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THE SYNTHESIS AND ENERGY BARRIERS TO RING INVERSION OF TRIAZOLO[4,3-d][1,4]BENZODIAZEPINONES

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The effect, on biological[1a-g] and physical[2a,b] properties, of fusing a 5- or 6-membered heterocycle onto the therapeutically important 1,4-benzodiazepine nucleus is a subject of current interest. While the synthesis of a variety of representative imidazolo-[3], oxazolo-[4], and triazolo[1,4]benzodiazepines[5,1d] have recently been described, the corresponding s-triazolo[4,3-d][1,4]-benzodiazepin-6-one and -3,6-dione ring systems, 4 and 5, have remained unknown.

We now wish to describe the syntheses of these novel heterocyclic systems by efficient, and generally applicable methods, as well as $\Delta F^{\ddagger}$'s associated with the ring inversion. Together with the isomeric series described in the accompanying paper,[6] they constitute the first examples of fully unsaturated monocyclic five-membered rings annelated to the "d" face of desphenyldiazepam.

Our initial "classical" approach[7] to 4 and 5, *via* the reaction of chloroimide 1 with hydrazine hydrate (refluxing benzene), gave, instead of the expected intermediate amidrazone 2a, the dihydro-as-triazinone 3 (mp = 166-167.5°).[8] On the assumption that 3 resulted from a transannular cleavage of the amide bond by the primary amino function in 2a, the reaction of chloroimide 1 with monoacyl hydrazines was investigated. Such "blocked" hydrazines should produce, as initial products, acylamidrazones incapable of attacking the amide bond. This approach was confirmed when the reaction of 1 with formylhydrazine (refluxing benzene or 1,2-dimethoxyethane, 12 hrs) furnished directly the desired 5H-s-triazolo[4,3-d][1,4]benzodiazepin-6-one 4a (mp = 273-275°, 84% yield), as the product of chloride displacement and subsequent cyclodehydration. The generality of this reaction for the preparation of 3-substituted derivatives shown by the synthesis of the 3-methyl and 3-phenyl analogs 4b (mp = 229-230°, 74%) and 4c (mp = 204-205.5°, 82%), *via* the appropriate acyl hydrazines.

Since this synthetic method does suffer from certain limitations (*e.g.*, the availability of the required hydrazides), the *in situ* generation of the elusive amidrazone 2a was investigated under conditions favoring its immediate reaction with external acyl derivatives. This route was ultimately successful, providing an alternate synthesis of a variety of triazoles not readily accessible by the original method. Thus, acid catalyzed removal of the t-BOC group in 2b (obtained from 1 by reaction with *tert*-butyl carbazate) in the presence of appropriate acyl derivatives (*i.e.*, refluxing trifluoroacetic acid/trifluoroacetic anhydride or oxalic acid/diethyl oxalate) afforded the corresponding 3-trifluoromethyl 4d (mp 186-187°, 70%) and 3-carbethoxy 4e (mp = 201-202°, 20%) derivatives presumably *via* amidrazone 2a.

The related 5H-s-triazolo[4,3-d][1,4]benzodiazepine-3,6-dione ring system 5a was synthesized by reacting 1 with ethyl carbazate (refluxing dioxane 7 hrs.) (mp = 268-269°, 85%). While 5a is potentially tautomeric with the 3-hydroxytriazole (4f), spectral evidence indicates that the dione (5a) is the predominent form, both in solution and as a solid. The uv spectrum of 5a [$\lambda_{Max\ nm}^{MeOH}$ 251, (ε= 17,900), 300 (3,680)] is similar to that of the alkylated derivatives which are incapable of tautomerism [*e.g.*, 5c, 253 (15,800), 302 (3,880)] and clearly different from the triazoles [*e.g.*, 4a, 231 (35,800), 250 (12,600), 298 (1,920)]. Similarly, the solid state ir spectrum of 5a exhibits two bands in the "carbonyl region" (ν_{Max}^{KBr} 1700, 1670 cm^{-1}) as does 5c (1690, 1670 cm^{-1}) while 4a shows only one (1675 cm^{-1}).

Alkylation of the triazolone ring in 5a was accomplished by refluxing its derived thallous salt in either methyl iodide (18 hrs.) or in a toluene solution of dimethylaminoethyl chloride (7 hrs.) to give the 2-methyl- or 2-(dimethylaminoethyl)triazolo-3,6-diones 5b (mp 292-294°, 17%) and 5c (mp of HCl salt = 284-285.5°, 71%). X-ray analysis of the methiodide derivative (5d, mp 249-250°dec.) of 5c confirmed that alkylation had indeed occurred on nitrogen as indicated and not on the oxygen atom at position-3.[9]

Additionally, the 3-substituted triazoles 4a-e are characterized in the nmr ($CDCl_3$) by an NCH_3 singlet (τ 6.6 to 6.7), a methylene singlet (τ 4.7 to 5.6) that varies in sharpness depending on the substituent at the 3-position, and three aromatic protons (τ 1.9 d, 2.3 q, 2.6 d). While the nmr spectra of the triazolone series 5a-c are essentially the same as those of 4, the resonance of the C-11 proton, is shifted to higher field (τ 1.9 → 2.2). This upfield shift is most probably due to the diminished anisotropic effect of the adjacent C=N bond relative to that of the fully delocalized triazole in 4.

A recent report[2b] indicates that annelation of an isoxazole ring to the "d" face of diazepam (*e.g.*, 6) exerts little influence on the ring inversion barrier of the seven-membered ring (ΔF^* = 17.6 for 6 *vs.* 17.7 kcal/mol for 2c). In contrast, preliminary results with 4 and 5 (employing temperature dependent nmr analysis[10] of the nonequivalent methylene protons) indicate a significant decrease in the free energy of activation for ring inversion (ΔF^* = 12.5-14.2 kcal/mol). The ΔF^* is slightly affected by the steric bulk of the 3-substituents (*e.g.*, 4a, ΔF^* = 13.1 kcal/mol and 4c, ΔF^* = 14.2). Thus, it is seen that replacement of the phenyl group in diazepam 2c, or the phenyl and isoxazolo groups in 6, with a fused triazole or triazolone ring (as in 4 and 5) results in a significant increase in the conformational mobility of the seven-membered ring, indicating that it is the phenyl group in 2c and 6 that is primarily responsible for the increased barrier (approx. 5 kcal/mol) to inversion of the seven-membered ring.

A comparison of the ΔF^*'s of 4 and 5 reveals that the ring inversion barrier is lower in the "3-oxo" triazolone series [*e.g.*, 5c, ΔF^* = 12.5 kcal/mol], and reflects the increased flexibility of the fused triazolone ring in 5 (due ot its exocyclic oxo double bond) relative to the triazole ring in 4 (with its more restraining 2,3-endocyclic double bond).

References and Notes

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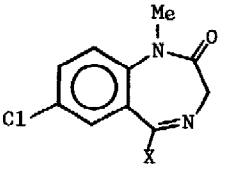
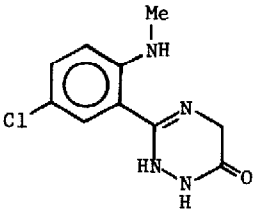


1, X = Cl
2a, X = $NHNH_2$
2b, X = $NHNHCOC(CH_3)_3$
2c, X = 



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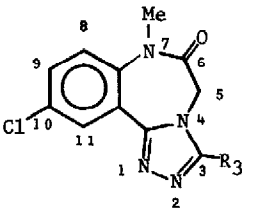
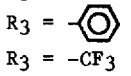
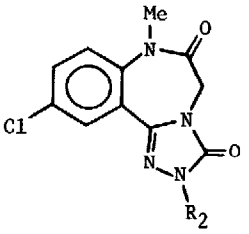
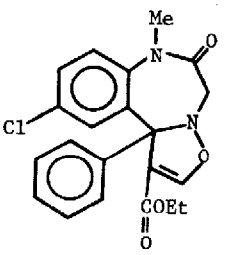


4a, R_3 = -H
4b, R_3 = -Me
4c, R_3 = 
4d, R_3 = $-CF_3$
4e, R_3 = $-CO_2Et$
4f, R_3 = OH ⇄ 5a



5a, R_2 = -H ⇄ 4f
5b, R_2 = -Me
5c, R_2 = $-(CH_2)_2NMe_2$
5d, R_2 = $-(CH_2)_2\overset{\oplus}{N}Me_3 \cdot I^{\ominus}$



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