Enamine Chemistry. V. Cycloaddition Reactions of Enamines Derived from Alicyclic Ketones

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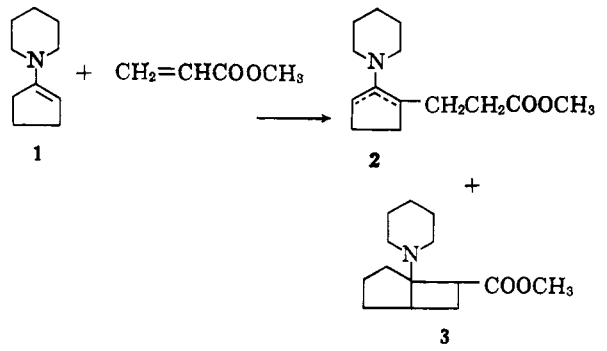
Received August 26, 1963

Enamines derived from alicyclic ketones react with methyl acrylate and diethyl maleate under mild conditions to give unstable cyclobutane derivatives. These cyclobutanes may be stabilized by conversion to the corresponding alcohols. Some further transformations of the cyclobutanes along with related simpler cyclobutanes are discussed.

Cycloaddition reactions of enamines derived from aldehydes and acyclic ketones have been reported.[1] We have found that under the proper conditions the reaction can be extended to include enamines derived from alicyclic ketones. These enamines react under mild conditions with methyl acrylate or diethyl maleate to give cyclobutane adducts which are thermally unstable.

When the cyclopentanone–piperidine enamine (1) and methyl acrylate are allowed to react in acetonitrile without controlling the temperature, the Stork alkylation product[2] (2) is obtained in 68% yield on distillation. When, however, the reaction mixture was maintained below 30°, the undistilled reaction mixture appeared, on the basis of its n.m.r. and infrared spectra, to contain both 2 and the cycloaddition product (3).

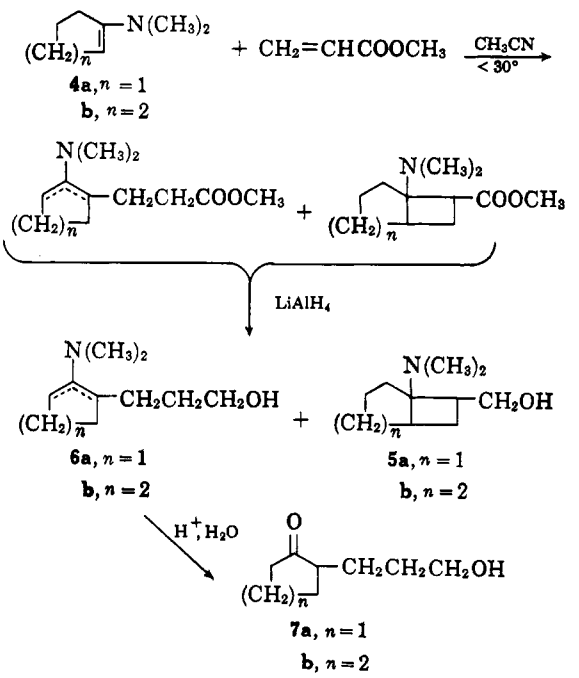


1 2 3

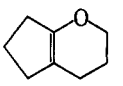
Similar reactions occurred when cyclohexanone enamines were substituted for the cyclopentanone enamine.

In order to demonstrate the presence of cycloaddition products in the enamine–methyl acrylate reaction mixtures, we carried out a sequence of reactions using the dimethylamine enamines of cyclopentanone **4a** and cyclohexanone **4b**.

Crude reaction mixtures from **4a** and **b** with methyl acrylate were stripped of solvent without heating them above 30° and then were subjected to reduction with lithium aluminum hydride under conditions which were shown not to affect the enamine double bond; for example, similar treatment of the cyclohexanone–pyrrolidine enamine gave an 86% recovery of the enamine. This treatment led to a mixture of **5** and **6** from which **5** was separated by means of acid-catalyzed hydrolysis of **6** to the keto alcohol **7**. This sequence afforded **5a** in 15.5% yield and **5b** in 21% yield based on methyl acrylate. The keto alcohol **7a** was converted



largely to pyran derivative **8**; no attempt to isolate **7b** was made.



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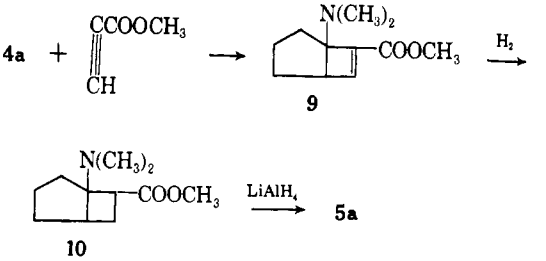
The structures of **5a** and **b** were assigned on the basis of their n.m.r. and infrared spectra as well as the independent synthesis of **5a** *via* another route. The adduct **9** derived from methyl propiolate and **4a**[3] was reduced catalytically at room temperature to the bicycloheptane (**10**) which was converted in 52% over-all yield to **5a** by lithium aluminum hydride.



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On very mild warming, **10**, which showed only a weak absorption in the double bond region, was converted to a mixture which contained the Stork adduct

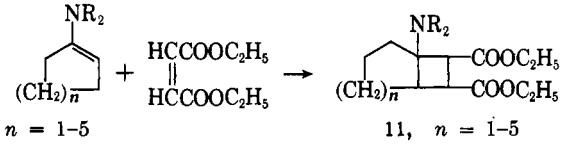
(1) Part IV of this series: K. C. Brannock, A. Bell, R. D. Burpitt, and C. A. Kelly, *J. Org. Chem.*, **29**, 801 (1964).

(2) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Am. Chem. Soc.*, **85**, 207 (1963).

(3) Part VI of this series: K. C. Brannock, R. D. Burpitt, V. W. Goodlett, and J. G. Thweatt, *J. Org. Chem.*, **29**, 818 (1964).

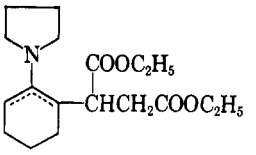
and which gave an infrared spectrum almost identical with that of the crude mixture obtained from **4a** and methyl acrylate.

Diethyl maleate was found to react rapidly and exothermically with a variety of alicyclic ketone enamines in acetonitrile and somewhat less rapidly in the absence of solvent. After the reactions had subsided, the infrared spectra of the reaction mixtures showed virtually no absorption in the double bond region. The reaction products thus appeared to be the cyclobutane adducts (**11**).



n = 1–5 **11**, n = 1–5

Cook has reported[4] the cyclohexanone–pyrrolidine enamine to react with diethyl maleate under more vigorous conditions, that is, refluxing the reactants alone or in a solvent to give the Stork adduct (**12**).



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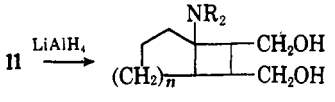
Our adducts (**11**) were, with few exceptions, nondistillable. Even on attempted molecular distillation most of them apparently dissociated into the reactants from which they were prepared, and the reactants recombined in the cold trap to regenerate the adducts (**11**). On heating they were converted more or less rapidly to the Stork products. Indeed, on standing at room temperature for about a year, the cyclopentanone, cyclohexanone, and cycloheptanone enamine adducts (**11**, n = 1, 2, and 3) had been converted largely to the Stork products, as indicated by their infrared spectra. The larger ring compounds (**11**, n = 4 and 5) appeared to be considerably more stable.

The adducts (**11**) could be converted to the stable diols (**13**) by reduction with lithium aluminum hydride.



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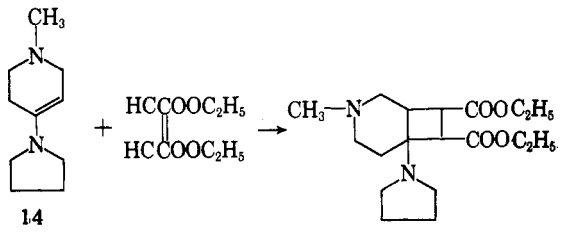
In this case it was not necessary to resort to a hydrolysis step to remove the Stork adduct, since the amount of the latter appeared to be negligible as compared to the methyl acrylate reactions.



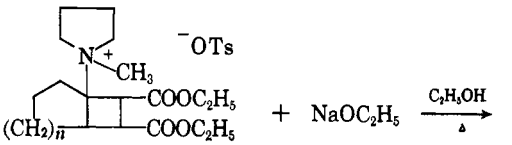
14 **15**

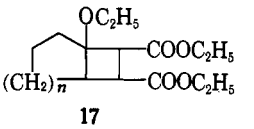
(4) A. G. Cook, Ph.D. thesis, University of Illinois, 1959.

We prepared one cyclobutane derivative (**15**) from an enamine of a heterocyclic ketone (**14**) and diethyl maleate(col. 1, bottom).

Based on spectral data, no cycloaddition occurred when ethyl crotonate was allowed to react with 1-(1-cyclopenten-1-yl)piperidine or 1-(1-cyclohexen-1-yl)-pyrrolidine under mild conditions.

Some Transformations of Cyclobutane Derivatives.—We found that, when the methyl p-toluenesulfonate salt (**16**) of the cyclobutane derivatives (**11**, where n = 1 or 2) were treated with alcoholic sodium ethoxide under reflux, the ethoxy substituted derivatives (**17**) were obtained. These presumably were formed by Hofmann-





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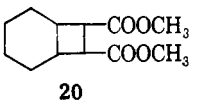
type elimination of the salts to give the bicyclo alkenes, followed by the base-catalyzed addition of alcohol.

Dimethyl bicyclo[4.2.0]oct-8-ene-7,8-dicarboxylate (**19**) was obtained by the treatment of the methyl p-toluenesulfonate salt (**18**) with aqueous sodium hydroxide solution. Hydrogenation of this compound gave the bicyclooctane (**20**), while distillation resulted in a cyclobutene-type rearrangement leading to the unsaturated ester (**21**).



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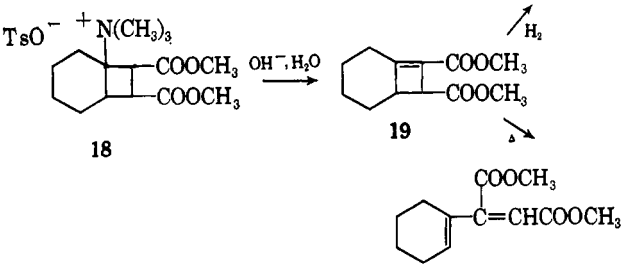
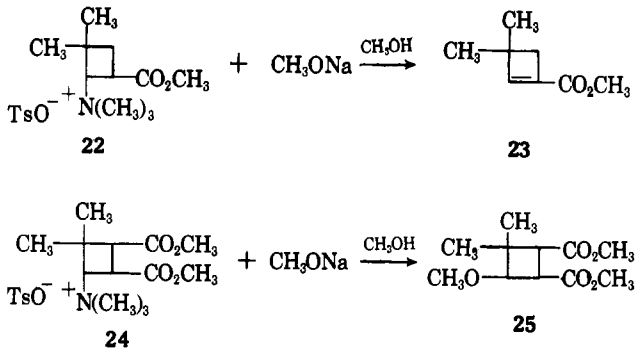


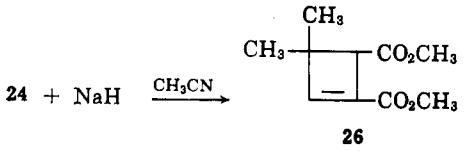
18 **19** **21**

The structures of these products were assigned on the basis of their elemental analyses and their infrared and n.m.r. spectra.

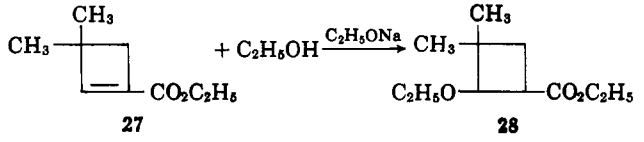
A study of the quaternary salts of simpler model compounds showed marked differences in their behavior. For example, when the methyl tosylate salt of methyl 2-dimethylamino-3,3-dimethyl cyclobutanecarboxylate (**22**) was treated with an equivalent of methanolic sodium methoxide, the elimination product (**23**) was obtained in good yield. In contrast to this result, analogous treatment of the quaternary salt of the corresponding diester (**24**) gave a good yield of dimethyl 3-methoxy-4,4-dimethylcyclobutane-1,2-dicarboxylate.



The cyclobutenedicarboxylate (**26**) could be obtained, however, by treating **24** with an equivalent of sodium hydride in a nonprotonic solvent.



A separate experiment showed that base-catalyzed addition of alcohol to the cyclobutene mono ester (**27**) did take place slowly, with ethyl 2-ethoxy-3,3-dimethylcyclobutanecarboxylate (**28**) being obtained in 40% yield after a reaction time of 18 days.



Experimental[5]

In several cases involving compounds which could not be purified because of their instability, no elemental analyses were obtained. In these cases we relied on n.m.r. and infrared spectral data.

Materials.—All of the enamines used in this investigation were prepared by previously described methods. The following new enamines were prepared.

1-Methyl-4-(1-pyrrolidinyl)-1,2,3,6-tetrahydropyridine was prepared in 70% yield by the method of Heyl and Herr,[6] b.p. 73–75° at 0.2 mm., $n^{20}D$ 1.5230.

Anal. Calcd. for $C_{10}H_{18}N_2$: N, 16.8. Found: N, 16.9.

N,N-Dimethyl-1-cyclohexen-1-ylamine was prepared by the method described for N,N-dimethyl-1-cyclopenten-1-ylamine.[3]

Dimethyl 3-dimethylamino-4,4-dimethylcyclobutane-1,2-dicarboxylate was prepared from dimethyl maleate and N,N-dimethylisobutenylamine as has been described for the diethyl ester.[1] It was obtained in 73% yield with b.p. 84–87° at *ca.* 0.5 mm., $n^{20}D$ 1.4559.

Anal. Calcd. for $C_{12}H_{21}NO_4$: C, 59.3; H, 8.7. Found: C, 59.5; H, 8.6.

Reactions of Alicyclic Ketone Enamines with Electrophilic Olefins. A. 1-(1-Cyclopenten-1-yl)piperidine with Methyl Acrylate.—1-(1-Cyclopenten-1-yl)piperidine (75.5 g., 0.5 mole), methyl acrylate (43 g., 0.5 mole), and acetonitrile (75 ml.) containing a pinch of hydroquinone were combined. An exothermic reaction occurred, and the temperature of the mixture rose to 70° within 11 min. After standing for 5.75 hr. at room temperature, the mixture was distilled to give 80 g. (68%) of methyl 2-piperidino-2-cyclopentene-1-propionate, b.p. 100–104° at *ca.* 0.5 mm., $n^{20}D$ 1.5011. The structure was assigned on the basis of the n.m.r. analysis which showed an olefinic proton resonance, though some of the 1-cyclopentene isomer may have been present.

Anal. Calcd. for $C_{14}H_{23}NO_2$: C, 70.9; H, 9.8. Found: C, 71.1; H, 9.8.

This reaction was repeated, and the temperature of the mixture was maintained below 30° by means of intermittent cooling. After the reaction mixture had stood for 4.5 hr. at room temperature, the solvent was removed by distillation under reduced pressure, keeping the temperature below 30°. The infrared spectrum of the undistilled material was different from the spectrum of the distilled compound above. The double bond absorption at 6.1 μ was not strong, as that in the above compound was. This product is apparently a mixture of methyl 2-piperidino-2-(or 1)-cyclopentene-1-propionate and methyl 1-piperidinobicyclo[3.2.0]heptane-7-carboxylate, based on analogy with the subsequently described results.

B. N,N-Dimethyl-1-cyclopenten-1-ylamine with Methyl Acrylate.—N,N-Dimethyl-1-cyclopenten-1-ylamine (55 g., 0.5 mole), methyl acrylate (43 g., 0.5 mole), and acetonitrile (150 ml.) containing a pinch of hydroquinone were allowed to react as described above, keeping the temperature of the mixture below 30°. After the solvent was removed, the residue (94 g.) was dissolved in anhydrous ether (100 ml.) and added dropwise to a slurry of lithium aluminum hydride (13 g., 0.34 mole) in anhydrous ether (300 ml.). The ether refluxed during this addition. The reaction mixture was allowed to stand overnight. Ethyl acetate (10 ml.) and water (75 ml.) were added, and the solids were removed by filtration. Evaporation of the ether from the filtrate on a steam bath left 101 g. of residue. This residue was mixed with water (200 ml.) and concentrated hydrochloric acid (50 g.) and heated on the steam bath for 3 hr. It then was cooled and extracted twice with ether (50 ml.); the aqueous phase was made basic with 10% sodium hydroxide solution, whereupon an oil separated. The oil was separated by extraction with ether and distilled to give 33 g. (39% based on 0.5 mole of methyl acrylate) of crude 1-dimethylaminobicyclo[3.2.0]heptane-7-methanol, b.p. 96–101° at *ca.* 1 mm., $n^{20}D$ 1.4912. The existence of a weak absorption band at 5.78–5.79 μ in the infrared spectrum of this material suggested the presence of a carbonyl component as an impurity.

The above reaction was repeated, using 0.47-mole quantities of starting materials. There was obtained 30 g. (38%) of crude 1-dimethylaminobicyclo[3.2.0]heptane-7-methanol, which likewise contained a carbonyl impurity.

The crude 1-dimethylaminobicyclo[3.2.0]heptane-7-methanol from the above two preparations (63 g., 0.37 mole) was dissolved in a solution of water (100 ml.) and concentrated hydrochloric acid (35 ml.), and the resulting solution was extracted seven times with 100-ml. portions of ether. Evaporation of the combined extracts on a steam bath left 23.5 g. of "neutral material."

The acidic aqueous phase was made basic with dilute sodium hydroxide solution, and the oily layer which separated was removed by extraction with ether. Distillation of this ether extract gave 27 g. of 1-dimethylaminobicyclo[3.2.0]heptane-7-methanol, b.p. 96–99° at *ca.* 0.5 mm., $n^{20}D$ 1.4975. The infrared spectrum had OH absorption at 3.1 and no absorption from 5.5 to 6.5 μ. The n.m.r. spectrum had OH absorption at 5.2 (singlet) and OCH_2– absorption at 3.4 p.p.m. (triplet). The infrared spectrum was identical with that of the material obtained from N,N-dimethyl-1-cyclopenten-1-ylamine and methyl propiolate by a series of transformations described subsequently.

Anal. Calcd. for $C_{10}H_{19}NO$: C, 70.9; H, 11.3. Found: C, 70.8; H, 11.2.

The "neutral material" (23.5 g.) from above was distilled through a 6-in. Vigreux column to give 11.6 g. of distillate, b.p. 38–82° at 1 mm. (mostly 38–40° at 1 mm.). The infrared spectrum of this material indicated the presence of small amounts of hydroxy and carbonyl impurities. The material was redistilled to give 3.5 g. of 2,3,4,5,6,7-hexahydrocyclopenta[*b*]pyran,[7] b.p. 32.5–33° at 2.5 mm., $n^{20}D$ 1.4872. The infrared spectrum had strong absorption at 5.85 μ. The n.m.r. spectrum contained OCH_2–absorption at 3.8 p.p.m. (triplet) and two broad absorptions due to six (lower field) and four protons.

Anal. Calcd. for $C_8H_{12}O$: C, 77.4; H, 9.7. Found: C, 77.0; H, 9.0.

This compound gave the 2,4-dinitrophenylhydrazone of 2-(3-hydroxypropyl)cyclopentanone, m.p. 157–158°.

Anal. Calcd. for $C_{14}H_{18}N_4O_5$: C, 52.2; H, 5.6. Found: C, 52.2; H, 5.6.

(5) Melting points were determined using a calibrated Fisher-Johns melting point apparatus. N.m.r. absorptions are reported in parts per million (p.p.m.) relative to tetramethylsilane.

(6) F. E. Heyl and M. E. Herr, *J. Am. Chem. Soc.*, **75**, 1918 (1953).

(7) See N. D. Zelinskiĭ and N. V. Elagina, *Dokl. Akad. Nauk SSSR*, **86**, 1117 (1952); *Chem. Abstr.*, **47**, 12271 (1953).

C. N,N-Dimethyl-1-cyclopenten-1-ylamine with Methyl Propiolate.—Methyl propiolate (28 g., 0.33 mole) was added slowly to N,N-dimethyl-1-cyclopenten-1-ylamine (38 g., 0.33 mole) in ether (100 ml.) over a 1-hr. period. The temperature was maintained below 35° during this time. The ether was removed by distillation under reduced pressure, keeping the temperature of the mixture below 35° and leaving 65 g. of methyl 1-dimethylaminobicyclo[3.2.0]hept-6-ene-7-carboxylate.[3]

Methyl 1-dimethylaminobicyclo[3.2.0]hept-6-ene-7-carboxylate (65 g., 0.33 mole) was dissolved in pentane (150 ml.) and hydrogenated at room temperature and 40 p.s.i., using 1 g. of 5% palladium-on-alumina catalyst. The catalyst was removed by filtration, and the solvent was removed by distillation (without heating above 30°) under reduced pressure, leaving 71 g. of crude methyl 2-dimethylaminobicyclo[3.2.0]heptane-7-carboxylate, $n^{20}D$ 1.4776.

This product (71 g.) was dissolved in ether, and the resulting solution was added slowly to a slurry of lithium aluminum hydride (11 g., 0.29 mole) in ether (300 ml.). The reaction mixture, after standing overnight at room temperature, was treated with ethyl acetate (to decompose excess hydride) followed by water (100 ml.). The solids were filtered and washed with ether. The filtrate was evaporated on the steam bath, leaving 77 g. of residue. The infrared spectrum of this residue showed the presence of hydroxy (3.0) and carbonyl (5.8) groups and weak unsaturation (6.1 μ). The 77 g. of residue was dissolved in a solution of concentrated hydrochloric acid (40 ml.) and water (200 ml.) and heated for 0.5 hr. on a steam bath. The mixture was cooled and extracted six times with 50-ml. portions of ether. Evaporation of the ether from the combined extracts on the steam bath left 4 g. of residue.

The aqueous layer was made basic with 20% sodium hydroxide solution and extracted twice with 50-ml. portions of ether. Distillation of the combined ether extracts gave, after removal of ether, 29 g. (52% yield, based on 0.3 mole of starting materials) of 1-dimethylaminobicyclo[3.2.0]heptane-7-methanol, b.p. 94–100° at 0.5–0.6 mm., $n^{20}D$ 1.4978. The infrared spectrum of this compound was identical with that of the compound obtained from the lithium aluminum hydride reduction of the adduct from methyl acrylate and N,N-dimethyl-1-cyclopenten-1-ylamine.

D. 1-(1-Cyclohexen-1-yl)pyrrolidine with Methyl Acrylate.—1-(1-Cyclohexen-1-yl)pyrrolidine (76 g., 0.5 mole), methyl acrylate (43 g., 0.5 mole), and acetonitrile (100 ml.) which contained a pinch of hydroquinone were combined. The temperature of the mixture rose to 60° within 20 min. Distillation of the mixture gave, after removal of solvent and 8 g. of forerun, 90 g. (80%) of methyl 2-(1-pyrrolidinyl)-2(or 1)-cyclohexene-1-propionate, b.p. 108–112° at *ca.* 0.5 mm., $n^{20}D$ 1.5072.

E. N,N-Dimethyl-1-cyclohexen-1-ylamine with Methyl Acrylate.—N,N-Dimethyl-1-cyclohexen-1-ylamine (62.5 g., 0.5 mole), methyl acrylate (43 g., 0.5 mole), and acetonitrile (150 ml.) which contained a pinch of hydroquinone were allowed to react, keeping the temperature of the mixture below 30° by means of intermittent cooling. The solvent was removed by distillation under reduced pressure, and the residue (92 g.) was reduced with lithium aluminum hydride (13 g., 0.34 mole) as described above for 1-dimethylaminobicyclo[3.2.0]heptane-7-methanol. The crude alcohol was heated on the steam bath for 2.5 hr. with a mixture of water (250 ml.) and concentrated hydrochloric acid (50 g.). This solution was cooled, extracted twice with 50-ml. portions of ether, and the acidic aqueous phase was made basic with 10% sodium hydroxide solution. The oil which separated was removed by extraction with ether. Distillation of the ether extracts gave, after removal of ether and a 2-g. forerun, 18.5 g. (21% based on starting methyl acrylate) of 1-dimethylaminobicyclo[4.2.0]octane-8-methanol, b.p. 103–107° at 1 mm., $n^{20}D$ 1.5043. The infrared and n.m.r. spectra were consistent with the assigned structure as described above for the homologous bicycloheptane derivative.

Anal. Calcd. for $C_{11}H_{21}NO$: C, 72.2; H, 11.5. Found: C, 72.1; H, 11.5.

F. 1-(1-Cyclopenten-1-yl)piperidine with Diethyl Maleate.—1-(1-Cyclopenten-1-yl)piperidine (75.5 g., 0.5 mole), diethyl maleate (86 g., 0.5 mole), and acetonitrile (125 ml.) were combined. An exothermic reaction occurred, and the temperature rose to a maximum of 63° within 17 min. After letting the mixture stand for 1 hr., the solvent was removed by distillation under reduced pressure, leaving 170 g. of crude diethyl 1-piperidinobicyclo[3.2.0]heptane-6,7-dicarboxylate. The infrared spectrum of this material showed no appreciable absorption between 5.9 and 6.5 μ.

Diethyl 1-piperidinobicyclo[3.2.0]heptane-6,7-dicarboxylate (161 g., 0.5 mole) was dissolved in ether (150 ml.), and the solution was added dropwise with stirring to lithium aluminum hydride (25 g., 0.66 mole) dissolved in ether (700 ml.). The addition, which required 5 hr., was done at such a rate as to maintain gentle refluxing of the ether. The reaction mixture was allowed to stand overnight. Ethyl acetate (50 ml.) was added to decompose excess hydride, then water (200 ml.) was added. The solids were collected and washed with ether; the combined ether filtrate and washings were evaporated on a steam bath. The residue crystallized to give 91 g. (76%) of 1-piperidinobicyclo-[3.2.0]heptane-6,7-dimethanol. A sample was purified by dissolving it in 10% hydrochloric acid solution, extracting it with ether to remove neutral impurities, making it basic with dilute sodium hydroxide solution, extracting it with ether, and evaporating it on a steam bath. Recrystallization of the residue from toluene gave white crystals, m.p. 109–110°.

Anal. Calcd. for $C_{14}H_{25}NO_2$: C, 70.3; H, 10.5; mol. wt., 239. Found: C, 70.6; H, 10.4; mol. wt., 242.

G. N,N-Dimethyl-1-cyclohexen-1-ylamine with Diethyl Maleate.—N,N-Dimethyl-1-cyclohexen-1-ylamine (75 g., 0.6 mole), diethyl maleate (103 g., 0.6 mole), and acetonitrile (100 ml.) were combined. An exothermic reaction occurred, and the temperature was maintained below 40° by means of intermittent cooling. After standing for 3.5 hr., the mixture was divided into two equal portions, and one portion was reduced as described below.

The other portion was distilled in an alembic-type pot molecular still to give 81 g. (91%) of diethyl 1-dimethylaminobicyclo[4.2.0]-octane-7,8-dicarboxylate, boiling at 65–67° at *ca.* 1–5 μ.

Anal. Calcd. for $C_{18}H_{27}O_4$: C, 64.7; H, 9.2; N, 4.7. Found: C, 64.5; H, 9.0; N, 4.5.

Diethyl 1-dimethylaminobicyclo[4.2.0]octane-7,8-dicarboxylate (90 g., *ca.* 0.3 mole) was reduced with lithium aluminum hydride (30 g., 0.79 mole) as described above for diethyl 1-piperidinobicyclo[3.2.0]heptane-6,7-dicarboxylate. Distillation of the crude product gave 27.5 g. (43%, based on starting diethyl maleate) of 1-dimethylaminobicyclo[4.2.0]octane-7,8-dimethanol, b.p. 160–165° at 1 mm.

A sample for analysis was redistilled and had b.p. 156–157° at *ca.* 0.5 mm., $n^{20}D$ 1.5140.

Anal. Calcd. for $C_{12}H_{23}NO_2$: C, 67.7; H, 10.9. Found: C, 67.6; H, 11.0.

H. 1-(1-Cyclohepten-1-yl)pyrrolidine with Diethyl Maleate.—1-(1-Cyclohepten-1-yl)pyrrolidine (30 g., 0.18 mole), diethyl maleate (31.2 g., 0.18 mole), and acetonitrile (75 ml.) were combined and allowed to stand at room temperature for 1 day. The solvent was removed by distillation under reduced pressure, leaving 61 g. of diethyl 1-(1-pyrrolidinyl)bicyclo[5.2.0]nonane-8,9-dicarboxylate, $n^{20}D$ 1.4932. The infrared spectrum showed strong carbonyl absorption at 5.8, and no absorption at 5.9–6.5 μ.

I. 1-(1-Cycloocten-1-yl)piperidine with Diethyl Maleate.—Similarly, 1-(1-cycloocten-1-yl)piperidine (13 g., 0.067 mole) and diethyl maleate (11.6 g., 0.067 mole) gave 24 g. of diethyl 1-piperidinobicyclo[6.2.0]decane-9,10-dicarboxylate, $n^{20}D$ 1.4918. The infrared spectrum supported the assigned structure as described above.

J. 1,2,3,6-Tetrahydro-1-methyl-4-(1-pyrrolidinyl)pyridine with Diethyl Maleate.—1,2,3,6-Tetrahydro-1-methyl-4-(1-pyrrolidinyl)pyridine (16.6 g., 0.1 mole) and diethyl maleate (17.2 g., 0.1 mole) were combined. The temperature of the mixture rose to a maximum of 66.5° after 5 min. and then dropped back to room temperature. After 3 hr. an infrared spectrum of the product showed no double bond absorption. The yield of diethyl 3-methyl-6-pyrrolidinyl-3-azabicyclo[4.2.0]octane-7,8-dicarboxylate, a viscous liquid with $n^{20}D$ 1.4893, was virtually quantitative.

Some Transformations of Cyclobutane Derivatives. A. Diethyl 1-Ethoxybicyclo[3.2.0]heptane-1,2-dicarboxylate.—1-(1-Cyclopenten-1-yl)pyrrolidine (50 g., 0.365 mole) was added to diethyl maleate (63 g., 0.365 mole) with stirring and cooling to prevent the temperature of the mixture from exceeding 40°, and the mixture was allowed to stand overnight. Upon adding methyl *p*-toluenesulfonate (68 g., 0.365 mole) to the crude diethyl 1-pyrrolidinylbicyclo[3.2.0]heptane-1,2-dicarboxylate, it was necessary to cool the mixture in a cold-water bath to prevent the temperature from rising above 60°. After standing for 2 hr., the reaction mixture had set to a glass. A solution of sodium ethoxide in ethanol was prepared from freshly cut sodium (8.6 g., 0.375 g.-atom) and ethanol (200 ml.). To this solution was

added, dropwise over a 0.5-hr. period, a solution of the quaternary salt in ethanol (200 ml.). The resulting slurry was refluxed for 2.5 hr., cooled, and poured onto ice (500 g.). The pH of the solution was adjusted to 6 with concentrated hydrochloric acid (26 ml.). The solution was extracted with four 250-ml. portions of ether. The combined extracts were dried over sodium sulfate and distilled *in vacuo* to obtain, after removing the ether, alcohol, and a small forerun, 64 g. (61%) of diethyl 1-ethoxybicyclo[3.2.0]heptane-1,2-dicarboxylate, b.p. 106–107° at 0.5 mm., $n^{20}D$ 1.4594.

Anal. Calcd. for $C_{15}H_{24}O_5$: C, 63.4; H, 8.5. Found: C, 63.4; H, 8.5.

B. Diethyl 1-Ethoxybicyclo[4.2.0]octane-1,2-dicarboxylate.—Similarly, the diethyl maleate–cyclohexenylpyrrolidine adduct gave a 57% yield of diethyl 1-ethoxybicyclo[4.2.0]octane-1,2-dicarboxylate, b.p. 127–130° at 0.7 mm., $n^{20}D$ 1.4658.

Anal. Calcd. for $C_{16}H_{26}O_5$: C, 64.5; H, 8.8. Found: C, 64.8; H, 8.8.

C. Dimethyl Bicyclo[4.2.0]oct-8-ene-7,8-dicarboxylate.—Dimethyl maleate (72 g., 0.5 mole) was added, all at once, to N,N-dimethyl-1-cyclohexen-1-ylamine (62.5 g., 0.5 mole) in acetonitrile (75 ml.). An exothermic reaction occurred, and the mixture was cooled to maintain the temperature at 40–45°. The mixture then was allowed to stand overnight. The solvent was removed *in vacuo*, and the remaining 132 g. of crude dimethyl 1-dimethylaminobicyclo[4.2.0]octane-7,8-dicarboxylate was treated with methyl *p*-toluenesulfonate (91 g., 0.49 mole), and the mixture was allowed to stand overnight. The resulting quaternary salt was dissolved in water (250 ml.), and the solution was filtered to remove a small quantity of solid (4.2 g.). The solution then was extracted with ether, and the aqueous layer was treated with 200 ml. of 10% sodium hydroxide solution. The oil which separated was removed by extraction with ether, and the extract was dried over magnesium sulfate. The filtered solution was stripped of ether leaving 52.5 g. (48%) of crude dimethyl bicyclo[4.2.0]-oct-8-ene-7,8-dicarboxylate. The n.m.r. spectrum showed two O-methyl absorptions at 3.55 and 3.6, but no other absorption below 3.2 p.p.m. The infrared spectrum showed a double bond absorption at 5.95 μ.

Anal. Calcd. for $C_{12}H_{16}O_4$: C, 64.3; H, 7.2. Found: C, 64.4; H, 7.3.

D. Dimethyl Bicyclo[4.2.0]octane-7,8-dicarboxylate.—Dimethyl bicyclo[4.2.0]oct-8-ene-7,8-dicarboxylate (21.8 g., 0.097 mole) was dissolved in a mixture of ether (25 ml.) and pentane (25 ml.) and hydrogenated at 40 p.s.i. and room temperature over 0.5 g. of 5% palladium-on-alumina catalyst. The catalyst was removed by filtration, and the filtrate was distilled to give, after removal of solvent, 16.4 g. (75%) of dimethylbicyclo[4.2.0]octane-7,8-dicarboxylate, b.p. 100° at 1 mm., $n^{20}D$ 1.4730. The infrared spectrum showed no absorption between 5.8 and 6.0 μ.

Anal. Calcd. for $C_{12}H_{18}O_4$: C, 63.7; H, 8.0; sapon. equiv., 113.1. Found: C, 63.8; H, 8.0; sapon. equiv., 113.6.

E. Dimethyl (1-Cyclohexen-1-yl)fumarate.—A portion of the crude dimethyl bicyclo[4.2.0]oct-8-ene-7,8-dicarboxylate (20 g., 0.089 mole) was distilled at 0.3 mm. to give, after removal of 3 g. of forerun, 13.5 g. (68%) of dimethyl (1-cyclohexen-1-yl)fumarate, b.p. 111–113° at 0.3 mm., $n^{20}D$ 1.5262. The n.m.r. spectrum showed a triplet at 6.2 and a singlet at 9.8 p.p.m. due to the cyclohexene and fumarate protons, respectively.

Anal. Calcd. for $C_{12}H_{16}O_4$: C, 64.3; H, 7.2. Found: C, 64.2; H, 7.4.

F. Methyl 3,3-Dimethyl-1-cyclobutene-1-carboxylate.—Methyl 3,3-dimethyl-2-dimethylaminocyclobutanecarboxylate (1000 g., 5.4 moles) in methanol (1 l.) was treated dropwise with a solution of methyl *p*-toluenesulfonate (1000 g., 5.38 moles) in methanol (100 ml.). The mixture was cooled intermittently with a cold-water bath to keep the temperature from going above 30°. The mixture then was allowed to stand overnight. The resulting solution of quaternary salt was treated with a solution of sodium methoxide (290 g., 5.38 moles) in methanol (850 ml.). After stirring for 1 hr., the mixture was filtered and the alcohol was removed *in vacuo*. Water (500 ml.) and ether (500 ml.) were added to the residue, and the ether layer separated after thorough shaking of the mixture. The aqueous layer was extracted once with 200 ml. of ether, and the combined ether layers were washed with 10% hydrochloric acid and dried over magnesium sulfate. The drying agent was filtered off; the filtrate was distilled to give, after removal of ether, methanol, and a small forerun, 599 g. (79%) of methyl 3,3-dimethyl-1-cyclobutene-1-carboxylate, b.p. 56–62° at 15–17 mm., $n^{20}D$ 1.4440.

Anal. Calcd. for $C_8H_{12}O_2$: C, 68.6; H, 8.6. Found: C, 68.6; H, 8.5.

G. Dimethyl 3-Methoxy-4,4-dimethylcyclobutane-1,2-dicarboxylate.—To a solution of dimethyl 4,4-dimethyl-3-dimethylaminocyclobutane-1,2-dicarboxylate (243 g., 1.0 mole) in methanol (150 ml.) was added methyl *p*-toluenesulfonate (186 g., 1.0 mole). The temperature of the mixture rose slowly to 35°. The mixture was allowed to stand overnight. A solution of sodium methoxide (54 g., 1.0 mole) in methanol (200 ml.) was added to the solution of quaternary salt. After the slightly exothermic reaction had subsided, the mixture was stirred for 2 hr. and filtered. The filtrate was distilled *in vacuo* to remove the alcohol, and the residue was treated with water (250 ml.) and ether (250 ml.). After thorough shaking, the ether layer was separated, dried over sodium sulfate, and distilled to give 191 g. (83%) of dimethyl 3-methoxy-4,4-dimethylcyclobutane-1,2-dicarboxylate, b.p. 62–65° at 0.10–0.15 mm., $n^{20}D$ 1.4483.

Anal. Calcd. for $C_{11}H_{18}O_5$: C, 57.4; H, 7.8. Found: C, 57.9; H, 8.0.

H. Dimethyl 4,4-Dimethyl-2-cyclobutene-1,2-dicarboxylate.—Methyl iodide (71 g., 0.5 mole) was added to a solution of dimethyl 4,4-dimethyl-3-dimethylaminocyclobutane-1,2-dicarboxylate (121.5 g., 0.5 mole) in acetonitrile (350 ml.). The reaction mixture was cooled to keep the temperature from exceeding 35°. The mixture then was allowed to stand overnight. This solution of quaternary salt was added to a suspension of sodium hydride (24 g. of a 51% dispersion in mineral oil) in anhydrous acetonitrile (100 ml.). An exothermic reaction occurred with vigorous evolution of gas. When the evolution of gas slowed, the mixture was heated to 60° for 1 hr. and then distilled *in vacuo* to 50° at 80 mm. When the residue was taken up in 400 ml. of water, an oily layer separated. The aqueous solution was extracted with two 300-ml. portions of ether, and the combined ether and organic layers were dried over sodium sulfate. The ether was distilled *in vacuo*, and the distillation was continued to give 65 g. (68%) of dimethyl 4,4-dimethyl-2-cyclobutene-1,2-dicarboxylate, b.p. 80–84° at 0.9 mm., $n^{20}D$ 1.4587.

Anal. Calcd. for $C_{10}H_{14}O_4$: C, 60.6; H, 7.1. Found: C, 60.3; H, 7.3.

I. Ethyl 2-Ethoxy-3,3-dimethylcyclobutanecarboxylate.—To ethyl 3,3-dimethyl-1-cyclobutene-1-carboxylate[1] (9.2 g., 0.060 mole) was added ethanol (2.74 g., 0.06 mole) and sodium hydride (0.2 g., 0.004 mole). When all of the sodium hydride had reacted, the mixture was warmed briefly on the steam bath and then allowed to stand for 18 days at room temperature. After filtration to remove a small amount of solid, the filtrate was washed with water and 10% hydrochloric acid solution. The combined aqueous washings were extracted with ether, and the ether was added to the original organic layer. The resulting ethereal solution was dried over Drierite. After filtration, distillation *in vacuo* gave, after removal of ether and a 0.9-g. forerun, 5.5 g. (46%) of ethyl 2-ethoxy-3,3-dimethylcyclobutanecarboxylate, b.p. 35.5–38° at *ca.* 0.5 mm., $n^{20}D$ 1.4290.

Anal. Calcd. for $C_{11}H_{20}O_3$: C, 66.0; H, 10.1. Found: C, 66.1; H, 10.0.