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INTRAMOLECULAR CYCLIZATION OF BIS-α-DIAZOKETONES: A NEW SYNTHESIS OF γ-TROPOLONE[a]

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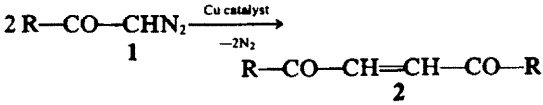
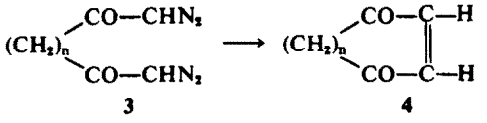
Abstract—Catalytic decomposition of bis-α-diazoketones (**3**, n = 3), in inert solvents, under high dilution affords cycloalk-2-ene-1,4-diones (**4**, n = 3). The method has been applied to a new synthesis of γ-tropolone **5** in five steps from glutaconic acid **6**.

INTRODUCTION[1]

Catalytic decomposition of α-diazoketones **1** by copper catalysts, in inert solvents, affords symmetrical *trans*-diacylethylenes **2**[2] which are formally dimers of the intermediate ketocarbene-copper complexes.



Although bis-α-diazoketones **3**, under similar conditions, could give cycloalk-2-ene-1,4-diones **4**, the success of such an intramolecular cyclization would depend not only upon some structural requirements, but also on the experimental conditions.



The cis-configuration of the double bond present in the cyclization product (**4**, n = 0 to 3), in contrast to the trans double bond observed in diacylethylenes **2**, would hardly be a serious impediment for the intramolecular reaction to take place since the trans-configuration is the result of a reaction run under thermodynamic control, and in fact the cis isomers can be isolated working under milder experimental conditions. For example,[2] whereas Cu-bronze-induced decomposition of diazomethyl-t-butylketone (**1**, R = CMe_3) in boiling benzene gives exclusively *trans*-1,2-dipivaloylethylene (**2**, R = CMe_3), the decomposition in the presence of Cu(I)-acetylacetonate at room temperature afforded a 3:1 mixture of trans- and cis-1,2-dipivaloylethylene. Although the cis isomer easily isomerizes, it could be characterized by NMR since the olefinic protons appear at τ 3·3 instead of 2·6 observed in the trans isomer. An observation very useful indeed for detecting the cyclization products of bis-α-diazoketones (see below) in the eluates from the chromatographic purification of the crude reaction mixtures.

Intramolecular cyclization of bis-α-diazoketones. In terms of ring strain, thermal stability (**4**, n = 1)[3] and the possibility of aromatization of the resulting cycloalk-2-ene-1,4-diones to hydroxy derivatives (**4**, n = 2 → hydroquinone), which would interfer with the intramolecular cyclization, the bis-α-diazoketone derived from glutaric acid (**3**, n = 3) appeared as the most suitable one to start with. On the other hand, whereas bis-α-diazoketones of type **3** with n ≥ 3 are easily prepared by reaction of diazomethane with the corresponding acid dichlorides,[4] the reaction follows a more complicated course[4,5] in the case of n = 0 to 2. However, Yates and Dewey[5] have prepared bis-α-diazoketones of the type $N_2CHCOCR_2COCHN_2$ (R ≠ H) by this method, and Newman and Wolf[6] have even prepared the bis-α-diazoketones corresponding to monosubstituted malonic acids, R—$CH(COCHN_2)_2$, with one active α-hydrogen.

Some unsuccessful attempts of intramolecular cyclizations of bis-α-diazoketones reported earlier[7] led us to explore the high dilution technique,[8] by very slow addition of a dilute solution of **3**, (n = 3) to a vigorously stirred suspension or solution of the copper catalyst.

Table 1 gives the results for the intramolecular cyclization of 1,7-bis-diazoheptane-2,6-dione (**3**, n = 3),[4] run under identical dilution conditions, but changing the solvent, the temperature and the nature of the copper catalyst. As anticipated, the best yields were obtained when the reaction was con-

[a]Taken in part from Doctoral Thesis of J. Valls (University of Barcelona, 1973). Financial support from Houghton-Hispania S.A. and Patronato "Juan de la Cierva" is gratefully acknowledged.

Table 1. Intramolecular cyclization of 1,7-bis-diazoheptane-2,6-dione

Solvent	Catalyst	Medium	Temp	Yield
toluene	Cu-bronze	heterogeneous	112°	20%
benzene	Cu(I) (acac)	heterogeneous	room temp.	15%
benzene	Cu(II) $(acac)_2$	homogeneous	65°	32%

ducted under strictly homogeneous conditions; i.e., using a soluble copper catalyst, such as Cu(II)-acetylacetonate.

The reaction product was isolated by column chromatography on silica, collecting all eluates showing τ 3·62 characteristic of *cis*-olefinic protons; the product was characterized as cyclohept-2-ene-1,4-dione (**4**, n = 3) by elementary analysis, UV, IR and NMR spectroscopy, and by its bis-2,4-dinitrophenylhydrazone.[Cf.7]

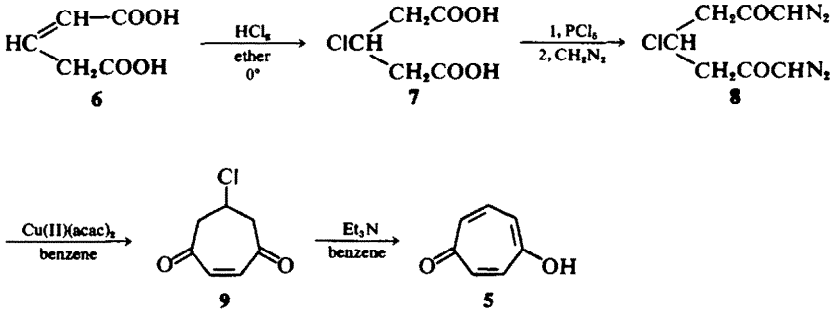
Taking into account the structural limitations discussed above and the fact that exploratory experiments (see Experimental) with the bis-α-diazoketone derived from dimethylmalonic acid failed to give 2,2-dimethylcyclopent-4-ene-1,3-dione, already known to be a fairly stable compound,[9] this method of intramolecular cyclization appears specially suited to seven-membered ring synthesis, *cf* 10.

Synthesis of γ-tropolone. γ-Tropolone **5**[11] which formally is the enol form of cyclohept-2,5-diene-1,4-dione, should be easily accessible by an intramolecular cyclization of a bis-α-diazoketone derived from a cis-glutaconic acid equivalent (in the classical biogenetic sense). Since preliminary experiments showed the facile interconversion between glutaconic and β-chloroglutaric esters,[1] we prepared the unknown[12] β-chloroglutaric acid **7** by addition of anhydrous hydrogen chloride to glutaconic acid **6** in ether solution, as starting material for a new synthesis of γ-tropolone **5**.

The reaction of β-chloroglutaric acid with excess oxalyl chloride afforded a 4:1 mixture of β-chloroglutaric anhydride and β-chloroglutaryl dichloride, the latter being the only product formed in the reaction with PCl_5 (93% yield). Treatment of β-chloroglutaryl dichloride with excess diazomethane in ether gave 1,7-bis-diazo-4-chloroheptane-2,6-dione **8** in 80% yield (m.p. 64–65°). Decomposition of this bis-α-diazoketone with Cu(II)-acetylacetonate in benzene solution at 65°, under the high dilution conditions described above, led to 6-chlorocyclohept-2-ene-1,4-dione **9** in 13–15·5% yield (12·6% in the presence of Cu(I)-acetylacetonate). This compound is only moderately stable even in benzene solution and the yields were estimated by dissolving an aliquot portion in 0·1 N sodium hydroxide solution and measuring the intensity at 359 nm (characteristic absorption of the γ-tropolone anion).[11] The purification was achieved by column chromatography on silica-gel: all benzene eluates with absorption at $\tau \sim 3{\cdot}7$ and/or 359 nm in 0·1 N sodium hydroxide solution were collected (> 93% recovery from yields estimated in the crude reaction mixture) and the solution was then concentrated.

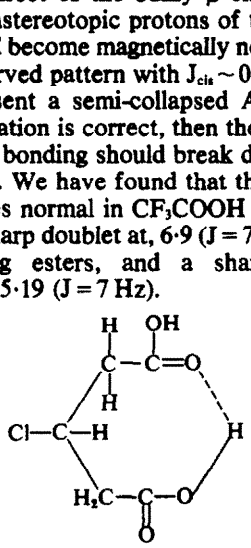
Elimination of HCl from 6-chlorocyclohept-2-ene-1,4-dione **9** by slow dropwise addition of Et_3N to the benzene solution afforded γ-tropolone **5** in 72% yield. Although quantitative yields of γ-tropolone could be obtained by spontaneous elimination of HCl, induced by careful concentration of the benzene solution in vacuo, the conditions are very critical and usually a sudden decomposition occurs leading to a complex mixture of hydroxyaryl aldehydes.

Spectroscopic considerations. Besides the singlet at τ 3·62, corresponding to the cis-olefinic protons, the NMR spectrum of cyclohept-2-ene-1,4-dione (**4**, n = 3) in CCl_4, at room temperature, shows two complex multiplets at τ 7·25 and 7·88 in a 2:1 ratio. However, when the sample (in α-chloronaphthalene) is slowly heated above 30° the two multiplets become more and more definite, and



at 150° a sharp triplet (4H, J = 6 Hz) and a quintuplet (2H, J = 6 Hz) are well apparent. Therefore, we must conclude that, in contrast to other seven-membered carbocyclic molecules (including cycloheptane,[13] cycloheptanone[14] and bullvalenetrione[10]) which are reputed to have rather low barriers to ring inversion, cyclohept-2-ene-1,4-dione (4, n = 3), with four interacting sp^2 carbon atoms, is a rather rigid molecule and undergoes, on the NMR time scale, a very slow ring inversion at room temperature.

The NMR spectrum of β-chloroglutaric 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 centered 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 **10** (similar to the eight-membered ring present in dimers of normal acids) which would be the preferred conformation as the result of a strong intramolecular hydrogen bond favoured by the buttressing effect of the bulky β-chlorine atom.[15] Then, the diastereotopic protons of the methylene groups would become magnetically non-equivalent, and the observed pattern with $J_{cis} \sim 0$ and $J_{trans} \sim 2·5$ would represent a semi-collapsed AB system. If this interpretation is correct, then the intramolecular hydrogen bonding should break down in strong acid solution. We have found that the NMR spectrum becomes normal in CF_3COOH solution, with the typical sharp doublet at, 6·9 (J = 7 Hz), as in the corresponding esters, and a sharp quintuplet centred at τ 5·19 (J = 7 Hz).



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EXPERIMENTAL

M.ps are uncorrected and have been determined on a Kofler microscope. UV, IR and NMR spectra were recorded on Perkin Elmer Spectrometers, Models 157-UV, 457, R-12 and R-10. Preparative GLC of cyclohept-2-ene-1,4-dione (4, n = 3) was performed with Perkin Elmer Gas Chromatograph, Model F-21, using a 200 cm × 1/4, with a 5% SE 30 on Chromosorb W column, at 150°.

Intramolecular cyclization of 1,7-*bis-diazoheptane*-2,6-*dione*: *Cyclohept*-2-*ene*-1,4-*dione* (4, n = 3)

(a) To a vigorously stirred soln of 0·80 g of Cu(II)-acetylacetonate in 550 ml anhyd benzene, under N_2 at 60–65°, was added dropwise over a period of 69 h (8 ml/h) a soln of 7·5 g (35 mmol) of 1,7-bis-diazoheptane-2,6-dione[4] in 550 ml anhyd benzene. After the addition was complete, stirring was continued for 8 h, the soln allowed to cool to room temperature, filtered and the solvent evaporated under vacuum. The remaining oily residue was chromatographed on silica-gel. Elution with benzene was continued until the peak at τ 3·62 (cis-olefinic protons) was not apparent in the eluates. The yellow benzene soln was evaporated to dryness, the oily residue dissolved in anhyd ether, resins filtered off, and the soln evaporated in vacuo once again. The residue (homogeneous to TLC) was evaporatively distilled at 135° (bath) at 18 torr to give 1·28 g (32·5% yield) of cyclohept-2-ene-1,4-dione (4, n = 3): UV (cyclohexane), λ_{max} 225 nm (ε 9410); IR (CCl_4), 3025, 2944, 1675 and 1615 cm^{-1}; NMR (CCl_4), τ 3·62 (s) (2H), 7·25 (complex m) (4H) and 7·88 (complex m) (2H).

The analytical sample was prepared by GLC and further distillation on a "tube à boules" (Büchi). Found: C, 67·10; H, 6·69. $C_7H_8O_2$ requires: C, 67·73; H, 6·50%. *Bis*-2,4-*dinitrophenylhydrazone*,[16] red crystals m.p. 270–272° (dec).[cf] (from dioxan) Found: C, 46·95; H, 3·38; N, 23·10. $C_{19}H_{16}N_8O_8$ requires: C, 47·11; H, 3·33; N, 23·10%.

(b) The decomposition of 1,7-bis-diazoheptane-2,6-dione in the presence of Cu-bronze was carried out under identical dilution conditions in solution of boiling toluene, the yield being 19·6%; in the presence of Cu(II)-acetylacetonate, in benzene soln, the reaction proceeded at room temperature to give 15% yield of cyclohept-2-ene-1,4-dione (4, n = 3).

Attempted intramolecular cyclization of 3,3-*dimethyl*-1,5-*bis-diazo-pentane*-2,4-*dione*

To a vigorously stirred soln of 0·90 g of Cu(II)-acetylacetonate in 900 ml anhyd benzene, under N_2 at 55–60°, was added dropwise over a period of 112 h a soln of 9·9 g (55 mmol) of crude 3,3-dimethyl-1,5-bis-diazopentane-2,4-dione (contaminated by 9% of the corresponding α-chloroketone, and prepared from dimethylmalonyl dichloride[17]) in 900 ml of anhyd benzene. After the addition was complete, stirring was continued for 10 h, the soln filtered and concentrated under vacuum to a volume of about 100 ml. Enough ether was added to precipitate resins, the soln filtered and the solvents eliminated under vacuum. The oily residue was chromatographed on silica-gel. Elution with benzene gave a chlorinated crystalline compound (1·16 g), m.p. 153–53·5°; IR (KBr), 1760 and 1725 cm^{-1}; NMR ($CDCl_3$), τ 5·22 (s) (1H), 6·15 (d, J = 3·4 Hz), 6·25–6·93 (AB system, J = 11 Hz) (2H), 8·70 (s) (3H), 8·77 (s) (3H), 8·84 (s) (3H) and 8·90 (s) (3H). Found: C, 59·10; H, 6·18; Cl, 12·16; MW 284–286 (MS). $C_{14}H_{17}ClO_4$ requires: C, 59·15; H, 6·03; Cl, 12·47%; MW 284·7. Further elution with benzene:ether (4:1) gave an oily fraction (4·0 g), shown to be a complex mixture of polymers of increasing molecular magnitude by TLC, which was not further investigated. No traces of 2,2-dimethylcyclopent-4-ene-1,3-dione[9] could be detected.

β-Chloroglutaric acid 7

A soln of 10·0 g (77 mmol) of glutaconic acid[18] in 600 ml of anhyd ether was saturated at 0° with anhyd hydrogen chloride. The soln was dried with $MgSO_4$ and evaporated to dryness in vacuo. The solid residue was recrystallized from ether-hexane to give 12·5 g (95% yield) of β-chloroglutaric acid 7,[12] mp 129–130°; IR (KBr) 3600–2100 (broad) and 1690 cm^{-1}; NMR (CF_3COOH), τ 5·18 (quintuplet, J = 7 Hz) (1H), 6·86 (d, J = 7 Hz) (4H). Found: C,

36·31; H, 4·23; Cl, 21·16. $C_5H_7ClO_4$ requires: C, 36·05; H, 4·24; Cl, 21·29%.

β-Chloroglutaryl dichloride

(a) *With oxalyl dichloride.* To 14·9 g (117 mmol) of recently distilled oxalyl dichloride, cooled with ice water, were added in small portions 4·0 g (24 mmol) of β-chloroglutaric acid. After evolution of HCl ceased, the reaction mixture was allowed to warm to room temperature and then refluxed for 6 h. Excess oxalyl dichloride was removed under vacuum and the residue distilled to give two fractions: (1) β-chloroglutaryl dichloride, b.p. 60–62°/0·45 torr (0·9 g, 18·3% yield) (see below), and (2) β-chloroglutaric anhydride, b.p. > 150·/0·45 torr (3·8 g, 77·4% yield); IR (CCl_4), 1825 and 1780 cm^{-1}; NMR (CCl_4), τ 5·32 (quintuplet, J = 4 Hz) (1H) and 6·78 (d, J = 4 Hz) 4H).

(b) *With PCl_5.* 6·5 g (39 mmol) of β-chloroglutaric acid were slowly added, in small portions, to 18·6 g (89 mmol) of PCl_5 cooled with ice water. After the addition was complete, the ice bath was removed and the mixture allowed to warm up. As reaction proceeded the mixture became more fluid and finally it was refluxed for 2–3 h. The reaction mixture was filtered and distilled to give 7·3 g (93% yield) of β-chloroglutaryl dichloride, b.p. 59–60°/0·3 torr; IR (CCl_4), 1795 cm^{-1}; NMR (CCl_4), τ 5·30 (quintuplet, J = 6·5 Hz) (1H) and 6·41 (d, J = 6·5 Hz) (4H).

1,7-Bis-diazo-4-chloroheptane-2,6-dione **8**

To a magnetically stirred soln of 12·5 g (297 mmol) of diazomethane in ether, cooled at − 5°, was added dropwise over a period of 70 min a soln of 10·1 g (50 mmol) of β-chloroglutaryl dichloride in 80 ml anhyd ether. After the addition was complete, stirring was continued overnight. The solvent and excess of diazomethane were removed in vacuo, the crystals filtered off and recrystallized from $CHCl_3$-CCl_4 to give 8·4 g (80% yield) of 1,7-bis-diazo-4-chloroheptane-2,6-dione, m.p. 64–65°; UV (EtOH), λ_{max} 253 and 274 nm (ε 16194 and 17350); IR (CH_2Cl_2), 2100, 1645, 1370 and 1340 cm^{-1}; NMR ($CDCl_3$), τ 4·53 (s) (2H), 5·17 (quintuplet, J = 6·8 Hz) (1H) and 7·1 (d, J = 6·8 Hz) (4H). (Found: C, 39·31; H, 3·24; Cl, 16·40; N, 26·6. $C_7H_7ClN_4O_4$ requires: C, 39·20; H, 3·29; Cl, 16·53; N, 26·12%.

Synthesis of γ-tropolone **5**

(1) *Intramolecular cyclization of 1,7-bis-diazo-4-chloroheptane-2,6-dione:* 6-chlorocyclohept-2-ene-1,4-dione **9**. To a vigorously stirred soln of 1·2 g of Cu(II)-acetylacetonate in 770 ml anhyd benzene, under nitrogen at 60–65°, was added dropwise over a period of 96 h a soln of 10·5 g (48·9 mmol) of 1,7-bis-diazo-4-chloroheptane-2,6-dione **8** in 770 ml anhyd benzene. After the addition was complete, stirring was continued for 12 h, the soln allowed to cool to room temperature, filtered and reduced in vacuo to a volume of 900 ml. The yield of the intramolecular cyclization, estimated by dissolving an aliquot portion into 0·1N sodium hydroxide solution and measuring the intensity at 359 nm (characteristic absorption of γ-tropolone anion[11]), was 13–15·5%.

The benzene soln was concentrated in vacuo to a volume of about 120 ml and chromatographed on silica-gel. The column was eluted with a 4:1 mixture of benzene-ether, collecting all fractions with the peak at τ ~ 3·7 characteristic of cis-olefinic protons and/or the characteristic absorption at 359 nm after extraction with 0·1 N sodium hydroxide. The recovery was > 93% of the cyclization product present in the original reaction mixture.

(2) *Dehydrochlorination of 7-chlorocyclohept-2-ene-1,4-dione: γ-tropolone* **5**. To a portion of the chromatographed benzene soln concentrated in vacuo to a volume of 250 ml and containing 378 mg of γ-tropolone (after trituration with 0·1 N sodium hydroxide soln) was added dropwise, with vigorous stirring, a soln of 0·9 ml of triethylamine in 10 ml benzene and stirring was continued for 24 h. The precipitate was filtered off, dissolved in 2N sodium hydroxide, the alkaline soln washed with ether, acidified with 2N HCl to pH 2–3 and evaporated to dryness under vacuum. The resulting solid residue (1·85 g) was sublimated at 140°/0·001 torr, to give 275 mg (72% yield) of pure γ-tropolone, m.p. 212°; UV (H_2O), λ_{max} 227 and 336 nm (ε 18939 and 12662); UV (0·1 N NaOH), λ_{max} 227 and 359 nm (ε 18722 and 18832); IR (KBr), 2460 (broad), 1640, 1597, 1440, 1400 and 1285 cm^{-1}; NMR (D_2O-NaOH, H_2O τ 5·3, as internal reference), τ 2·79 (double d, J = 9·4 Hz) (1H), 2·94 (double *d* long-range meta-coupling, J ~ 1·7 Hz) (2H), and 3·46 and 3·67 (unsymmetrical d, J = 9·4 Hz; long-range meta-coupling, J ~ 1·7 Hz) (2H).

Eventually, quantitative yields of γ-tropolone were obtained by spontaneous elimination of HCl induced by careful concentration of the chromatographed benzene soln in vacuo.

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