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THE SYNTHESIS OF TRIAZOLO[1,5-d][1,4]BENZODIAZEPINONES AND TRIAZOLO[4,3-d][1,4]BENZODIAZEPINONES, NEW COMPOUNDS WITH CNS ACTIVITY

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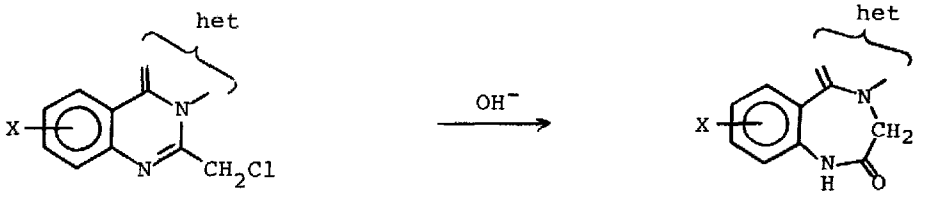
Several years ago we observed[1] that 2-(chloromethyl)-3-aryl-4-quinazolinones, when treated with aqueous alkali, undergo a ring expansion reaction to the known[2-6] 4-aryl-1,4-benzodiazepinedione ring system.

In view of the current interest in compounds derived from the 1,4-benzodiazepine nucleus[7], we extended our investigations to determine whether certain condensed chloromethylquinazoline derivatives 1 would undergo a similar reaction to form the corresponding condensed benzodiazepinones 2.

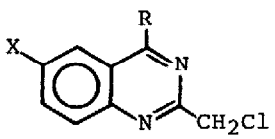


1 2

"het" represents a fused 5- or 6-membered heterocyclic ring

We now wish to describe the ring expansion reaction of certain chloromethyltriazoloquinazolines, 1.

The necessary 2-(chloromethyl)-4-hydrazinoquinazoline starting materials 3c and 3d were prepared by reacting the corresponding 4-chloro compounds 3a and 3b[8] with hydrazine hydrate.



3a, R = Cl, X = H, mp 95-96°C
3b, R = Cl, X = Cl, mp 92-95°C
3c, R = NH-NH_2, X = H, mp 138-140°C (dec)
3d, R = NH-NH_2, X = Cl, mp 163-165°C (dec)

On refluxing with triethyl orthoformate, 3c and 3d were transformed into the corresponding 5-chloromethyl-1,2,4-triazolo[4,3-c]quinazolines, 4a and 4b. Warming of 4 in ethyleneglycol monomethylether resulted in a rearrangement to the isomeric 5-(chloromethyl)triazolo[1,5-c]quinazolines 5, which are the thermodynamically more stable of the two ring systems. The isomers 4 and 5 can be distinguished by their nmr spectra.[9] The triazolo[4,3-c]quinazolines 4 are characterized by a 3-H singlet at ∿9.6τ, whereas the corresponding 2-H singlet of the isomeric triazolo[1,5-c]quinazolines 5 appears at a higher field (τ ∿8.7).

The reaction of 4 and 5 with aqueous sodium hydroxide (in dioxane or DMF) at room temperature resulted in ring expansion to give a mixture of the triazolo-1,4-benzodiazepinone 9 accompanied by minor amounts of 8. The simultaneous formation of both isomeric compounds 8 and 9 (from either 4 or 5) follows from the proposed mechanism indicated in Scheme 1, wherein anions 6 and 7 are presumed to be in equilibrium with each other.

In the case of 5b, both isomeric products, 8b and 9b, were isolated from the ring expansion reaction. The major product A has a mp of 228°C, while the minor isomer B has a mp of 335°(dec). Both A and B were methylated by treatment with sodium methoxide and subsequent reaction with methyl iodide. The methyl derivative 11b obtained from A has a mp of 139-141°C; the corresponding derivative 10b obtained from B has a mp of 278-280°C. The structures of A and B were unequivocally established by comparison of their methyl derivatives with a sample of 10b which had been obtained by an unambiguous route described in the accompanying paper.[10] The methyl derivative obtained from the isomer B proved to be identical (mp, mixture mp, ir,

nmr) with an authentic sample of 10b. Consequently isomer B was assigned formula 8b and isomer A formula 9b. As in the case of the triazoloquinazolines, the isomeric triazolobenzodiazepines can be distinguished on the basis of their nmr spectra. Compounds 8 are characterized by a 3-H singlet at ~8.8τ, whereas the 2-H singlet of the isomeric compounds, 9, appears at a higher field (τ~8.1 - 8.2).

Members of the novel triazolo[1,5-d]benzodiazepine series are potent CNS agents. For example, 11b produces a significant effect at 50 mg/kg *per os* in a rat conflict procedure which is predictive of antianxiety activity.[11]

REFERENCES

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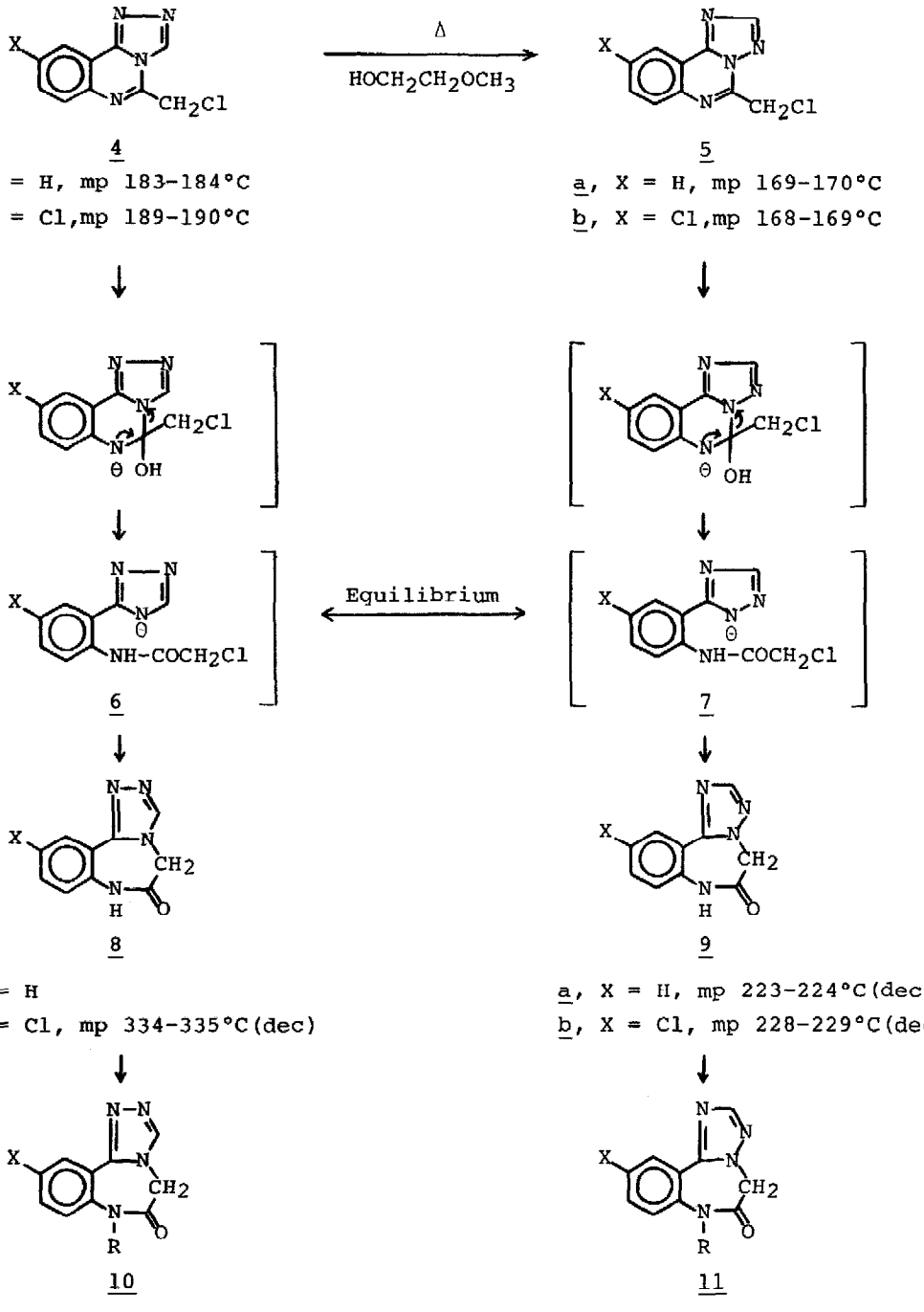
SCHEME 1



4

a, X = H, mp 183-184°C
b, X = Cl, mp 189-190°C

5

a, X = H, mp 169-170°C
b, X = Cl, mp 168-169°C

6 ⟷ 7

8

a, X = H
b, X = Cl, mp 334-335°C(dec)

9

a, X = H, mp 223-224°C(dec)
b, X = Cl, mp 228-229°C(dec)

10

a, X = H, R = CH_3
b, X = Cl, R= CH_3, mp 278-280°C

11

a, X = H, R= CH_3, mp 212-213°C
b, X = Cl, R= CH_3, mp 139-141°C