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SYNTHESIS AND PROOF OF STRUCTURE OF A NOVEL 1,4-BENZODIAZEPINE

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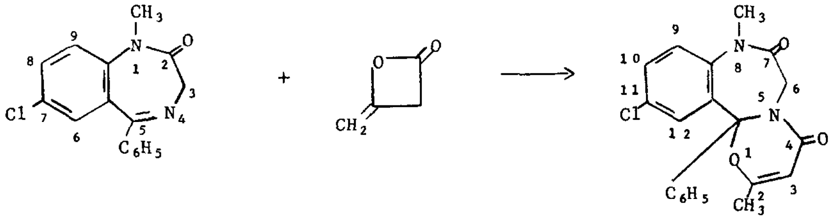
Current interest in the 1,4-benzodiazepine area[1] prompts us to report the synthesis and determination of the structure of 11-chloro-8,12b-dihydro-2,8-dimethyl-12b-phenyl-4H[1,3]-oxazino[3,2-d][1,4]benzodiazepine-4,7(6H)-dione (II).[2]

Compound II was obtained in high yield, as colorless prisms melting at 182-183.5° (s170°), from the condensation of 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (I)[3] with acetyl chloride and triethylamine in ether or with diketene in acetone.

Of several possible structures, the adduct was assigned structure II on the basis of 1) ir, uv, nmr and mass spectroscopic evidence summarized below, and 2) an independent x-ray structure determination.



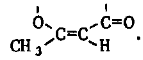
I II

From elemental analyses and mass spectrum compound II was assigned the molecular formula $C_{20}H_{17}ClN_2O_3$ suggesting the addition of two ketene (CH_2CO) units. The mass spectrum showed doublets in accord with the presence of one chlorine atom (M^+: 368, 370; M-43: 325, 327; M-84: 284, 286) and indicated a stepwise cleavage under electron impact to regenerate I.

The uv absorption (in EtOH) shifted to 202 nm (ε40,600), 241 (18,400) indicating loss of conjugation in II as compared to the starting material [uv of I in EtOH:λ_{max} 229 (32,500), sh 253 (16,400), 314 (2,350)].

The ir showed increased intensity of carbonyl absorption in the C=O region at 1670-1685 cm^{-1} as compared to I.

The nmr spectrum of adduct II was compared to that of I (Table 1). The protons of I were all present in II. In addition, the spectrum of the adduct contained an isolated weakly coupled AX_3 system which was verified by spin decoupling and by isotope substitution.[4] The A-proton quartet (δ5.38, J~0.5 Hz) was in the vinyl-hydrogen region, and the X_3-proton doublet (δ1.88) was in the vinyl-methyl region. The magnitude of the coupling constant was suggestive of four-bond allylic coupling, $H\text{-}C{=}C\text{-}CH_3$.

From the chemical shifts, the coupling constants and mass spectral data the addend was judged to be  $\mathrm{(\overset{|}{O})(CH_3)C{=}CH(\overset{|}{C}{=}O)}$.

The addend was placed on the C=N for several reasons. The uv and the chemical shift of the N-methyl of the adduct both indicated some loss of conjugation. The AB pattern attributed to the methylene in the 7-membered ring of II was significantly changed from that of I. The AB coupling had increased in magnitude from -10.7 to -14.0 Hz indicating loss of an α,β double bond.[5] The A and B hydrogens were shifted farther apart and the signals were sharper indicating a more rigid system than observed in I.[6]

The addend was oriented as shown in II on the basis of polarity considerations; an observed spin tickling of one of the methylene hydrogens upon strong irradiation of the vinyl hydrogen; and rationalization of the downfield shift of the C_{12} hydrogen (as compared to the C_6 hydrogen of I) owing to the proximity of the O_1 atom in II.

Table 1. NMR Spectral Data[a]

	Compound II		Compound I	
	δ	J	δ	J(Hz)
N-methyl	2.50		3.40	
ring methylene	3.34	-14.0	3.80	-10.7
	5.39		4.83	
C-12 aromatic	8.22	2.5	multiplet centered at 7.5	
C-10 aromatic	7.54	2.5,8.5		
C-9 aromatic	7.17	8.5		
phenyl	7.29			
vinyl methyl	1.88	0.5	-	
vinyl hydrogen	5.38	0.5	-	

[a] Spectra were observed at 60 and 100 MHz on solution in d-chloroform.

Table 2. Crystal Data

a = 8.644 Å ± 0.005 Å
b = 13.135 ± 0.005
c = 16.985 ± 0.005
β = 114.28° ± 0.1°
Space Group P $2_1/c$
Z = 4
D (obs) = 1.391 $g.cm.^{-3}$
D (calc) = 1.378

Simultaneously with the spectroscopic work mentioned above, the crystal structure of II was determined by x-ray diffraction. The crystals were found to be monoclinic with crystal data shown in Table 2.

Intensities of 2958 independent reflections were measured on an automated diffractometer using nickel-filtered Cu K radiation. Direct analysis of a sharpened Patterson function served to locate the chlorine and several lighter atoms. The remaining atoms were found in a three-dimensional electron density synthesis. The structure was refined by multiple-matrix least squares. Elemental assignments were verified by temperature factor studies. Anisotropic temperature factors were introduced for C, N, O, and Cl atoms. Hydrogens were located using a three-dimensional difference Fourier synthesis. The final agreement index, $R = \Sigma(|F_o|-|F_c|)/\Sigma|F_o|$, was 0.071.

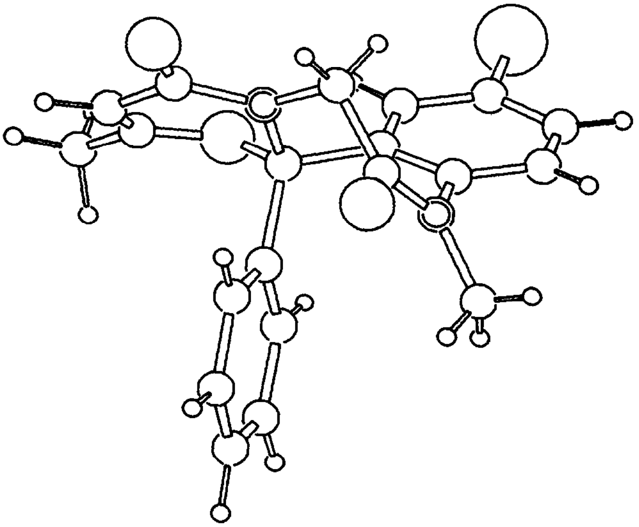


Figure. Drawing of II from x-ray results.

A drawing of II prepared from x-ray results is shown in the Figure. The seven-membered ring is in a boat conformation. This conformation has also been found in the x-ray structure of I.[7] A rather striking feature of the molecule is that the phenyl group is approximately perpendicular to the remainder of the molecule which is rather flat. The two amide groups are almost planar, adding considerably to the rigidity of the molecular conformation. The molecule appears to be held quite rigidly in the conformation illustrated.

An alternate conformation for the molecule may be proposed in which the $O_1 - C - C - C_{12}$ torsion angle is about -80°, (versus about +8° in the conformation found by x-ray), and the seven-membered ring--still a boat--is bent towards the phenyl (instead of away from the phenyl). A study via space-filling models shows that on steric grounds this alternate conformation is considerably less favorable because of very close contacts to the ortho hydrogens of the phenyl ring and the hydrogen on C_{12} of the chlorobenzene moiety. Also, because of the rigidity of the system, conversion via a "ring flip" mechanism between the found and alternate conformations probably is not possible at the temperatures at which the molecule is stable.[8]

REFERENCES

1. For the most recent reviews see L. H. Sternbach, *Angew. Chem. Intern.* Ed. Engl., **10**, 34 (1971); A. V. Bogatskiii and S. A. Andronati, *Russ. Chem. Rev.* (English Transl.), **39**, 1064 (1970).
2. Generic USAN name: ketazolam (The Upjohn Company); U. S. patent 3,573,282 issued March 30, 1971.
3. Valium®, diazepam (Hoffmann-La Roche Inc.); L. H. Sternbach, R. Ian Fryer, W. Metlesics, E. Reeder, G. Sach, G. Saucy and A. Stempel, *J. Org. Chem.*, **27**, 3788 (1962).
4. The required 2-CD_3, 3-D adduct II was prepared by the reaction of I with d_3-acetyl chloride and triethylamine and melted at 146-148°. It was supported by satisfactory analytical data, ir, uv, nmr and mass spectra.
5. A. A. Bothner-By in "Advances in Magnetic Resonance", Vol. 1, J. S. Waugh, ed., Academic Press, New York, 1965, p. 195; R. C. Cookson, T. A. Crabb, J. J. Frankel and J. Hudec, *Tetrahedron* Suppl. No. 7, 355 (1966); R. C. Cookson and T. A. Crabb, *Tetrahedron*, **24**, 2385 (1968).
6. W. Sadée, *Arch. Pharm.*, **302**, 769 (1969); W. Bley, P. Nuhn and G. Benndorf, ibid., **301**, 444 1968); P. Nuhn and W. Bley, *Pharmazie*, **22**, 532 (1967); A. Mannschreck, G. Rissmann, F. Vögtle and D. Wild, *Chem. Ber.*, **100**, 335 (1967).
7. A. Camerman and N. Camerman, *Science*, **168**, 1457 (1970).
8. The authors wish to thank Mr. Lloyd G. Laurian for able technical assistance, Mr. Paul A. Meulman for ir spectra, and Mrs. Betty F. Zimmer for uv spectra.