.8)
H(11)		61(3)	265(2)	407(4)	4.1(0.7)
H(12)		81(3)	182(2)	245(5)	4.2(0.7)
H(13)	C(9)	−64(2)	200(2)	602(4)	3.5(0.7)
H(14)	C(10)	−162(3)	299(3)	725(5)	6.0(0.9)
H(15)	C(11)	−43(3)	414(3)	1026(6)	6.8(1.0)
H(16)	C(12)	141(3)	431(3)	1120(5)	5.9(0.9)
H(17)	C(13)	238(2)	324(2)	976(4)	3.0(0.6)
H(18)	N(4)	561(3)	84(3)	599(5)	5.6(0.9)
H(19)	N(5)	347(3)	183(3)	202(5)	5.5(0.9)
H(20)	C(18)	591(2)	397(2)	812(4)	3.8(0.7)
H(21)		501(3)	439(2)	641(5)	4.5(0.8)
H(22)	C(20)	414(4)	377(4)	876(7)	10.2(1.4)
H(23)		356(3)	302(3)	683(6)	6.7(1.0)
H(24)		454(3)	257(3)	852(6)	7.2(1.1)
H(25)	C(21)	670(3)	482(2)	635(5)	4.1(0.7)
H(26)	C(25)	704(3)	247(3)	388(6)	7.7(1.1)
H(27)		608(3)	273(3)	225(6)	7.2(1.1)

a) The atoms to which the hydrogen atoms are bonded.

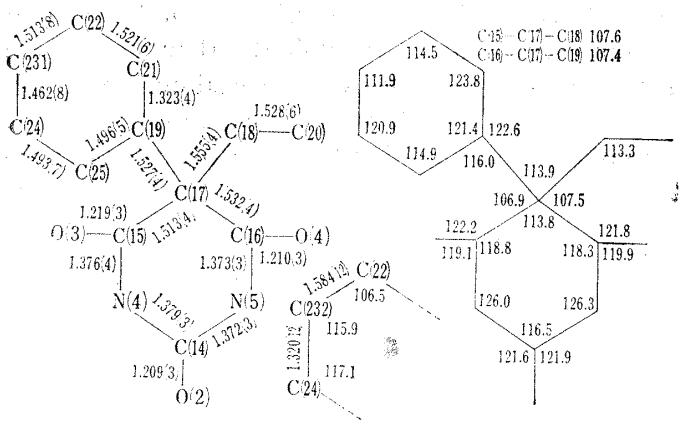

Fig. 3. Bond Lengths (Å) and Bond Angles with Their Estimated Standard Deviations for Cyclobarbital

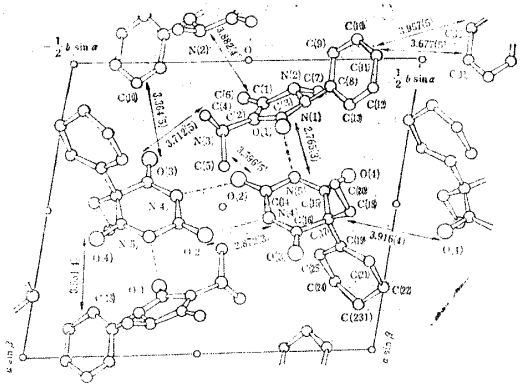

Fig. 4. The Molecular Arrangement viewed along the *c*-Axis and Intermolecular Atomic Distances (Å)

The hydrogen bonds are shown by broken lines.

TABLE III. Least-Squares Plane

	1. Equation of plane[a]			
Plane[b]	A	B	C	D
1	−0.85682	−0.33252	0.40413	−0.4176
2	−0.21028	−0.68297	0.73101	1.3821
3	−0.78680	0.05922	0.79272	−2.1640
Plane	2. Displacements from the plane (Å × 10^3)			
1	C(1) −29, C(2) 5, C(3) 22, N(1) −40, N(2) 42; atoms not forming the plane, C(6) −103, C(7) −778, N(3) 76, C(8) 479, O(1) 138			
2	C(8) 12, C(9) −11, C(10) 2, C(11) 8, C(12) −7, C(13) −3			
3	C(14) −13, N(4) −3, N(5) 1, C(15) 27, C(16) 23, C(17) −35; atoms not forming the plane, O(2) −22, O(3) 94, O(4) 84			

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 cyclobarbital.

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 pyrazolone ring (Table III). The structure is also very similar to that of antipyrine.[6]

Molecular Structure of Cyclobarbital

The structure of the cyclobarbital crystal at the stage of R=0.15 was reported as a note by Bideau, *et al.*[7] and has not been completely refined to be compared with the structure of this complex. The bond lengths and angles of the barbituric acid moiety of the complex, however, agree quite well with those of other barbiturates.[8] A slight folding of the pyrimidine ring plane[9] is also recognized along C(15)—C(16) line at an angle of about 5°.

The Crystal Structure

The intermolecular atomic distances and the arrangement of molecules in the crystals are shown in Fig. 4. The short distances between the carbonyl and imino groups, O(1)·····

6) T.P. Singh and M. Vijayan, *Acta Crystallogr., Sect. B*, **29**, 714 (1973).
7) J.P. Bideau and M. Artaud, *C. R. Acad. Sc. Paris, Ser. C*, **271**, 906 (1970).
8) B.M. Craven, E.A. Vizzini, and M.M. Rodorigues, *Acta Crystallogr., Sect. B*, **25**, 1978 (1969); B.M. Craven and E.A. Vizzini, *ibid.*, **25**, 1993 (1969).
9) B.M. Craven, C. Cusatis, G.L. Gartland, and E.A. Vizzini, *J. Mol. Struct.*, **16**, 331 (1973).

H(19)—N(5) 2.765 Å (O(1)·····H(19) 1.82 Å) and O(2)·····H(18)—N(4) 2.872 A (O(2)·····H(18) 1.93 Å), suggest hydrogen bonds. Two aminopyrine and two cyclobarbital molecules are thus linked by hydrogen bonds in the series of aminopyrine-cyclobarbital-cyclobarbital-aminopyrine, while the hydrocarbon groups, phenyl and cyclohexenyl groups, are in contact with one another; these molecular interactions are quite similar to those of aminopyrine-barbital system in spite of its different crystal symmetry. No other close contacts or stackings of molecules are observed.

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