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PROTONATION OF METHANE(TRI-α-DIAZOACETONE) IN ACID SOFTENING SOLVENTS

ACID AND BASE-INDUCED INTRAMOLECULAR CYCLIZATIONS OM METHANE(TRI-CHLOROACETONE) TO TRIOXAADAMANTANE AND TRIASTERANE DERIVATIVES[a]

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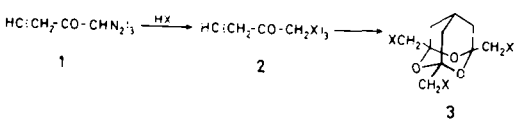
Abstract—Controlled protonation of methane(tri-α-diazoacetone) (1) leads to open-chain tricarbonyl compounds 2, which can be cyclized by acids to 2,4,9-trioxaadamantanes 3. On the other hand, the base-induced cyclization of methane(tri-chloroacetone) (2, X = Cl) leads to a triasterane derivative: 1-hydroxymethyltetracyclo-[3.3.1.0^{4,6}]nona-3,7-dione (4).

INTRODUCTION

Stetter and Stark[1] reported that protonation of methane(tri-α-diazoacetone) (1) either with aqueous concentrated hydrochloric or hydrobromic acid gives 1,3,5-tri(halomethyl)-2,4,9-trioxaadamantanes (3) instead of the expected open-chain triketones 2 (X = Cl or Br) (Scheme 1). These results are in agreement with those reported earlier by Stetter and Dohr,[2] and those of Raasch and Krespan[3] who concluded that tricarbonyl compounds of structure 2 spontaneously and irreversibly cyclize to 2,4,9-triosaadamantanes 3.

We found,[4a] however, that the cyclization is an acid-catalyzed reaction similar to the intermolecular trimerization of acetaldehyde to paraldehyde (Scheme 2), and that open-chain tricarbonyl compounds 2 can be isolated, starting from methane(tri-α-diazoacetone) (1), provided that protonation takes place under strictly controlled conditions: namely, in the presence of highly basic organic solvents, such as dimethylformamide DMF, dimethylsulfoxide DMSO and hexamethylfosforic triamide (HMPT).

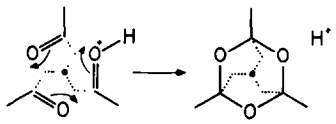
In contrast to the superacids,[5] which are "hard acids" that protonate α-diazoketones exclusively at the O atom ("hard base"),[6] the conjugated acids of DMF, DMSO and HMPT are, apparently, "soft acids" that protonate the tris-α-diazoketone 1 at the C atom ("soft base") rather than at oxygen, otherwise the cyclization product would be isolated. Alternatively, DMF, DMSO and HMPT can be considered as "acid-softening solvents" in the sense that strong acids in solution of either one of them cannot protonate "hard bases" such as the C=O groups, and therefore cannot promote the cyclization of methane(tri-acetones) 2 to 2,4,9-trioxaadamantanes 3 (cf. Scheme 2).



1 2 3

Scheme 1.

[a] Taken in part from Doctoral Thesis of E. Herranz, University of Barcelona (1975).



Scheme 2.

Exploratory experiments with anhydrous methanesulfonic acid shows that the best results were obtained working with HMPT,

solvent	2 (X = OMs), yield
DMF	11.3%
DMSO	11.2%
HMPT	19.2%

All the experiments were performed by dropwise addition of a solution of methane(tri-α-diazoacetone) in THF to a magnetically stirred solution of equimolecular amounts of acid and the basic solvent at room temperature.

When the same procedure was applied to aqueous concentrated hydrochloric and hydrobromic acids, using HMPT as the acid-softening solvent, the corresponding open-chain triketones 2 (X = Cl or Br) were obtained in 47 nad 43% yield, respectively. The yields were increased to 81.6 and 60.5%, by filtering the mixture through a column packed with Dowex 50W × 8, which efficiently removes all traces of HMPT, and then extracting the product with methylene dichloride.

Table 1 gives the results for the reaction of methane(tri-α-diazoacetone) with acids in different conditions. It can be seen that H_2O competes effectively with anions of low nucleophilicity (MsO^- and ClO_4^-) to give the corresponding hydroxy derivative.

Acid and base-induced cyclizations

The open-chain tricarbonyl compounds 2 (X = Cl, Br, MsO) could be quantitatively cyclized to 2,4,9-trioxaadamantanes 3 by refluxing a dimethoxyethane (DME) solution, in the presence of catalytic amounts of *p*-toluenesulfonic acid. The chloro- and the bromo-derivatives were identical with those prepared by the

Table 1. Protonation of $HC(CH_2\text{-}CO\text{-}CHN_2)_3$

Acid	Solvents	Triketones 2		Trioxaadamantane, 3	
		m.p.	yield	m.p.	yield
HCl	DMFT/HF/H_2O	85°	81.6%	-	-
HCl	H_2O^+	-	-	105-6°	70%
HBr	DMFT/HF/H_2O	70-1°	60.5%	-	-
HBr	H_2O^+	-	-	128-9°	71.2%
MeSO$_3$H	DMFT/HF	118-20°	19.2%	-	-
MeSO$_3$H	CH_2Cl_2	-	-	173-5°	4.6%
MeSO$_3$H	H_2O	-	-	114°++	10.8%
$HClO_4$	H_2O	-	-	114°++	13%

+ As in ref. 1 (yields have been improved, however).

++ as 1,3,5-tri(hydroxymethyl)-2,4,9-trioxaadamantane (3, X = OH), dec. p. in a sealed capillary.

method previously described by Stetter and Stark[1] (Table 1).

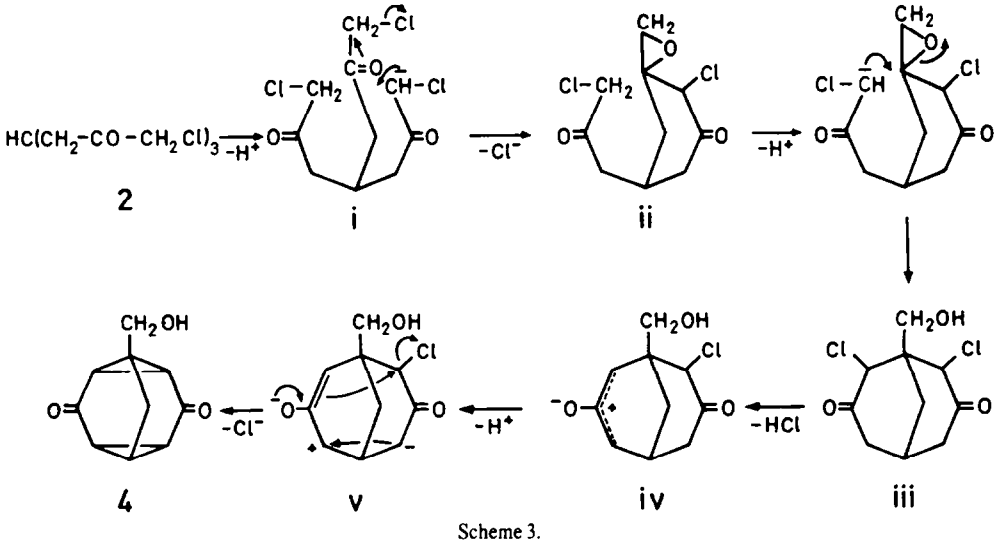
The reaction of methane(tri-chloroacetone) (2, X = Cl) under Favorskii conditions, however, leads to a water soluble, highly crystalline compound, m.p. 107–108°, the yields depending upon the nucleophilicity of the base used: 78% yield with potassium t-butoxide in t-butyl alcohol, and 46% yield with sodium methoxide in methanol. It is obvious that intermolecular nucleophilic reactions compete effectively with the intramolecular reactions involved in the cyclization process in the latter case.

The compound has been characterized as 1-hydroxymethyl-tetracyclo[3.3.1.$0^{2,8}$.$0^{4,6}$]nona-3,7-dione (4) by spectroscopic techniques and the preparation of some derivatives (Experimental), as well as by the following mechanistic considerations.

In α-chloroketones and C–H bond (α) adjacent to both the CO group and the Cl atom is significantly more acidic (about 2 pK_a units)[7a] than C–H bonds (α′) adjacent only to a CO group. However, removal of one of the former protons (α) leads to a relatively stable anion which usually does not undergo further chemical changes, but through and equilibrium with the protonated form the α′ anion is formed which will lead to the characteristic products of the Favorskii rearrangement.[8]

In the reaction of methane(tri-chloroacetone) with bases (Scheme 3) however, once the more stable anion (i) is formed, it can react intramolecularly with a CO group of another side-chain (six atoms apart), with simultaneous attack of the resulting alkoxide to the adjacent C atom and elimination of chloride, to give an epoxide (ii),[7b] which, after a further nucleophilic attack of the carbanion of the third side-chain, leads to a bicyclic primary alcohol (iii). Dehydrochlorination of this alcohol, induced by excess base, gives an oxyallyl dipolar ion (iv),[9] which finally undergoes an "anomalous Favorskii rearrangement" (v) to the triasterane derivative 4.

The observed spectroscopic properties (Experimental) are in agreement with the proposed triasterane structure.[10] Further confirmation was obtained by NMR in the presence of a lanthanide shift reagent,[11] such as



Scheme 3.

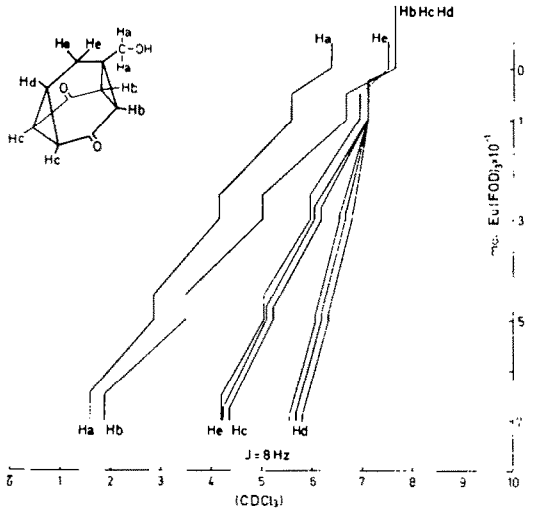


Fig. 1.

$Eu(FOD)_3$, which produces a nearly first-order NMR spectrum (Fig. 1) in which the observed couplings between H_c and H_d ($A \sim 0°$) and H_d and H_e ($A \sim 55°$) are in agreement with those expected: $J = 8$ Hz and $J < 2$ Hz, respectively.

EXPERIMENTAL

Unless otherwise stated m.ps were determined on a Kofler microscope and are uncorrected.

UV spectra have been recorded with a Pye-Unicam Spectrophotometer, SP 500, and the IR with Perkin-Elmer Spectrophotometers, Model 457 and 257.

The NMR spectra have been recorded with a Perkin-Elmer Spectrometer, Model R-12. Finally, mass spectra have been obtained on a AEI MS 902S Spectrometer at 70 eV (only peaks higher than 5% are reported).

Reaction of methant(tri-α-diazoacetone) with acids

(A) *Anhydrous methanesulfonic acid*: 1,3,5 - *tri(mesyloxymethyl)* - 2,4,9 - *trioxaadamantane*, 3 (X = MsO). A soln of methane(tri - α - diazoacetone)[12] (535 mg; 2 mmol) in 20 ml CH_2Cl_2 was added dropwise to a magnetically stirred soln of methanesulfonic acid (0.53 ml; 8.1 mmol) in 10 ml Ch_2Cl_2. After stirring for a further 12 hr, the mixture was neutralized with $NaHCO_3$ aq, the organic layer separated, dried and concentrated under vacuum. The oily residue was dissolved in chloroform and, after a few days, the soln afforded 40 mg (4.6% yield) of 1,3,5-tri(mesyloxymethyl) - 2,4,9 - trioxaadamantane, m.p. 173–175° (from acetone); IR (KBr), 1375, 1355, 1175, 1155, 1095, 1015 and 845 cm^{-1}; NMR (C_5D_5N), τ 5.63 (s) (6H), 6.69 (s) (9H), 7.85 (m, $J \sim 2.7$ Hz) (1H) and 8.04 (d, $J \sim 2.7$ Hz) (6H) (Found: C, 33.76; H, 4.86; S, 20.28. $C_{13}H_{22}O_{12}S_3$ requires: C, 33.47; H, 4.75; S, 20.62).

(B) *Aqueous hydrochloric acid*: 1,3,5 - *tri(chloromethyl)* - 2,4,9 - *trioxaadamantane*, 3 (X = Cl). As in Ref. 1, 70% yield of 1,3,5 - tri(chloromethyl) - 2,4,9 - trioxaadamantane, m.p. 105–106° (capillary); IR (CH_2Cl_2), 1325, 1260, 1220, 1110, 1075, 1000, 950, 900 and 740 cm $^{-1}$; NMR ($CDCl_3$), τ 6.57 (s) (6H), 7.3 (m, $J \sim 3.3$ Hz) (1H) and 7.98 (d, $J \sim 3.3$ Hz) (6H).

(C) *Aqueous hydrobromic acid*: 1,3,5 - *tri(bromomethyl)* - 2,4,9 - *trioxaadamantane*, 3 (X = Br). As in Ref. 1, 71.2% yield of 1,3,5 - tri(bromomethyl) - 2,4,9 - trioxaadamantane, m.p. 128–129° (capillary); IR (KBr), 1320, 1270, 1245, 1205, 1090, 1055, 990, 900 and 880 cm^{-1}; NMR ($CDCl_3$), τ 6.70 (s) (6H), 7.37 (m, $J \sim 3.3$ Hz) (1H) and 8.01 (d, $J \sim 3.3$ Hz) (6H).

(D) *Aqueous methanesulfonic acid*: 1,3,5 - *tri(hydroxymethyl* - 2,4,9 - *trioxaadamantane*, 3 (X = OH). To a magnetically stirred soln of methanesulfonic acid (1 ml) in 20 ml water were added, in small portions, methane(tri - α - diazoacetone) (520 mg). After stirring for a further 12 hr, the mixture was neutralized with $NaHCO_3$, saturated with NaCl and the soln continuously extracted with CH_2Cl_2 for 72 hr. The organic soln was dried and evaporated to dryness to give an oily residue that afforded 50 mg (10.8% yield) of 1,3,5 - tri(hydroxymethyl) - 2,4,9 - trioxaadamantane, m.p. 114° dec. (sealed capillary), when treated with acetone; IR (KBr), 3340, 3280, 1095, 1055 and 1015 cm^{-1}; NMR (C_5H_5N), τ 6.09 (s) (6H), 7.5 (m, $J \sim 3.3$ Hz) (1H) and 7.74 (d, $J \sim 3.3$ Hz) (6H) (Found: C, 51.46; H, 6.89. $C_{10}H_{16}O_6$ requires: C, 51.71; H, 6.94%).

(E) *Aqueous perchloric acid*: 1,3,5 - *tri(hydroxymethyl)* - 2,4,9 - *trioxaadamantane*, 3 (X = OH). Working as described in (D), the same product was isolated in 13% yield.

Reaction of methane(tri - α - diazoacetone) with acids in the presence of HMPT

(A') *Anhydrous methanesulfonic acid*: *methane(tri - mesyloxyacetone)*, 2 (X = MsO). A soln of methane(tri - α - diazoacetone) (445 mg; 1.6 mmol) in 20 ml anhyd THF was added dropwise to a magnetically stirred soln of methanesulfonic acid (0.33 ml; 4.8 mmol) in 10 ml anhyd. THF, containing 0.89 ml (4.8 mmol) of HMPT. After stirring for a further 2 hr, the mixture was filtered through a column packed with Dowex 50W × 8, 50–100 mesh, previously swollen with water. The resulting heterogenous mixture was treated with CH_2Cl_2, the organic layer dried and concentrated under vacuum. The residue, dissolved in chloroform, afforded 116–147 mg (15–19% yield) of methane(trimesyloxyacetone), m.p. 118–120°; IR (KBr), 1735, 1370, 1345, 1175, 1020, 1010, 1000 and 985 cm^{-1}; NMR (*d*-DMSO), τ 5.15 (s) (6H), 6.82 (s) (9H) and 7.44 (interference with solvent) (Found: C, 33.76; H, 4.86; S, 20.28. $C_{13}H_{22}O_{12}S_3$ requires: C, 33.47; H, 4.75; S, 20.62%).

(B') *Aqueous hydrochloric acid*: *methane(tri-chloroacetone)*, 2 (X = Cl). A soln of methane(tri - α - diazoacetone) (500 mg; 1.9 mmol) in 10 ml THF was added dropwise to a magnetically stirred soln of 32% HCl aq (0.56 ml; 5.7 mmol; density 1.16) in 25 ml THF, containing 1 ml (5.7 mmol) of HMPT. After stirring for a further 12 hr, the mixture was treated as described above (A') to give a solid residue, which was recrystallized from MeOH affording 432 mg (81% yield) of methane(tri-chloroacetone), m.p. 85°; IR (CH_2Cl_2), 1720 cm $^{-1}$; NMR ($CDCl_3$), τ 5.97 (s) (6H) and 7.22 (d) (7H) (Found: C, 41.88; H, 4.54; Cl, 37.33. $C_{10}H_{13}O_3Cl_3$ requires: C, 41.76; H, 4.55; Cl, 37.04%).

(C') *Aqueous hydrobromic acid*: *methane(tri-bromoacetone)*, 2 (X = Br). Operating as described above (A'), from methane(tri - α - diazoacetone) (500 mg; 1.9 mmol) 40% HBr (0.84 ml; 5.7 mmol; density 1.38) and 1 ml (5.7 mmol) of HMPT, were obtained 485 mg (60.5% yield) of methane(tri-bromoacetone), m.p. 70–71° (from chloroform); IR (CH_2Cl_2), 1740 and 1725 cm^{-1}; NMR ($CDCl_3$), τ 6.17 (s) (6H) and 7.2 (*pseudo*singlet) (7H) (Found: C, 28.95; H, 3.08; Br, 54.04. $C_{10}H_{13}O_3Br_3$ requires: C, 28.53; H, 3.09; Br, 56.95%).

Acid-induced intramolecular cyclization of methane(tri-acetones) to 2,4,9-trioxaadamantanes, 3 (X = Cl, Br, MsO)

A soln of 10 mg of $HC(CH_2–CO–CH_2X)_3$ (X = Cl, Br, MsO) in 5 ml DME, containing catalytic amounts of *p*-toluenesulfonic acid, was heated under reflux for 48 hr. The solvent was removed under vacuum and the residue identified as the corresponding trioxaadamantane by IR and NMR spectroscopy. In all the cases the isomerization proceeds in quantitative yields.

Base-induced intramolecular cyclization of methane(tri-chloroacetone) to 1 - hydroxymethyl-tetracyclo-[3.3.1.0^{2,8}.0^{4,6}]nona - 3,7 - dione, 4

To a magnetically stirred soln of t-BuOK in t-BuOH (from 224 mg of K and 5 ml t-BuOH) was added dropwise, in a 4 hr period, a soln of methane(tri-chloroacetone) (500 mg; 1.74 mmol) in 100 ml anhyd THF. After stirring for a further 12 hr, the mixture was poured 0.2 M H_2SO_4 (25 ml), the organic solvents eliminated under vacuum, the aqueous soln saturated with NaCl and then continuously extracted with ether for 4-5 days. The oily residue from the ether soln (286 mg) was dissolved in CH_2Cl_2, adsorbed on silica (28 g) and eluted with CH_2Cl_2: MeOH mixtures (100:0 to

95:5),[b] to give 242 mg (78% yield)[c] of **4** which, after purification by TLC on silica and elution with CH_2Cl_2:MeOH 95:5, gave m.p. 107–108°; UV (CH_3OH), λ_{max} 274 (ϵ = 225); IR (KBr), 3350, 3250, 3080, 3060 and 1695 (sh), 1680, 1653; NMR ($CDCl_3$), τ 6.38 (s) (2H), 7.0 (broad s)(1H), 7.50 and 7.63 (*pseudo*doublet) (7H) (Found: C, 67.68; H, 5.40. $C_{10}H_{10}O_3$ requires: C, 67.41; H, 5.66%).

MS: 178 (23.3) (M^+), 149 (8.3), 148 (18.3), 147 (100), 135 (5.8), 132 (10), 131 (15), 121 (14.1), 121.4 (m*), 120 (20.8), 119 (32.5), 107 (9.1), 105 (7.9), 104 (13.3), 103 (19.1), 95 (7.5), 93 (6.6), 92 (7.5), 91 (50), 81 (7.5), 79 (18.3), 78 (15.8), 77 (16.6), 71 (5), 69 (5.8), 68 (6.6), 67 (7), 66 (6.6), 65 (17.5), 63 (6.6), 57 (9.1), 55 (15.8), 53 (11.6), 52 (6.6), 51 (11.6), 50 (5.4), 44 (10.8), 43 (6.6), 41 (15.8), 40 (6.25), 39 (30), 31 (91.6), 30 (7), 28 (8.3).

Acetate, m.p. 99–101°; IR (KBr), 1730, 1680 and 1250 cm^{-1}; NMR ($CDCl_3$), τ 6.0 (S) (2H), 7.4–7.8 (complex m) (7H), 7.95 (s) (3H) (Found: C, 65.50; H, 5.72. $C_{12}H_{12}O_4$ requires: C, 65.45; H, 5.49).

MS: 220 (14.1) (M^+), 178 (5.4), 161 (11.8), 160 (82.2), 149 (5.9), 148 (6.5), 147 (12.7), 133 (10.6), 132 (35.7), 131 (30), 119 (7.3), 105 (16.2), 104 (36.2), 103 (14.4), 91 (20.4), 79 (9.5), 78 (20.3), 77 (14.6), 65 (10.4), 55 (17.4), 53 (13.5), 44 (6.8), 43 (100), 41 (6.2), 40 (5.7), 39 (23.4), 32 (45), 29 (5.3).

Mesylate, m.p. 143–145° (capillary); IR (KBr), 1680, 1345 and 1175 cm^{-1}; NMR ($CDCl_3$), τ 5.90 (s) (2H), 6.95 (s) (3H), 7.3–7.7 (broad d) (7H) (Found: C, 51.33; H, 4.45; S, 12.12. $C_{11}H_{12}O_5S$ requires: C, 51.44; H, 4.71; S, 12.49).

1 - *Chloromethyl-tetracyclo*[3.3.1.$0^{2,8}$.$0^{4,6}$]*nona* - 3,7 - *dione* (prepared with PCl_5 in ether), m.p. 120–122° (capillary); IR (KBr), 1680 and 710 cm^{-1}; NMR ($CDCl_3$), τ 6.5 (s) (2H), 7.42 (d, J ~ 1.3 Hz) (2H) and 7.62 (broad s) (5H) (Found: C, 61.01; H, 4.60; Cl, 17.71. $C_{10}H_9O_2Cl$ requires: C, 61.08; H, 4.61; Cl, 18.03).

MS: 198 (14.1), 196 (43.3) (M^+), 168 (11), 162 (10.9), 161 (100), 160 (7.7), 149 (6.9), 148 (5.4), 147 (48.1), 134 (6.6), 133 (62.1), 132 (6), 131 (7.6), 119 (23.7), 105 (41.6), 104 (10.1), 103 (17.3), 91 (36.3), 82 (11.3), 81 (7), 79 (28.5), 78 (17.7), 77 (26.2), 68 (5.1), 65 (13.4), 63 (7.5), 57 (6.2), 55 (43.5), 53 (16.1), 52 (15.5), 51 (33.7), 50 (10.6), 43 (12.1), 41 (6), 40 (7), 39 (34.2), 36 (7.6), 32 (31.2).

[b] Eventually, the methylene dichloride fractions afforded a few mg of 1,3,5 - tri(chloromethyl) - 2,4,9 - trioxaadamantane.

[c] 46% yield with sodium methoxide in methanol.

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