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1,6-Dihydro-3(2*H*)-pyridinones. II.[1] Synthesis of 2-Azabicyclo[2.2.2]octanes by the Reaction of *N*-Substituted 1,6-Dihydro-3(2*H*)-pyridinones with 1,3-Dicarbonyl Compounds[2]

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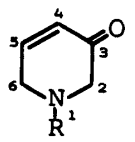
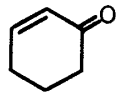
Base-catalyzed reaction of *N*-substituted 1,6-dihydro-3(2*H*)-pyridinones (**1** and **2**) with some 1,3-dicarbonyl compounds (**8a**—**e**) resulted in exclusive formation of the 2-azabicyclo[2.2.2]octan-7-ones (**5** and **6**), while a similar treatment of **1** with dimethyl acetonedicarboxylate (**8f**) gave the 3-azabicyclo[3.3.1]nonan-7-one (**10f**) as a sole product. On deethoxycarbonylation under acidic conditions, the azabicyclooctanecarboxylates (**5a**, **5c**, **6a**, and **6c**) afforded the 3-azabicyclo[3.3.1]nonanes (**13** and **16**) and/or the 2-azabicyclo[2.2.2]octanes (**14**, **15**, **17**, and **18**). On the other hand, ketalization of a mixture of **17** and **18** with ethylene glycol provided the diketal (**23**), which was derived into the monoketone (**24**) upon treatment with 98% formic acid. Haloform reaction of **24** followed by esterification yielded the ester (**26**), which was transformed into the aldehyde (**28**) by sodium borohydride reduction and subsequent PCC oxidation. An acidic hydrolysis of **28** directly furnished the desired 2-azabicyclo[2.2.2]octanone derivative (**7**), a possible synthon for the Iboga alkaloids.

Keywords——dihydropyridinone; Claisen rearrangement; haloform reaction; 1,3-dicarbonyl compound; Michael addition; aldol condensation; deethoxycarbonylation; 2-azabicyclo[2.2.2]octane; 3-azabicyclo[3.3.1]nonane

In the previous papers,[1,3] we reported the first synthesis of *N*-substituted 1,6-dihydro-3(2*H*)-pyridinones (**1** and **2**), which possess many active reaction centers able to undergo electrophilic or nucleophilic reactions for the formation of various carbon–carbon bonds at



1 : R = CO_2Et
2 : R = SO_2Me



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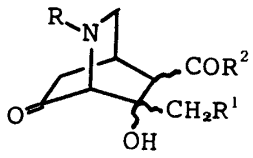

5 : R = CO_2Et
6 : R = SO_2Me

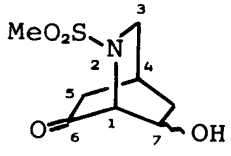

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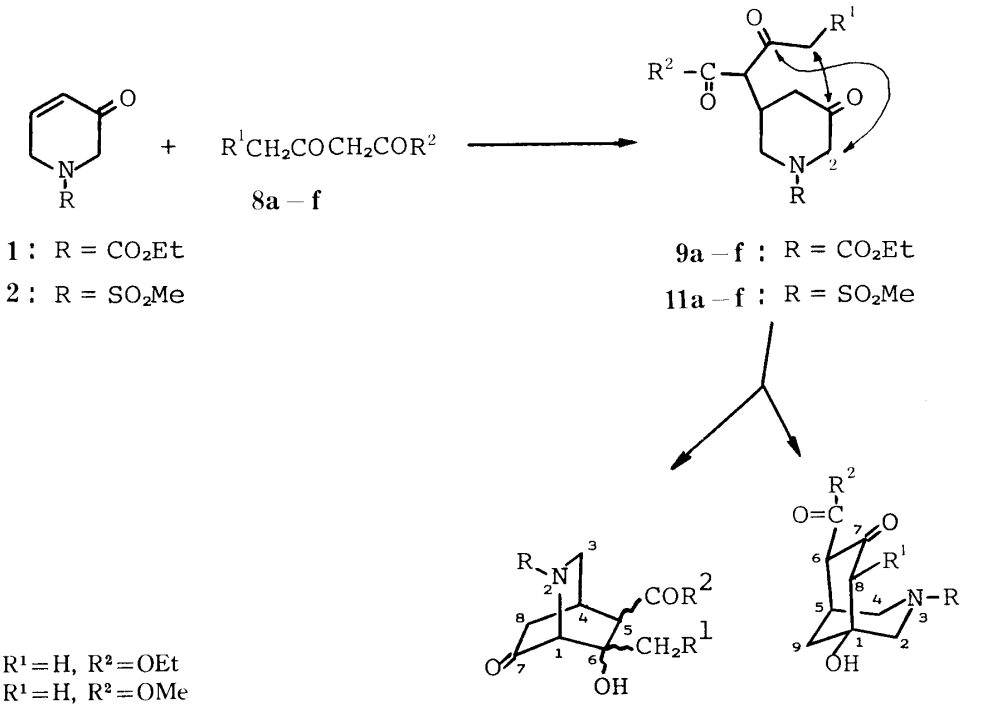
Chart 1

any position of the ring. 2-Cyclohexenone (**3**), the homocyclic analogue of **1**, is well known to give a bicyclo[3.3.1]nonanone compound (**4**) on treatment with ethyl acetoacetate in the presence of base.[4] This result is very interesting in that two carbon–carbon bonds are created by a single operation. This paper describes the reactions of **1** and **2** with some 1,3-dicarbonyl compounds resulting in almost exclusive cyclization to 2-azabicyclo[2.2.2]octanones (**5** and **6**) in contrast with the result using 2-cyclohexenone, and also describes a synthesis of 7-hydroxy-2-methanesulfonyl-2-azabicyclo[2.2.2]octan-6-one (**7**) from **6**.

Reaction of *N*-Substituted 1,6-Dihydro-3(2*H*)-pyridinones (1 and 2) with 1,3-Dicarbonyl Compounds in the Presence of Base

Treatment of ethyl 1,6-dihydro-3(2*H*)-pyridinone-1-carboxylate (**1**) with ethyl acetoacetate (**8a**) in ethanol containing 0.1 equivalent of sodium ethoxide at room temperature provided the labile Michael adduct (**9a**) in 80% yield. On being passed through an alumina column, the adduct (**9a**) easily cyclized to the 2-azabicyclo[2.2.2]octanone (**5a**) instead of the 3-azabicyclo[3.3.1]nonanone (**10a**) in 88% yield. The structure of **5a** was confirmed by the spectral data. Namely, its proton nuclear magnetic resonance (^{1}H-NMR) spectrum exhibited a singlet at 1.56 ppm due to the C_6-methyl protons, and the infrared (IR) spectrum showed a carbonyl band at 1735 cm^{-1} owing to the ester and ketone functions.[5] It is noteworthy that the expected product (**10a**) was not detectable in this reaction. On the other hand, distillation of **5a** under reduced pressure resulted in exclusive transformation into the original Michael adduct (**9a**). Reaction of **1** with methyl acetoacetate (**8b**) under the same condition followed by chromatography on alumina gave also the azabicyclooctanone (**5b**) in 73% yield, and this was also directly obtained by the reaction of **1** with **8b** in the presence of 1 equivalent of sodium ethoxide in a rather low yield (45%).

Similar abnormal cyclizations into the azabicyclo[2.2.2]octanones (**5** and **6**) were observed in the reactions of **1** and **2** with some other 1,3-dicarbonyl compounds (**8a—e**) and can be



a: R^1=H, R^2=OEt
b: R^1=H, R^2=OMe
c: R^1=Me, R^2=OEt
d: R^1=H, R^2=Me
e: R^1=H, R^2=NHPh
f: R^1=CO_2Me, R^2=OMe

Chart 2

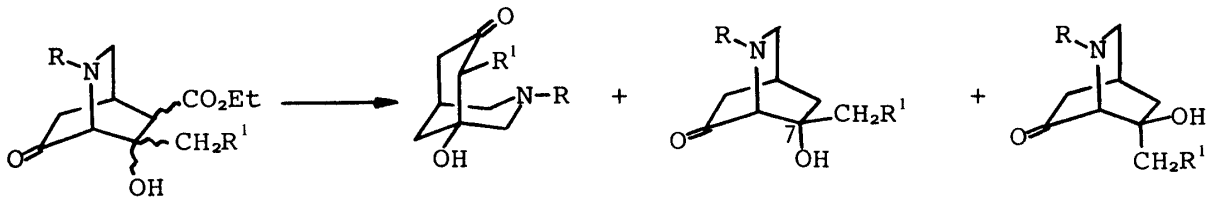
interpreted in terms of high acidity of the C_2-hydrogen in **1** and **2** due to the electron-withdrawing character of the *N*-substituents. In the case of the reaction of **1** with **8a**, the Michael adduct (**9a**), the C_2-proton of which is more acidic than the terminal methyl proton, results in exclusive carbon–carbon bond formation between the ring carbon (C-2) and the methyl ketone carbonyl carbon to afford **5a**. On this basis, it is not surprising that the Michael adduct (**9f**), the C_2-proton of which is less acidic than the methylene proton of the terminal β-keto ester, gives the 3-azabicyclononanone rather than the 2-azabicyclooctanone. In fact, treatment of **1** with **8f** in ethanol in the presence of 0.1 equivalent of sodium ethoxide at room temperature directly afforded the azabicyclononanone (**10f**) in 64% yield, and this was also obtained in 63% yield by the same reaction in the presence of triethylamine instead of sodium ethoxide. The IR spectrum showed a series of absorption bands at 1740, 1690, 1668, and 1621 cm^{-1} characteristic of a enolizable β-keto ester group.[6] The elemental analysis and other spectral features are in good accord with the structure **10f**.

Table I. Base-catalyzed Reaction of *N*-Substituted 1,6-Dihydro-3(2*H*)-pyridinones (**1** and **2**) with 1,3-Dicarbonyl Compounds (**8**)

Substrate	1,3-Dicarbonyl compound	Base	Product (Yield; %)
1	**8a**	NaOEt	**5a** (70)
1	**8b**	NaOEt	**5b** (73)
1	**8c**	NaOEt	**5c** (60)
1	**8d**	NaOEt	**5d** (60)
1	**8e**	NaOEt	**5e** (58)
1	**8f**	NaOEt	**10f** (64)
1	**8f**	Et_3N	**10f** (63)
2	**8a**	NaOEt	**6a** (75)
2	**8c**	NaOEt	**6c** (52)

Deethoxycarbonylation of the 2-Azabicyclo[2.2.2]octanecarboxylates (5a, 5c, 6a, and 6c)

The 2-azabicyclo[2.2.2]octane ring system is of great interest because the ring system constitutes a partial structure of the Iboga alkaloids. Since it is essential to remove the ester group at C_5 in **5c** or **6c** in order to synthesize these alkaloids, we have examined acidic hydrolysis of the carboxylates (**5a**, **5c**, **6a**, and **6c**). Heating of **5a** with 10% hydrochloric acid in acetic acid provided three products, **13a**, **14a**, and **15a**, in 20, 24, and 4% yields, respectively. The stereochemistry in **14a** and **15a** was determined from the fact that the C_7-methyl signal (1.25 ppm) of **15a** appeared at higher field than that (1.35 ppm) of **14a** in the ^1H-nuclear magnetic resonance (NMR) spectra owing to a diamagnetic effect of the C_6-carbonyl group.[7] On the other hand, hydrolysis of **5c** under the same conditions as mentioned above resulted in exclusive formation of the 3-azabicyclo[3.3.1]nonanone derivative (**13c**) in 80% yield. On similar



5: R = CO_2Et
6: R = SO_2Me

13: R = CO_2Et
16: R = SO_2Me

14: R = CO_2Et
17: R = SO_2Me

15: R = CO_2Et
18: R = SO_2Me

a: R^1 = H **c**: R^1 = Me

Chart 3

hydrolysis, the *N*-sulfonamide derivatives (**6a** and **6c**) gave results analogous to those obtained with the *N*-ethoxycarbonyl derivatives (**5a** and **5c**) (Table II).

The above deethoxycarbonylation reaction presumably proceeds as follows: in the case of **5a**, it is initially hydrolyzed to afford the carboxylic acid (**19**), which then undergoes retro-aldol reaction to give **20**, and decarboxylation of the β-keto acid is followed by cyclization to provide **13a**, **14a**, and **15a**. It is surprising that, on deethoxycarboxylation, **5c** or **6c** gave none of the desired 2-azabicyclo[2.2.2]octanone products.[8]

Table II. Deethoxycarbonylation of the 2-Azabicyclo [2.2.2]-octanecarboxylates (**5a**, **5c**, **6a**, and **6c**)[a]

Substrate	Reaction time (h)	Products (Yield; %)		
5a	3	**13a** (20)	**14a** (24)	**15a** (3)
5c	3	**13c** (80)	—	—
6a	3	—	**17a** + **18a** (35)[b]	
6c	1	**16c** (56)	—	—

a) Treatment of the carboxylate with 10% HCl and AcOH under reflux. *b*) Obtained as an inseparable diastereoisomeric mixture.

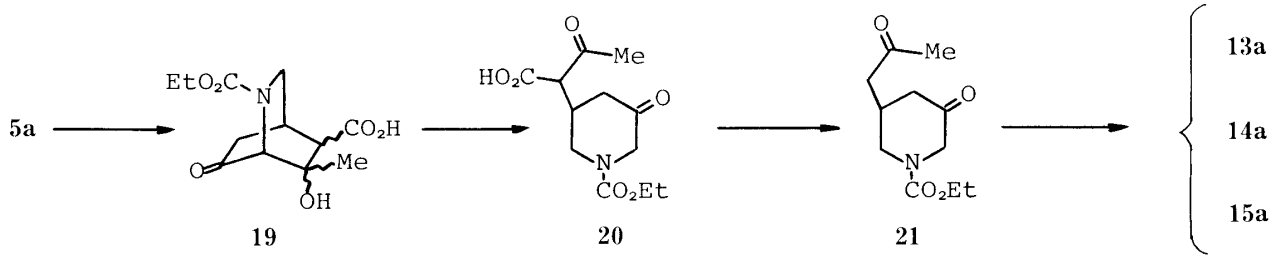
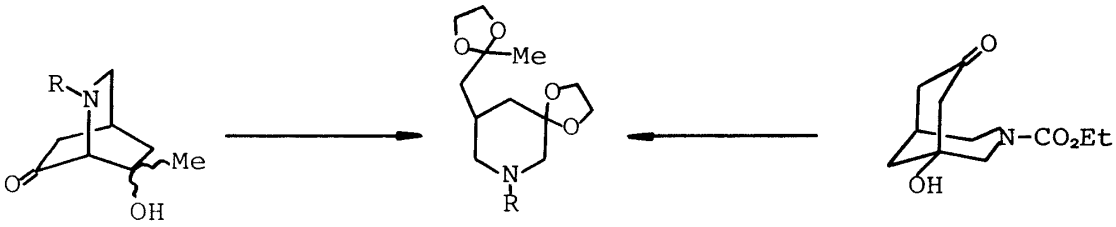


Chart 4

Synthesis of 7-Hydroxy-2-methanesulfonyl-2-azabicyclo[2.2.2]octan-6-one (7)

In the foregoing section, it was shown that acidic hydrolysis of the 2-azabicyclo[2.2.2]-octanecarboxylates (**5c** and **6c**) afforded exclusively the 3-azabicyclo[3.3.1]nonanes (**13c** and **16c**) rather than the 2-azabicyclo[2.2.2]octanes (**14c**+**15c** and **17c**+**18c**), which would be possible key intermediates for the synthesis of Iboga alkaloids. We next attempted to synthesize the title compound (**7**), a potential synthon for the Iboga alkaloids.

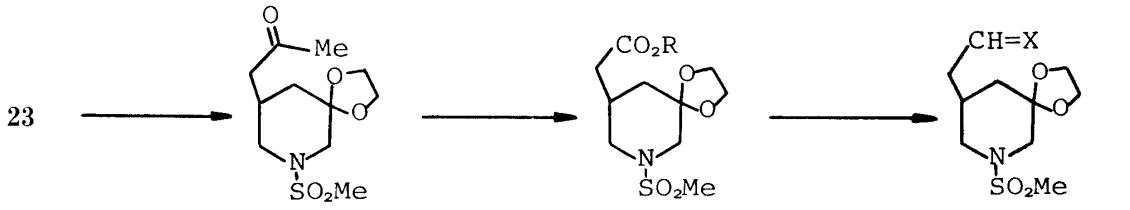
On treatment with ethylene glycol in the presence of *p*-toluenesulfonic acid as a catalyst in boiling benzene, either a mixture of **14a** and **15a** or **13a** gave the same diketal (**22**) in 76 or 50% yield, respectively. On similar treatment, a mixture of **17a** and **18a** afforded the diketal (**23**) in 69% yield. A short reaction of **23** with 98% formic acid provided the monoketone (**24**) in 86% yield; the ^{1}H-NMR spectrum of **24** exhibited a singlet at 2.14 ppm due to the acetyl group. The ketone (**24**) was subjected to haloform reaction in the usual way[9] to afford the carboxylic acid (**25**) in 92% yield. Esterification of **25** with diazomethane was followed by reduction of the ester (**26**) with lithium aluminum hydride in tetrahydrofuran to give the alcohol (**27**) in 77% yield. On oxidation with pyridinium chlorochromate (PCC)[10] in the presence of sodium acetate, the alcohol (**27**) gave the aldehyde (**28**), mp 114—115°C, in 78% yield. Acidic hydrolysis of **28** furnished the desired azabicyclooctanone (**7**) *via* **29** in 72% yield. Its mass spectrum showed a parent peak at *m/e* 219 and the infrared (IR) spectrum showed a hydroxy band at 3400 cm^{-1} and a carbonyl band at 1735 cm^{-1}.[5] The ring system was further confirmed by preparation of the benzoyl derivative (**30**), mp 147—148°C, the ^{1}H-NMR spectrum of which exhibited a doublet (J=4.5 Hz) at 4.26 ppm attributable to the C_1-proton, precluding the possible structural isomer (**31**).



14a, 15a : R = CO_2Et
17a, 18a : R = SO_2Me

22 : R = CO_2Et
23 : R = SO_2Me

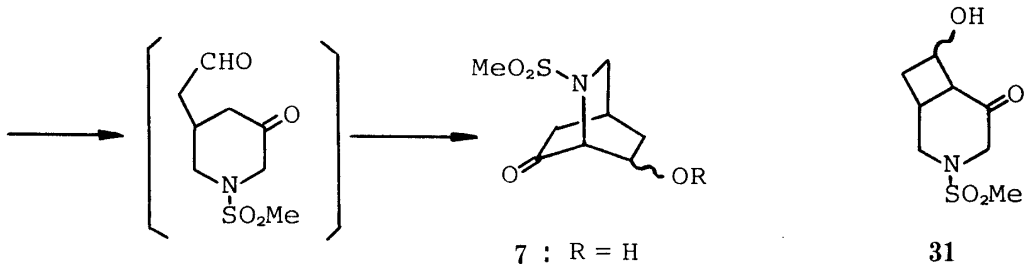
13a



24

25 : R = H
26 : R = Me

27 : X = OH, H
28 : X = O



29

7 : R = H
30 : R = COPh

31

Chart 5

The above synthesis *via* an aldol reaction provides a novel method for construction of the 2-azabicyclo[2.2.2]octane ring system.

Experimental

All melting points are uncorrected. IR spectra were measured with a Hitachi IR-G and a JASCO A-102 spectrometers. Mass spectra (MS) were taken with a Hitachi M-80 mass spectrometer (direct inlet, at 70 eV). ^{1}H-NMR spectra were recorded with a JEOL PMX-60 and FX-100 spectrometers using tetramethylsilane as an internal standard. The following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, ddd=doublet of doublets of doublets, br=broad. All organic extracts were dried over anhydrous sulfate. Column chromatography was carried out with Kieselgel 60 (70—230 mesh, Merck) and Aluminiumoxid 90 (Aktivitätsstufe II-III, 70—230 mesh, Merck).

Ethyl 5-Ethoxycarbonyl-6-hydroxy-6-methyl-7-oxo-2-azabicyclo[2.2.2]octane-2-carboxylate (5a)——Ethyl acetoacetate (**8a**; 90 mg) and 0.2 N ethanolic NaOEt solution (0.35 ml) were added to a stirred solution of **1** (118 mg) in abs. EtOH (2 ml) under a stream of N_2. The reaction mixture was allowed to stand at room temperature for 3 h, then neutralized with AcOH. The solvent was removed *in vacuo* and the residue was taken up in $CHCl_3$ (50 ml). The $CHCl_3$ layer was washed with sat. $NaHCO_3$ and brine, and dried. Evaporation of the solvent left an oily residue, which was chromatographed on silica gel with $CHCl_3$ to afford 167 mg (80%) of ethyl 5-(1-ethoxycarbonyl-2-oxopropyl)-3-oxopiperidine-1-carboxylate (**9a**) as a colorless oil. The product gave a positive $FeCl_3$ test. IR ν_{max}^{film} cm^{-1}: 1725, 1685 (CO). ^{1}H-NMR δ ($CDCl_3$): 2.27 (3H, s, $COCH_3$). The above crude product (92 mg) was chromatographed on alumina with C_6H_6–EtOH (10: 1) to afford 81 mg (88%) of **5a** as an oil. The product gave a negative $FeCl_3$ test. IR ν_{max}^{film} cm^{-1}: 3350 (OH), 1730, 1695,

1680 (CO). ^{1}H-NMR δ ($CDCl_3$): 1.56 (3H, s, C_6–CH_3), 1.76 (1H, s, OH). The tosylhydrazone: mp 209—211°C (from EtOH). *Anal.* Calcd for $C_{21}H_{29}N_3O_7S$: C, 53.95; H, 6.25; N, 8.99. Found: C, 53.88; H, 6.45; N, 8.75.

Ethyl 6-Hydroxy-5-methoxycarbonyl-6-methyl-7-oxo-2-azabicyclo[2.2.2]octane-2-carboxylate (5b)——a) In the Presence of 0.1 eq of NaOEt: A mixture of **1** (240 mg), methyl acetoacetate (**8b**) (165 mg; 1 eq.), 0.2 N ethanolic NaOEt solution (0.7 ml), and abs. EtOH (5 ml) was stirred in a stream of N_2 at room temperature for 3 h. Work-up as usual gave crude **9b** [^{1}H-NMR δ ($CDCl_3$): 2.24 (3H, s, $COCH_3$)], which was chromatographed on alumina with C_6H_6–EtOH (10: 1) to afford 294 mg (73%) of **5b** as a colorless oil. IR ν_{max}^{film} cm^{-1}: 1735, 1700, 1685 (CO). ^{1}H-NMR δ ($CDCl_3$): 1.25 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 1.55 (3H, s, C_6–CH_3), 1.72 (1H, s, OH), 3.74 (3H, s, OCH_3). The tosylhydrazone: mp 209—211°C (from EtOH–acetone). *Anal.* Calcd for $C_{20}H_{27}N_3O_7S$: C, 52.97; H, 6.00; N, 9.27. Found: C, 52.98; H, 6.18; N, 9.27.

b) In the Presence of 1 eq of NaOEt: A mixture of **1** (150 mg), methyl acetoacetate (**8b**) (104 mg; 1 eq), 0.2 N ethanolic NaOEt solution (4.5 ml), and abs. EtOH (5 ml) was stirred in a stream of N_2 at room temperature for 15 min. Work-up as usual followed by chromatography on silica gel with $CHCl_3$ gave 113 mg (45%) of **5b**.

Ethyl 5-Ethoxycarbonyl-6-ethyl-6-hydroxy-7-oxo-2-azabicyclo[2.2.2]octane-2-carboxylate (5c)——A mixture of **1** (750 mg), ethyl 3-oxovalerate[11] (**8c**; 640 mg), 0.2 N ethanolic NaOEt solution (2.2 ml), and abs. EtOH (20 ml) was stirred at room temperature for 2 h. Work-up as usual gave 820 mg (60%) of **5c** as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400 (OH), 1740, 1695 (CO). ^{1}H-NMR δ ($CDCl_3$): 1.00 (3H, t, J=6 Hz, C_6–$CH_2C\underline{H}_3$), 1.25 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 1.30 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 1.76 (2H, q, J=6 Hz, C_6–$C\underline{H}_2$-CH_3). The tosylhydrazone: mp 184—185°C (from EtOH). *Anal.* Calcd for $C_{22}H_{31}N_3O_7S\cdot 1/4H_2O$: C, 54.38; H, 6.53; N, 8.65. Found: C, 54.38; H, 6.43; N, 8.49.

Ethyl 5-Acetyl-6-hydroxy-6-methyl-7-oxo-2-azabicyclo[2.2.2]octane-2-carboxylate (5d)——A mixture of **1** (226 mg), acetylacetone (**8d**; 134 mg), 0.2 N ethanolic NaOEt solution (0.66 ml), and abs. EtOH (5 ml) was stirred at room temperature for 3 h. Work-up as usual gave 215 mg (60%) of **5d** as a colorless oil. IR ν_{max}^{film} cm^{-1}: 1745, 1710, 1680 (CO). ^{1}H-NMR δ ($CDCl_3$): 1.28 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 1.68 (3H, s, C_6–CH_3), 2.30 (3H, s, $COCH_3$). The bistosylhydrazone: mp 202—209°C (from EtOH). *Anal.* Calcd for $C_{27}H_{35}N_5O_7S_2\cdot 1/4H_2O$: C, 52.83; H, 5.83; N, 11.31. Found: C, 53.00; H, 5.84; N, 11.46.

Ethyl 6-Hydroxy-6-methyl-7-oxo-5-phenylcarbamoyl-2-azabicyclo[2.2.2]octane-2-carboxylate (5e)——A mixture of **1** (65 mg), acetoacetanilide (**8e**; 61 mg), 0.2 N ethanolic NaOEt solution (0.2 ml), and abs. EtOH (3 ml) was stirred at room temperature for 3 h. Work-up as usual gave 69 mg (58%) of **5e** as a diastereoisomeric mixture, which was separated by alumina preparative TLC (with C_6H_6–EtOH 10: 1).

The less polar isomer: mp 73—78°C (from hexane). IR ν_{max}^{KBr} cm^{-1}: 1745, 1690, 1635 (CO). ^{1}H-NMR δ ($CDCl_3$): 1.24 (3H, s, C_6–CH_3), 1.24 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 8.56—8.77 (1H, br, NH). The tosylhydrazone: mp 228—229°C (from EtOH). *Anal.* Calcd for $C_{25}H_{30}N_4O_6S$: C, 58.36; H, 5.88; N, 10.89. Found: C, 58.19; H, 6.01; N, 10.59.

The more polar isomer: mp 174—177°C (from C_6H_6). IR ν_{max}^{KBr} cm^{-1}: 1740, 1700—1660 (CO). ^{1}H-NMR δ ($CDCl_3$): 1.24 (3H, t, J=7 Hz, OCH_2CH_3), 1.43 (3H, s, C_6–CH_3), 7.85 (1H, s, NH). *Anal.* Calcd for $C_{18}H_{22}N_2O_5$: C, 62.41; H, 6.40; N, 8.09. Found: C, 62.29; H, 6.40; N, 7.85.

Ethyl 1-Hydroxy-6,8-dimethoxycarbonyl-7-oxo-3-azabicyclo[3.3.1]nonane-3-carboxylate (10f)——a) In the Presence of NaOEt: A mixture of **1** (384 mg), dimethyl acetonedicarboxylate (**8f**; 395 mg), 0.2 N ethanolic NaOEt solution (1.1 ml), and abs. EtOH (7 ml) was stirred at room temperature for 3 h. Work-up as usual gave 497 mg (64%) of **10f** as colorless crystals, mp 110—112°C (from iso-propyl ether). The product gave a positive $FeCl_3$ test. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1740, 1690, 1668 (CO), 1621 (C=C). ^{1}H-NMR δ ($CDCl_3$): 3.79 (3H, s, OCH_3), 3.77 (3H, s, OCH_2), 12.00 (1H, br s, OH). MS *m/e*: 343 (M^+), 195 (base). *Anal.* Calcd for $C_{15}H_{21}NO_8$: C, 52.47; H, 6.17; N, 4.08. Found: C, 52.64; H, 6.21; N, 4.24.

b) In the Presence of Triethylamine: A mixture of **1** (139 mg), dimethyl acetonedicarboxylate (**8f**; 143 mg), Et_3N (0.172 ml), and abs. EtOH (5 ml) was stirred at 85°C for 45 min. Work-up as usual gave 177 mg (63%) of **10f**, which was identical with the sample obtained in a) on the basis of TLC and IR comparisons.

5-Ethoxycarbonyl-6-hydroxy-2-methanesulfonyl-6-methyl-2-azabicyclo[2.2.2]octan-7-one (6a)——A mixture of **2** (347 mg), ethyl acetoacetate (**8a**; 290 mg), 0.2 N ethanolic NaOEt solution (1 ml), and abs. EtOH (10 ml) was stirred at room temperature for 3 h. Work-up as usual gave 453 mg (75%) of **6a** as a colorless oil. IR ν_{max}^{film} cm^{-1}: 3475 (OH), 1735 (CO), 1340, 1160 (SO_2). ^{1}H-NMR δ ($CDCl_3$): 1.30 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 1.67 (3H, s, C_6–CH_3), 2.71 (3H, s, SCH_3), 4.20 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$).

5-Ethoxycarbonyl-6-ethyl-6-hydroxy-2-methanesulfonyl-2-azabicyclo[2.2.2]octan-7-one (6c)——A mixture of **2** (147 mg), ethyl 3-oxovalerate (**8c**; 100 mg), 0.2 N ethanolic NaOEt solution (0.4 ml), and abs. EtOH (10 ml) was stirred at room temperature for 1 h. Work-up as usual gave 140 mg (52%) of **6c** as a colorless oil, which solidified on standing overnight. Recrystallization from ether afforded colorless plates, mp 117—118°C. IR ν_{max}^{KBr} cm^{-1}: 3480 (OH), 1725, 1700 (CO), 1340, 1155 (SO_2). ^{1}H-NMR δ ($CDCl_3$): 1.00 (3H, t, J=7 Hz, C_6–$CH_2C\underline{H}_3$), 1.29 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 2.01 (2H, q, J=7 Hz, C_6–$C\underline{H}_2CH_3$), 2.71 (3H, s, SCH_3), 4.16 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$). *Anal.* Calcd for $C_{13}H_{21}NO_6S$: C, 48.90; H, 6.63; N, 4.39. Found: C, 48.59; H, 6.53; N, 4.62.

Ethyl 1-Hydroxy-7-oxo-3-azabicyclo[3.3.1]nonane-3-carboxylate (13a) and Ethyl 7-Hydroxy-7-methyl-6-oxo-2-azabicyclo[2.2.2]octane-2-carboxylate (14a and 15a)——A mixture of **5a** (1.06 g), 10% HCl (15 ml), and glacial AcOH (15 ml) was heated under reflux for 3 h. The solvent was removed *in vacuo* and the residue was neutralized by addition of aqueous K_2CO_3 solution. The resulting mixture was extracted with $CHCl_3$ (30 ml×3) and the extract was washed with brine and dried. Evaporation of the solvent gave an oily residue, which was chromatographed on alumina with $CHCl_3$–EtOH (50: 1). The first fraction afforded **15a** (20 mg; 3%) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400 (OH), 1735, 1675 (CO). ^{1}H-NMR δ ($CDCl_3$): 1.25 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 1.25 (3H, s, C_7–CH_3), 4.10 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$). MS *m/e*: 227 (M^+). The second fraction afforded **14a** (195 mg; 24%) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400 (OH), 1735, 1675 (CO). ^{1}H-NMR δ ($CDCl_3$): 1.25 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 1.35 (3H, s, C_7–CH_3), 4.08 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$). The tosylhydrazone: mp 184—185°C (from EtOH). *Anal.* Calcd for $C_{18}H_{25}N_3O_5S\cdot 1/4H_2O$: C, 54.06; H, 6.43; N, 10.51. Found: C, 54.31; H, 6.56; N, 10.69. The third fraction afforded **13a** (160 mg; 20%) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3350 (OH), 1680 (CO). ^{1}H-NMR δ ($CDCl_3$): 1.23 (3H, t, J=6 Hz, $OCH_2C\underline{H}_3$), 2.00 (2H, br s, C_9–H), 4.03 (2H, q, J=6 Hz, $OC\underline{H}_2CH_3$). MS *m/e*: 227 (M^+).

Ethyl 1-Hydroxy-8-methyl-7-oxo-3-azabicyclo[3.3.1]nonane-3-carboxylate (13c)——A mixture of **5c** (280 mg), 10% HCl (3 ml), and glacial AcOH (10 ml) was heated under reflux for 3 h. Work-up as usual gave an oily residue, which was chromatographed on alumina with $CHCl_3$ to give 173 mg (80%) of **13c** as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400 (OH), 1710 (CO). ^{1}H-NMR δ ($CDCl_3$): 1.15 (3H, d, J=7 Hz, C_8–CH_3), 1.25 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 4.05 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$).

7-Hydroxy-2-methanesulfonyl-7-methyl-2-azabicyclo[2.2.2]octane-6-one (17a and 18a)——A mixture of **6a** (453 mg), 10% HCl (3 ml), and glacial AcOH (10 ml) was heated under reflux for 3 h. Work-up as usual gave an oily residue, which was chromatographed on silica gel with $CHCl_3$ to give 130 mg (35%) of an inseparable diastereoisomeric mixture of **17a**+**18a** as a solid. Recrystallization from C_6H_6 afforded colorless plates, mp 116.5—117.5°C. IR ν_{max}^{KBr} cm^{-1}: 1720 (CO), 1335, 1150 (SO_2). ^{1}H-NMR δ ($CDCl_3$): 1.23 and 1.46 (1: 2, total 3H, each s, C_7–CH_3), 2.73 and 2.83 (2: 1, total 3H, each s, SCH_3). *Anal.* Calcd for $C_9H_{15}NO_4S$: C, 46.35; H, 6.48; N, 6.01. Found: C, 46.23; H, 6.32; N, 6.21.

1-Hydroxy-3-methanesulfonyl-8-methyl-3-azabicyclo[3.3.1]nonan-7-one (16c)——A mixture of **6c** (140 mg), 10% HCl (2 ml), and glacial AcOH (2 ml) was heated under reflux for 1 h. Work-up as usual gave a crystalline residue, which was recrystallized from C_6H_6–MeOH to give 61 mg (56%) of **16c** as colorless plates, mp 185—186°C. IR ν_{max}^{KBr} cm^{-1}: 3350 (OH), 1675 (CO), 1325, 1155 (SO_2). ^{1}H-NMR δ ($CDCl_3$): 0.93 (3H, d, J=7 Hz, C_8–CH_3), 2.76 (3H, s, SCH_3). *Anal.* Calcd for $C_{10}H_{17}NO_4S$: C, 48.58; H, 6.93; N, 5.67. Found: C, 48.37; H, 6.94; N, 5.84.

Ethyl 9-(2-Ethylenedioxypropyl)-1,4-dioxa-7-azaspiro[4.5]decane-7-carboxylate (22)——a) From Ethyl 7-Hydroxy-7-methyl-6-oxo-2-azabicyclo[2.2.2]octane-2-carboxylate (**14a**+**15a**): A mixture of **14a**+**15a** (630 mg), ethylene glycol (0.7 ml), *p*-TsOH (20 mg), and C_6H_6 (60 ml) was heated under reflux for 1 h while water was removed using a Dean–Stark apparatus. The cooled reaction mixture was washed with sat. $NaHCO_3$ and water, and dried. Evaporation of the solvent left an oily residue, which was chromatographed on alumina with $CHCl_3$ to give 660 mg (76%) of the diketal (**22**) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1680 (CO). ^{1}H-NMR δ ($CDCl_3$): 1.23 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 1.30 (3H, s, $\begin{matrix}O\\O\end{matrix}\!\!>\!\overset{|}{C}\!-\!CH_3$), 3.91 (8H, s, $OCH_2CH_2O\times 2$), 4.10 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$). High resolution MS *m/e*: Calcd for $C_{14}H_{23}NO_6$: 301.1524. Found: 301.1529.

b) From Ethyl 1-Hydroxy-7-oxo-3-azabicyclo[3.3.1]nonane-3-carboxylate (**13a**): A mixture of **13a** (80 mg), ethylene glycol (0.2 ml), *p*-TsOH (trace), and C_6H_6 (20 ml) was heated under reflux for 24 h using a Dean–Stark apparatus. Work-up as usual gave 55 mg (50%) of **22**, which was identical with the above sample on the basis of TLC and IR comparisons.

9-(2-Ethylenedioxypropyl)-7-methanesulfonyl-1,4-dioxa-7-azaspiro[4.5]decane (23)——A mixture of **17a**+**18a** (293 mg), ethylene glycol (0.25 ml), *p*-TsOH (10 mg), and C_6H_6 (30 ml) was heated under reflux for 5.5 h using a Dean–Stark apparatus. Work-up as usual gave an oily residue, which was chromatographed on alumina with C_6H_6 to give 261 mg (69%) of **23** as colorless needles, mp 139—140°C (from EtOH). IR ν_{max}^{KBr} cm^{-1}: 1320, 1145 (SO_2). ^{1}H-NMR δ ($CDCl_3$): 1.30 (3H, s, $\begin{matrix}O\\O\end{matrix}\!\!>\!\overset{|}{C}\!-\!CH_3$), 2.83 (3H, s, SCH_3), 3.88 (4H, s, OCH_2-CH_2O), 3.93 (4H, s, OCH_2CH_2O). *Anal.* Calcd for $C_{13}H_{23}NO_6S$: C, 48.59; H, 7.22; N, 4.36. Found: C, 48.48; H, 7.23; N, 4.41.

7-Methanesulfonyl-9-(2-oxopropyl)-1,4-dioxa-7-azaspiro[4.5]decane (24)——A solution of **23** (153 mg) in 98% HCO_2H (1 ml) was allowed to stand under ice cooling for 3 min. A small amount of ice water was added to the solution and the resulting mixture was neutralized with K_2CO_3 then extracted with $CHCl_3$ (15 ml×2). The extract was washed with brine, dried, and concentrated to give a crystalline solid, which was recrystallized from C_6H_6 to afford 114 mg (86%) of **24** as colorless needles, mp 163—164°C. IR ν_{max}^{KBr} cm^{-1}: 1700 (CO), 1320, 1145 (SO_2). ^{1}H-NMR δ ($CDCl_3$): 2.13 (3H, s, $COCH_3$), 2.94 (3H, s, SCH_3), 3.97 (4H, s, OCH_2CH_2O). *Anal.* Calcd for $C_{11}H_{19}NO_3S$: C, 47.65; H, 6.86; N, 5.05. Found: C, 47.40; H, 6.83; N, 5.19.

7-Methanesulfonyl-1,4-dioxa-7-azaspiro[4.5]decane-9-acetic Acid (25)——A sodium hypobromite solution (1.5 ml) [prepared from 10% NaOH (9 ml) and bromine (0.3 ml) according to the literature][9] was added

dropwise to a stirred solution of **24** (546 mg) in dioxane (30 ml) and water (10 ml) below 10°C. Stirring was continued for 30 min at the same temperature, then the mixture was heated under reflux for 10 min and cooled. The pH of the mixture was adjusted to 8 by addition of conc. HCl and the solvent was removed *in vacuo*. Water (10 ml) was added to the residue and the resulting mixture was washed with ether (10 ml × 2) and acidified with conc. HCl. The aqueous mixture was extracted with AcOEt (15 ml × 5) and the extract was washed with brine and dried. Evaporation of the solvent left 503 mg (92%) of the crude carboxylic acid (**25**), which was used for the next step without further purification. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3650—2400 (CO_2H), 1685 (CO), 1325, 1145 (SO_2).

Methyl 7-Methanesulfonyl-1,4-dioxa-7-azaspiro[4.5]decane-9-acetate (**26**)——An ethereal diazomethane solution (10 ml; *ca.* 3 eq) was added to the carboxylic acid (**25**; 140 mg) and the mixture was allowed to stand at room temperature for 1 h. Evaporation of the solvent *in vacuo* left an oily residue, which was chromatographed on silica gel with $CHCl_3$ to give 113 mg (77%) of the ester (**26**) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1725 (CO), 1325, 1145 (SO_2). ^{1}H-NMR δ ($CDCl_3$): 2.89 (3H, s, SCH_3), 3.66 (3H, s, OCH_3), 3.97 (4H, s, OCH_2-CH_2O).

9-(2-Hydroxyethyl)-7-methanesulfonyl-1,4-dioxa-7-azaspiro[4.5]decane (**27**)——A mixture of **26** (110 mg), $LiAlH_4$ (60 mg), and abs. THF (5 ml) was stirred at room temperature for 1 h. Excess $LiAlH_4$ and the complex were decomposed by addition of aqueous sat. Rochelle salt solution. The inorganic salt was filtered off and washed thoroughly with $CHCl_3$. The combined organic layers were dried and concentrated to leave an oily residue, which was chromatographed on silica gel with $CHCl_3$ to give 77 mg (77%) of **27** as a colorless oil. On standing overnight, the oil solidified. Recrystallization from C_6H_6 afforded colorless plates, mp 102—103°C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400 (OH), 1330, 1145 (SO_2). ^{1}H-NMR δ ($CDCl_3$): 2.85 (3H, s, SCH_3), 3.94 (4H, s, OCH_2CH_2O). *Anal.* Calcd for $C_{10}H_{19}NO_5S$: C, 45.28; H, 7.22; N, 5.28. Found: C, 45.02; H, 7.27; N, 5.57.

7-Methanesulfonyl-9-(2-oxoethyl)-1,4-dioxa-7-azaspiro[4.5]decane (**28**)——PCC (49 mg) and NaOAc (42 mg) were added to a stirred solution of **27** (40 mg) in purified CH_2Cl_2 (2 ml). The mixture was further stirred at room temperature for 3 h and passed through a short column packed with Florisil. The column was washed thoroughly with ether. The combined eluates were concentrated *in vacuo* and the residue was chromatographed on silica gel with $CHCl_3$ to give 31 mg (78%) of **28** as a colorless oil, which solidified on standing overnight. Recrystallization from C_6H_6 afforded colorless needles, mp 114—115°C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2720 (CHO), 1720 (CO), 1330, 1145 (SO_2). ^{1}H-NMR δ ($CDCl_3$): 2.93 (3H, s, SCH_3), 3.99 (4H, s, OCH_2CH_2O), 9.77 (1H, s, CHO). *Anal.* Calcd for $C_{10}H_{17}NO_5S$: C, 45.62; H, 6.51; N, 5.32. Found: C, 45.43; H, 6.37; N, 5.12.

7-Hydroxy-2-methanesulfonyl-2-azabicyclo[2.2.2]octan-6-one (**7**)——A mixture of **28** (30 mg), 10% HCl (1 ml), and acetone (10 ml) was heated under reflux for 16 h. The solvent was removed *in vacuo* and the residue was taken up in $CHCl_3$ (20 ml). The $CHCl_3$ layer was washed with brine, dried, and concentrated to give an oily residue, which was chromatographed on silica gel with $CHCl_3$–EtOH (50: 2) to give 18 mg (72%) of **7** as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400 (OH), 1735 (CO), 1340, 1150 (SO_2). ^{1}H-NMR δ ($CDCl_3$): 2.79 (3H, s, SCH_3), 3.96 (1H, d, J=5 Hz, C_1–H), 4.47 (1H, m, C_7–H). MS *m/e*: 219 (M^+). High resolution MS *m/e*: Calcd for $C_8H_{12}NO_3S$ (M^+-OH): 202.0536. Found: 202.0518.

7-Benzoyloxy-2-methanesulfonyl-2-azabicyclo[2.2.2]octan-6-one (**30**)——A mixture of the alcohol (**7**; 22 mg), benzoyl chloride (30 mg), Et_3N (30 mg), and CH_2Cl_2 (10 ml) was heated under reflux for 12 h. The reaction mixture was washed with 3% HCl, brine, sat. $NaHCO_3$, and brine, and dried. The solvent was evaporated off *in vacuo* and the residue was chromatographed on silica gel with $CHCl_3$ to afford 28 mg (87%) of **30** as colorless needles, mp 147—148°C (from C_6H_6–hexane). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1740, 1715 (CO), 1600, 1580 (aromatic), 1345, 1155 (SO_2). ^{1}H-NMR δ ($CDCl_3$): 2.85 (3H, s, SCH_3), 3.30 and 3.58 (2H, AB-q, J=11 Hz, C_3–H), 4.26 (1H, d, J=4.5 Hz, C_1–H), 5.56 (1H, ddd, J=9, 4.5, 2.5 Hz, C_7–H), 7.4—8.0 (5H, m, Ar–H). MS *m/e*: 323 (M^+), 105 (base). *Anal.* Calcd for $C_{15}H_{17}NO_5S$: C, 55.72; H, 5.30; N, 4.30. Found: C, 55.79; H, 5.34; N, 4.17.

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