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THE STRUCTURE OF THE PRODUCTS WHEN α-BROMOACETOARENONES REACT WITH 3-(*N,N*-DIMETHYLAMINO)PROPAN-1-OL.

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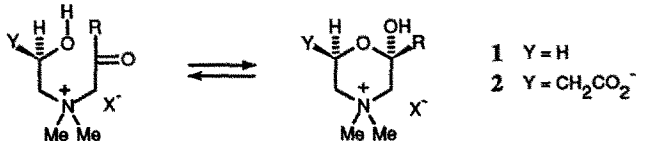
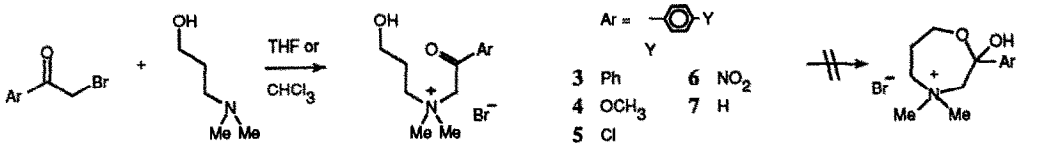
Abstract. 3-(*N,N*-Dimethylamino)propan-1-ol readily reacts at room temperature with aryl α-bromoacetophenones to form *N*-(3-hydroxypropyl)-*N,N*-dimethyl-*N*-[2-oxo-2-arylethyl]ammonium bromides in yields up to 89%. Contrary to a previous report (*J. Med. Chem.* **1966**, *9*, 211-213), the seven-membered ring hemiketal is not formed. An X-ray structure of the 4-phenylphenyl compound shows the open form.

Hemiketal morpholinium (hemicholiniums), **1**, salts show potent biological activity.[1] Our recent kinetic studies[2] of three aryl derivatives have quantified the dynamic ring-chain tautomerism that others had demonstrated over fifty years ago.[3] We have used this ring as a template in the design of carnitine acyltransferases inhibitors, **2**.[4]



A report[5] of the analogous seven-membered ring (hemiketal 1,4-oxazepinium) prompted us to reexamine this chemistry to design potential enzyme inhibitors and to measure the equilibrium between the open and closed forms. Unfortunately, we found no evidence of the closed form.



3-(*N,N*-Dimethylamino)propan-1-ol readily reacts at room temperature with aryl α-bromoacetophenones

to form *N*-(3-hydroxypropyl)-*N*,*N*-dimethyl-*N*-[2-oxo-2-arylethyl]ammonium bromides, **3** - **7**, in yields up to 89%.[6,7] Contrary to the previous report, we find no evidence for the seven-membered ring. All IR spectra contain strong carbonyl stretching absorptions (1682-1701 cm^{-1}). All ^{13}C NMR spectra have resonances for carbonyl carbons (189.6-191.6 ppm) but no resonances for hemiketal carbons (94.4-94.6 ppm). All ^{1}H NMR spectra have singlets at 5.3-5.4 ppm for a methylene between a quaternary ammonium ion and a carbonyl and no pair of doublets at 3.2-3.7 ppm for methylene between a quaternary carbon and a hemiketal carbon. We have determined the crystal structures of **3**-**7**; all are open forms, e.g., **3**.[8] (Figure 1)

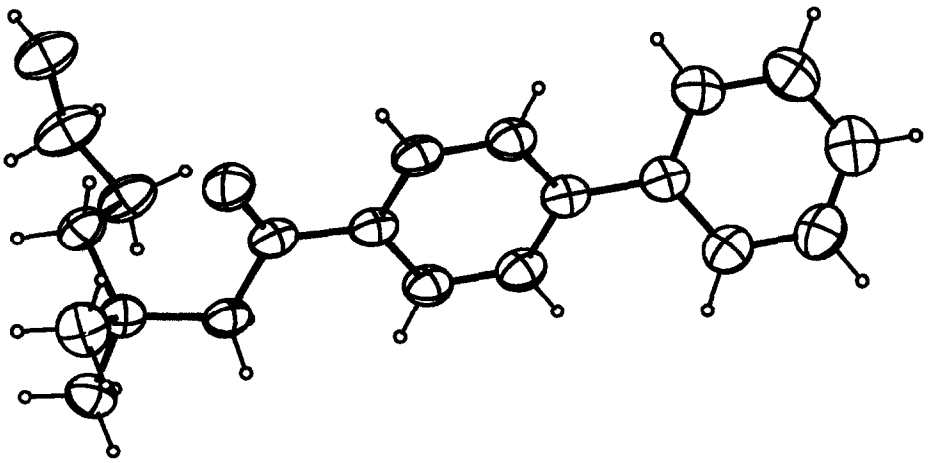


Figure 1. X-ray crystal structure of *N*-(3-hydroxypropyl)-*N*,*N*-dimethyl-*N*-[2-oxo-2-(4-phenylphenyl)ethyl]ammonium bromide, **3**; bromide omitted.

In the previous study,[5] they claimed for **3** and Y = OH, "The proposed structures were confirmed by the absence of carbonyl absorption . . ." The experimental section contained no spectroscopic data. They also contrasted their results with an earlier speculation[9] that a seven-membered ring would not form in similar compounds. In our hands, preparation of **3** by their procedure or our modification gave the same product. We preferred the modification because of milder conditions, shorter reaction times, and the improved yields.

We find no evidence of ring formation, even for the most favorable case, **6**. Our kinetic study suggests that electron withdrawing groups on the aryl ring strongly favor the cyclic structure in the equilibrium. We support the original speculation[9] that seven-membered rings are unfavorable. We can only conclude that the claim for a 1,4-oxazepinium hemiketal suffered by the lack of today's rapid and powerful methods for structure elucidation.

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6. **General Procedure:** A solution of the α-bromo 4-substituted (Ph, 0.52 g, 2 mmol; OCH_3, 0.2 g, 1 mmol; Cl, 0.27 g, 1 mmol; NO_2, 0.17 g, 1 mmol; and H, 0.2 g, 1 mmol) acetophenones (prepared by the procedure of Langley) in freshly distilled dry THF (3 mL) was dropwise added to a solution of 3-(*N,N*-dimethylamino)propan-1-ol (Ph, 0.22 mL, 2 mmol; OCH_3, 0.12 mL, 1 mmol; Cl, 0.14 mL, 1 mmol; NO_2, 0.13 mL, 1 mmol; H, 0.12 mL, 1 mmol) in freshly distilled dry THF (3 mL) at 25°C. A white solid precipitates during the first 0.5 to 1 min of stirring, separated by filtration and washed with cold THF. The white solid thus obtained is recrystallized from *i*-PrOH:THF (1:1) (**1** and **5**); from benzene:*i*-PrOH (1:1) (**2**), from methanol (**3**), and from benzene:*i*-PrOH:methanol (1:1:1) (**4**). Melting points are uncorrected. IR spectra were recorded as thin layer on a KBr pellet. ^1H NMR and ^{13}C NMR spectra were determined in DMSO-d_6 at 200 MHz.

N-(3-Hydroxypropyl)-N,N-dimethyl-N-[2-oxo-2-(4-phenylphenyl)ethyl]ammoniumBromide (**3**) (0.64 g, 89%) mp 174-175 °C (lit.[5] mp 168-170 °C); ^1H NMR: 8.10 (d, 2H), 7.91 (d, 2H), 7.80-7.76 (m, 2H), 7.56-7.44 (m, 3H), 5.43 (s, 2H), 4.81 (t, 1H), 3.76-3.68 (m, 2H), 3.52-3.44 (m, 2H), 3.33 (s,

6H), 1.93-1.88 (m, 2H); ^{13}C NMR: 191.0, 145.9, 138.4, 133.1, 129.1, 128.8, 128.7, 127.0, 65.0, 63.0, 57.6, 51.3, 25.5; IR: 3352, 3016, 2947, 2884, 1692, 1602 cm^{-1}. Anal. Calcd. for $C_{19}H_{24}BrNO_2$: C 60.32, H 6.39, N 3.70. Found: C 59.99, H 6.37, N 3.68.

N-(3-Hydroxypropyl)-N,N-dimethyl-N-[2-oxo-2-(4-methoxyphenyl)ethyl]ammoniumBromide (4) (0.23 g, 70%) mp 194-195 °C; ^{1}H NMR: 7.98 (d, 2H), 7.12 (d, 2H), 5.26 (s, 2H), 4.79 (t, 1H), 3.86 (t, 3H), 3.71-3.62 (m, 2H), 3.47-3.42 (m, 2H), 3.28 (s, 6H), 1.90-1.87 (m, 2H); ^{13}C NMR 189.6, 164.3, 130.6, 127.2, 114.2, 64.6, 62.9, 57.6, 55.8, 51.3, 25.5; IR: 3389, 3014, 2927, 2882, 1680, 1605 cm^{-1}. Anal. Calcd. for $C_{14}H_{22}BrNO_3$: C 50.60, H 6.69, N 4.22. Found: C 50.86, H 6.73, N 4.32.

N-(3-Hydroxypropyl)-N,N-dimethyl-N-[2-oxo-2-(4-chlorophenyl)ethyl]ammonium Bromide (5) (0.30 g, 74%) mp 191-193 °C; ^{1}H NMR 8.02 (d, 2H), 7.70 (d, 2H), 5.34 (s, 2H), 4.80 (t, 1H), 3.71-3.62 (m, 2H), 3.49-3.44 (m, 2H), 3.28 (s, 6H), 1.91-1.83 (m, 2H); ^{13}C NMR 190.4, 139.6, 133.1, 130.0, 129.1, 65.0, 63.2, 57.6, 51.3, 25.4; IR: 3295, 3092, 2917, 2872, 1695, 1590 cm^{-1}. Anal. Calcd. for $C_{13}H_{19}BrClNO_2$: C 46.37, H 5.70, N 4.16. Found: C 46.55, H 5.46, N 4.96.

N-(3-Hydroxypropyl)-N,N-dimethyl-N-[2-oxo-2-(4-nitrophenyl)ethyl]ammonium Bromide (6) (0.24 g, 62%) mp 174-175 °C; ^{1}H NMR 8.41 (d, 2H), 8.24 (d, 2H), 5.45 (s, 2H), 4.79 (t, 1H), 3.73-3.64 (m, 2H), 3.51-3.43 (m, 2H), 3.31 (s, 6H), 1.94-1.86 (m, 2H); ^{13}C NMR 190.6, 150.6, 138.9, 129.6, 123.9, 65.5, 63.3, 57.6, 51.3, 25.4; IR: 3247 (br), 3046, 2947, 2867, 1701, 1605 cm-1. Anal. Calcd. for $C_{13}H_{19}BrN_2O_4$: C 44.96, H 5.53, N 8.07. Found: C 44.83, H 5.59, N 8.06.

N-(3-Hydroxypropyl)-N,N-dimethyl-N-[2-oxo-2-phenylethyl]ammonium Bromide (7) (0.20 g, 66%) mp 112-114 °C; ^{1}H NMR 8.04-7.99 (m, 2H), 7.74-7.71 (m, 1H), 7.63-7.55 (m, 2H) 5.44 (s, 2H), 4.78 (t, 1H), 3.75-3.66 (m, 2H), 3.50-3.42 (m, 2H), 3.32 (s, 6H), 1.92-1.84 (m, 2H); ^{13}C NMR: 191.5, 134.7, 134.3, 128.9, 128.0, 65.1, 63.0, 57.6, 51.2, 25.5; **IR** 3380 (b), 3060, 2917, 1692, 1597, 1450 cm^{-1}. Anal. Calcd. for $C_{13}H_{20}BrNO_2$: C 51.67, H 6.67, N 4.63. Found: C 51.83, H 6.73, N 4.55.

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8. $C_{19}H_{24}NO_2Br$, FW = 378.3, monoclinic space group $P2_{1/c}$, a = 10.942(2), b = 11.376(1), c = 14.859(1) Å, β = 91.88°, V = 1848.5(6) Å^3, Z = 4, D_c = 1.359 g cm^{-3}, T = 25 °C, μ(CuKα) = 31.0 cm^{-1}, R = 0.037 for 2934 observed data.

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