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THE TRIAZINO[4,3-d][1,4]BENZODIAZEPINE-3,4,7-TRIONE RING SYSTEM: SYNTHESIS AND RING INVERSION BARRIER

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Current interest in the chemical,[1a] physical,[1b] and biological[1c] properties of tricyclic 1,4-benzodiazepines prompts us to report the synthesis and energy barrier (ΔF^*) to ring inversion of the novel triazino[4,3-d][1,4]benzodiazepine-3,4,7-trione ring system 4. In addition to their utility as precursors of other novel heterocycles, these tricyclic triazinones are of particular interest as semi-rigid models for conformational studies of the seven-membered ring and its influence on physical[1d] and biological[1e] properties.

Of the possible approaches to annelated triazinones analogous to 4, the method involving condensation of an amidrazone with appropriate dicarbonyl compounds[3] was originally considered but found impractical in this case due to the relative instability of 1b.

Initial attempts to prepare 4a by condensing chloroimide 1a[4] with oxamic hydrazide 2a in either refluxing benzene or 1,2-dimethoxyethane (DME) were frustrated by a general lack of reactivity. In contrast, a relatively rapid reaction occurred when dimethylformamide (DMF) was employed as the solvent, resulting in essentially complete reaction of 1a with 2a after 30 min at 100°. The major product of the reaction, however, was not the triazino[4,3-d][1,4]benzodiazepine-3,4,7-trione, 4a, but rather the fused five-membered triazolo[4,3-d][1,4]benzodiazepin-6-one, 3a[2] (mp 303-304°), resulting from cyclodehydration of the intermediate acyl amidrazone 1d.

To avoid this problem we investigated the *in situ* generation of amidrazone 1b in the presence of appropriate oxalic acid derivatives with a view to generating intermediates (*e.g.*, 1e) favoring cyclization to the alternate six-membered ring compound. Thus, addition of the imino-nitrogen to the ester carbonyl of 1e and elimination of ethanol to yield a triazine would be expected to compete more effectively with attack on the adjacent amide carbonyl and dehydration to the triazole. Accordingly, the *t*-BOC derivative 1c was prepared (from 1a and *t*-butyl carbazate, in refluxing benzene), and reacted with a mixture of ethyl oxalate and oxalic acid at 90°. Fractional crystallization of the water and ether insoluble portion of the reaction mixture afforded two products in equiv-

alent (20%) yield. The more soluble product proved to be the five-membered 3-carbethoxy triazole 3b (mp 201-202°).

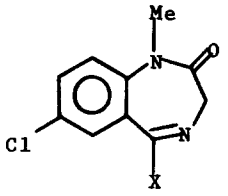
The other product A (indistinct mp 342-365 decomp.) possessed an empirical formula of $C_{12}H_9ClN_4O_3$ which was consistent with either the carboxy triazole 3c or the trione 4a. Analysis of the NMR spectrum (DMSO-d_6, normal probe temperature) of A indicated the presence of an AB quartet (J = 14.0 Hz) at τ4.93 and 5.91 for the methylene protons, in contrast to the singlet at τ4.6-4.9 observed with triazoles 3a, b and d. In addition, the IR spectrum of A, which lacked the characteristic carboxylic acid group absorptions, was compatible with the tricyclic triazino structure 4a, while the UV spectrum [λ_{max} (MeOH) 215 nm (ε 26,800), 348 (16,400), 305 (8,570)] was also distinctly different from that of the triazoles [e.g., 3a, λ_{max} (MeOH) 236 nm (ε 35,600), 300 (2,510)]. On the basis of these data, the second product A was tentatively assigned the annelated triazinedione structure 4a.

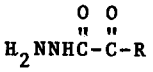
Attempts to improve the yield of 4a by modification of the leaving group on the oxalyl moiety led to the discovery that the reaction of 1a with the morpholino hydrazide 2b (in DMF at 100°) furnished the desired triazinedione 4a in high (84%) yield. In contrast to the triazole formation observed with 2a, the major product in this case arises from the alternate cyclization of the intermediate acylamidrazone 1f to give the fused six-membered triazino ring system 4a. Analysis of the mother liquors revealed the presence of minor amounts of the triazole amide 3d (7%, mp 200.5-201°).

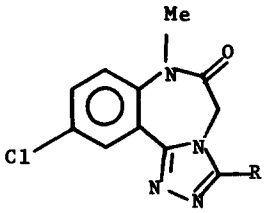
Selective alkylation of 4a at the 2-position was accomplished by reacting the derived thallous salt and the appropriate alkyl halide in refluxing toluene, to give, for example, the 2-methyl (68%, mp 350-353°), 2-benzyl (58%, mp 241-243°) and 2-(2-dimethylamino)ethyl (24%, mp 224-225°) derivatives 4b - 4d. Single crystal X-ray analysis[6] of the hydrobromide salt 4e (mp 295-297°) of 4d, unequivocally established that alkylation had occurred on nitrogen as indicated and confirmed the six-membered triazino structure of 4e (and, therefore, that of 4a).

The AB quartets assigned to the methylene protons of the seven-membered rings of 4a (as above) and 4d (τ 6.67, 4.76, J = 14.0 Hz, C_6D_5Br) exhibited temperature dependent NMR spectra. The rate constants at the collapse temperatures (t_c°) of 150° and 145°, calculated utilizing $k_c = (\pi/\sqrt{2})\sqrt{\Delta\nu^2 + 6J^2}$, gave energy barriers to inversion (ΔF*) of 20.7 and 19.9 kcal/mol for 4a and 4d, respectively.[7]

Thus, annelation of the triazinedione ring to the 1,4-benzodiazepinone nucleus resulted in a significant increase in the conformational rigidity of the seven-membered ring relative to that observed in the analogous fused triazolone 5 (ΔF* = 12.5 kcal/mol),[8] the related isoxazole 6 (ΔF* = 17.6 kcal/mol)[1d] and diazepam 1g (ΔF* = 17.7 kcal/mol).[1d]







1a, X = Cl

1b, X = $NHNH_2$

1c, X = $NHNHCOC(Me_3)_3$

1d, X = $NHNHCOCONH_2$

1e, X = $NHNHCOCOOEt$

1f, X = 

1g, X = Ph

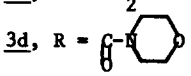
2a, R = NH_2

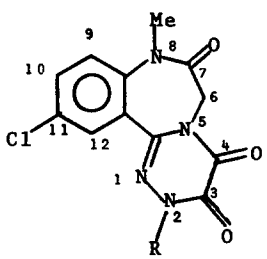
2b, R = 

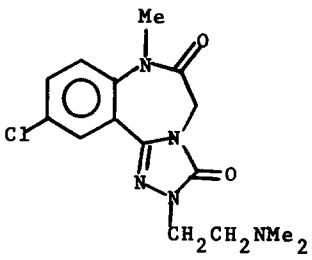
3a, R = $CONH_2$

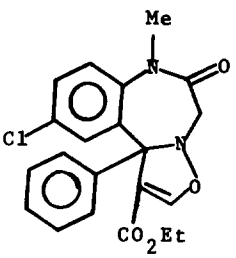
3b, R = $COOEt$

3c, R = CO_2H

3d, R = 







4a, R = H

4b, R = Me

4c, R = CH_2Ph

4d, R = $(CH_2)_2N\text{-}Me_2$

4e, R = $(CH_2)_2NMe_2$. HBr

5

6

Higher values of ΔF^* for the ring inversion process in 4 suggest not only a high energy transition state but also low potential energy in the ground state.[9] Increased resonance delocalization of the π system in the bridgehead lactam in 4 relative to 5 is expected to impart a greater degree of coplanarity to the three groups attached to the bridgehead nitrogen. This lowers the potential energy in the ground state and increases the rigidity of 4 relative to 5 by several kcal/mol. In addition, the increased rigidity of 4, presumably, also stems from the repulsive dipole-dipole interactions, in the transition state, of the adjacent carbonyl groups having strong anisotropic effects.

References and Footnotes

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6) The single crystal X-ray crystallographic studies of 4e were carried out at Squibb by Dr. J. Z. Gougoutas (U. of Minnesota) and Mrs. B. Toeplitz. The crystals have space group C_c with a = 19.328, b = 11.536, c = 16.063 Å, β = 144° and Z = 4. The R factor, after least squares refinement, is 0.107. Further refinements of the X-ray data are pending and will be published elsewhere.

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