Intramolecular Cyclization of Bis-α-diazoketones: a New Synthesis of 4-Hydroxytropone

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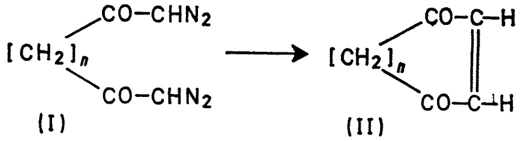
Summary The catalytic decomposition of bis-α-diazoketones, in inert solvents, under the high dilution conditions of Ruggli–Ziegler, affords cycloalk-2-ene-1,4-diones; the method was applied to the synthesis of 4-hydroxytropone (γ-tropolone).



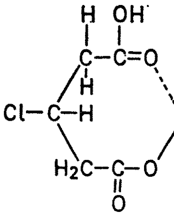
The catalytic decomposition of α-diazoketones in inert solvents affords *trans*-1,2-diacylethylenes,[1] which formally are "dimers" of the intermediate ketocarbene–copper complexes. Bis-α-diazoketones (I), under similar conditions, should give cycloalk-2-ene-1,4-diones (II) by an intramolecular cyclization, the newly formed double bond having *cis*-configuration.

In terms of ring strain and of the possibility of enolization (or aromatization) of the resulting cycloalk-2-ene-1,4-diones to hydroxy-derivatives, which would interfere with the intramolecular cyclization,† bis-α-diazoketones derived from glutaric acids (I; $n = 3$) appeared to be the most suitable ones to start with.

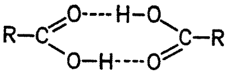
1,7-Bis-diazoheptane-2,6-dione,[2] in boiling toluene with copper-bronze catalyst, under the high dilution conditions of Ruggli–Ziegler, affords cyclohept-2-ene-1,4-dione (II; $n = 3$) in 20% yield of pure, distilled product, b.p. 100° (bath)/15 mm; λ_{max} (cyclohexane) 225 nm (ϵ 9400); ν_{max} (CCl_4) 1680 (C=O stretching), 1615 (C=C stretching), and 900 cm^{-1} (*cis*-CH=CH); τ ($CDCl_3$) 3·47 (s, 2H)‡ and complex multiplets centred at 7·25 and 7·9 (6H). The yields of the intramolecular cyclization are increased up to 32% by using soluble copper chelates[3] as catalyst.

This reaction is the first reported example of a successful intramolecular cyclization of a bis-α-diazoketone. The early claim in which the authors[4] reported the isolation of cyclohept-2-ene-1,4-dione as the bis-2,4-dinitrophenylhydrazone derivative in 2·3% yield, must be questioned since the reported m.p. (259—260°) is not in agreement with that we found (m.p. 270—272°) for the bis-2,4-dinitrophenylhydrazone prepared from pure dione.

This new method of intramolecular cyclization of bis-α-diazoketones was applied to the synthesis of 4-hydroxytropone (γ-tropolone). For this, we had to prepare β-chloroglutaric acid as the starting material. Although β-chloroglutaric acid esters are well known,[5] no such data concerning to the free acid are available.[6] Attempts to hydrolyse the esters led to glutaconic acid. However, we found that glutaconic acid, in anhydrous ether solution, easily adds gaseous HCl to give β-chloroglutaric acid in quantitative yields as a white solid, m.p. 129–130°. The n.m.r. spectrum of this acid in D_2O solution shows unsymmetrical bands at τ 6·95 (s) and 7·05 (d, J 2·5 Hz) in a 2 : 1 ratio, and a complex multiplet centred at 5·2. Since the splitting at τ 7 is not observed in the corresponding methyl or ethyl esters, which give the expected doublet at τ 7·15 (J 7 Hz) for the protons of the methylene groups, we explain it in terms of a cyclic structure (III) [similar to the eight-membered ring (IV) present in "dimers" of normal acids], which would be the preferred conformation as the result of a strong intramolecular hydrogen bonding favoured by the buttressing-effect of the bulky β-chlorine atom.[7] Then, the diastereotopic protons[8] of the methylene groups would become magnetically nonequivalent, and the observed pattern with J_{cis} *ca.* 0 and J_{trans} *ca.* 2·5 would represent a "semi-collapsed AB system."



(III)



(IV)

If this interpretation is correct, then the intramolecular hydrogen bonding should break down in strong acid solution; we have found that the n.m.r. spectrum becomes "normal" in $CF_3{\cdot}CO_2H$ solution, with the typical sharp doublet at τ 6·9 (J 7 Hz), as in the corresponding esters, and a sharp quintuplet centred at τ 5·19 (J 7 Hz).

The reaction of β-chloroglutaric acid with an excess of oxalyl chloride affords a mixture of β-chloroglutaric anhydride (low m.p. solid, b.p. 89—90°/0·4 mm) and β-chloroglutaryl dichloride (b.p. 49—50°/0·3 mm), the latter being the only product formed in the reaction with PCl_5. Treatment of β-chloroglutaryl dichloride with a threefold molar excess of diazomethane gives the 1,7-bisdiazo-4-chloroheptane-2,6-dione (m.p. 65—66°; ν_{max} (CCl_4) 2100 cm^{-1}, in 80% yield. Decomposition of this bis-α-diazoketone with copper acetylacetonate in benzene solution at 65°, under the high dilution conditions, leads to 6-chlorocyclohept-2-ene-1,4-dione. This compound is only moderately stable in benzene solution and it could be isolated in about 15% yield by column chromatography on silica-gel, and characterized by n.m.r. spectroscopy (sharp singlet at τ 3·7 in benzene solution, typical of the *cis*-olefinic protons). Elimination of HCl from 6-chlorocyclohept-2-ene-1,4-dione either spontaneously, induced by careful concentration of the benzene eluates *in vacuo*, or promoted by weak bases (Et_3N), leads to 4-hydroxytropone (γ-tropolone) in high yields (70—75%). The conditions in the former case are very critical, otherwise complex mixtures of hydroxy and aromatic aldehydes are formed.

4-Hydroxytropone, after sublimation at 140°/0·001 mm, has m.p. 212°; λ_{max} (H_2O) 227 and 336 (ϵ 18,938 and 12,662) and (0·1N-NaOH) 227 and 359 nm (ϵ 18,722 and 18,832); ν_{max} (KBr) 2460 (br), 1640 (w), 1597, 1440, 1400, and 1285 cm^{-1}, in agreement with the data previously reported.[9] The n.m.r. spectrum of the anion (NaOH solution; H_2O as internal reference) shows a double doublet at τ 2·60, 2·77, 2·81, and 2·88 (the last one overlaps with the next peak) (1H, J 9·4 Hz), a peak at 2·94 (2H), and an unsymmetrical doublet at 3·46 and 3·67 (2H, J 9·4 Hz), the bands of the last four protons appearing further split by long-range *meta*-coupling (J *ca.* 1·7 Hz).

Correct analyses were obtained for all the reported compounds.

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† If $n = 2$, for example, the primary formed cyclohex-2-ene-1,4-dione will enolize to hydroquinone which will then react with the bis-α-diazoketone still present in the mixture, to give complex linear co-polymers.

‡ Compare with the olefinic protons of *trans*-1,2-diacylethylenes which, owing to the diamagnetic anisotropy of C=O groups, are found at τ 2·6 (ref. 1b).

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