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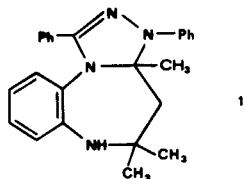
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The crystal structure of the title compound is described.

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Introduction.

In the course of our studies concerned with the synthesis of novel benzodiazepines with an additional fused heterocyclic nucleus [1], we have prepared the 3a,4,5,6-tetrahydro-3a,5,5-trimethyl-1,3-diphenyl-3H-1,2,4-triazolo[4,3-a][1,5]benzodiazepine (**1**) via the [3 + 2] cycloaddition reaction of diphenylnitrile imine [2] with 2,3-dihydro-2,2,4-trimethyl-1H-1,5-benzodiazepine [3]. The structure of **1** has been assigned principally on the basis of ¹³C- and ¹H-nmr analysis [1c].



The current X-ray study was undertaken to confirm the structural assignment made and to establish the influence of the "a" fusion of the five-membered ring on the conformation of the benzodiazepine system. Only few crystal structures of tricyclic benzodiazepines are reported in the literature [4], in comparison with the worldwide interest in the preparations and pharmaceutical properties of heterocyclic - particularly five-atom - fused benzodiazepine ring systems [5]. To the best of our knowledge these X-ray studies [4] are restricted to 1,4- and 2,4-benzodiazepine derivatives, a part from a recent paper [4j] concerning the structure determination of 2a-pbromophenyl-2a,3-dihydro-4-methylthio-2-phenoxy-2H-azeto[1,2-a][1,5]benzodiazepin-1-one.

X-Ray Structural Investigation.

Crystals of the title compound **1**, suitable for X-ray diffraction, were obtained by slow evaporation of a diethyl ether-light petroleum (7:3) solution at room temperature.

The crystallographic data are as follows: C₂₅H₂₈N₄O (C₂₅H₂₆N₄·H₂O), M = 400.50, a = 10.225(2), b = 10.371(2), c = 11.847(2) Å, α = 113.67(1), β = 107.79(1), γ = 95.67(1)°, triclinic, space group P $\bar{1}$, Z = 2, D_c = 1.26

g/cc, U = 1060 Å³, F(000) = 428, μ(Cu-K_α) = 6 cm⁻¹.

A total of 2006 independent observed reflections [$|F_o| > 3\sigma(|F_o|)$, θ ≤ 50°] were measured on a Nicolet R3m diffractometer with Cu-K_α radiation (graphite monochromator) and using ω-scans. The structure was solved by direct methods and the non-hydrogen atoms refined anisotropically. The hydrogen atoms on N(6) and O(27) (the water of solvation) were located from a ΔF map, and re-

Table I

Atom Coordinates (× 10⁴) and Temperature Factors (Å² × 10³)

atom	x	y	z	U
C(1)	7530(2)	820(2)	5818(2)	39(1) [a]
N(2)	7370(2)	-441(2)	4880(2)	45(1) [a]
N(3)	7562(2)	-202(2)	3852(2)	55(1) [a]
C(3a)	7919(2)	1369(2)	4209(2)	41(1) [a]
C(4)	6773(2)	1686(2)	3255(2)	42(1) [a]
C(5)	6726(2)	3259(2)	3566(2)	40(1) [a]
N(6)	6618(2)	4052(2)	4880(2)	42(1) [a]
C(6a)	7791(2)	4472(2)	6083(2)	37(1) [a]
C(7)	8352(2)	5938(2)	6995(2)	47(1) [a]
C(8)	9417(2)	6364(2)	8220(2)	51(1) [a]
C(9)	9958(2)	5351(2)	8552(2)	51(1) [a]
C(10)	9436(2)	3900(2)	7655(2)	48(1) [a]
C(10a)	8345(2)	3447(2)	6436(2)	39(1) [a]
N(11)	7769(2)	1949(2)	5517(1)	45(1) [a]
C(12)	9450(2)	1888(2)	4386(2)	53(1) [a]
C(13)	7968(2)	4115(2)	3481(2)	52(1) [a]
C(14)	5354(2)	3202(3)	2545(2)	56(1) [a]
C(15)	7451(2)	-1371(2)	2688(2)	41(1) [a]
C(16)	6975(2)	-2786(2)	2465(2)	46(1) [a]
C(17)	6808(2)	-3950(2)	1286(2)	55(1) [a]
C(18)	7119(2)	-3756(2)	310(2)	56(1) [a]
C(19)	7606(2)	-2374(2)	525(2)	55(1) [a]
C(20)	7791(2)	-1189(2)	1694(2)	53(1) [a]
C(21)	7359(2)	975(2)	7053(2)	40(1) [a]
C(22)	6543(2)	1858(2)	7583(2)	49(1) [a]
C(23)	6346(2)	1917(3)	8705(2)	60(1) [a]
C(24)	6961(3)	1121(3)	9304(2)	64(1) [a]
C(25)	7780(3)	261(3)	8789(2)	63(1) [a]
C(26)	7969(2)	178(2)	7667(2)	51(1) [a]
O(27)	4046(2)	3102(2)	5133(2)	68(1) [a]

[a] Equivalent isotropic U defined as one third of the trace of the orthogonalised U_{ij} tensor.

fined isotropically. All other hydrogen positions were idealized (C-H 0.96 Å), isotropic thermal parameters were assigned, $U(\text{H}) = 1.2 U_{eq}(\text{C})$, and these hydrogen atoms were allowed to ride on their parent carbon atoms. The methyl groups were refined as rigid bodies. Refinement converged to give $R = 0.037$, $R_w = 0.046$ [$w^{-1} = \sigma^2(F_o) + 0.00108 F_o^2$]. The scattering factors were taken from the literature.

The final atomic coordinates and temperature factors for non-hydrogen atoms, bond distances and angles are reported in Tables I-III. Lists of hydrogen fractional coordinates and anisotropic thermal factors and of the observed and calculated structure factors are available on request. A view of the molecule is supplied in the Figure.

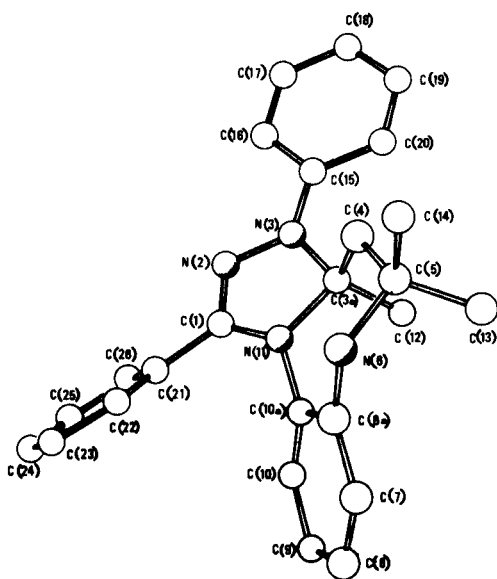


Figure. A perspective drawing of the molecule with the numbering scheme.

Discussion.

The X-ray crystallographic structure determination reported here confirms the assignment of structure **1** obtained by nmr analysis.

The seven-membered ring adopts a chair conformation which can be described in terms of the dihedral angles between four least-squares planes: plane 1, the five atoms of the fused triazole ring (planar to a good approximation); plane 2, four atoms C(5), N(6), N(11), C(3a); plane 3, the three atom moiety C(3a), C(4), C(5) of the seven-membered ring; plane 4, eight atoms [the fused benzene ring and two nitrogen atoms N(6) and N(11)]. The dihedral angles between these planes are as follows: p.1-p.2 35.6, p.1-p.3 120.4, p.1-p.4 125.4, p.2-p.3 126.2, p.2-p.4 130.8, p.3-p.4 5.2°. Most of all this last value is indicative of a flattening

Table II

Bond Lengths (Å)

C(1)-N(2)	1.286(2)	C(1)-N(11)	1.374(3)
C(1)-C(21)	1.473(3)	N(2)-N(3)	1.400(3)
N(3)-C(3a)	1.484(3)	N(3)-C(15)	1.386(2)
C(3a)-C(4)	1.524(3)	C(3a)-N(11)	1.484(3)
C(3a)-C(12)	1.526(3)	C(4)-C(5)	1.531(3)
C(5)-N(6)	1.485(3)	C(5)-C(13)	1.529(3)
C(5)-C(14)	1.524(3)	N(6)-C(6a)	1.419(2)
C(6a)-C(7)	1.392(2)	C(6a)-C(10a)	1.399(3)
C(7)-C(8)	1.383(3)	C(8)-C(9)	1.371(4)
C(9)-C(10)	1.374(3)	C(10)-C(10a)	1.385(3)
C(10a)-N(11)	1.420(2)	C(15)-C(16)	1.389(3)
C(15)-C(20)	1.399(4)	C(16)-C(17)	1.378(3)
C(17)-C(18)	1.370(4)	C(18)-C(19)	1.363(4)
C(19)-C(20)	1.375(3)	C(21)-C(22)	1.392(3)
C(21)-C(26)	1.382(3)	C(22)-C(23)	1.382(4)
C(23)-C(24)	1.371(4)	C(24)-C(25)	1.376(4)
C(25)-C(26)	1.371(4)		

Table III

Bond Angles (°)

N(2)-C(1)-N(11)	114.2(2)	N(2)-C(1)-C(21)	120.9(2)
N(11)-C(1)-C(21)	124.7(2)	C(1)-N(2)-N(3)	106.2(2)
N(2)-N(3)-C(3a)	112.2(1)	N(2)-N(3)-C(15)	119.9(2)
C(3a)-N(3)-C(15)	127.8(2)	N(3)-C(3a)-C(4)	109.9(1)
N(3)-C(3a)-N(11)	98.2(2)	C(4)-C(3a)-N(11)	108.8(2)
N(3)-C(3a)-C(12)	111.0(2)	C(4)-C(3a)-C(12)	116.9(2)
N(11)-C(3a)-C(12)	110.5(1)	C(3a)-C(4)-C(5)	120.2(1)
C(4)-C(5)-N(6)	111.6(2)	C(4)-C(5)-C(13)	113.7(2)
N(6)-C(5)-C(13)	110.3(1)	C(4)-C(5)-C(14)	107.3(1)
N(6)-C(5)-C(14)	105.4(2)	C(13)-C(5)-C(14)	108.1(2)
C(5)-N(6)-C(6a)	121.0(2)	N(6)-C(6a)-C(7)	119.8(2)
N(6)-C(6a)-C(10a)	121.9(1)	C(7)-C(6a)-C(10a)	118.1(2)
C(6a)-C(7)-C(8)	120.8(2)	C(7)-C(8)-C(9)	120.5(2)
C(8)-C(9)-C(10)	119.5(2)	C(9)-C(10)-C(10a)	120.8(2)
C(6a)-C(10a)-C(10)	120.1(2)	C(6a)-C(10a)-N(11)	118.5(1)
C(10)-C(10a)-N(11)	121.3(2)	C(1)-N(11)-C(3a)	108.8(1)
C(1)-N(11)-C(10a)	126.6(2)	C(3a)-N(11)-C(10a)	120.2(2)
N(3)-C(15)-C(20)	120.2(2)	N(3)-C(15)-C(2)	122.3(2)
C(16)-C(15)-C(20)	117.5(2)	C(15)-C(16)-C(17)	120.4(2)
C(16)-C(17)-C(18)	121.6(2)	C(17)-C(18)-C(19)	118.5(2)
C(18)-C(19)-C(20)	121.3(3)	C(15)-C(20)-C(19)	120.7(2)
C(1)-C(21)-C(22)	121.4(2)	C(1)-C(21)-C(26)	119.4(2)
C(22)-C(21)-C(26)	119.2(2)	C(21)-C(22)-C(23)	119.8(2)
C(22)-C(23)-C(24)	120.3(2)	C(23)-C(24)-C(25)	119.9(3)
C(24)-C(25)-C(26)	120.4(3)	C(21)-C(26)-C(25)	120.4(2)

Table IV

Hydrogen Bonds X-H...Y

X	H	Y	X-H(Å)	Y-H(Å)	X-H...Y(°)
O(27)	H(27a)	N(6)	2.86	1.94	156
O(27)	H(27b)	N(2)	2.98	2.05	159
N(6)	H(6)	O(27) ¹	3.10	2.12	176

of the chair conformation which alleviates the unfavourable synaxial interference between C(12) and C(13) methyl groups: the C(12)...C(13) interatomic distance is 3.23 Å in

the crystal of the title compound, while the inspection of a Dreiding model of the ideal chair structure shows a distance of roughly 2.5 Å between the carbon atoms of the two axial methyl groups. A similar flattening of the chair conformation was suggested [6] for the 2,3,4,5-tetrahydro-2,2,4-trimethyl-1*H*-1,5-benzodiazepine in the solution state. The alternative twist-boat conformation of the heptatomic ring in **1** is probably unfavoured by the steric hindrance which one methyl group bonded to C(5) would experience on behalf of N(11).

There is no conjugation between the triazole ring and the phenyl substituent at C(1). Owing to steric inhibition, mainly caused by the fused benzene nucleus, the C(1)-phenyl ring is rotated from the mean plane of the triazole ring [torsion angle N(11)-C(1)-C(21)-C(22) = 43°] while N(3)-phenyl ring is nearly coplanar to the pentatomic one, with the torsion angle C(3a)-N(3)-C(15)-C(20) = 5°. The nitrogen atom N(3) has an almost planar configuration, while N(11) shows a flattened pyramidal structure, their deviations from the planes containing the adjacent atoms being 0.01 and 0.17 Å respectively. One water molecule of crystallization is involved in hydrogen bonds, as reported in Table IV.

The bond distances in the heptatomic ring are in agreement with corresponding values found in the strictly related 1,4,5,6-tetrahydro-1-hydroxy-5,5-dimethyl-1-phenyl-3-phenylaminopyrrolo[1,2-*a*][1,5]benzodiazepin-2-one [1d], a part from the lengths of the bonds involving C(3a), which is differently hybridized in the aforesaid pyrrolobenzodiazepinone with respect to the title compound **1**. In particular, the C(3a)-N(11) bond distances [1.484(3) Å in **1**] is sen-

sibly shortened [to 1.352(8) Å] in the related pyrrolobenzodiazepinone, owing to the suggested electron delocalization over the pyrrole ring [1d]. Other bond lengths in **1** are what one would expect for such a molecule and require no special comment.

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REFERENCES AND NOTES

- [1a] M. C. Aversa, P. Giannetto, A. Ferlazzo and G. Romeo, *J. Chem. Soc., Perkin Trans. 1*, 2701 (1982); [b] M. C. Aversa and P. Giannetto, *J. Chem. Soc., Perkin Trans. 2*, 81 (1984); [c] M. C. Aversa, A. Ferlazzo, P. Giannetto and F. H. Kohnke, *Synthesis*, 230 (1986); [d] M. C. Aversa, P. Giannetto, A. Ferlazzo and G. Bruno, *J. Chem. Soc., Perkin Trans. 2*, in press.
- [2] R. Huisgen, M. Seidel, G. Wallbillich and H. Knupfer, *Tetrahedron*, **17**, 3 (1962).
- [3] W. Ried and P. Stahlhofen, *Chem. Ber.*, **90**, 815 (1957).
- [4a] J. B. Hester, Jr., D. J. Duchamp and C. G. Chidester, *Tetrahedron Letters*, 1609 (1971); [b] J. Szmuszkovicz, C. G. Chidester, D. J. Duchamp, F. A. MacKellar and G. Slomp, *ibid.*, 3665 (1971); [c] R. Jaunin, W. E. Oberhänsli and J. Hellerbach, *Helv. Chim. Acta*, **55**, 2975 (1972); [d] P. C. Wade, B. R. Vogt and M. S. Puar, *Tetrahedron Letters*, 1699 (1977); [e] R. I. Fryer, J. Blount, E. Reeder, E. J. Trybulski and A. Walser, *J. Org. Chem.*, **43**, 4480 (1978); [f] P. C. Wade, T. P. Kissick, B. R. Vogt and B. Toeplitz, *ibid.*, **44**, 84 (1979); [g] P. C. Wade, B. R. Vogt, B. Toeplitz and M. S. Puar, *ibid.*, **44**, 88 (1979); [h] J. B. Hester, Jr., P. VonVoigtlander and G. N. Evenson, *J. Med. Chem.*, **23**, 873 (1980); [i] Y. Okada, T. Takebayashi, M. Hashimoto, S. Kasuga, S. Sato and C. Tamura, *J. Chem. Soc., Chem. Commun.*, 784 (1983); [j] M. Soriano-Garcia, R. A. Toscano, E. Cortes and R. Martinez, *Acta Cryst.*, **C40**, 1460 (1984).
- [5] E. Schulte, *Dtsch. Apoth. Ztg.*, **115**, 1253, 1828 (1975); A. Nawojski, *Wiad. Chem.*, **31**, 753 (1977); M. Artico, *Boll. Chim. Farm.*, **119**, 455, 505 (1980); and references cited therein.
- [6] P. W. W. Hunter and G. A. Webb, *Tetrahedron*, **29**, 147 (1973).