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REACTION OF α-DIKETONES WITH ETHANOLAMINE

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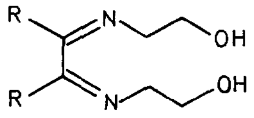
Summary: Butanedione and ethanolamine react to yield 4,8-diaza-1,5-dioxadecalin 3, 2,3-epoxy-8-aza-1,4,5-trioxadecalin 4, and 2-hydroxy-1,6-dihydro-oxazine 5a according to the molar ratios of the reagents. With benzil and 1-phenyl-1,2-propanedione only the related oxazines 5 are obtained in equilibrium with their open-chain tautomers.

The reactions of various α-diketones with ethanolamine and C-substituted ethanolamines have been reported in connection with the synthesis of metallic complexes of polydentate Schiff bases. Adekeye et al.[1] claim that α-diimines 1 are obtained in the reactions of butanedione and benzil with ethanolamine. Dieck and Dietrich[2] report the synthesis of bisoxazolidine 2 by reaction of butanedione and (S)-2-amino-1-butanol.

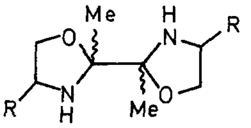
Totally different results are reported here for the reactions of butanedione, benzil, and 1-phenyl-1,2-propanedione with ethanolamine. We also describe the unique behaviour of butanedione as compared to the other diketones studied. In the first case the molar ratios of the reagents have a remarkable influence on the nature and proportions of the resulting products, 3, 4, and 5a[3]. Thus, in ethanolamine excess (molar ratio = 2) 4,8-diaza-1,5-dioxadecalin 3 is obtained as the main product, while with butanedione in excess (molar ratio = 1.5) 2,3-epoxy-8-aza-1,4,5-trioxadecalin 4 is isolated as the predominant product[4]. Equimolar amounts of reagents lead to a mixture of 3 and 5a in 35 and 50% respectively.

^{1}H and ^{13}C n.m.r. data of compounds 3 and 4 reveal the existence of only one diastereoisomer in each case, despite the chiral character of both bridge-head carbon atoms, and allow us to make an unequivocal identification of their structures. The ^{1}H n.m.r. spectra of both 3 and 4 show an ABCD system for the peripheral methylene protons[5]. Coupling constants for compound 3 clearly allow us to discard the bisoxazolidine (type 2) structure and provide unambiguous evidence for the morpholino-morpholine framework having the trans configuration (Table). Thus, a coupling constant value of 12 Hz is



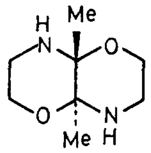
1

R = Me, Ph



2

R = Et



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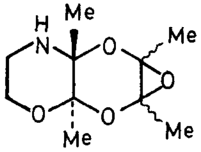

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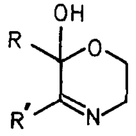

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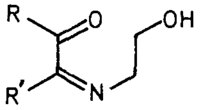


6

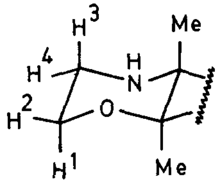
a : R = R'= Me

b : R = R'= Ph

c : R = Ph, R'= Me

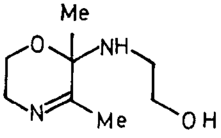
characteristic of $^3J_{aa}$ and values of 1.0 Hz and 3.1-3.8 Hz are consistent with $^3J_{ee}$ and $^3J_{ae}$, respectively, for a morpholine ring of fixed configuration[6]. To our knowledge, this is the first trans-morpholino-morpholine structure to be reported[7]. Also, it has been shown that, in solution, 3 is in equilibrium with 7, the bicyclic tautomer being predominant[8] (80%). From similar considerations based on spectral parameters a trans-morpholino-dioxane structure is assigned

Table.- Coupling constants within the CH_2-CH_2 moiety of compounds 3 and 4.



Comp.	$J_{1.2}$	$J_{3.4}$	$J_{1.3}$	$J_{1.4}$	$J_{2.3}$	$J_{2.4}$
3	-11.2	-11.1	12.0	3.1	3.8	1.0
4	-11.3	-14.9	12.8	4.8	6.5	0.5

to compound 4 (Table). Differences in the vicinal couplings between 3 and 4, can be easily accounted for by accepting a slight flattening (-8° in the torsion angle N-C-C-O) of the chair, according to the results provided by the application of the empirical formulation of the Karplus equation put forward by Haasnoot *et al.*[9]. The large difference observed in the geminal coupling $^2J_{3.4}$ between 3 and 4 must be a consequence of a change in the orientation of the N lone pair of electrons with respect to the adjacent methylene group brought about by the bulky groups in the second ring. An equatorial position of the lone pair in 4 would be required to match the observed highly negative value of $^2J_{3.4}$ in 4[10], which is indirectly evidenced by the observation of a long range coupling (1.1 Hz) between the methyl group at 1.42 p.p.m. (CH_3-C9) and the NH proton (axial) in 4. The formation of 4 may arise through the intermediate *vic*-diol 8 formed by 1,2-addition of ethanolamine to butanedione as shown in Scheme[11].



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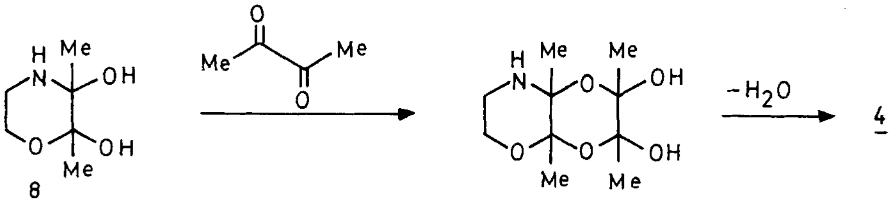

Scheme

With benzil and 1-phenyl-1,2-propanedione whatever the molar ratios of the reagents and experimental conditions (catalyst, solvent and temperature) the related 2-hydroxy-5,6-dihydro-oxazines, 5b and 5c are obtained[12]. In solution, equilibrium with the related open-chain α-iminoketone tautomer 6 is observed.

The extension of the above reaction to other α-dicarbonyl compounds and ethanolamines and the study of the tautomerism observed are now under consideration.

Acknowledgements. We thank Prof. J. Barluenga for communication of some unpublished results[7b].

References and Notes

1. S. B. Adekeye, E. O. Erinoso, and B. N. Ghose, An. Quím., **79B**, 353 (1983).
2. H. tom Dieck and J. Dietrich, Chem. Ber., **117**, 694 (1984).
3. Reaction was carried out in either ether or benzene at room temperature. Compound 3, m.p. 106-108°C (AcOEt); yield : 46% of pure product; ^{13}C n.m.r. ($DCCl_3$, δ) : 21.85 (2xCH_3), 39.27 (N-CH_2), 63.38 (O-CH_2),84.22(N-C-O) ^{1}H n.m.r. ($DCCl_3$, δ) : 1.40 (s, 2xCH_3), 2.43 (m, H^4), 3.45 (m, H^3),

3.77 (m, H^2), 3.94 (m, H^1).
Compound 4, m.p. 89-91°C (AcOEt-hexane); yield : 50% of pure product; ^{13}C n.m.r. ($DCCl_3$, δ) : 10.49 and 12.32 (CH_3-C9 and CH_3-C10) , 16.04 and 17.12 ($CH_3-\underset{O}{C—C}-CH_3$), 41.99 (C8), 57.93 (C7), 93.63 (C9), 97.50 (C10), 103.51 (C2 and C3). ^1H n.m.r. ($DCCl_3$, δ) : 1.35 (s, CH_3-C10), 1.42 (d, J = 1.1 Hz, CH_3-C9), 1.54 and 1.56 (s, $CH_3-\underset{O}{C—C}-CH_3$), 3.02 (m, H^4), 3.05 (q, J = 1.1 Hz, NH), 3.34 (m, H^3), 3.47 (m, H^2), 3.94 (m, H^1).
Compound 5a, m.p. 74-76°C (Benzene); ^{13}C n.m.r. ($DCCl_3$, δ) : 21.37 ($\underline{C}H_3$-C-O), 25.76 ($\underline{C}H_3$-C=N), 47.03 (N-CH_2), 57.37 (O-CH_2), 91.7 (O-C-OH), 169.6 (C=N).
Correct analysis for all compounds.

4. 5a appears as minor product in both cases as indicated by the ^1H n.m.r. of the reaction mixture.

5. At 360 MHz. The ABCD patterns for compounds 3 and 4 were subjected to a complete analysis by using the LAOCOON-3 program. Calculations were carried out on a IBM/UM 370 computer. The reported coupling constants are considered to be accurate within ±0.06 Hz.

6. For related oxygen compounds see : B. Fuchs, A. Ellencweig, and U. Burkert, *Tetrahedron*, **40**, 2011 (1984).

7 *cis*-Heterodecalines related to 3 have been recently reported : (a) A. Le Rouzic, D. Raphalen, D. Papillon, and M. Kerfanto, *Tetrahedron Lett.*, 1853 (1985); J. Barluenga, F. Aznar, R. Liz, and C. Casal, *Chem. Ber.*, in the press.

8. I.r. ($HCCl_3$) : ν (C=N) 1660 cm^{-1}; ^{13}C n.m.r. ($DCCl_3$) : δ (C=N) 169.43; ^1H n.m.r. ($DCCl_3$, δ) : 1.45 (s, CH_3-C-O), 2.04 (t, J = 1.7, CH_3-C=N), 2.78 (m, ^2J = 12.93, ^3J = 4.9 and 5.3, CH_2-NH), 3.54 (m, ^3J = 5.0 and 8.3, CH_2-N=C), 3.63 (t, ^3J = 5.1, CH_2-OH). These signals appear neatly resolved in the 360 MHz spectrum of 3.

9. C. A. G. Haasnoot, F. A. A. M. de Leeuw, and C. Altona, *Tetrahedron*, **36**, 2783 (1980).

10. P. J. Chivers and T. A. Crabb, *Tetrahedron*, **26**, 3389 (1970).

11. Reactions of butanedione with some diols and polyols yielding 1,4-dioxane derivatives have been previously reported. See, for instance : (a) O. Neunhoeffer and H. Paul, *J. Prakt. Chem.*, [4], **4**, 257 (1957); (b) J. Gelas and A. Thiallier, *Carbohyd. Res.*, **30** (1), 21 (1973).

10. In nearly quantitative yield in both cases. 5b, m.p. 91-92°C (AcOEt-hexane). 5c, m.p. 104-106°C (Benzene).

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