Robinson-Mannich Annelation of Cyclohexane-1,3-dione

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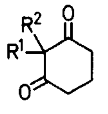
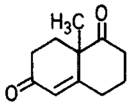
Recent observations by Patterson and Reusch[1] prompt us to report other aspects of the above annelation reaction. When cyclohexane-1,3-dione (**1a**) was submitted to reaction with an equivalent amount of 1-diethylamino-3-butanone in refluxing benzene in the presence of pyridine and the mixture worked up by acidification [conditions under which the bicyclic ketone **2** is obtained[2] in good yield from 2-methylcyclohexane-1,3-dione (**1b**)], β(2-methyl-7-oxo-3,4,4a,5,6,7-hexahydronaphthalene-1)-propanoic acid (**3**) is obtained in 45–50% yield (based on **1a**). When 2 equivalents of 1-dimethylamino-3-butanone are used, the yield of **3** is increased to 90–95%. The same acid (**3**) resulted from the alkaline cleavage of bis-adduct **1d** obtained earlier by Nazarov and Zavyalov[3] (by 1,4-addition of **1a** to butenone in the presence of sodium carbonate), or by simply refluxing compound **1d** with diethylamine in benzene.



1a $R^1 = R^2 = H$
b $R^1 = H$; $R^2 = CH_3$
c $R^1 = H$; $R^2 = -CH_2-CH_2-\overset{O}{\overset{\|}{C}}-CH_3$
d $R^1 = R^2 = -CH_2-CH_2-\overset{O}{\overset{\|}{C}}-CH_3$



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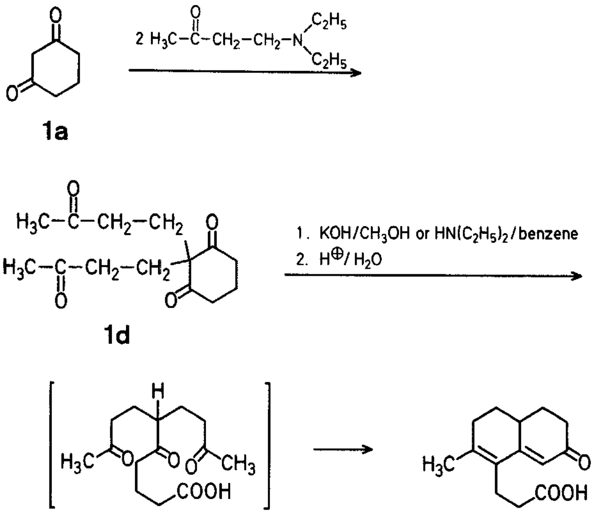


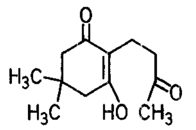
1a

1d

3

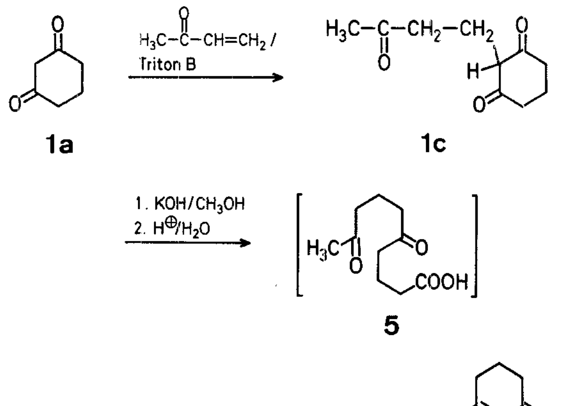
The structure of **3** was confirmed by analytical and spectral data. Compound **3** is probably formed by ring cleavage of the bis-adduct **1d**, followed by cyclodehydration involving apparently enamines at some stage cf. Ref.[4]).

The fact that acid **3** is the major product formed whether one or two equivalents of Mannich base are used implies that the initially formed monoadduct **1c** is more readily annelated than the dione **1a**. The annelation of dimedone under the same conditions gives only the monoadduct[7] which exists as **4** as evidenced by spectrometrical data.

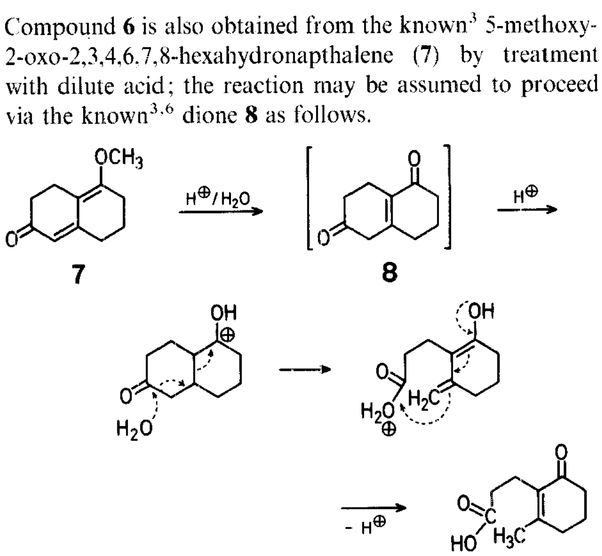


4

When the annelation of **1a** was carried out with butenone in the presence of Triton-B, the product surprisingly was a different acid β(2-methyl-6-oxocyclohexene-1)-propanoic acid, **6**); in addition, minor amounts of the mono-adduct **1c** were obtained. Acid **6** has earlier been synthesized[5] via alkylation of ethyl 1-methyl-3-oxocyclohex-1-ene-6-carboxylate with ethyl 2-bromopropanoate. In the above reaction it is probably formed by cleavage of the primary addition product **1c**; compound **1c** can also be prepared using different conditions and was found to undergo conversion into **6** upon treatment with either base or acid, probably via **5**.



Compound **6** is also obtained from the known[3] 5-methoxy-2-oxo-2,3,4,6,7,8-hexahydronapthalene (**7**) by treatment with dilute acid; the reaction may be assumed to proceed via the known[3,6] dione **8** as follows.



β(2-Methyl-7-oxo-3,4,4a,5,6,7-hexahydronaphthalene-1)-propanoic Acid (3):

A mixture of cyclohexane-1,3-dione (**1a**; 5.6 g, 0.05 mol), 1-diethylamino-3-butanone (7 g, 0.05 mol), pyridine (6 ml), and benzene (50 ml) was refluxed for 18 hr. The reaction mixture was cooled, washed with dilute hydrochloric acid, water, and saturated sodium chloride solution, dried, and freed from solvent. The resultant crude yellow solid (6 g) was recrystallized from aqueous methanol to give colorless crystals; yield: 5 g; m.p. 163–164°.

$C_{14}H_{18}O_3$	calc.	C 71.8	H 7.7
(234.3)	found	71.9	H 8.0

I.R. (KBr): ν_{max} = 1725, 1620, 1600 cm^{-1}.

U.V. (ethanol): λ_{max} = 297 nm (ε = 24000).

^{1}H-N.M.R. (CDCl$_3$): δ = 1.95 (s, 7H, 4- and 5-CH$_2$—, CH$_3$), 2.2–2.6 (m, 9H, other —CH$_2$—, 4a-CH), 6.1 (s, 1H, 8-CH), 10.9 (s, 1H, COOH).

^{1}H-N.M.R. (pyridine): δ = 1.82 ppm (s, 3H).

Mass Spectrum: m/e = 234 (M$^+$, intensity: 90%).

Semicarbazone: m.p. 205–207° (from ethanol).

$C_{15}H_{21}O_3N_3 \cdot C_2H_5OH$	calc.	C 60.5	H 8.07
(337.4)	found	60.9	7.90

U.V. (ethanol): λ_{max} = 303 nm (ε = 19580).

When 2 equivalents of 1-diethylamino-3-butanone were used, the yield of **3** was 11 g.

Compound **3** was also obtained in 60% yield by heating 2,2-bis-[3-oxobutyl]-1,3-dioxocyclohexane (**1d**) with methanolic potassium hydroxide or with diethylamine in benzene, and subsequent treatment with acid to remove basic material.

β(2-Methyl-6-oxocyclohexene-1)-propanoic Acid (6):

Method A; from Cyclohexane-1,3-dione (**1a**): A mixture of **1a** (7.8 g, 0.07 mol), butenone (4.9 g, 0.07 mol), methanol (30 ml), and methanolic Triton-B (0.8 ml, 40%) was refluxed for 7 hr. The solvent was then removed, the residue treated with aqueous sodium hydrogen carbonate, and extracted with ether to remove neutral material. The aqueous layer was cooled, acidified with dilute hydrochloric acid, and extracted with ether. The extract was evaporated and the residual pale yellow solid (6 g) recrystallized from petroleum ether to give pale-yellow needles; yield: 5.0 g (40%); m.p. 93–95°.

$C_{10}H_{14}O_3$	calc.	C 65.9	H 7.7
(182.2)	found	65.6	8.0

I.R. (CHCl$_3$): ν_{max} = 1695, 1613 cm^{-1}.

^{1}H-N.M.R. (CDCl$_3$): δ = 1.92 (s, 3H, CH$_3$), 2.26 (m, 10H, CH$_2$), 7.6 ppm (s, 1H, COOH).

Mass Spectrum: m/e = 182 (M$^+$, intensity: 26%).

The compound was identical (I.R., m.p., and mixture m.p.) with a sample prepared by the method of Ref.[5].

Method B; from 1,3-Dioxo-2-(3-oxobutyl)-cyclohexane (**1c**): A mixture of compound **1c** (1.82 g) and a 10% solution (20 ml) of potassium hydroxide in methanol was refluxed on the water bath for 2 hr. The solvent was removed under reduced pressure and the residue taken up in water. The mixture was extracted with ether, the aqueous phase acidified with dilute hydrochloric acid, extracted with ether, and the extract dried with magnesium sulfate. Uopn removal of solvent, the product crystallized; yield: 1 g.

Method C; from 5-Methoxy-2-oxo-2,3,4,6,7,8-hexahydronaphthalene (**7**): To a solution of compound **7** (4.5 g) in ether (15 ml), 3% hydrochloric acid (15 ml) was added and the mixture stirred at room temperature for 3 hr. The organic layer was separated and worked up as above; yield: 3 g (60%).

5,5-Dimethyl-1,3-dioxo-2-(3-oxobutyl)-cyclohexane (4):

Compound **4** was obtained from 5,5-dimethylcyclohexane-1,3-dione (5.0 g, 0.04 mol) and 1-dimethylamino-3-butanone (5.0 g, 0.04 mol) following the method used for the preparation of compound **3**; yield of **4**: 6.0 g (60%); m.p. 93°.

I.R. (CHCl$_3$): ν_{max} = 3670 and 3600 (OH), 1697 and 1610 cm^{-1} (C=O).

U.V. (ethanol): λ_{max} = 263 nm (ε = 13960).

^{1}H-N.M.R. (CDCl$_3$): δ = 1.0 (s, 6H, *gem*-di-CH$_3$), 1.5 (s, enolic OH), 2.1 (s, 3H, —CO—CH$_3$), 2.1–2.8 ppm (m, 8H, —CH$_2$—).

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