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A NEW SYNTHETIC ROUTE TO BENZODIAZEPINES

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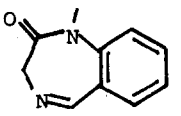
Observation of the psychosedative and tranquilizing properties of certain benzodiazepine derivatives (structure 1) has provoked extensive synthetic and



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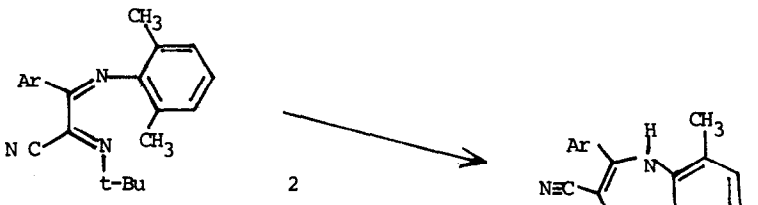
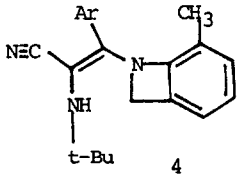
biological work on these compounds.[1] In the course of exploring the chemistry of some unsymmetrically substituted diimines obtained from the reaction of certain imines with isocyanides,[2] we have discovered a new entry into the 1,4-benzodiazepine structure. Reaction of 2 with a catalytic amount of potassium t-butoxide in refluxing diglyme for 10 hours yielded an isomeric substance in 62% yield. We have assigned the 4,5-dihydro-1-H-1,4-benzodiazepine structure (3) to the product on the basis of spectral and chemical evidence.[3]



2 3

Ar = O_2N–

The nmr spectrum of the product indicated that only one of the two ring methyl groups was still intact. In addition to the singlet at 2.12 δ (3H) there was another singlet at 4.22 δ (2H). Other peaks included N-H(5.72 δ), t-Bu(1.19 δ) and 7 aryl ring hydrogens. The latter region was resolvable into the AB quartet of the p-substituted ring and a complex three proton multiplet. The infra-red spectrum showed intense peaks at 2.94 μ (NH) and 4.53 μ (C≡N) The unaltered presence of the cyano group and the NO_2 substituted ring require that the former aryl methyl group now be attached to one of the remaining two carbons or two nitrogens (structures 3-6).



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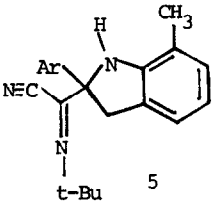

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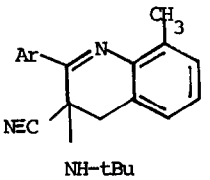

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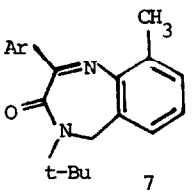
The deshielded position of the methylene group (4.22 δ ,N-CH_2-Ar) and the observation of no imine absorption in the infra-red spectrum served to rule out structures 5 and 6. Inspection of the mass spectrum of the isomer revealed no peaks attributable to the pendant side chain of 4. Moreover, the isomer showed none of the pronounced thermal and nucleophilic sensitivity expected of the benzoazetine structure.[4]

Further confirmation of the enamine moiety of 3 was found in its facile oxidation by methanolic NaOCl to a product ($C_{20}H_{21}N_3O_3$) in 70% yield. This compound, which had a carbonyl group (6.08μ), lacked both N-H and C≡N peaks. Its nmr spectrum now showed the methylene group as an symmetrical AB quartet centered at 4.20 δ (J=15.5 Hz, $\Delta\nu$=26.2 Hz). We assign structure 7 to this compound. Such a compound would arise from halogenation of the eneamine with subsequent deprotonation to give 8.[5] The lone pair assisted ionization would ultimately lead to hydrolsis of 8 and formation of 7. Models of 7 indicate both different environments for the two methlyene protons and a barrier to

their interconversion (if planarity of the amide function is assumed) which is absent in 3.



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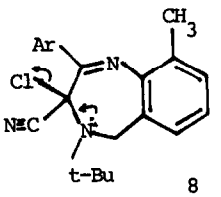

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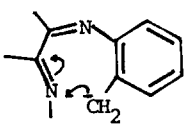
From a mechanistic point of view, this cyclization may be viewed as an inverse nucleohilic attack on an imine bond (9). More appropriately, it is an electrocyclic (thermal conrotatory) cyclization. Work to delineate the



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necessary and sufficient conditions required for such cyclizations and their further application to heterocyclic synthesis is now in progress.

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REFERENCES

1. G.A. Archer and L.H. Sternbach, Chem. Rev., 68, 747 (1968); L.H. Sternbach, L.O. Randall, R. Banziger and H. Lehr in "Drugs Affecting the Central Nervous System", A. Burger, Ed., Dekker; New York, New York, 1968, p. 237

2. J.C. Gill, Ph.D. Thesis, University of Florida, Gainesville, Florida, 1972.

3. Satisfactory elemental analyses, mass spectra, etc. were obtained for all new compounds.

4. cf. E.M. Burgess and L. McCullagh, J. Am. Chem. Soc., 88, 1580 (1966).

5. cf. J. Szmuskovicz, Advances in Organic Chemistry, 4, 60 (1963).