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AN X-RAY STUDY OF THE RING INVERSION IN 1,3,4,5-TETRAHYDRO-5-PHENYL-2H-1,4-BENZODIAZEPIN-2-ONES CAUSED BY CARBAMOYLATION

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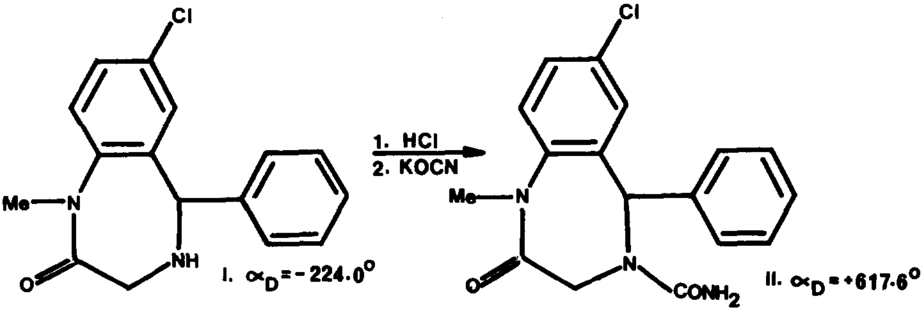
The specific rotation (α_D = +617.6°) of a new compound (II), (+) 4-carba-moyl-7-chloro-1,3,4,5-tetrahydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one obtained from the reaction of (-) 7-chloro-1,3,4,5-tetrahydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (I) with potassium cyanate[1], was found to be different both in magnitude and sign from that of I (α_D = -224.0°). This phenomenon could not be explained on the basis of n.m.r. and chemical studies. For this reason the crystal structures of both I and II have been determined.



Compound I, $C_{16}H_{15}N_2OCl$ is monoclinic, space group $P2_1$ with a = 11.348(3), b = 8.334(3), c = 7.638(2) Å, β = 97.42(2)°, M = 286.76, U = 716.3 Å^3, D_c = 1.33 g.cm^{-3}, Z = 2. 1670 independent reflexions were collected on an automatic Syntex $P2_1$ four-circle diffractometer (Mo-K_α radiation, $\bar{\lambda}$ = 0.7107 Å, graphite monochromator). The structure was solved with MULTAN[2] and refined to R = 0.058 for 1591 reflexions with $I - 1.96\sigma(I) \geq 0$.

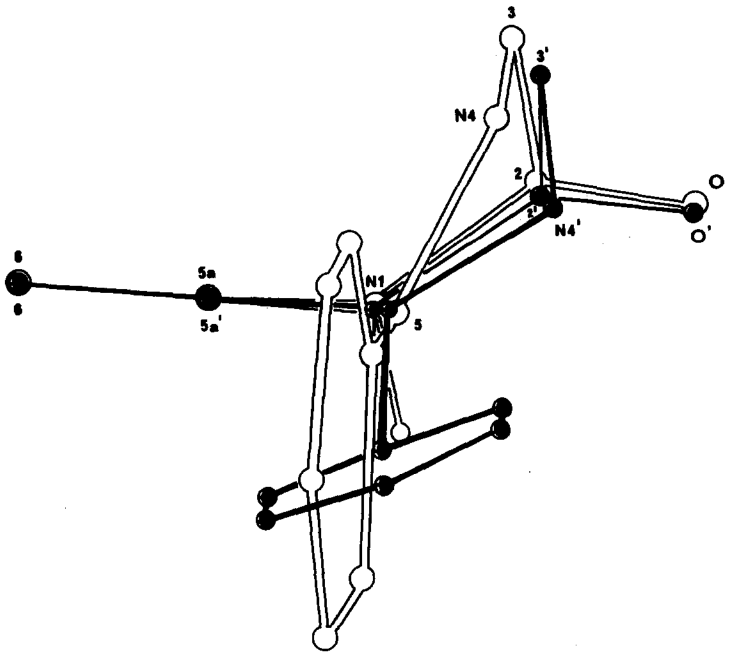


Figure 1. Projection of compound I (open lines) superimposed upon the structure of 7-dechloro-diazepam (full lines) along the C(5a)-C(9a) bonds (cf. Figure 3). The bare numbers are for carbon atoms. Atoms 5a and 6 represent the plane of the condensed benzene rings.

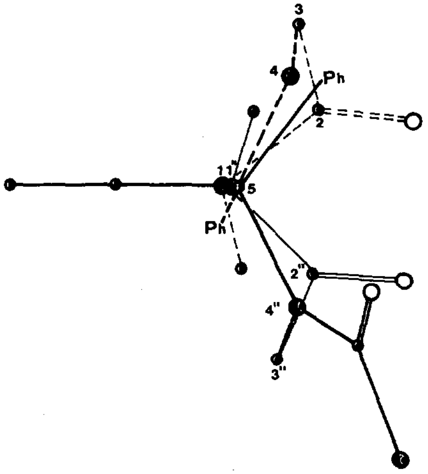


Figure 2. Projection of compound II (solid lines) superimposed upon the structure of compound I (broken lines) along the C(5a)-C(9a) bonds. The C(5)-phenyl rings are marked by Ph.

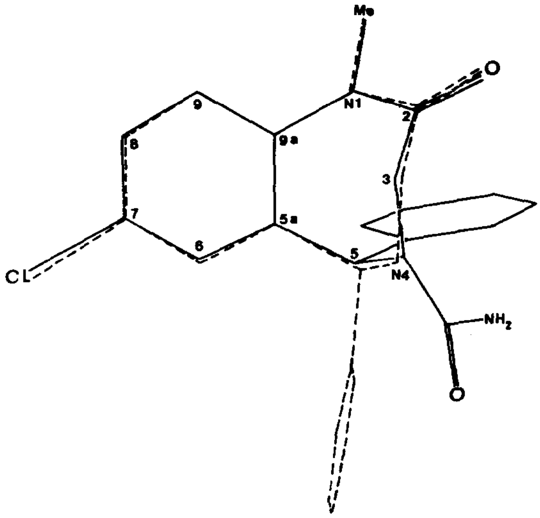


Figure 3. Projection of the superimposed structures of I (broken lines) and II (solid lines) perpendicular to the plane of the condensed benzene rings. The conventional atomic numbering of the benzodiazepine moiety is presented.

Compound II, $C_{17}H_{16}N_3O_2Cl$, is orthorhombic, space group $P2_12_12_1$ with *a* = 10.458(2), *b* = 17.060(4), *c* = 18.148(4) Å, M = 329.79, U = 3238.2 $Å^3$, D_c = 1.35 $g.cm^{-3}$, Z = 8. 4274 independent reflexions were collected on the same diffractometer. The structure of the molecule was developed by a recycling procedure. Starting phases to the tangent formula were derived from the positions of chlorine atoms obtained from a Patterson map. Isotropic refinement by the least-squares led to the present R = 0.12 for 2036 reflexions.

The conformation of I agrees with that of its 4-methyl-derivative.[3] It is also similar to that of 1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-ones, e.g. 7-dechloro-diazepam[4] depicted together in Figure 1. As can be seen, the position of the 5-phenyl group is equatorial or *quasi-equatorial*, respectively, and they are at the opposite side of the condensed benzene ring with respect to the *bows* of the boat shaped seven-membered rings. The difference between them is only that the seven-membered ring in I resembles a twist boat, while it has a nearly plane-symmetrical boat shape in the latter type of molecule owing to the rigidity of the 4,5 double bond.[4]

The conformations of the two II molecules in the asymmetric unit show only slight differences. They are, however, significantly different from that of I as shown in Figure 2. The position of the C(5)-phenyl ring relative to the seven-membered ring, unlike in (I), is *pseudoaxial*. The change of the position of the C(5)-phenyl group (Figure 3) involves the inversion of the seven-membered ring. A similar conformation to that of II was found earlier in Ketazolam[5,6] which is also a 4-acyl derivative of I. In that case the acyl moiety is part of an unsaturated ring fused in positions 4,5. These observations suggest that introducing an acyl (e.g. carbamoyl) group in position 4 results in an *inversion* of the seven-membered ring in tetrahydro-1,4-benzodiazepines owing to the steric hindrance of the entering acyl group fixed in its position by conjugation.

References

1. L. Kisfaludy, J. Röhricht, L. Ürögdi, L. Szporny, É. Pálosi, *Hung.P*. 160.769; J. Röhricht, L. Kisfaludy, L. Ürögdi, É. Pálosi, Sz. Szeberényi and L. Szporny, *Hung.P.Appl*. RI-538.
2. G. Germain, P. Main, M.M. Woolfson, *Acta Cryst.*, A27, 368 (1971).
3. J. Karle and I. Karle, *J. Amer. Chem. Soc*. 89, 804 (1967).
4. L.H. Sternbach, F.D. Sancilio and J.F. Blount, *J. Med. Chem*. 17, 374 (1974), and references therein.
5. J. Szmuszkovicz, C.G. Chidester, D.J. Duchamp, F.A. MacKellar and G. Slomp, *Tetrahedron Letters*, 3665 (1971).
6. D.J. Duchamp, 1976, Personal communication.

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