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Cyclization of 4-Acetyl-1-dialkylamino-1-cyclohexenes to 4-(Dialkylamino)bicyclo[2.2.2]octan-2-ones¹

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An acid-catalyzed cyclization of 4-acetyl-1-dialkylamino-1-cyclohexenes leading to 4-(dialkylamino)bicyclo[2.2.2]octan-2-ones has been reported.

In a previous publication,² we reported an acid-catalyzed cyclization of 4-acetyl-1-methoxy-1-cyclohexene leading to 4-methoxybicyclo[2.2.2]octan-2-one. We would now like to describe a novel cyclization³ of 4-acetyl-1-dialkylamino-1-cyclohexenes leading to 4-(dialkylamino)bicyclo[2.2.2]octan-2-ones.

Reaction of 4-acetyl-4-methyl-1-cyclohexanone (2) with morpholine in boiling benzene afforded 4-acetyl-4-methyl-1-morpholino-1-cyclohexene (5).⁵ Treatment of 5 with a catalytic amount of acetic acid at 180–205° for 7.5 hr gave 1-methyl-4-morpholinobicyclo[2.2.2]octan-2-one (9) in 70% yield. The transformation could be carried out without isolating enamine 5. Thus, a reaction of a toluene solution of 4-acetyl-4-methyl-1-cyclohexanone (2) with morpholine in the presence of *p*-toluenesulfonic acid furnished 9 in 71% yield.

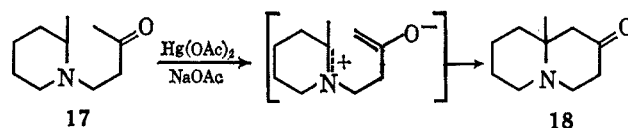
An analogous cyclization was carried out with other secondary amines. Reaction of 4-acetyl-4-methyl-1-cyclohexanone (2) with piperidine in the presence

of an acid catalyst furnished 1-methyl-4-piperidino-bicyclo[2.2.2]octan-2-one (10), and with pyrrolidine 1-methyl-4-pyrrolidinobicyclo[2.2.2]octan-2-one (11). Variations in substituents in the 4 position of the 4-acetyl-1-cyclohexanone structure had little influence on the reaction. Reaction of 4-acetyl-1-cyclohexanone (1) and 4-acetyl-4-phenyl-1-cyclohexanone (3) each with secondary amines such as morpholine, pyrrolidine, or piperidine gave the 4-(dialkylamino)bicyclo[2.2.2]octan-2-ones, respectively. Table I summarizes the physical constants of the 4-(dialkylamino)bicyclo[2.2.2]octan-2-ones (6–13).

Assignments of structures for cyclization products are based on the nmr and infrared spectra (*cf.* Table I). The nmr spectra of cyclization products confirmed the presence of an isolated methylene group α to the carbonyl group, τ 7.50–7.80; a bridgehead hydrogen for compounds 6, 7, and 8, τ 7.75–7.90; a tertiary methyl group for compounds 9, 10, and 11, τ 9.06–9.14; a phenyl group for compounds 12 and 13, τ 2.74–2.75. Infrared spectra of cyclization products confirmed the presence of a carbonyl group (*cf.* Table I).

It appears that cyclization⁶ of 4-acetyl-1-dialkylamino-1-cyclohexenes proceeds *via* iminium ions in a way that is formally analogous to the cyclization² of 4-acetyl-1-methoxy-1-cyclohexene (14) leading to 4-methoxybicyclo[2.2.2]octan-2-one (15). The mechanism involves reaction of an iminium ion and an enolate anion⁸ (*cf.* 16). Reaction of iminium ions are known to undergo rapid attack by a wide variety of nucleophilic agents.¹⁰

(6) The cyclization may be compared with that⁷ of a Mannich base (17) leading to compound 18 in the presence of mercuric acetate and sodium acetate.

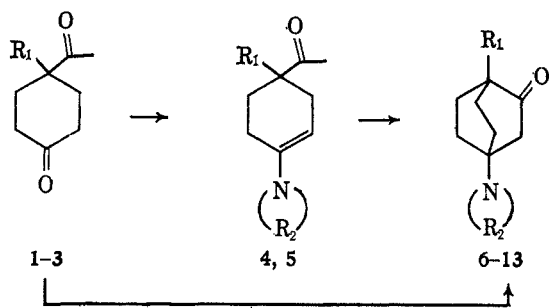


(7) F. Bohlman and O. Schmidt, *Chem. Ber.*, **97**, 1354 (1964).

(8) The mechanism of Mannich reaction presumably involves reaction of an iminium ion derived by a condensation of a carboxyl compound with an amine and an active methylene group.⁹

(9) T. S. Cummings and J. R. Shelton, *J. Org. Chem.*, **25**, 419 (1960). Also see, H. Böhme and H. Ellenberg, *Chem. Ber.*, **92**, 2976 (1959).

(10) The reaction of iminium ion with Grignard reagents, lithium alkyls, and potassium cyanide [N. J. Leonard and A. S. Hay, *J. Am. Chem. Soc.*, **78**, 1984 (1956); R. M. Scribner, *J. Org. Chem.*, **30**, 3203 (1965)], and with 3-bromopropylamine leading to a synthesis of tetrahydropyridine nuclei [R. F. Parcell, *J. Am. Chem. Soc.*, **81**, 2596 (1959); R. D. Parcell and F. P. Hauck, *J. Org. Chem.*, **28**, 3468 (1963)] has been reported.



- 1, R₁ = H
 2, R₁ = CH₃
 3, R₁ = C₆H₅
 4, R₁ = H; R₂ = (CH₂)₂O(CH₂)₂
 5, R₁ = CH₃; R₂ = (CH₂)₂O(CH₂)₂
 6, R₁ = H; R₂ = (CH₂)₂O(CH₂)₂
 7, R₁ = H; R₂ = CH₂(CH₂)₃CH₂
 8, R₁ = H; R₂ = CH₂(CH₂)₂CH₂
 9, R₁ = CH₃; R₂ = (CH₂)₂O(CH₂)₂
 10, R₁ = CH₃; R₂ = CH₂(CH₂)₃CH₂
 11, R₁ = CH₃; R₂ = CH₂(CH₂)₂CH₂
 12, R₁ = C₆H₅; R₂ = (CH₂)₂O(CH₂)₂
 13, R₁ = C₆H₅; R₂ = CH₂(CH₂)₃CH₂

(1) Bridged Ring Compounds. VI. Paper V: K. Morita and Z. Suzuki, *J. Org. Chem.*, **31**, 233 (1966).

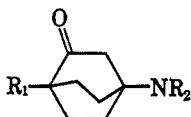
(2) K. Morita and T. Kobayashi, *ibid.*, **31**, 229 (1966).

(3) An acid-catalyzed condensation of an enamine with aldehydes has been reported to furnish α,β -unsaturated aldehydes.⁴

(4) N. V. Volkova and A. A. Yasnikov, *Dokl. Acad. Nauk SSSR*, **149**, 94 (1963).

(5) K. Morita, M. Nishimura, and H. Hirose, *J. Org. Chem.*, **30**, 3011 (1965).

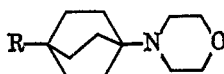
TABLE I
PHYSICAL CONSTANTS OF 4-(DIALKYLAMINO)BICYCLO[2.2.2]OCTAN-2-ONES



Compd	R ₁	R ₂	Mp, °C	Infrared, cm ⁻¹ (ν _{C=O}) ^a	Nmr, τ		Yield, %	Calcd, %			Found, %		
					Methylene α to C=O	Bridgehead		C	H	N	C	H	N
6	H	(CH ₂) ₂ O(CH ₂) ₂	106-107 ^a	1723	7.72	Overlap (H)	82	68.86	9.15	6.69	68.76	9.11	6.52
7	H	CH ₂ (CH ₂) ₃ CH ₂	58-64 ^{b,c}	1731	7.68	7.75 (H)	44	75.31	10.21	6.76	75.56	10.23	6.78
8	H	CH ₂ (CH ₂) ₂ CH ₂	63-65 ^{b,c}	1729	7.80 ^e	7.90 ^e (H)	55	74.57	9.91	7.25	74.85	9.82	7.26
9	CH ₃	(CH ₂) ₂ O(CH ₂) ₂	64-66 ^{c,d}	1729	7.70	9.06 (CH ₃)	71	69.92	9.48	6.27	69.87	9.45	6.26
10	CH ₃	CH ₂ (CH ₂) ₃ CH ₂	68 ^{b,c}	1727	7.80 ^e	9.14 ^e (CH ₃)	90	75.97	10.47	6.33	76.08	10.50	6.34
11	CH ₃	CH ₂ (CH ₂) ₂ CH ₂	56-59 ^c	1726	7.78 ^e	9.13 ^e (CH ₃)	61	75.31	10.21	6.76	75.12	10.16	6.70
12	C ₆ H ₅	(CH ₂) ₂ O(CH ₂) ₂	164-165.5 ^a	1716	7.53	2.74 (C ₆ H ₅)	75	75.75	8.12	4.91	75.56	8.46	5.06
				1725									
13	C ₆ H ₅	CH ₂ (CH ₂) ₃ CH ₂	164-165 ^a	1715	7.50	2.75 (C ₆ H ₅)	62	80.52	8.89	4.94	80.12	8.95	4.92
				1723									

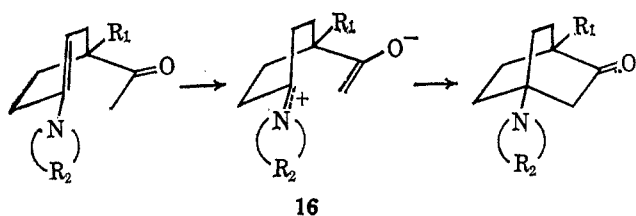
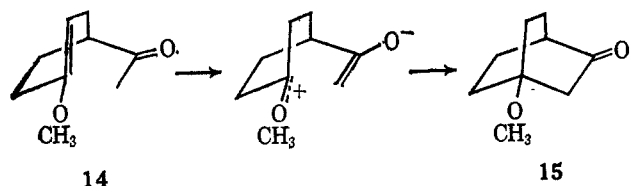
^a Recrystallized from ether. ^b With previous softening. ^c Recrystallized from petroleum ether. ^d Recrystallized from ether-petroleum ether. ^e In carbon tetrachloride.

TABLE II
PHYSICAL CONSTANTS OF 4-(BICYCLO[2.2.2]OCT-1-YL)MORPHOLINES



Compd	R	Mp, °C	Nmr, τ ^a		Formula	Calcd, %			Found, %		
			Methylene in the bicyclic ring	Bridgehead		C	H	N	C	H	N
20	H	78-79	8.47	...	C ₁₂ H ₂₁ NO	73.79	10.84	7.17	73.63	10.88	7.05
21	CH ₃	59.5-61	8.55	9.23 (CH ₃)	C ₁₃ H ₂₃ NO	74.59	11.08	6.69	74.52	11.34	6.70
22	C ₆ H ₅	171-172	8.21	2.80 (C ₆ H ₅)	C ₁₈ H ₂₅ NO	79.66	9.29	5.16	79.50	9.32	5.12
			8.28								

^a In carbon tetrachloride.



Spencer and his associates¹¹ studied the mechanism of an amine-catalyzed¹² intramolecular aldol condensation of 2-methyl-2-(3-oxobutyl)cyclohexane-1,3-dione (19) and predicted the enamine-as-nucleophile mechanism rather than the iminium ion-as-electrophile mechanism.¹⁴

Wolff-Kishner reduction of 4-morpholinobicyclo[2.2.2]octan-2-one (6), of 1-methyl-4-morpholinobicyclo[2.2.2]octan-2-one (9), and of 4-morpholino-1-phenylbicyclo[2.2.2]octan-2-one (12) gave 4-(bicyclo[2.2.2]oct-1-yl)morpholine (20), 4-(4-methylbicyclo[2.2.2]oct-1-yl)morpholine (21), and 4-(4-phenylbicyclo[2.2.2]oct-1-yl)morpholine (22), respectively, in good yields. Table II summarizes physical constants of the resulting amines. Table III lists the pK_a values of 4-(dialkylamino)bicyclo[2.2.2]octan-2-ones and bicyclo[2.2.2]oct-1-ylamines. It was observed that an introduction of an oxo group in the bicyclic

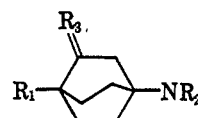
(11) T. A. Spencer, H. S. Neel, T. W. Flechtner, and R. A. Zayle, *Tetrahedron Letters*, No. 43, 3889 (1965).

(12) Amine alone and a mixture¹³ of amine and acetic acid have been used as catalysts for aldol condensation.

(13) Cf. P. Wieland and K. Miescher, *Helv. Chim. Acta*, **33**, 2215 (1950).

(14) Cf. T. I. Crowell and D. W. Peck, *J. Am. Chem. Soc.*, **75**, 1075 (1953).

TABLE III
THE pK_a VALUES OF BICYCLO[2.2.2]OCTYLAMINES^a



Compd	R ₁	R ₂	R ₃	pK _a
6	H	(CH ₂) ₂ O(CH ₂) ₂	O	6.27
7	H	CH ₂ (CH ₂) ₃ CH ₂	O	9.15
8	H	CH ₂ (CH ₂) ₂ CH ₂	O	9.15
9	CH ₃	(CH ₂) ₂ O(CH ₂) ₂	O	6.42
10	CH ₃	CH ₂ (CH ₂) ₃ CH ₂	O	9.13
11	CH ₃	CH ₂ (CH ₂) ₂ CH ₂	O	9.10
12	C ₆ H ₅	(CH ₂) ₂ O(CH ₂) ₂	O	6.09
13	C ₆ H ₅	CH ₂ (CH ₂) ₃ CH ₂	O	8.79
20	H	(CH ₂) ₂ O(CH ₂) ₂	H ₂	8.55
21	CH ₃	(CH ₂) ₃ O(CH ₂) ₂	H ₂	8.50
22	C ₆ H ₅	(CH ₂) ₂ O(CH ₂) ₂	H ₂	7.70

^a Determined by Mr. K. Miura by half-neutralization method in aqueous hydrochloric acid in the presence of potassium chloride. Titration with standard potassium hydroxide was followed with a Metrohm potentiometer Type E336.

[2.2.2]oct-1-yl)morpholine (20), 4-(4-methylbicyclo[2.2.2]oct-1-yl)morpholine (21), and 4-(4-phenylbicyclo[2.2.2]oct-1-yl)morpholine (22), respectively, in good yields. Table II summarizes physical constants of the resulting amines. Table III lists the pK_a values of 4-(dialkylamino)bicyclo[2.2.2]octan-2-ones and bicyclo[2.2.2]oct-1-ylamines. It was observed that an introduction of an oxo group in the bicyclic

TABLE IV
 PHYSICAL CONSTANTS OF BICYCLO[2.2.2]OCTYLAMINE PICRATES

Parent amine	Picrate mp dec, °C	Formula	Calcd, %			Found, %		
			C	H	N	C	H	N
6	207.5–209.0	C ₁₈ H ₂₂ N ₄ O ₉	49.31	5.06	12.78	49.41	4.98	12.54
7	199–200	C ₁₉ H ₂₄ N ₄ O ₈	52.29	5.54	12.84	52.15	5.52	12.55
8	204.5–205.5	C ₁₈ H ₂₂ N ₄ O ₈	51.18	5.25	13.27	51.30	5.32	13.08
9	216–218	C ₁₉ H ₂₄ N ₄ O ₉	50.44	5.35	12.39	50.25	5.41	12.15
10	228–229	C ₂₀ H ₂₆ N ₄ O ₈	53.33	5.82	12.44	53.43	5.81	12.35
11	220	C ₁₉ H ₂₄ N ₄ O ₈	52.29	5.54	12.84	52.01	5.46	12.89
12	228	C ₂₄ H ₂₈ N ₄ O ₉	56.03	5.09	10.89	55.65	5.19	10.73
13	207–208	C ₂₅ H ₂₈ N ₄ O ₈	58.58	5.51	10.93	58.42	5.64	10.85
20	236–237	C ₁₈ H ₂₄ N ₄ O ₈	50.94	5.70	13.20	50.66	5.84	13.10
21	219.5–220	C ₁₉ H ₂₆ N ₄ O ₈	52.05	5.98	12.78	52.41	6.06	12.74
22	233–236	C ₁₈ H ₂₈ N ₄ O ₈	57.59	5.64	11.20	57.36	5.76	11.06

ring (in the γ position with respect to the nitrogen atom) resulted in a decrease of basic strength of tertiary amines by about 2 p*K*_a units (compare 6 and 20, 9 and 21, and also 12 and 22) and of phenyl group at the other side of a bridgehead position resulted in a slight decrease of basic strength of tertiary amines (compare 6 and 12, 7 and 13, and 20 and 22). The base-weakening effect exerted by a carbonyl and a phenyl group can be associated with their electron-withdrawing inductive effects. Transmission of substituent effects in a bicyclo[2.2.2]octane system has been studied.¹⁵

Experimental Section¹⁶

4-Acetyl-4-methyl-1-morpholino-1-cyclohexene (5).—This material was prepared according to the method already described,⁵ bp 131–132° (1.5 mm), *n*_D²⁰ 1.5070.

Anal. Calcd for C₁₃H₂₁NO₂: C, 69.92; H, 9.48; N, 6.27. Found: C, 69.69; H, 9.43; N, 6.38.

4-Acetyl-1-morpholino-1-cyclohexene (4).—A mixture of 3.0 g (0.021 mole) of 4-acetyl-1-cyclohexanone (1),² 2.0 g (0.023 mole) of morpholine, and 80 ml of benzene was heated at reflux using a Bidwell–Sterling moisture trap to collect water of reaction. After 16 hr the slight excess of the calculated amount of water had collected in the trap. The solvent and excess morpholine were evaporated; the residue was distilled *in vacuo*, giving 3.7 g (87.5%) of monoamine (4), bp 137–138° (2 mm), *n*_D²⁰ 1.5190.

Anal. Calcd for C₁₂H₁₉NO₂: C, 68.86; H, 9.15; N, 6.69. Found: C, 68.42; H, 9.26; N, 6.71.

Cyclization of 4-Acetyl-4-methyl-1-morpholino-1-cyclohexene (5).—Two drops of glacial acetic acid were added to 1.35 g of 4-acetyl-4-methyl-1-morpholino-1-cyclohexene (5) and the mixture was heated at 180–205° for 7.5 hr. After cooling, the reaction mixture was absorbed on a column containing 7 g of alumina (Sumitomo Kagaku Co., 100 mesh) packed in petroleum ether (bp 35–65°). Elution with 4:1 petroleum ether–ether mixture and recrystallization gave 0.98 g (70.4%) of 1-methyl-4-morpholinobicyclo[2.2.2]octan-2-one (9).¹⁷

General Procedure for Preparation of 1-Substituted 4-(Dialkylamino)bicyclo[2.2.2]octan-2-ones. A. With Acetic Acid.—To a benzene solution of 4-acetyl-1-cyclohexanone (1), 4-acetyl-4-methyl-1-cyclohexanone (2), or 4-acetyl-4-phenyl-1-cy-

clohexanone (3) was added secondary amine and acetic acid, and the mixture was heated at reflux using a Bidwell–Sterling moisture trap to collect water of reaction. After 10 to 16 hr, the slight excess of the calculated amount of water had collected in the trap. After the removal of benzene, the mixture was heated at 130–150° for 3 to 10 hr. After cooling, the mixture was passed through an alumina column. Crystalline material was collected from fractions eluted with 4:1 petroleum ether–ether. Recrystallization gave 4-(dialkylamino)bicyclo[2.2.2]octan-2-ones in yields specified in Table I. Physical constants of the products are recorded in Table I.

In the preparation of 4-piperidinobicyclo[2.2.2]octan-2-one (7), 4-pyrrolidinobicyclo[2.2.2]octan-2-one (8), and 1-methyl-4-pyrrolidinobicyclo[2.2.2]octan-2-one (11), crude products were distilled before alumina chromatography. These exhibited the following boiling points: 7, 125–129° (1.5 mm); 8, 114–117° (1.5 mm); 11, 116–117° (2.0 mm).

B. With *p*-Toluenesulfonic Acid.—A toluene solution of an acetylcyclohexanone derivative and a secondary amine was heated at reflux using a Bidwell–Sterling moisture trap to collect water of reaction. After the slight excess of the calculated amount of water had been collected in the trap, *p*-toluenesulfonic acid was added to the reaction mixture and then heated at reflux for 12–18 hr. The mixture was neutralized with aqueous potassium carbonate and diluted with ether. The extract was dried over potassium carbonate and concentrated. The residue was chromatographed on alumina as described above. Recrystallization from solvent specified in Table I gave 4-(dialkylamino)bicyclo[2.2.2]octan-2-ones in yields specified in Table I.

The Wolff–Kishner Reduction.—A stirred mixture of 1.30 g (0.0062 mole) of 4-morpholinobicyclo[2.2.2]octan-2-one (6), 2.0 g (0.036 mole) of potassium hydroxide, 2.0 g of 80% hydrazine hydrate, and 20 ml diethylene glycol was heated at 100–110° for 1.5 hr. The condenser was then set for downward distillation and the temperature of the bath raised to 180–200°, where it was maintained for 2.5 hr. and a distillate was obtained. The distillate, bp 97–100°, was diluted with 20 ml of water and the mixture was extracted with two 25 ml- portions of ether. The residue of the above distillation was poured into 100 ml of water, and the mixture was extracted with three 70-ml portions of ether. The combined extracts were washed with 30 ml of water, dried over anhydrous sodium carbonate, and concentrated. The residue (1.2 g) exhibited no infrared absorption in the C=O and NH regions. Sublimation followed by recrystallization from petroleum ether (bp 35–60°) gave 1.1 g of 4-(bicyclo[2.2.2]oct-1-yl)morpholine (20), mp 78–79° (*cf.* Table II).

The reduction of 1-methyl-4-morpholinobicyclo[2.2.2]octan-2-one (9) and 4-morpholino-1-phenylbicyclo[2.2.2]octan-2-one (12) was carried out in the same way and there were obtained 4-(4-methylbicyclo[2.2.2]oct-1-yl)morpholine (21) and 4-(4-phenylbicyclo[2.2.2]oct-1-yl)morpholine (22) in 78 and 89% yields, respectively (*cf.* Table II).

Picrates.—To a 1.5% solution of picric acid in ether was added an ether solution of tertiary amines and precipitated crystals were collected and recrystallized from absolute methanol. Physical constants of resulting picrates are given in Table IV.

(15) (a) J. D. Roberts and W. T. Moreland, *J. Am. Chem. Soc.*, **75**, 2167 (1953); (b) H. D. Holtz and L. M. Stock, *ibid.*, **86**, 5188 (1964); (c) C. F. Wilcox, Jr., and J. S. McIntyre, *J. Org. Chem.*, **30**, 777 (1965).

(16) Melting points were obtained on Büchi melting point apparatus and are uncorrected. Nmr spectra were obtained with Varian A-60 instrument using deuteriochloroform, except where specified otherwise, as a solvent and tetramethylsilane as internal standard. Carbonyl frequencies were determined on a Perkin-Elmer Model 125 spectrophotometer and calibrated from internal standard of polystyrene peak at 1603 cm⁻¹.

(17) *Cf.* Table I.