Formation and *X*-Ray Crystal Structure of 5,6-Dihydro-1-hydroxy-5,5-dimethyl-1-phenyl-3-phenylamino-1*H*-pyrrolo[1,2-*a*][1,5]benzodiazepin-2(4*H*)-one†

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The reaction of 2,3-dihydro-2,2,4-trimethyl-1*H*-1,5-benzodiazepine (**1**) with (*Z*)-*N*-(benzoylmethylene)aniline *N*-oxide in anhydrous benzene at room temperature gave 5,6-dihydro-1-hydroxy-5,5-dimethyl-1-phenyl-3-phenylamino-1*H*-pyrrolo[1,2-*a*][1,5]benzodiazepin-2(4*H*)-one (**2**), accompanied by several by-products. The structure of compound (**2**), the first example of a tetrahydropyrrolo[1,2-*a*][1,5]benzodiazepine derivative, was established by an *X*-ray crystallographic analysis. A mechanism for its formation is suggested.

Many benzodiazepine derivatives bearing further condensed heterocyclic nuclei are of pharmacological importance. In our search for new benzodiazepines with a heterocyclic ring fused to the seven-mumbered one,[1] we have investigated the reactivity of nitrones towards 2,3-dihydro-1*H*-1,5-benzodiazepine derivatives. We report here the isolation of the major product from the reaction of compound (**1**)[2] with an excess of (*Z*)-*N*-(benzoylmethylene)aniline *N*-oxide[3] and its identification as 5,6-dihydro-1-hydroxy-5,5-dimethyl-1-phenyl-3-phenylamino-1*H*-pyrrolo[1,2-*a*][1,5]benzodiazepin-2(4*H*)-one (**2**) (the yield of pure product does not exceed 20%). Tetrahydropyrrolo-[1,2-*a*][1,5]benzodiazepine derivatives have apparently not been prepared previously. However, 4*H*-pyrrolo[1,2-*a*][1,5]-benzodiazepin-5(6*H*)-one is formed in low yield by reaction between 1-(*o*-acetamidophenyl)-2-dimethylaminomethylpyrrole methiodide and potassium cyanide.[4]

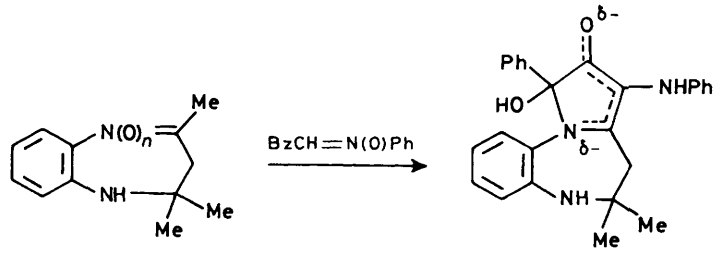
The benzodiazepine (**1**) was treated in anhydrous benzene with an excess of the nitrone at room temperature under nitrogen. The solvent was evaporated off and the reaction mixture was subjected to repeated column and layer chromatography. The main product (**2**), $C_{26}H_{25}N_3O_2$, was obtained as yellow prisms, m.p. 134—136 °C (from methanol). The i.r. spectrum (Nujol mull) suggested the presence of a carbonyl group conjugated with an unsaturated system ($\nu_{max.}$ 1 657 cm^{-1}) and possibly amino and hydroxy groups (3 250 and 3 380 cm^{-1}). The ^1H n.m.r. spectrum (CD_3OD) showed an AB system (δ_A 2.86, δ_B 2.54, J_{AB} −12.0 Hz), and only two methyl signals (two singlets at 1.38 and 1.32), in the range for the geminal 2-methyl groups in the starting material (**1**).[5] The AB system may be attributed to the methylene protons, which resonate as a singlet in the bicyclic product (**1**) and become magnetically inequivalent in tricyclic derivatives.[1c] The structure (**2**) was established unambigously by *X*-ray analysis (see later).

The formation of (**2**), which is stabilized by an extended delocalization of the N(11) lone pair towards O(19) (see the Figure for atom labelling), may be rationalized as follows. First the nitrone acts as an oxygen donor[6a] towards the benzodiazepine (**1**), the 5-oxide (**3**) of which undergoes dipole–dipole interaction[6b] with unchanged nitrone, yielding the intermediate tricyclic dioxadiazine (**4**) (not isolated). Intramolecular rearrangement of a tautomer of (**4**) affords (**5**), which contains a –C(OH)Ph–CO– moiety in the six-membered heterocyclic ring: this suggested rearrangement [(**4**) to (**5**)] is reminiscent in part of that observed in the reaction of the same nitrone with allene[7] or ketene dimer.[3a] Then ring contraction occurs, involving the angular methyl group, to yield the intermediate (**6**). The final product (**2**) is formed from (**6**) by dehydration, which follows the migration of the phenylhydroxyamino group from C(2) to C(3).

† *Supplementary data available* (SUP 56596, 4 pp.): full list of bond angles, temperature factors, hydrogen co-ordinates. For details of Supplementary Publications see Instructions for Authors, *J. Chem. Soc., Perkin Trans. 2*, 1986, Issue no. 1.

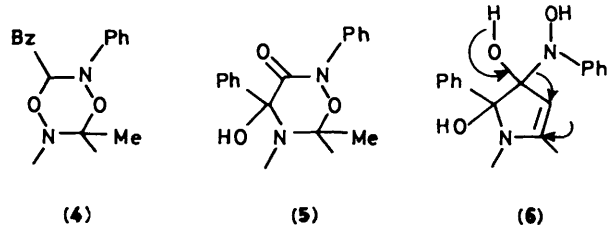
Table 1. Fractional atomic co-ordinates (× 10^4), with e.s.d.s in the least significant digits in parentheses, for compound (**2**)

	x	*y*	*z*
C(1)	1 453(9)	1 128(5)	6 277(6)
C(2)	102(11)	742(5)	5 267(6)
C(3)	−1 618(9)	1 176(5)	5 289(6)
C(3a)	−1 442(9)	1 781(5)	6 193(6)
C(4)	−2 847(10)	2 398(5)	6 588(7)
C(5)	−2 530(10)	3 226(5)	5 919(7)
C(6a)	555(7)	3 247(4)	7 153(5)
C(7)	1 358(7)	3 901(4)	7 841(5)
C(8)	2 577(7)	3 757(4)	8 913(5)
C(9)	2 992(7)	2 959(4)	9 295(5)
C(10)	2 189(7)	2 304(4)	8 607(5)
C(10a)	970(7)	2 448(4)	7 536(5)
C(13)	2 010(6)	518(5)	7 288(6)
C(14)	3 841(6)	205(5)	7 361(6)
C(15)	4 297(6)	−408(5)	8 264(6)
C(16)	2 923(6)	−709(5)	9 093(6)
C(17)	1 093(6)	−396(5)	9 019(6)
C(18)	636(6)	217(5)	8 117(6)
C(21)	−3 294(6)	1 073(5)	3 177(5)
C(22)	−5 016(6)	933(5)	2 522(5)
C(23)	−5 149(6)	1 002(5)	1 158(5)
C(24)	−3 562(6)	1 212(5)	450(5)
C(25)	−1 841(6)	1 353(5)	1 106(5)
C(26)	−1 707(6)	1 284(5)	2 469(5)
C(27)	−3 118(12)	3 196(6)	4 520(8)
C(28)	−3 630(12)	3 873(6)	6 664(9)
C(30)	1 855(15)	2 952(8)	2 934(9)
N(6)	−490(8)	3 402(5)	5 992(6)
N(11)	264(8)	1 787(0)	6 817(5)
N(20)	−3 231(9)	1 000(5)	4 501(6)
O(12)	3 058(7)	1 454(4)	5 704(5)
O(19)	569(7)	166(5)	4 585(5)
O(29)	1 770(8)	2 615(5)	4 164(5)



(1; n = 0)
(3; n = 1)

(2)



(4) (5) (6)

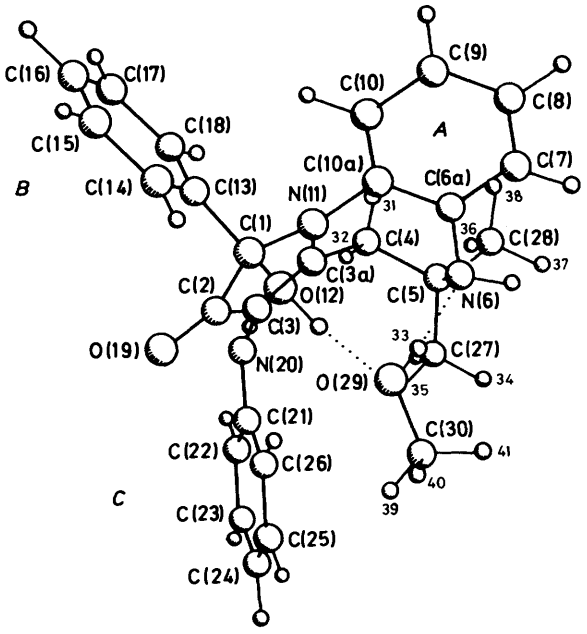


Figure. Stereodiagram of (2) with the atomic notation used in the Tables; hydrogen atoms have the same numbers as the atoms to which they are attached, unless otherwise stated

Table 2. Bond lengths (Å) for compound (2), with e.s.d.s in the least significant digits in parentheses

C(1)–C(2)	1.525(10)	C(1)–C(13)	1.482(10)
C(1)–N(11)	1.484(8)	C(1)–O(12)	1.398(9)
C(2)–C(3)	1.412(10)	C(2)–O(19)	1.223(10)
C(3)–C(3a)	1.357(10)	C(3)–N(20)	1.410(9)
C(3a)–C(4)	1.482(11)	C(3a)–N(11)	1.352(8)
C(4)–C(5)	1.538(11)	C(5)–C(27)	1.476(11)
C(5)–C(28)	1.530(12)	C(5)–N(6)	1.475(9)
C(6a)–C(10a)	1.395(9)	C(6a)–N(6)	1.404(8)
C(10a)–N(11)	1.395(7)	C(21)–N(20)	1.355(8)
C–C(aromatics)	1.395	C(30)–O(29)	1.372(11)

Table 3. Selected bond angles (°) for compound (2), with e.s.d.s in parentheses

C(1)–C(2)–C(3)	108.0(6)	C(1)–C(2)–O(19)	121.9(7)
C(3)–C(2)–O(19)	130.1(6)	C(2)–C(3)–C(3a)	108.3(6)
C(2)–C(3)–N(20)	125.2(6)	C(3a)–C(3)–N(20)	126.5(6)
C(3)–C(3a)–N(11)	113.0(6)	C(3)–C(3a)–C(4)	129.2(6)
C(4)–C(3a)–N(11)	117.8(5)	C(3a)–C(4)–C(5)	112.0(6)
C(4)–C(5)–C(27)	111.0(7)	C(4)–C(5)–C(28)	108.0(6)
C(4)–C(5)–N(6)	107.7(6)	C(27)–C(5)–C(28)	111.5(7)
C(27)–C(5)–N(6)	107.9(6)	C(28)–C(5)–N(6)	110.5(6)
C(5)–N(6)–C(6a)	120.2(5)	C(10a)–C(6a)–N(6)	120.6(5)
C(6a)–C(10a)–N(11)	120.8(4)	C(3a)–N(11)–C(10a)	123.9(4)
C(1)–N(11)–C(3a)	109.2(4)	C(1)–N(11)–C(10a)	124.1(3)
N(11)–C(1)–O(12)	110.6(6)	C(2)–C(1)–N(11)	101.5(5)
C(2)–C(1)–C(13)	110.0(6)	C(2)–C(1)–O(12)	112.3(5)
C(13)–C(1)–O(12)	110.1(5)	C(3)–N(20)–C(21)	123.8(6)

Table 4. Some torsion angles (°) for compound (2), with e.s.d.s in parentheses

C(1)–N(11)–C(10a)–C(10)	−51.3(8)
C(3)–N(20)–C(21)–C(22)	−175.8(6)
C(3a)–C(3)–N(20)–C(21)	114.9(9)
C(3a)–C(4)–C(5)–C(27)	73.6(8)
C(3a)–C(4)–C(5)–C(28)	−163.8(6)
C(3a)–N(11)–C(1)–C(13)	−118.5(6)
C(3a)–N(11)–C(1)–O(12)	118.2(6)
C(3a)–N(11)–C(10a)–C(6a)	−34.1(8)
C(10a)–C(6a)–N(6)–C(5)	72.3(8)
N(11)–C(1)–C(13)–C(14)	−137.9(6)
N(11)–C(3a)–C(4)–C(5)	82.2(8)

An extensive chromatographic separation of the crude reaction mixture allowed the isolation, along with (2), of small amounts of unchanged (1) and several by-products, all showing merely aromatic peaks in their n.m.r. spectra.

X-Ray Crystal Structure of Compound (2).—A general view of the molecule with the labelling of the atoms is shown in the Figure. Atomic co-ordinates and their estimated standard deviations are in Table 1. Bond distances and selected bond and torsion angles are given in Tables 2—4.

The molecule (2) possesses a 1,5-benzodiazepine system, the *a* edge of which is fused to a pyrrole nucleus. The molecular packing is mainly due to van der Waals interactions and intermolecular hydrogen bonds involving O(12), O(19), N(20), and N(6) (Table 5). There are also two intramolecular hydrogen bonds involving one molecule of methanol of crystallization [O(29)···N(6) 2.802, O(29)···O(12) 2.616 Å].

The seven-membered ring has a boat conformation which can be described with respect to the least-squares plane through the fused benzene ring (*A*): the displacements of N(6) and N(11) from this plane are 0.155 and 0.074 Å, while C(3a), C(4), and

Table 5. Hydrogen bonds for compound (2)

A–H · · · D	A · · · D(Å)	A–H · · · D(°)
O(12)–H(12) · · · O(29)i	2.62(1)	165.3(4)
O(29)–H(29) · · · N(6)i	2.80(1)	166.0(4)
N(20)–H(20) · · · O(12)ii	3.02(1)	169.0(5)
N(6)–H(6) · · · O(19)iii	2.95(1)	168.3(4)

Symmetry code: (i) x, y, z; (ii) $x - 1, y, z$; (iii) $-x, y + \frac{1}{2}, -z + 1$.

C(5) are out of plane by −0.48, −1.53, and −0.94 Å, respectively. The five-membered ring is planar to a good approximation, O(19) and N(20) being 0.014 and −0.024 Å out of plane. The aromatic rings *A*, *B*, and *C* make angles of 45.7, 92.5, and 117.4° respectively with the plane containing the pyrrole nucleus.

The C(10a)–N(11) and C(6a)–N(6) bond distances [1.395(7) and 1.404(8) Å, respectively] agree with corresponding values for related compounds.[8] Although N(11) displays a tetrahedral rather than a trigonal configuration, being −0.135 Å out of the plane C(1)–C(3a)–C(10a), the modifications of bond lengths in the N(11)–C(3a)–C(3)–C(2) moiety suggest an extended electron delocalization over the system. Other bond lengths are what one would expect for such a molecule.

Experimental

M.p.s were determined with a Kofler hot-plate apparatus. I.r. spectra were taken for Nujol mulls with a Perkin-Elmer 225 spectrophotometer and ^{1}H n.m.r. spectra were determined for solutions in $CDCl_3$ or CD_3OD with a Varian EM 360 A instrument (internal standard $SiMe_4$). T.l.c. was performed on silica gel sheets (Stratocrom SIF Carlo Erba) and Merck 60 PF_{254} silica plates, developed with diethyl ether–ethyl acetate (95:5), and column chromatography on Riedel-de Haën silica gel S (0.063—0.2 mm; 70—230 mesh ASTM).

5,6-Dihydro-1-hydroxy-5,5-dimethyl-1-phenyl-3-phenylamino-1H-pyrrolo[1,2-a][1,5]*benzodiazepin-2(4H)-one* (**2**).—The benzodiazepine[2] (**1**) (1.9 g, 10 mmol) and (*Z*)-*N*-(benzoylmethylene)aniline *N*-oxide[3a] (2.7 g, 1.2 mmol) in anhydrous benzene (30 ml) were stirred at room temperature in the dark under nitrogen for 24 h. The solvent was evaporated off under reduced pressure, and the brown residue was subjected to column chromatography with light petroleum–diethyl ether (1:1), then with 100% diethyl ether, to give small amounts of (**1**) and several by-products. Final elution with diethyl ether–ethyl acetate (95:5) gave the *pyrrolobenzodiazepinone* (**2**) (1.0 g), which was further purified by preparative t.l.c. (Found: C, 76.0; H, 6.1; N, 10.5. $C_{26}H_{25}N_3O_2$ requires C, 75.9; H, 6.1; N, 10.2%); m.p. 134—136 °C (from methanol); $\nu_{max.}$ 3 380, 3 250, 1 657, 1 448, and 1 357 cm^{-1}; δ(CD_3OD) 1.32 and 1.38 (each 3 H, s, 5-Me), 2.54 and 2.86 (each 1 H, ABq, J −12 Hz, 4-H), and 6.5—8.0 (14 H, m, ArH).

Crystal Structure Analysis of the Pyrrolobenzodiazepinone (**2**).—*Crystal data.* $C_{27}H_{29}N_3O_3$, M = 443.5. Monoclinic, a = 7.087(1), b = 16.387(3), c = 10.193(2) Å, β = 91.44(1)°, U = 1 183.5(4) Å^3, Z = 2, D_c = 1.24 g cm^{-3}, $F(000)$ = 472. Space group $P2_1$, μ = 0.76 cm^{-1} for Mo-K_α radiation, λ = 0.710 69 Å.

Crystals suitable for *X*-ray analysis were obtained by slow evaporation of a methanolic solution. A crystal of dimensions 0.2 × 0.2 × 0.4 mm was used for the measurement at 23 °C with a Siemens-Stoe four-circle diffractometer. Accurate unit-cell dimensions and crystal orientation matrices were obtained from least-squares refinement of 2θ, ω, χ, and φ values of 22 reflections in the range 14 ⩽ 2θ ⩽ 26°. Crystal and electronic stability was confirmed by the constancy of three reference reflections, the intensities of which were monitored every 120 min. Of 1 648 independent reflections, measured by the ω/θ scan technique in the range 3 ⩽ 2θ ⩽ 46°, 1 301 having net intensity $I \geqslant 3\sigma(I)$ were used in the structure refinement. Lorentz and polarization corrections were made, but not absorption corrections.

Structure determination. The structure was solved by direct methods with the MULTAN 80 system;[9] the following calculations were mainly carried out by the SHELX-76[10] and PARST[11] systems of programs. All the H atoms were found from the difference Fourier map. However, only the H atoms involved in hydrogen bonds were actually refined; the others were assigned calculated positions (C–H distance 1.08 Å). The structure was refined by the full-matrix least-squares method; anisotropic temperature factors were introduced for all non-hydrogen atoms except those belonging to the aromatic rings. These were refined as rigid groups and restricted to their normal geometry (D_{6h} symmetry, C–C 1.395 Å) by using the group refinement procedure. Each ring was assigned six variable positional parameters, and each ring carbon atom was assigned an individual isotropic thermal parameter. The final R value was $[\Sigma||F_o| - |F_c||/\Sigma|F_o| = 0.06$ and R_w was $[\Sigma w(|F_o| - |F_c|)^2/\Sigma w|F_o|^2]^{\frac{1}{2}} = 0.064$. The weighting scheme used in the last refinement cycles was $w = 3.251/[\sigma^2(F_o) + 0.000\,01\ F_o^2]$. Refinement of possible enantiomers showed no difference in R value and no assignment of absolute configuration could be made. Final difference map peaks were in the range 0.3—0.5 e Å^{-3}. Scattering factors for the non-hydrogen atoms were taken from Cromer and Mann[12] and for H from Stewart.[13]

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