Structural Studies of Analgesics and Their Interactions. Part 4.[1] Crystal Structures of Phenylbutazone and a 2:1 Complex between Phenylbutazone and Piperazine

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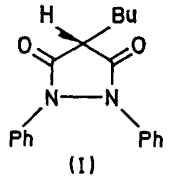
The *X*-ray crystal structures of 4-butyl-1,2-diphenylpyrazolidine-3,5-dione (phenylbutazone) (I), and its 2:1 complex (II) with piperazine have been determined by direct methods and the structures refined to *R* 0.096 (2 300 observed reflections measured by diffractometer) and 0.074 (2 494 observed reflections visually estimated). Crystals are monoclinic. space group $P2_1/c$; for (I) a = 21.695(4). b = 5.823(2). c = 27.881(4) Å. β = 108.06 (10)°. Z = 8. and for (II) a = 8.048(4). b = 15.081(4), c = 15.583(7) Å. β = 95.9(3)°. Z = 2. The two crystallographically independant molecules in the structure of (I) are similar except for the conformation of the butyl group. which is disordered in one of the molecules. In the pyrazolidinedione group. the two C–C bonds are single and the two C–O bonds double. The two nitrogen atoms in the five-membered ring are pyramidal with the attached phenyl groups lying on the opposite sides of the mean plane of the ring. The phenylbutazone molecule in (II) exists as a negative ion owing to deprotonation of C-4. C-4 is therefore trigonal and the orientation of the Bu group with respect to the pyrazolidinedione group is considerably different from that in (I); there is also considerable electron delocalization along the C–O and C–C bonds. These changes in geometry and electronic structure may relate to biological activity. The doubly charged cationic piperazine molecule exists in the chair form with the nitrogen atoms at the apices. The crystal structure of (II) is stabilized by ionic interactions and N–H • • • O hydrogen bonds.

THE discovery that all mild anti-inflammatory and anti-pyretic analgesics, despite their diverse chemical structues, inhibit prostaglandin biosynthesis has led to a hypothesis that their therapeutic action is based on this inhibition.[2,3] A knowledge of the three-dimensional structures of these drug molecules and the nature of their non-covalent interactions, together with associated changes in molecular geometry and electronic structure may give a better understanding of the molecular mechanism of their action. We have therefore carried out *X*-ray structural studies on some anti-inflammatory and analgetic pyrazolones and their crystalline complexes,[1,4,5] and we report here the structures of a pyrazolidinedione derivative, namely, 4-butyl-1,2-diphenylpyrazolidine-3,5-dione (I) (phenylbutazone), and its 2:1



(I)

crystalline complex (II) with piperazine. Preliminary reports have been published.[6,7]

[1] Part 3, T. P. Singh and M. Vijayan, *Acta Cryst.*, 1976, **B32**, 2432.
[2] R. J. Flower and J. R. Vane, *Nature*, 1972, **240**, 410.
[3] R. J. Flower, *Pharmacol. Rev.*, 1974, **26**, 33.
[4] T. P. Singh and M. Vijayan, *Acta Cryst.*, 1973, **B29**, 714.
[5] T. P. Singh and M. Vijayan, *Acta Cryst.*, 1974, **B30**, 557.
[6] T. P. Singh and M. Vijayan, *Acta Cryst.*, 1975, **A31**, S51.
[7] T. P. Singh and M. Vijayan, *Current Sci.*, 1975, **44**, 698.

EXPERIMENTAL

Thin needle-like crystals of (I) were grown by the controlled evaporation of its solution in ethyl alcohol. Large yellowish crystals of the complex were obtained by the slow evaporation of the components in methanol. The space group and unit-cell dimensions were determined by oscillation and Weissenberg photographs.

Crystal Data.—(*a*) *Phenylbutazone*, (I). $C_{19}H_{20}N_2O_2$, $M = 307.2$. Monoclinic, $a = 21.695 \pm 0.004$, $b = 5.823 \pm 0.002$, $c = 27.881 \pm 0.004$ Å, $\beta = 108.06 \pm 0.10°$, $U = 3\,348.57$ Å^3, $D_m = 1.211$ g cm^{-3} (by flotation), $Z = 8$, $D_c = 1.218$ g cm^{-3}. Space group $P2_1/c$. Cu-K_α radiation, $\lambda = 1.5418$ Å; μ (Cu-K_α) = 6.44 cm^{-1}.

(b) *Phenylbutazone : piperazine*, 2 : 1. (II). $2C_{19}H_{20}N_2O_2,C_4H_{10}N_2$, $M = 700.47$. Monoclinic, $a = 8.048 \pm 0.004$, $b = 15.081 \pm 0.004$, $c = 15.583 \pm 0.007$ Å, $\beta = 95.9 \pm 0.3°$, $U = 1881.31$ Å^3, $D_m = 1.238$ g cm^{-3} (by flotation), $Z = 2$, $D_c = 1.237$ g cm^{-3}. Space group $P2_1/c$. Cu-K_α radiation; $\mu r_c = 0.34$, $\mu r_b = 0.36$.

The intensity data from crystals of (I) were collected on a Hilger and Watts four-circle diffractometer at the Laboratory of Molecular Biophysics, Oxford, from a needle-like specimen of mean radius 0.10 mm mounted along the *b* axis by use of nickel-filtered copper radiation. The ordinate-analysis procedure [8] was employed to measure intensities by use of ω scan. The diffraction pattern faded off rapidly at high angles and data were collected only up to a Bragg angle of 57°. Of the 4 315 independent reflections measured within this range, the intensities of 2 300 reflections had $I > 3\sigma(I)$ and were used for structure determination and refinement. Data were corrected for Lorentz and polarization factors. The normalized structure factors for the reflections were calculated using the scale factor and the overall temperature factor obtained from Wilson's statistics.

The intensity data from crystals of (II) were recorded on multiple-film equi-inclination Weissenberg photographs corresponding to reciprocal levels *hk*0—13 and *h*0—1*l* by use of Cu-K_α radiation from nearly cylindrical specimens of mean radii 0.047 and 0.053 cm cut and ground along the *c* and *b* axes respectively. Intensities were estimated visually by comparison with calibrated film strips. Of a total of 4 283 independent reflections in the copper sphere 3 722 were recorded, of which 2 494 were in the measurable range. Corrections were made for the Lorentz and polarization factors and for spot size. The two sets of data were also corrected for absorption according to the analytical formula of Palm.[9] Common reflections in the two data sets were used for interlevel scaling. The absolute scale and the overall temperature factor were initially obtained from Wilson's statistics and normalized structure factors, $|E|$ values, then derived.

Structure Determination of (I).—The crystals contain two crystallographically non-equivalent phenylbutazone molecules which meant that the positions of 46 non-hydrogen atoms had to be determined. After several unsuccessful attempts at structure analysis by the symbolic-addition procedure [10] and an unweighted multisolution method, the structure was finally solved by use of the programme MULTAN [11] (modified by Ramakumar and Murthy for the IBM 360/44), followed by conventional Fourier techniques. The structure was refined, first isotropically and then anisotropically, to R 0.105 by use of a locally modified version of a block-diagonal structure factor least-squares programme written by Professor R. Shiono.

Disordered Butyl Group.—An examination of the molecular dimensions at this stage showed that the bond lengths and angles in the butyl group of molecule (B) [molecules (A) and (B) are indicated in Figure 1] deviated substantially from standard values thus casting doubts on the positioning of the atoms. The orientation of this butyl group with respect to the rest of the molecule was also very different from that of the butyl group in molecule (A). Structure factors were then calculated for atoms other than those of the two butyl groups and were used to compute a difference-Fourier map. In this, peaks corresponding to the butyl group of molecule (A) appeared at exactly the same positions as those obtained from the SFLS refinement. No revision of these atomic positions was therefore necessary. The peaks corresponding to the butyl group of molecule (B), however, indicated disorder, with two peaks of nearly equal heights associated with each of the three terminal atoms in

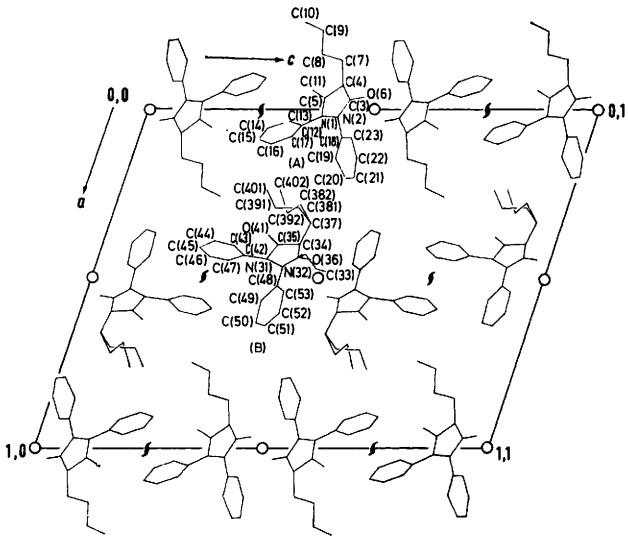


FIGURE 1 Crystal structure of phenylbutazone (I) viewed along the *b* axis

the group. Atoms corresponding to both these orientations of the butyl group were introduced in the subsequent refinement. In the next few cycles of refinement, the temperature factors of these two sets of atoms were held constant and the occupancy factors refined instead. The occupancy factors of all six atoms (two sets of three) converged to *ca.* 0.5 indicating that the statistical weights of the two orientations were nearly equal. In further anisotropic refinements, each of these six atoms was assigned an occupancy factor of 0.5. The R value came down to 0.097 in three more cycles. In the final cycle, parameter shifts were much smaller than the corresponding standard deviations for all the atoms.

At this stage, the positions of all the hydrogen atoms, except those of the disordered butyl group of molecule (B) and those attached to the terminal carbon atom in the butyl group of molecule (A), were calculated from geometrical considerations, and given the isotropic temperature factors of the heavy atom to which each was attached. Hydrogen-

[8] H. C. Watson, D. M. Shotton, J. M. Cox, and H. Muirhead, *Nature*, 1970, **225**, 806.
[9] J. H. Palm, *Acta Cryst.*, 1964, **17**, 1326.
[10] I. L. Karle and J. Karle, *Acta Cryst.*, 1966, **21**, 849.
[11] G. Germain, P. Main, and M. M. Woolfson, *Acta Cryst.*, 1971, **A27**, 368.

atom parameters were also included in the final structure-factor calculations, but were not refined. The final R was 0.096 for 2 300 observed reflections.

The weighting function used in the final cycles had the form: [12] $w = |1/F_o^2|$ if $F_o \geqslant 4\ F_{min}$, and $w = |\frac{1}{4}\ F_{min}^2|$ if $F_o < 4\ F_{min}$, where $F_{min} = 8.0$. Scattering factors for non-hydrogen atoms were taken from ref. 13, and for hydrogen from ref. 14. The final positional parameters of the non-hydrogen atoms are listed in Table 1.

TABLE 1

Final positional co-ordinates ($\times 10^4$) of non-hydrogen atoms in the structure of phenylbutazone (I), with standard deviations in parentheses

Atom	x	y	z
N(1)	239(6)	3 796(25)	3 902(4)
N(2)	252(6)	5 784(27)	4 207(4)
C(3)	−283(8)	5 768(36)	4 386(6)
C(4)	−684(9)	3 633(36)	4 176(6)
C(5)	−340(9)	2 609(35)	3 831(6)
C(6)	−381(6)	7 166(28)	4 671(4)
C(7)	−1 414(9)	4 118(45)	3 917(7)
C(8)	−1 528(9)	4 765(47)	3 456(8)
C(9)	−2 281(14)	6 246(63)	3 247(10)
C(10)	−2 427(14)	7 882(64)	2 813(12)
C(11)	−516(6)	1 064(25)	3 537(5)
C(12)	488(7)	4 073(32)	3 480(5)
C(13)	349(8)	6 050(33)	3 194(5)
C(14)	571(9)	6 184(33)	2 764(6)
C(15)	938(8)	4 381(35)	2 658(6)
C(16)	1 070(9)	2 409(36)	2 954(6)
C(17)	853(8)	2 254(34)	3 385(6)
C(18)	874(8)	6 683(31)	4 479(5)
C(19)	1 442(8)	5 358(35)	4 527(6)
C(20)	2 033(9)	6 269(41)	4 819(7)
C(21)	2 079(10)	8 366(41)	5 057(7)
C(22)	1 510(10)	9 681(35)	5 001(6)
C(23)	888(9)	8 841(35)	4 708(6)
N(31)	4 468(6)	10 967(26)	3 717(5)
N(32)	4 675(7)	9 063(25)	4 051(4)
C(33)	4 406(8)	9 290(34)	4 446(6)
C(34)	4 039(8)	11 479(33)	4 380(6)
C(35)	4 048(8)	12 319(32)	3 870(6)
C(36)	4 506(6)	7 942(35)	4 790(4)
C(37)	3 347(9)	11 403(41)	4 454(7)
C(381)	2 911(21)	9 607(99)	4 093(18)
C(382)	2 768(22)	10 608(97)	4 013(18)
C(391)	2 767(25)	9 255(99)	3 591(22)
C(392)	2 947(15)	8 065(61)	3 940(14)
C(401)	2 330(21)	7 401(86)	3 281(17)
C(402)	2 306(21)	7 042(89)	3 523(17)
O(41)	3 745(6)	13 915(22)	3 629(4)
C(42)	4 342(28)	10 487(33)	3 179(6)
C(43)	4 064(9)	8 388(35)	2 987(6)
C(44)	3 918(9)	8 029(36)	2 463(7)
C(45)	4 060(10)	9 761(39)	2 161(7)
C(46)	4 346(9)	11 830(40)	2 373(7)
C(47)	4 491(9)	12 218(35)	2 900(6)
C(48)	5 299(7)	8 095(33)	4 101(6)
C(49)	5 728(8)	9 374(35)	3 915(6)
C(50)	6 344(9)	8 447(37)	3 971(6)
C(51)	6 518(10)	6 314(39)	4 214(6)
C(52)	6 073(10)	5 121(37)	4 404(6)
C(53)	5 454(9)	6 010(34)	4 341(6)

Structure Analysis of the Complex (II).—The unit cell contains four molecules of phenylbutazone and two of piperazine. The multiplicity of space group $P2_1/c$ is four-fold and, hence, the asymmetric unit should consist of one phenylbutazone molecule and half a piperazine molecule situated at a centre of inversion.

The structure was determined by direct methods by use of MULTAN and was refined, first isotropically and then anisotropically, to R 0.102. A difference-Fourier map, computed at this stage, revealed the positions of all the hydrogen atoms. In the subsequent refinement, positional parameters and the isotropic thermal parameters of the hydrogen atoms were included. Refinement was terminated when all the shifts became much smaller than the corresponding estimated standard deviations; R was then 0.074 for 2 494 observed reflections. The weighting function used in the final cycle had the form: [15] $1/(a + bF_o + cF_o^2)$ where $a = 1.0$, $b = 0.040\ 3$, and $c = -0.000\ 1$. The computer programmes and the form factors used in the analysis

TABLE 2

Final positional co-ordinates ($\times 10^4$ for non-hydrogen and $\times 10^3$ for hydrogen atoms) in the structure of the complex (II), with estimated standard deviations in parentheses

Atom	x	y	z
N(1)	2 342(7)	2 818(4)	3 568(3)
N(2)	1 985(7)	3 345(4)	2 818(3)
C(3)	3 236(8)	3 147(4)	2 278(4)
C(4)	4 118(8)	2 418(5)	2 613(5)
C(5)	3 565(8)	2 193(4)	3 390(4)
O(6)	3 416(7)	3 612(3)	1 630(3)
C(7)	5 524(10)	1 983(6)	2 182(5)
C(8)	4 921(12)	1 319(7)	1 478(6)
C(9)	4 435(13)	460(7)	1 882(6)
C(10)	3 742(19)	−246(10)	1 210(11)
O(11)	3 958(6)	1 576(3)	3 915(3)
C(12)	972(8)	2 621(4)	4 058(4)
C(13)	1 348(9)	2 360(5)	4 904(4)
C(14)	83(12)	2 225(6)	5 423(5)
C(15)	−1 572(12)	2 357(6)	5 113(6)
C(16)	−1 922(10)	2 599(6)	4 231(6)
C(17)	−680(9)	2 723(5)	3 708(5)
C(18)	1 385(9)	4 225(4)	2 921(5)
C(19)	1 456(10)	4 635(5)	3 722(5)
C(20)	829(12)	5 496(6)	3 778(6)
C(21)	111(13)	5 925(6)	3 047(7)
C(22)	24(12)	5 518(6)	2 274(7)
C(23)	653(10)	4 662(5)	2 195(5)
C(24)	3 277(9)	5 099(5)	154(5)
N(25)	4 604(7)	4 999(4)	876(3)
C(26)	6 038(9)	4 470(5)	603(5)
H(13)	257(10)	225(5)	513(5)
H(14)	26(12)	202(6)	606(6)
H(15)	−248(11)	229(7)	550(6)
H(16)	−309(11)	267(6)	395(6)
H(17)	−92(11)	288(7)	312(5)
H(19)	187(11)	430(6)	425(6)
H(20)	95(11)	580(6)	436(5)
H(21)	−38(14)	654(8)	307(7)
H(22)	−56(12)	588(7)	174(6)
H(23)	64(10)	435(6)	164(5)
H(71)	632(10)	169(6)	260(5)
H(72)	627(11)	241(6)	191(6)
H(81)	586(12)	122(7)	104(6)
H(82)	387(12)	157(8)	110(7)
H(91)	365(12)	62(7)	233(6)
H(92)	551(12)	25(7)	226(6)
H(101)	467(17)	40(10)	78(9)
H(102)	342(17)	−87(10)	153(9)
H(103)	276(17)	−1(10)	87(9)
H(241)	286(11)	449(6)	−3(6)
H(242)	234(10)	546(6)	37(5)
H(251)	417(9)	470(5)	135(5)
H(252)	497(10)	558(6)	104(5)
H(261)	570(10)	387(6)	460(5)
H(262)	700(10)	444(6)	113(5)

[12] E. W. Hughes, *J. Amer. Chem. Soc.*, 1941, **63**, 1737.
[13] D. T. Cromer and J. T. Waber, *Acta Cryst.*, 1965, **18**, 104.
[14] R. F. Stewart, E. R. Davidson, and W. T. Simpson, *J. Chem. Phys.*, 1965, **42**, 3175.
[15] D. W. J. Cruickshank, A. Bujosa, F. M. Lovell, and M. R. Truter, 'Computing Methods and the Phase Problem in *X*-Ray Analysis,' eds. R. Pepinsky and J. M. Robertson, Pergamon, Oxford, 1961, p. 45.

were the same as those used in the structure determination of the crystals of phenylbutazone. Final positional parameters are given in Table 2. Observed and calculated structure factors for both (I) and (II), and atom thermal parameters are listed in Supplementary Publication No. SUP 21874 (28 pp., 1 microfiche).*

RESULTS

The crystal structures of phenylbutazone (I) viewed down the *b* axis and that of the complex (II) projected along the *a* axis are shown in Figures 1 and 2. Perspective views of the two crystallographically independent molecules in (I) are shown in Figure 3. Figure 4 shows the corresponding view of the phenylbutazone molecule in (II). Bond lengths and angles, not corrected for thermal vibrations, of the phenylbutazone molecules in (I) and (II) are given in Figures 5 and 6 respectively. The equations of the mean planes for different planar groupings in the structures were calculated by Blow's method.[16] The phenyl rings are planar, displacements of atoms from the mean planes being $\ll 3\sigma$. The deviations of atoms in the pyrazolidine ring are small, though significant in a few instances, in both structures. The dihedral angles which define the geometry of

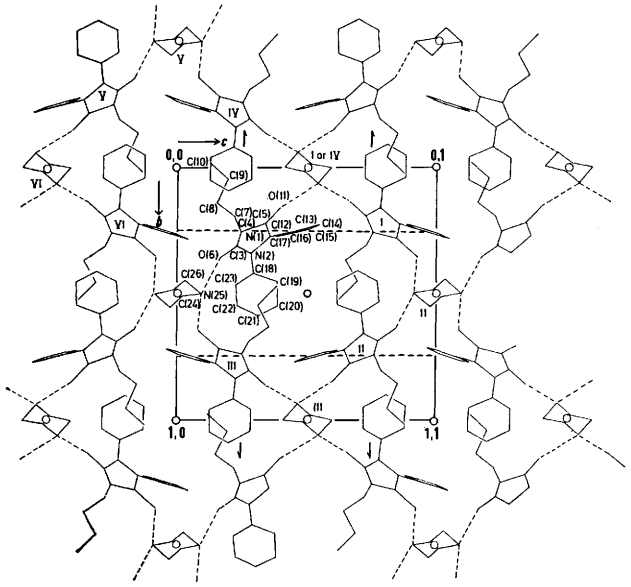


FIGURE 2 The crystal structure of the complex (II) as viewed along the *a* axis. Hydrogen bonds are shown by broken lines. Molecules are at the following equivalent positions: I, x, $\frac{1}{2}-y$, $\frac{1}{2}+z$; II, $1-x$, $1-y$, $1-z$; III, $1-x$, $\frac{1}{2}+y$, $\frac{1}{2}-z$; IV, $1-x$, $\frac{1}{2}+y-1$, $\frac{1}{2}-z$; V, $1-x$, $-y$, $-z$; and VI, x, $\frac{1}{2}-y$, $\frac{1}{2}+z-1$

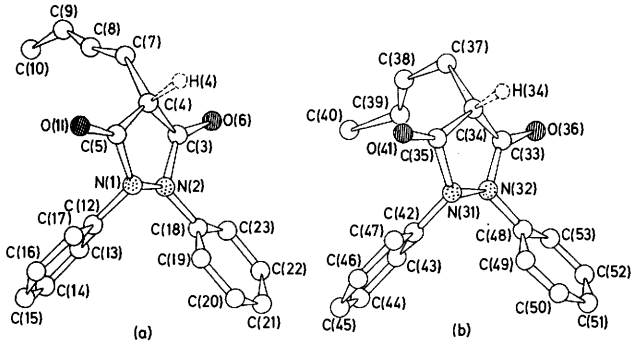


FIGURE 3 Perspective views of (a) molecule (A) and (b) molecule (B) in the crystals of (I). In molecule (B), the average positions of atoms in disordered butyl group are used for clarity

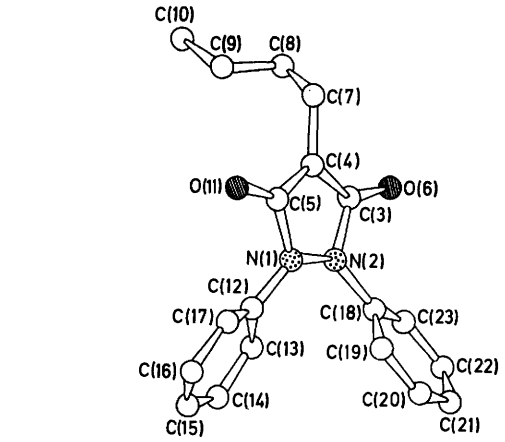


FIGURE 4 Perspective view of the phenylbutazone molecule in (II)

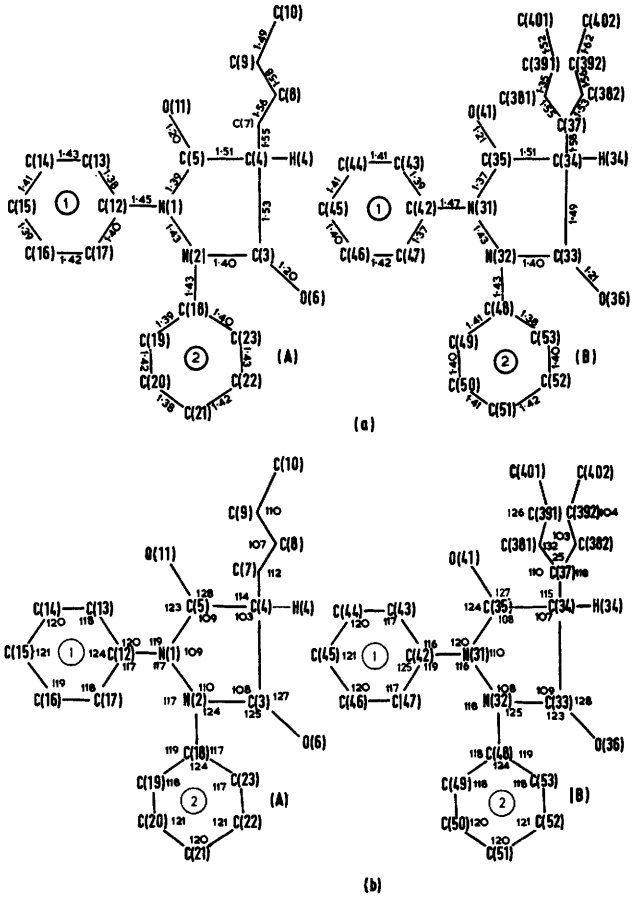


FIGURE 5 (a) Bond lengths (Å) and (b) bond angles (°) of phenylbutazone molecules in (I). Mean estimated standard deviations: C–O 0.02, N–N 0.02, N–C 0.02, and C–C 0.03 Å, angles 1—2°; mean for disordered atoms of the Bu group in molecule (B) 0.06 Å and 4—6°. Additional angles: C(3)–C(4)–C(7) 114, C(33)–C(34)–C(37) 117°

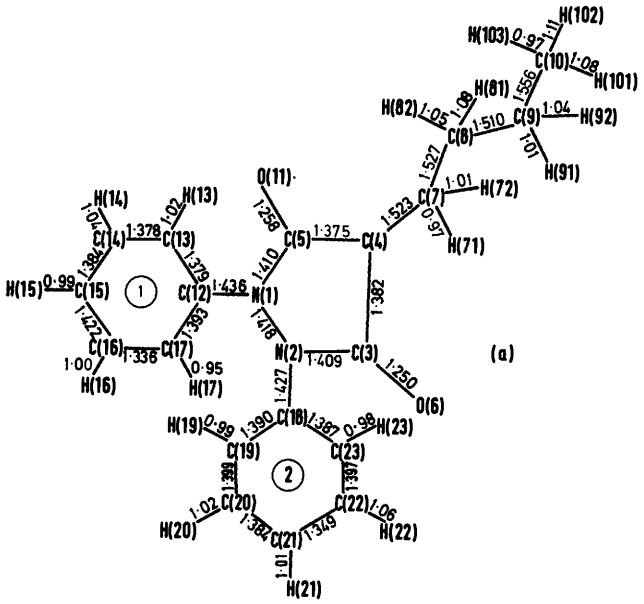
* See Notice to Authors No. 7 in *J.C.S. Perkin II*, 1976, Index issue.

[16] D. M. Blow, *Acta Cryst.*, 1960, **13**, 168.

TABLE 3

Dihedral angles (°) in the phenylbutazone molecule in (I) and (II), with estimated standard deviations in parentheses

Plane (1)	Plane (2)	(I) Molecule (A)	(I) Molecule (B)	(II)
C(12)–N(1)–N(2)	N(1)–N(2)–C(18)	−65(2)	−67(2)	−62.2(0.7)
C(12)–N(1)–C(5)	N(1)–C(5)–O(11)	31(3)	33(3)	30.3(0.8)
C(18)–N(2)–C(3)	N(2)–C(3)–O(6)	30(3)	33(3)	29.3(0.9)
O(6)–C(3)–C(4)	C(3)–C(4)–C(7)	54(3)	49(3)	4.2(1.0)
O(11)–C(5)–C(4)	C(5)–C(4)–C(7)	−46(3)	−42(3)	−4.3(1.0)
5-Membered ring	Ph ring (1)	66	61	41.4
5-Membered ring	Ph ring (2)	40	42	42.0



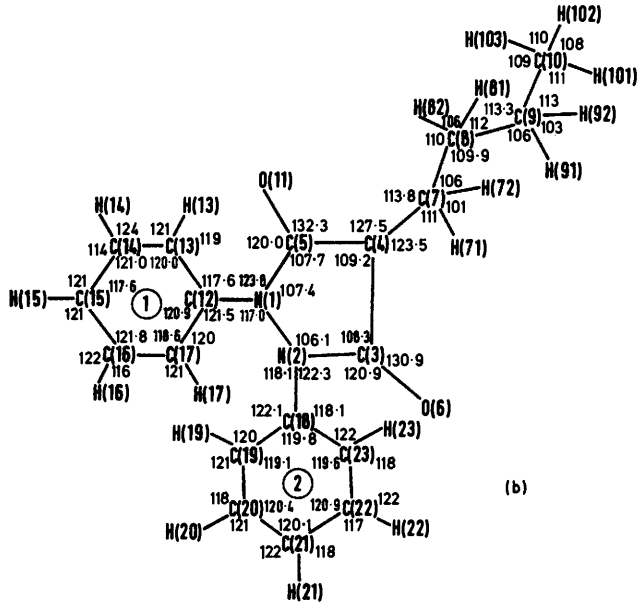


FIGURE 6 (a) Bond lengths (Å) and (b) bond angles (°) in the phenylbutazone molecule of the complex (II). Mean estimated standard deviations: C–O 0.008, N–N 0.007, N–C 0.009, C–C 0.010, C–H 0.09 Å; for angles involving non-hydrogen atoms 0.4—0.7 (Bu group 0.7—1.0), C–C–H 5, and H–C–H 8°. Additional angles : H(102)–C(10)–C(9) 111, H(103)–C(10)–H(101)109, H(82)–C(8)–C(9) 108, H(81)–C(8)–C(7) 110, H(91)–C(9)–C(10) 115, H(92)–C(9)–C(8) 105, H(71)–C(7)–C(8) 109, H(72)–C(7)–C(4) 114°

the phenylbutazone molecules in both structures are given in Table 3. Table 4 lists bond lengths and angles in the centrosymmetric piperazine molecule in (II).

TABLE 4

Bond lengths (Å) and angles (°) in the piperazine molecule of (II), with estimated standard deviations in parentheses

(*a*) Distances			
C(24)–N(25)	1.477(8)	N(25)–H(251)	0.97(7)
N(25)–C(26)	1.501(9)	N(25)–H(252)	0.96(8)
C(26)–C(24′)	1.500(9)	C(26)–H(261)	0.97(8)
C(24)–H(241)	1.01(9)	C(26)–H(262)	1.06(7)
C(24)–H(242)	1.02(8)		
(*b*) Angles			
N(25)–C(24)–C(26′)	110.4(6)	H(251)–N(25)–H(252)	110(7)
C(24)–N(25)–C(26)	110.8(5)	H(251)–N(25)–C(26)	109(5)
N(25)–C(26)–C(24′)	110.4(6)	H(252)–N(25)–C(24)	107(5)
H(241)–C(24)–H(242)	110(7)	H(252)–N(25)–C(26)	110(5)
H(241)–C(24)–N(25)	109(5)	H(261)–C(26)–N(25)	111(5)
H(241)–C(24)–C(26′)	108(5)	H(261)–C(26)–H(262)	108(7)
H(242)–C(24)–C(26′)	112(5)	H(261)–C(26)–C(24′)	110(5)
H(242)–C(24)–C(26′)	112(5)	H(262)–C(26)–N(25)	109(4)
H(242)–C(24)–N(25)	108(5)	H(262)–C(26)–C(24′)	109(4)
H(251)–N(25)–C(24)	110(5)		

DISCUSSION

Molecular Dimensions of Phenylbutazone in (I).—In the pyrazolidinedione moiety in each molecule, the two C–C bonds and the N–N bonds have lengths appropriate to single bonds whereas the two C–O bonds are double. The two N–C bonds, though formally single, are much shorter than a normal N–C single bond. The dimensions of the phenyl rings and the butyl group of molecule (A) are as expected, but some dimensions of the disordered butyl group of molecule (B) deviate substantially from standard values. However, these deviations are not statistically significant on account of the high standard deviations.

The two hetero-nitrogen atoms in the molecule are pyramidal and the attached phenyl groups lie on opposite sides of the plane of the five-membered ring. One of the carbon atoms in the ring is tetrahedral in each molecule with a butyl group and a hydrogen atom attached to it. The two other carbon atoms are sp^2 hybridized. Phenyl ring (1), which lies on the same side of the plane of the five-membered ring as does the butyl group, is inclined with respect to the five-membered ring at 66° in molecule (A) and 61° in molecule (B); corresponding values for phenyl ring (2) are 40 and 45°.

Except for the presence of a butyl group at the 4-position, the phenylbutazone molecule may be expected to have two-fold symmetry about an axis passing through the mid-point of the N–N bond and the tetrahedral

carbon atom at the 4-position. However, the substitution of the butyl group at this tetrahedral carbon atom prevents this symmetry, and also makes the environment of the two phenyl groups attached to the nitrogen atoms dissimilar. The orientation, with respect to the five-membered ring, of phenyl ring (1) is different from that of phenyl ring (2) in both molecules. The fact that the nature and magnitude of this difference are the same in both the crystallographically independent molecules leads one to believe that it is perhaps an inherent structural characteristic of the molecule and not the result of crystal packing alone.

Molecular Dimensions of Phenylbutazone in the Complex (II) *compared with those in* (I).—The phenylbutazone molecule in the structure exists as a negative ion on account of the deprotonation of the ring carbon atom C(4), as a consequence of formation of the complex. This deprotonation causes significant structural differences between the anionic phenylbutazone molecule in the complex (II) and the neutral molecules in the crystals

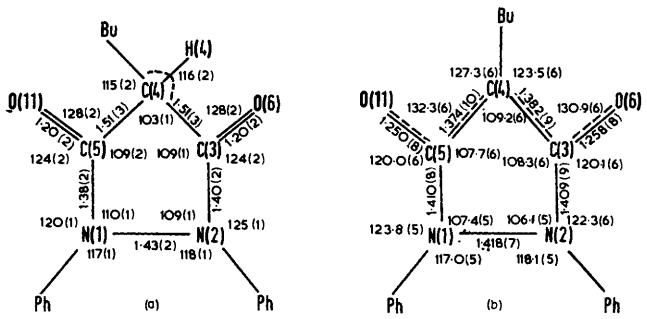


FIGURE 7 (a) Mean dimensions of the pyrazolidinedione moiety in the crystals of (a) phenylbutazone (I) and (b) the complex (II), with estimated standard deviations in parentheses

of (I). In (I), carbon atom C(4) is tetrahedral whereas in the complex it is trigonal resulting in different orientations of the butyl group in the two cases. As can be seen from Figure 7, the molecular dimensions of the pyrazolidinedione moiety in the two structures also differ substantially. In the anionic molecule in the complex, the excess electron is delocalized over the two C–O and two C–C bonds, giving them partial double-bond character. Yet another difference between the two structures pertains to the exocyclic angles about the atoms C(3) and C(5). In the complex, the exocyclic angles about C(3) and C(5) are substantially different whereas in the free phenylbutazone molecule they are nearly equal. The hybridization state of C(4) changes from sp^3 to sp^2 on complex formation resulting in increased steric interaction between the butyl carbon atom C(7) and the two oxygen atoms. This leads to the enlarging of angles adjacent to C(4) and consequent reduction of those adjacent to the nitrogen atoms in the complex (II) when compared to values in (I).

The two-fold symmetry of the 1,2-diphenylpyrazolidine-3,5-dione part of the molecule is restored by the deprotonation of C(4). In the anionic phenylbutazone molecule, the two phenyl groups are oriented with respect to the plane of the pyrazolidine moiety at nearly equal angles, unlike the situation in phenylbutazone. The C(4)–C(7) bond lies in the plane of the five-membered ring and the butyl group has no preferred orientation with respect to this plane; therefore, unlike the situation in free phenylbutazone, the two phenyl groups are structurally indistinguishable.

The crystal structure of a 1 : 1 complex between phenylbutazone and *N*-methylpiperazine has been reported recently.[17] The phenylbutazone molecule in this complex is also anionic, with C(4) deprotonated, and has molecular dimensions in close agreement with those found in the present study.

Biological Relevance of Structural Changes in Phenylbutazone.—The deprotonation at C(4) occurs in (II) as a result of complex formation with the basic piperazine molecule. However, deprotonation of the phenylbutazone molecule is likely to occur when it approaches carrier proteins or the prostaglandin synthetase system as a result of its interaction with basic amino-acid residues. The accompanying changes in the molecule could conceivably be of crucial importance in its protein-binding properties and its inhibitory action against prostaglandin synthetase.

The Piperazine Molecule.—The centrosymmetric piperazine molecules in the structure of (II) exist in the doubly charged cationic state with two hydrogen atoms attached to each of the two nitrogen atoms in the molecule. The dimensions of the molecule (Table 4) are comparable to those reported previously.[17-21] The molecule exists in the chair form with the nitrogen atoms at the apices. Each nitrogen atom deviates from the plane of the four carbon atoms in the ring by 0.287 ± 0.007 Å.

Crystal Packing.—The crystal structure of phenylbutazone (Figure 1) is stabilized by van der Waals interactions. All contact distances are normal and there are no unusual features in the crystal packing.

In the structure of (II) (Figure 2), the deprotonated anionic phenylbutazone molecules occupy general positions whereas the doubly protonated cationic piperazine molecules are located at the centres of inversion at 1/2,-1/2,0. The structure is stabilized by ionic interactions and hydrogen bonds involving the NH_2 groups of the piperazine molecules and the carbonyl oxygen atoms of the phenylbutazone molecules. The parameters of the two crystallographically independent hydrogen bonds in the structure are given in Table 5.

The structure consists of hydrogen-bonded sheets stacked along the *a* axis. Each sheet contains two types of loops, one connecting phenylbutazone molecules at *x,y,z* and equivalent positions (I)—(III) with piper-

[17] J. Toussaint, O. Dideberg, and L. Dupont, *Acta Cryst.*, 1973, **B30**, 590.
[18] J. K. Dattagupta and N. N. Saha, *Indian J. Phys.*, 1970, **44**, 561.
[19] S. Kashino, *Acta Cryst.*, 1973, **B29**, 1836.
[20] E. J. Email and G. M. Sheldrick, *Acta Cryst.*, 1973, **B29**, 2027.
[21] K. Fukayama, S. Kashino, and M. Haisa, *Acta Cryst.*, 1973, **B29**, 2713.

azine molecules in the same positions, and the other connecting phenylbutazone molecules at x,y,z and positions (III)—(V) and piperazine molecules in the same positions (equivalent positions are defined in the caption to Figure 2). When the sheet repeats itself along the a direction, an infinite number of loops of the same type are stacked, one above the other, along the a axis, resulting in column-like arrangements. Thus, the crystal structure can also be described as consisting of columns, with shared surfaces, running parallel to the a axis. The surface of each column is primarily made up of hydrogen bonds and atoms bearing positive or negative charges whereas the interior of each column is filled with non-polar phenyl rings and butyl groups.

TABLE 5

Hydrogen-bond distances (Å) and angles (°) in the structure of the complex (II), with estimated standard deviations in parentheses

	Distances			Angles	
i j k	d_{ij}	d_{jk}	d_{ik}	i–j–k	k–i–j
N(25)–H(251) · · · O(6)	0.97(8)	1.82(8)	2.627(8)	139(6)	27(4)
N(25)–H(252) · · · O(11^{III})	0.96(8)	1.73(8)	2.650(8)	162(6)	12(5)

O(11^{III}) is at $1 - x, \frac{1}{2} + y, \frac{1}{2} - z$.

We thank Professor G. N. Ramachandran for his interest in the work, the University Grants Commission, India, for financial support, and the Council of Scientific and Industrial Research, India, for the award of a Senior Research Fellowship (to T. P. S.).

[6/484 *Received*, 10*th March*, 1976]