The Mannich Reaction of Alicyclic α-Diketones. A Novel Synthesis of 2-Hydroxy-3-methyl-2-cyclohexen-1-one[1]

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A new synthesis of 2-hydroxy-3-methyl-2-cyclohexen-1-one (**1**) is described. The Mannich reaction of cyclohexane-1,2-dione (**2**) or 2-morpholino-2-cyclohexen-1-one (**3**) with morpholine and formalin gave a Mannich base (**4**), which was then hydrogenolized to afford **1**. However, the Mannich reaction of **1** merely gave a bis-Mannich base (**22**), which was then similarly hydrogenolized to afford 3,6-dimethyl-2-hydroxy-2-cyclohexen-1-one (**7**) along with 3,6-dimethyl-2-hydroxy-6-morpholinomethyl-2-cyclohexen-1-one (**26**); 2-hydroxy-3,6,6-trimethyl-2-cyclohexen-1-one could not be obtained under these conditions. The Mannich reaction of other alicyclic α-diketones and the hydrogenolysis of their Mannich bases are also described.

2-Hydroxy-3-methyl-2-cyclohexen-1-one (**1**) has been known as a flavor constituent in coffee aroma.[2] Previous papers have described several routes to synthesize **1** from 2-ethoxycarbonyl-2-methylcyclohexanone.[3]

In this paper, we will investigate the orientation and reactivities of several alicyclic α-diketones in the Mannich reaction for the synthesis of **1**.

The Mannich reaction of cyclohexane-1,2-dione (**2**),[4] which exists almost entirely in the enolic form[5] with 1 equivalent of both morpholine and formalin in dioxane, afforded 2-hydroxy-3-morpholinomethyl-2-cyclohexen-1-one (**4**) in a good yield.

Furthermore, 2-hydroxy-3,6-bismorpholinomethyl-2-cyclohexen-1-one (**5**) was easily obtained by the treatment of **2** with two equivalents of both morpholine and formalin. On the other hand, the Mannich reaction of cyclopentane-1,2-dione with excess morpholine and formalin in dioxane have been shown to give 2-hydroxy-3-morpholinomethyl-2-cyclopenten-1-one (**6**) as the sole product. This is supposed to be attributable to the significant difference in the solubility of the mono-Mannich bases, **4** and **6**.

The Mannich base **4** was hydrogenolized with zinc powder in glacial acetic acid to give **1** in a 51% yield. Similarly, the Mannich base **5** afforded 3,6-dimethyl-2-hydroxy-2-cyclohexen-1-one (**7**) by a similar hydrogenolysis.

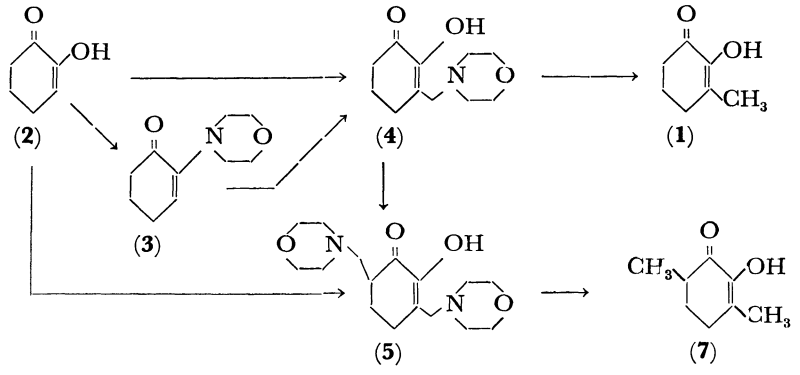
Then we examined the Mannich reaction of 2-morpholino-2-cyclohexen-1-one (**3**). Enaminoketone (**3**) could be obtained by refluxing **1** with morpholine in benzene.

The Mannich reaction of **3** with morpholine and formalin in various solvents, for example, dioxane, ethanol, and isopropyl ether, resulted in recovery of only the starting material. However, **4** was successfully attained in a good yield by the refluxing of **3** with morpholine hydrochloride and with paraformaldehyde in dioxane–ethanol, while no bis-Mannich base (**5**) could be isolated even when **3** was treated with two molar equiv. of both morpholine hydrochloride and paraformaldehyde.

Although no 2-morpholino-3-morpholinomethyl-2-cyclohexen-1-one could be obtained, the above results suggest that the substrate underwent morpholinomethylation in the form of enaminoketone. On the other hand, the Mannich reaction of 2-morpholino-2-cyclopenten-1-one with morpholine and formalin did not afford the corresponding mono-Mannich adduct, but it did readily give the bis-Mannich base.[6]

Enaminoketone may be represented by three principally contributing resonance structures.[7] The Mannich reactions of enaminoketones have revealed an interesting relationship between the product and the ring size, but the detail are uncertain. Cycloalkanones have been shown to give the corresponding Mannich bases by treatment with paraformaldehyde and with secondary amine hydrochloride.[8]

Since **3** is enolizable, it can not easily be determined whether the morpholinomethylation occurs at the enol site or at the enamine site. Therefore, we studied the Mannich reactions of nonenolizable ketons such as 6-ethoxycarbonyl-6-methyl-2-cyclohexen-1-one (**9**).[3]



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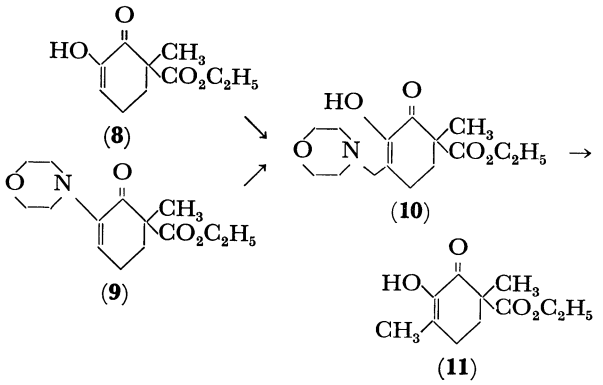
6-Ethoxycarbonyl-2-hydroxy-6-methyl-2-cyclohexen-1-one (**8**) easily reacted with morpholine and formalin in dioxane at room temperature to give a Mannich base (**10**); this base was then hydrogenolized to afford 6-ethoxycarbonyl-2-hydroxy-3,6-dimethyl-2-cyclohexen-1-one (**11**).



Under the same conditions, **9** did not react even when warmed at 55 °C. However, **9** reacted with morpholine hydrochloride and with formalin in dioxane-water at room temperature to form **10**. In this case, however, it is not clear whether the substrate undergoes morpholinomethylation in the form of **9** or **8**, which is formed after the hydrolysis of **9** under the present reaction conditions.[3] At least these results imply that α-diketone is more subject to morpholinomethylation than is enaminoketone.

On the basis of these results, it may be supposed that the Mannich reactions of enolizable enaminoketons proceed *via* electrophilic substitution by morpholinomethylation through the hydrogen-bonded complex between enol and amino nitrogen.[9]

Then we examined the Mannich reactions of 2-hydroxy-3-methyl-2-cycloalken-1-ones. Tonari and his co-workers[10] reported the Mannich reaction of 2-hydroxy-3-methyl-2-cyclopenten-1-one (**12**) to give a mono-Mannich adduct (**14**) in a 30% yield and obtained 2-hydroxy-3,5-dimethyl-2-cyclopenten-1-one by subsequent hydrogenolysis. However, their characterization of the mono-Mannich base was inadequate. Therefore, we reexamined the Mannich reaction of **12** with various secondary amines.

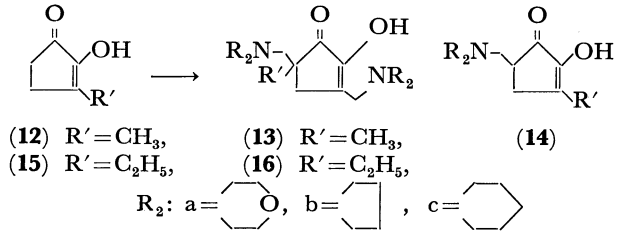
The Mannich reaction of **12** under the conditions previously reported[10] afforded 2-hydroxy-5-methyl-3,5-bismorpholinomethyl-2-cyclopenten-1-one (**13a**) in a 34% yield. The melting point of this crude crystals was compatible with the reported[10] mp of 115—6°C. The structure of **13a** was confirmed by analytical and spectral data, and no mono-adduct (**14**) could be obtained. This reaction was examined with various ratios of reagents; these ratios are shown in Table 1. Moreover, we examined the Mannich reaction of 3-ethyl-2-hydroxy-2-cyclopenten-1-one (**15**) under the various conditions listed in Table 1.

When diketone (**15**) was treated with equimolar amounts of formalin and morpholine in dioxane at room temperature, 5-ethyl-3,5-bis-morpholinomethyl-2-cyclopenten-1-one (**16**) was obtained as the sole product; the best yield was attained with two molar equivalents of both formalin and morpholine.

Table 1. The Mannich reaction of **12** and **15** under various conditions

Formalin (equiv.)	Amine	(equiv.)	Mannich base	Yield[a] (%)
1.0	Morpholine hydrochloride	1.0	**13a**	34.8[b]
1.0	Morpholine	1.0	**13a**	38.4
2.0	Morpholine	2.0	**13a**	70.3
1.0	Pyrrolidine	1.0	**13b**	34.5
2.0	Pyrrolidine	2.0	**13b**	53.6
2.0	Piperidine	2.0	**13c**	90.0
1.0	Morpholine	1.0	**16a**	30.9
2.0	Morpholine	2.0	**16a**	85.3
2.0	Pyrrolidine	2.0	**16b**	40.8
2.0	Piperidine	2.0	**16c**	80.6

a) Yields are based on diketone. b) Procedure by Tonari and coworkers.[10]

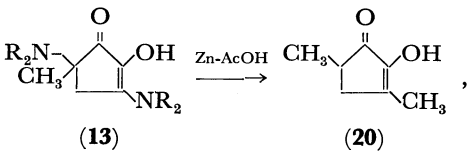


(**12**) R′=CH_3, (**13**) R′=CH_3, (**14**)
(**15**) R′=C_2H_5, (**16**) R′=C_2H_5,
R_2: a=O, b=, c=

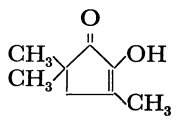
The chemical properties and analytical characterization of **13** and **16** are summarized in Table **2**.

Then we studied the Mannich reactions of 2-cyclopentnones derived from **12**. The Mannich reaction of 2-pyrrolidino-5-methyl-2-cyclopenten-1-one (**17**)[11] with both formalin and pyrrolidine at −10 °C provided the bis-Mannich base (**13b**). However, efforts to introduce an aminomethyl group into such 2-cyclopenteneones with an electron-withdrawing group as 2-acetoxy-3-methyl-2-cyclopenten-1-one (**18**)[12] or 1-methyl-3-oxo-1-cyclopenten-2-yl *p*-toluene sulfonate (**19**) failed.

The hydrogenolysis of the Mannich bases **13a**—**c** with zinc powder in glacial acetic acid at 80 °C for 5 hr was accompanied by deaminomethylation to afford 3,5-dimethyl-2-hydroxy-2-cyclopenten-1-one (**20**); no trimethyl derivative (**21**) could be obtained under these conditions.



(**13**) (**20**)



(**21**)

Then we examined the Mannich reaction of **1**. When **1** was treated with equimolar amounts of both morpholine and formalin, 2-hydroxy-6-methyl-3,6-bis-morpholinomethyl-2-cyclohexen-1-one (**22**) was obtained along with the recovered **1**.

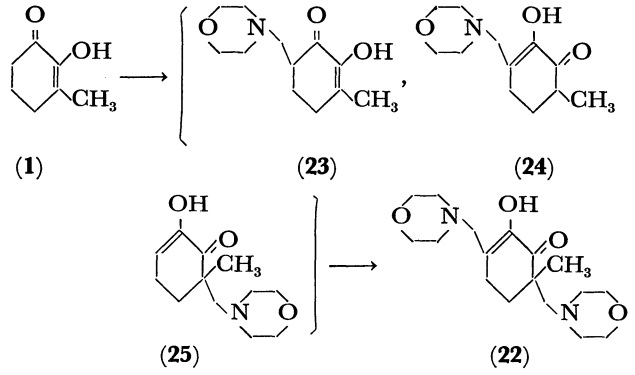
The analytical data of **22** agreed with the $C_{17}H_{28}N_2O_4$

Table 2. Identification of bis-mannich bases

Compd.	mp. (°C)	IR(KBr) (cm^{-1}) O-H	IR(KBr) (cm^{-1}) C=O	IR(KBr) (cm^{-1}) C=C	UV_{max} (EtOH) nm (ε)	NMR ($CDCl_3$) δ_{ppm}[b]	Anal. Found (Calcd) C%	H%	N%
13a	123—123.5[a]	3400 (2600—2300)[c]	1690	1650	262(7100)	1.06(s, 3H), 2.12—2.92 (m, 12H), 3.55—3.90 (m, 10H), 7.71(s, 1H)	62.07 (61.91)	8.56 (8.44)	8.39 (8.63)
13b	110.5—111.5[d]	3380 (2650—2300)[c]	1690	1660	260(6990)	1.11(s, 3H), 1.50—2.05 (m, 8H), 2.09—2.99(m, 12H), 3.55(m, 2H), 7.60 (s, 1H)	69.25 (69.03)	9.42 (9.41)	9.77 (10.06)
13c	135[a]	3400 (2650—2400)[c]	1700	1665	262(10800)	1.05(s, 3H), 1.15—1.93 (m, 12H), 2.09—2.95(m, 12H), 3.38(m, 2H), 8.87 (s, 1H)	70.61 (70.55)	9.85 (9.87)	8.95 (9.14)
16a	157—158[a]	3450 (2650—2450)[c]	1700	1660	265(7880)	0.76(t, 3H, 6.8Hz), 1.30 —1.97(m, 2H), 2.18—2.95 (m, 12H), 3.40—3.94(m, 10H), 7.85(bs, 1H)	63.21 (62.94)	8.66 (8.70)	8.63 (8.63)
16b	113—114[d]	3450 (2650—2350)[c]	1700	1665	265(5980)	0.74(t, 3H, 6.8Hz), 1.34 —2.06(m, 10H), 2.16—3.06 (m, 12H), 3.53(m, 2H), 8.46 (s, 1H)	69.59 (69.83)	9.64 (9.65)	9.33 (9.58)
16c	133—114[a]	3400 (2650—2400)[c]	1700	1660	264(6690)	0.75(t, 3H, 6.8Hz), 1.30 —1.92(m, 14H), 2.05—2.85 (m, 12H), 3.35(m, 2H), 8.43(s, 1H)	71.21 (71.21)	10.16 (10.06)	8.63 (8.74)

a) Recrystallization from ethanol. b) TMS was used as an internal standard. c) Hydrogen-bonded O-H. d) Recrystallization from petroleum ether-ethanol.

formula, and the structure was assigned on the basis of its IR, NMR, and UV spectra. This reaction was run with the various ratios of reagents listed in Table 3; the best yield was obtained with 2 molar equivalents of both morpholine and formaline.



(1) (23) (24)

(25) (22)

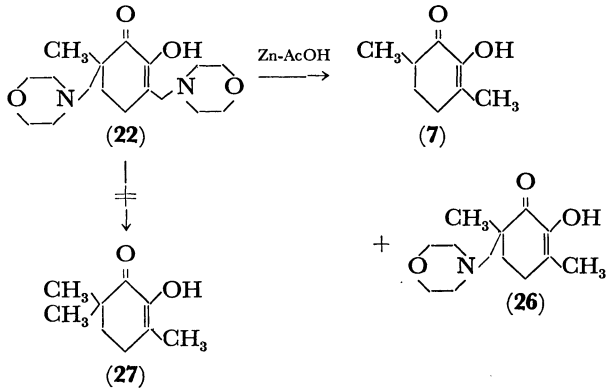
Table 3. The Mannich reaction of **1** under various conditions in dioxane

Morpholine (equiv.)	Formalin (equiv.)	Reaction Temp. (°C)	Reaction Time (hr)	Yield (**22**)[a] (%)
1.0	1.0	27—28 and 55—56	2.5 5.0	40[b]
1.6	1.6	34—35 and 55—56	22.0 3.0	67[b]
2.0	2.0	25—27	60.0	79.2

a) Isolated yield based on diketone. b) Diketone 1 was recovered.

In no case, could any mono Mannich adducts (**23**, **24**, or **25**) be isolated. These results imply that the second morpholinomethylation is faster than the first.

The hydrogenolysis of **22** with zinc powder in acetic acid at 73—76 °C for 6 hr also afforded a demorpholinomethylation product (**7**) (60%) and 2-hydroxy-3,6-dimethyl-6-morpholinomethyl-2-cyclohexen-1-one (**26**) (6.8%). Under these conditions, no trimethyl diketone (**27**) could be isolated.



(22) (7) (26) (27)

On the basis of these facts, it was supposed that the Mannich bases with a tertiary aminomethyl group could easily undergo deaminomethylation[13] in the hydrogenolyses described above.

The NMR spectra of 6-substituted-2-cyclohexenones (**7**, **11**, and **26**) indicate that the allylic methyl protons appear as a doublet (J=0.6 Hz) at 1.83—1.89 ppm. Further work is under way to elucidate the reason for the splitting of these allylic methyl protons.

Experimental

All the melting points are uncorrected. The IR spectra were recorded with a Hitachi Model 215 spectrophotometer, and the UV spectra, with a Hitachi Model EPS-3T spectrophotometer. The NMR spectra were obtained on a JEOL Model C-60H spectrometer, with tetramethylsilane as the internal reference. The mass spectra were determined on a Hitachi RMU-6E spectrometer.

*2-Morpholino-2-cyclohexen-1-one (**3**).* A mixture of 4.6 g (41 mmol) of cyclohexane-1,2-dione, 4.5 g (51 mmol) of morpholine, and 100 ml of benzene was refluxed, while the water was removed, for 5 hr. After the removal of the benzene and the surplus morpholine, the residue was solidified. Recrystallization from isopropyl ether–ethanol gave 6.7 g (90.4%) of **3** as colorless crystals; mp 52.5—53 °C (lit,[14] mp 53—54 °C); IR(KBr) 3050 (=C–H), 1667 (C=O), 1605 cm^{-1} (C=C); NMR (CCl_4) δ *ca.* 1.95 (m, 2H), *ca.* 2.30 (m, 4H), *ca.* 2.70 (m, 4H), *ca.* 3.60 (m, 4H), 5.69 (t, 1H, J=3.9 Hz); UVmax (95% EtOH) 294 nm (ε=2450). Found: C, 66.24; H, 8.24; N, 7.58%. Calcd for $C_{10}H_{15}NO_2$; C, 66.27; H, 8.38; N, 7.73%.

*2-Hydroxy-3-morpholinomethyl-2-cyclohexen-1-one (**4**). A):* To a mixture of 2.80 g (25 mmol) of cyclohexane-1,2-dione in 3 ml of dioxane and 2.18 g (25 mmol) of morpholine, formalin (2.0 g, (25 mmol)) was added drop by drop, at room temperature and the mixture was then stirred for 3 hr. After the removal of the dioxane *in vacuo*, the residue was solidified. Recrystallization from isopropyl ether–ethanol gave 4.6 g (87.1%) of colorless crystals of **4**; mp 72—73 °C; IR(KBr) 3400 (O–H), 1665 (C=O), 1643 cm^{-1} (C=C); NMR (CCl_4) δ *ca.* 1.96 (m, 2H), *ca.* 2.38 (m, 8H), 3.08 (s, 2H), *ca.* 3.55 (m, 4H), *ca.* 5.73 (s, 1H); UVmax (95% EtOH) 274 nm (ε=8670). Found: C, 62.52; H, 8.06; N, 6.55%. Calcd for $C_{11}H_{17}NO_3$: C, 62.54; H, 8.11; N, 6.63%.

B): A mixture of 18.1 g (10 mmol) of **3**, 1.48 g (12 mmol) of morpholine hydrochloride, 0.36 g (4 mmol) of paraformaldehyde in 10 ml of dioxane, and 5 ml of ethanol was stirred for 6 hr under reflux. After cooling, the precipitated morpholine hydrochloride was separated, and the resulting mixture was diluted with ether, washed with water, and dried. After the evaporation of the solvent, trituration with isopropyl ether gave 1.75 g (83%) of **4**.

*2-Hydroxy-3,6-bismorpholinomethyl-2-cyclohexen-1-one (**5**).* To a mixture of 2.80 g (25 mmol) of **2** in 3 ml of dioxane and 5.22 g (60 mmol) of morpholine, formalin (4.8 g, (60 mmol)) in 1 ml of dioxane was added, drop by drop, at room temperature and the mixture was then stirred for 4.5 hr. After the removal of the dioxane *in vacuo*, the residual solid was recrystallized from isopropyl ether–ethanol to afford 6.28 g (85.2%) of **5**: mp 126.5—7.5 °C; IR (KBr) 3320 (O–H), 1672 (C=O), 1641 cm^{-1} (C=C); NMR (CCl_4) δ *ca.* 2.0 (m, 3H), 2.20—2.55 (m, 12H), 2.76 (s, 1H), 3.10 (s, 2H), *ca.* 3.45 (m, 8H); UVmax (95% EtOH) 277 nm (ε=6680). Found: C, 61.83; H, 8.53; N, 9.19%. Calcd for $C_{16}H_{26}N_2O_4$: C, 61.91; H, 8.44; N, 9.03%.

*2-Hydroxy-3-methyl-2-cyclohexen-1-one (**1**).* A mixture of 2.32 g (11 mmol) of **4**, 18.5 ml of glacial acetic acid, and 4.8 g (73 mg-atom) of zinc powder was stirred at 78—80 °C for 5 hr. After the zinc had then been filtered off and the acetic acid had been removed under reduced pressure, a small amount of water was added. The solution was subsequently extracted with chloroform. After drying, the chloroform was removed and the residue was chromatographed on a silica gel column. Elution with benzene–ethyl acetate (10 : 1) yielded 0.71 g (51.4%) of **1**; mp 60.5—61.5 °C (lit, [5] mp 63 °C). The spectral data were identical with those of an authentic sample.[3]

*2-Hydroxy-3,6-dimethyl-2-cyclohexen-1-one (**7**).* A mixture of 3.83 g (13 mmol) of **5**, 30 ml of acetic acid, and 8.45 g (0.13 g-atom) of zinc powder was stirred at 75—76 °C for 5 hr. After the zinc had then been filtered off and the acetic acid had been removed under reduced pressure, a small amount of water was added and the solution was extracted with chloroform. After drying, the solvent was evaporated and the residue was chromatographed on a silica gel column using benzene–ethyl acetate (10 : 1) to give 0.36 g (20%) of **7**; mp 61.5—62.5 °C; IR (KBr) 3420 (O–H), 1675 (C=O), 1650 cm^{-1} (C=C): NMR (CCl_4) δ 1.13 (d, 3H, J=7.0 Hz), 1.83 (d, 3H, J=0.6 Hz), 1.6—2.7 (m, 5H), 5.90 (s, 1H); UVmax (95% EtOH) 273 nm (ε=11900); mass *m/e* (%) 140 (41), 111 (80), 70 (83), 41 (100). Found: C, 68.08; H, 8.91%. Calcd for $C_8H_{12}O_2$: C, 68.55; H, 8.63%.

*6-Ethoxycarbonyl-2-hydroxy-3,6-dimethyl-2-cyclohexen-1-one (**11**). A):* To a mixture of 1.0 g (5 mmol) of **8** in 5 ml of dioxane and 0.40 g (5 mmol) of morpholine, formalin (0.4 g, (5 mmol)) in 1 ml of dioxane was added, at 14—15 °C and the mixture was then stirred for 3 hr. After removal of the dioxane *in vacuo*, we obtained a crude Mannich base (**10**) which was used without further purification for the next step. A mixture of the crude **10**, 18 ml of acetic acid, and 1.64 g (25 mg-atom) of zinc powder was stirred at 72—74 °C for 7 hr. After the zinc had then been filtered off and the acetic acid had been removed under reduced pressure, a small amount of water was added. After extraction with chloroform and drying with magnesium sulfate, the solvent was evaporated and the residue was chromatographed on a silica gel column. Subsequent elution with benzene–ethyl acetate (10 : 1) yielded 0.28 g (26%) of **11**; mp 46—48 °C; IR(KBr) 3440 (O–H), 1715, 1670 (C=O), 1640 cm^{-1} (C=C); NMR ($CDCl_3$) δ 1.22 (t, 3H, J=7.0 Hz), 1.40 (s, 3H), 1.89 (d, 3H, J=0.6 Hz), *ca.* 2.36 (m, 3H), 4.13 (q, 2H, J=7.0 Hz), 5.99 (s, 1H). Found: C, 61.87; H, 7.30%. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60%.

B): A mixture of 1.34 g (5 mmol) of **9**, 5 ml of dioxane, 0.62 g (5 mmol) of morpholine hydrochloride, and 0.40 g (5 mmol) of formalin was stirred at 50—55 °C for 4 hr. After having been worked up, the resulting mixture gave 1.20 g of crude **10**. To this Mannich base, 18 ml of acetic acid and 1.64 g (25 mg-atom) of zinc powder was added, the mixture was then stirred for 7 hr at 75 °C. A subsequent work-up in a manner similar to that described above afforded 266 mg (25%) of **11**.

*The Mannich Reaction of **12** with Secondary Amines: 2-Hydroxy-5-methyl-3,5-bismorpholinomethyl-2-cyclopenten-1-one (**13a**).* To 5.6 g (0.05 mol) of **12** in 50 ml of dioxane and 8.7 g (0.1 mol) of morpholine, a 8.1 g portion (0.1 mol) of formalin was added, drop by drop, at 0 °C. The mixture was then stirred at room temperature for several hours and allowed to stand overnight. After the subsequent removal of the dioxane under reduced pressure, the residue was solidified. Recrystallization from ethanol afforded 10.9 g (70.3%) of **13a**: mp 123—123.5 °C. The results with individual compounds under various conditions are shown in Table 1. The analytical data for **13a**—**c** are presented in Table 2.

*The Mannich Reaction of **15** with Secondary Amines: 5-Ethyl-2-hydroxy-3,5-bismorpholinomethyl-2-cyclopenten-1-one (**16**).* To 2.6 g (21 mmol) of **15** in 20 ml of dioxane and 3.7 g (42 mmol) of morpholine, formalin (3.4 g, (42 mmol)) was added at O °C. The mixture was then stirred at room temperature for several hours and kept overnight. The precipitated solid was recrystallized from ethanol to give 5.8 g (85.3%) of **16a**; mp 157—158 °C. The other results under various conditions are

shown in Table 1, while individual analytical data for **16a—c** are presented in Table 2.

*The Mannich Reaction of **17**: 2-Hydroxy-5-methyl-3,5-bispyrrolidinomethyl-2-cyclopenten-1-one (**13b**).* To 10.0 g (60 mmol) of **17** in 30 ml of dioxane and 8.6 g (0.12 mol) of pyrrolidine, a 9.8 g portion (0.12 mol) of formalin was slowly added, drop by drop at −10 °C, after while the mixture was stirred for 6 hr. The mixture was then stirred for 30 min at room temperature. After the subsequent removal of the solvent *in vacuo*, the resulting solid was recrystallized from petroleum ether–ethanol (10 : 1) to give 7.8 g (45.9%) of **13b**; mp 110.5—111.5 °C.

*1-Methyl-3-oxo-1-cyclopenten-2-yl p-Toluene Sulfonate (**19**).* To a stirred solution of 13.7 g (0.072 mol) of *p*-toluensulfonyl chloride in 4.7 g of pyridine, 6.7 g (0.06 mol) of **12** in 2.4 g of pyridine was added, drop by drop, with ice-water-bath cooling. The mixture was then stirred for 5 hr at 14—15 °C and the resulting mixture was poured into 60 ml of ice water. The precipitated crystals were filtered and recrystallized from petroleum ether–ethanol to afford 8.0 g (50.3%) of **19**; IR (KBr) 1710 (C=O), 1640 (C=C), 1585 cm^{-1} (aromatic (C=C); UVmax (99% EtOH) 229.5 nm (ε=24500); NMR ($CDCl_3$) δ 2.06 (s, 3H), 2.19—2.81 (m, 4H), 7.40 (m, 4H). Found: C, 58.97; H, 5.43%. Calcd for $C_{13}H_{14}O_4S$: C, 58.63; H, 5.30%.

*3,5-Dimethyl-2-hydroxy-2-cyclopenten-1-one (**20**). A)*: A mixture of 31.0 g (0.1 mol) of **13a**, 250 ml of glacial acetic acid, and 65.4 g (1 g-atom) of zinc powder was stirred at 80 °C for 5 hr. After the zinc had then been filtered off and the acetic acid removed *in vacuo*, 30 ml of water was added. The solution was then extracted with chloroform. After drying, the chloroform was evaporated and the residue was recrystallized from water to afford 5.1 g (40.5%) of **20**; mp 91—92.5 °C (lit,[6] mp 91—92 °C); IR (KBr) 3250 (O–H), 1690 (C=O), 1640 cm^{-1} (C=C); NMR ($CDCl_3$) δ 1.14 (d, 3H, J=7.5 Hz), 1.97 (t, 3H, J=0.6 Hz), 2.50 (m, 3H), 6.79 (s, 1H): UV max (99% EtOH) 261 nm (ε=12100). mass *m/e* (%) 126 (100), 111 (42), 83 (38), 79 (44), 56 (51). Found: C, 66.61; H, 8.10%. Calcd for $C_7H_{10}O_2$: C, 66.65; H, 7.99%.

B): Similarly, from 3.5 g (12.6 mmol) of **13b**, 35 ml of acetic acid, and 8.2 g (0.126 g-atom) of zinc powder, 0.50 g (31.4%) of **20** was obtained.

C): Similarly, from 3.10 g (10 mmol) of **13c**, 40 ml of acetic acid, and 6.5 g (0.1 g-atom) of zinc powder, 0.70 g (55.6 %) of **20** was obtained.

*2-Hydroxy-6-methyl-3,6-bismorpholinomethyl-2-cylohexen-1-one (**22**).* To a mixture of 0.60 g (4.75 mmol) of **1** in 3 ml of dioxane and 0.825 g (9.5 mmol) of morpholine, formalin (0.78 g, (9.5 mmol)) in 1 ml of dioxane was added slowly drop by drop at room temperature, and the mixture was stirred for 60 hr. After the removal of the dioxane *in vacuo*, the residue was diluted with a small amount of isopropyl ether to give white crystals. Recrystallization from isopropyl ether–ethanol afforded 1.22 g (79.8%) of **22**; mp 112—113 °C; IR (KBr) 3300 (O–H), 1674 (C=O), 1648 (C=C); NMR ($CDCl_3$) δ 1.05 (s, 3H), 1.6—2.3 (m, 4H), *ca.* 2.45 (m, 10H), 2.77 (s, 1H), *ca.* 3.69 (m, 8H); UVmax (99% EtOH) 274.5 nm (ε=8800). Found: C, 62.96; H, 8.68; N, 9.00%. Calcd for $C_{17}H_{28}N_2O_4$: C, 62.94; H, 8.70; N, 8.63%.

*Hydrogenolysis of **22** in Glacial Acetic Acid with Zinc Powder.* A mixture of 1.20 g (3.7 mmol) of **22**, 9 ml of glacial acetic acid, and 2.0 g (30.6 mg-arom) of zinc powder was stirred at 73—76 °C for 6 hr. After the zinc had then been filtered off and the acetic acid removed *in vacuo*, a small amount of water was added. The solution was then extracted with chloroform. After drying, the solvent was evaporated and the residue was chromatographed on 12 g of silica gel, using a 10 : 1 mixture of benzene–ethyl acetate as the eluent. An early fraction afforded 0.31 g (59.8%) of **7**: mp 61.5—62.5 °C. This compound was identical with the **7** derived from **4** as has been described above.

A later fraction gave 60 mg (6.8%) of **26**; mp 70—72 °C; IR (KBr) 3420 (O–H), 1670 (C=O), 1640 cm^{-1} (C=C); NMR (CCl_4) δ 1.00 (s, 3H), 1.83 (d, 3H, J=0.6 Hz), 1.90—3.0 (m, 10 H), *ca.* 3.49 (m, 4H), *ca.* 5.70 (broad s, 1H); UV_{max} (95% EtOH) 275 nm (ε=11800). Found: C, 65.58; H, 9.13; N, 5.88%. Calcd for $C_{13}H_{21}NO_3$: C, 65.25; H, 8.84; N, 5.85%.

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