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THE REMARKABLY FACILE REARRANGEMENT OF A 2,3,5,6-TETRAKETOPIPERAZINE TO 4,5-DIOXOIMIDAZOLIDINE-2-CARBOXYLIC ACID DERIVATIVES AND ITS REVERSAL

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Reaction of N,N'-dibenzyl-2,3,5,6-piperazinetetraone (1) with boiling ethanol gives ethyl N,N'-dibenzyl-4,5-dioxoimidazolidine-2-carboxylate (2a). Analogous rearrangement products are formed with methyl, n-propyl, n-butyl, and isopropyl alcohols, and ethylene glycol. In the last case the cleavage product N,N'-dibenzyloxamide is also formed. Thermolysis of 2a results in loss of ethanol and regeneration of 1.

Treatment of N,N'-dibenzyl-2,3,5,6-piperazinetetraone (1)[1] with boiling ethanol for 6 hours led to its quantitative conversion to a compound, $C_{20}H_{20}N_2O_5$, m.p. 140-142°C, which is assigned structure 2a on the basis of its spectra (see Table). The occurrence of ring contraction was vouchsafed by the shift of the carbonyl-stretching bands of 1 at 5.87 and 5.92 μ (KBr) to 5.68 μ (KBr) [5.70 and 5.74 μ ($CHCl_3$)] in the i.r. spectrum of 2a, which also shows a hydroxyl-stretching band at 2.90 μ. The presence of a hydroxyl group was confirmed by the ^1H n.m.r. spectrum of the product, which shows a one-proton signal at δ 5.80 that is absent after D_2O treatment. This spectrum also gives clear evidence of the presence of a CH_2CH_3 group, although both the CH_2 and CH_3 proton signals are at unusually high field for a $CO_2CH_2CH_3$ group (vide infra). Further, the benzyl protons give rise to an AB system in contrast to those of 1 in accord with the prochirality of 2a. The ^{13}C n.m.r. spectrum of 2a corroborates the assigned

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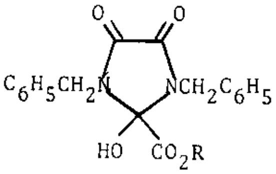
*Dedicated to Professor Tetsuji Kametani on the occasion of his retirement from the Chair of Organic Chemistry at the Pharmaceutical Institute of Tohoku University.

TABLE. Infrared and ^{1}H nuclear magnetic resonance spectra of compounds 2a-2f



	R	λ_{max}^{KBr}, μ[a]	δ[b]
2a	CH_3CH_2	5.68	0.57 (t, J 7 Hz, 3H), 2.95 (q, J 7 hz, 2H), 4.23 (d, J 15 Hz, 2H), 4.90 (d, J 15 Hz, 2H), 5.80[c] (s, 1H), 7.25 (s, 10H)
2b	CH_3	5.72	2.63 (s, 3H), 4.28 (d, J 15 Hz, 2H), 4.97 (d, J 15 Hz, 2H), 5.87[c] (s, 1H), 7.28 (s, 10H)
2c	$CH_3CH_2CH_2$	5.76	0.53 (t, J ~6 Hz, 3H), 0.93 (m, 2H), 2.96 (t, J 6 Hz, 2H), 4.32 (d, J 15 Hz, 2H), 4.92 (d, J 15 Hz, 2H), 5.73[c] (s, 1H), 7.30 (s, 10H)
2d	$CH_3CH_2CH_2CH_2$	5.74	0.8 (t, J 7 Hz, 3H), 2.97 (t, J 7 Hz, 2H), 4.28 (d, J 15 Hz, 2H), 4.91 (d, J 15 Hz, 2H), 5.59[c] (s, 1H), 7.30 (s, 10H)
2e	$(CH_3)_2CH$	5.70	0.65 (d, J 6 Hz, 6H), 4.05 (m, 1H), 4.47 (d, J 15 Hz, 2H), 4.68 (d, J 15 Hz, 2H), 5.93[c] (s, 1H), 7.32 (s, 10H)
2f	CH_2CH_2OH	5.70	3.30 (m, 4H) 4.41 (d, J 15 Hz, 2H), 4.60 (d, J 15 Hz, 2H), 7.23 (s, 11H), 8.67[c] (s, 1H)[d]

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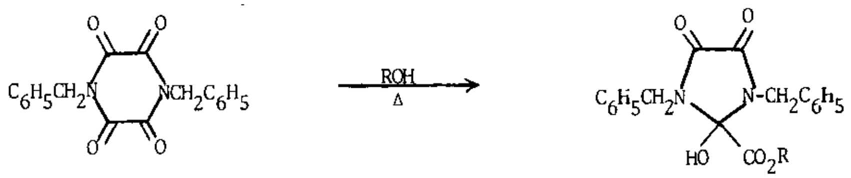
[a] Position of major C=O band is given: in all cases this is accompanied by satellites and/or shoulders. [b] In $CDCl_3$ unless otherwise specified. [c] Absent after D_2O treatment. [d] In DMSO-d_6; additional 1H OH signal falls under benzylic signals.



1

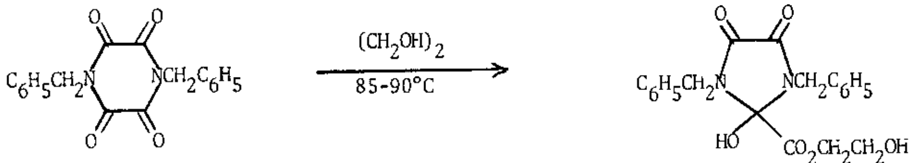
2 a R = C_2H_5
b R = CH_3
c R = n-C_3H_7
d R = n-C_4H_9
e R = i-C_3H_7

structure, showing the presence of two different types of carbonyl carbon [δ 157.3 (s), 164.5 (s)], a quaternary carbon [δ 91.1 (s)], and an O-ethyl group [δ 12.8 (q), 62.2 (t)]. The mass spectrum of 2a shows, inter alia, peaks corresponding to the loss of fragments OC_2H_5, HOC_2H_5, and $HCO_2C_2H_5$ from the molecular ion.

Heating of 2a under reduced pressure (0.05 Torr) at 160°C led to sublimation of a product that was shown to be 1 by spectroscopic comparison; the reconversion of 2a to 1 was quantitative.

The generality of the rearrangement of 1 to 2a was demonstrated by the conversion of 1 to 2b-2e by treatment with the corresponding alcohol. In each case a solution of 1 in the alcohol was boiled at reflux for 6 hours, when conversion was complete, except in that of isopropyl alcohol, which gave a mixture of 2e and unconsumed 1. The i.r. and ^{1}H n.m.r. spectra of compounds 2b-2e (Table) clearly indicate that they are analogues of 2a. Again the signals of the alkoxy protons are at unusually high field. These upfield shifts can be attributed to shielding resulting from the "folding over" of the aromatic ring of one of the benzylic groups.[2]

Two earlier accounts have appeared concerning the reaction of tetraketopiperazines with nucleophilic reagents: N,N'-diaryl-2,3,5,6-piperazinetetraones have been reported to give N,N'-diaryloxamides with boiling aniline[3] and with ethylene and trimethylene glycol.[4] We have therefore examined the reaction of 1 with ethylene glycol. The reaction was carried out at 85°C for 5 days followed by 2 days at 95°C and gave N,N'dibenzyloxamide (3)[1] together with a compound, $C_{20}H_{20}N_2O_6$ (60%), whose spectra (Table) showed it to be 2f, analogous to 2a-2e. Heating of 2f as in the case of 2a reconverted it to 1.



1

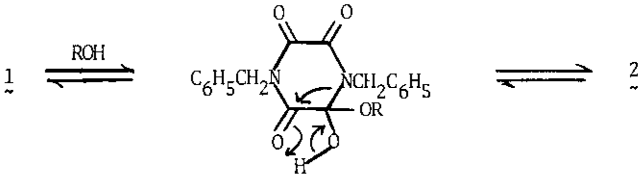
2f

+

$C_6H_5CH_2NHCOCONHCH_2C_6H_5$

3

The formation of products of type 2 from 1 is readily interpretable in terms of a benzilic acid type rearrangement via 4.[5] Such rearrangements usually require



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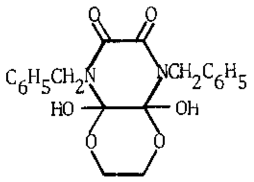

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the use of basic conditions;[5] the remarkably mild conditions in the present case must reflect the destabilization of 1 by dipole-dipole interactions. The circumstance that oxamide formation was only observed in the case of reaction with ethylene glycol suggests that this proceeds via formation of an intermediate of type 5. The thermal reconversion of 2a to 1 must proceed via an intermediate of type 4 and be favoured by an entropic driving force.

ACKNOWLEDGEMENT

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