Enamine Chemistry. VI. Reactions with Propiolates[1]

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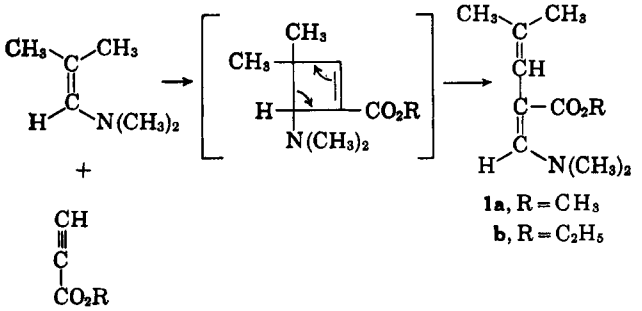
Received August 26, 1963

The reaction of a variety of enamines with propiolates was studied. With a few exceptions the reaction products were those derived from the cyclobutene rearrangement of cycloaddition products initially formed. Methods are described for the conversion of several cyclic ketones (with the exception of cyclohexanone) to their higher homologs containing two more carbon atoms in the ring.

Cycloaddition reactions of enamines with electrophilic olefins have been reported previously.[2] Extension of the cycloaddition reaction to include reactions of enamines with acetylenedicarboxylates also has been described.[3,4] The reactions of enamines with propiolates are more complex and will be discussed separately in this paper.

In general, the reactions of propiolates with a number of enamines involved initial cycloadditions to form cyclobutene derivatives. These cyclobutenes rearranged, in most cases spontaneously, to form products whose structures depended on the starting enamine and on the reaction conditions. Since the results differed greatly depending on the enamine used, the reactions of the various enamines will be discussed separately.

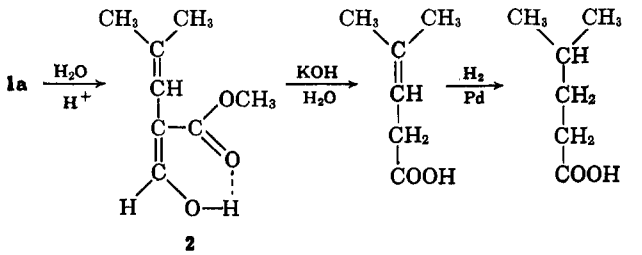
When N,N-dimethylisobutenylamine was allowed to react with methyl or ethyl propiolate, the products expected from cyclobutene rearrangement of the presumed intermediate cycloaddition products were obtained in about 50% yield. When a propiolate was



1a, R = CH_3
b, R = C_2H_5

added to the enamine, only a small amount of high-boiling material was formed. Addition of enamine to a propiolate, however, yielded, in addition to the 3-pentenoate (**1**), 29% of an unidentified higher-boiling product formed by reaction of 1 mole of enamine with 2 moles of propiolate.

The structure of **1a** was proved by stepwise hydrolysis to 4-methyl-3-pentenoic acid and hydrogenation of this acid to 4-methylvaleric acid. Both **1a** and the initial hydrolysis product (**2**) had infrared and n.m.r. spectra which supported the assignment of structure.



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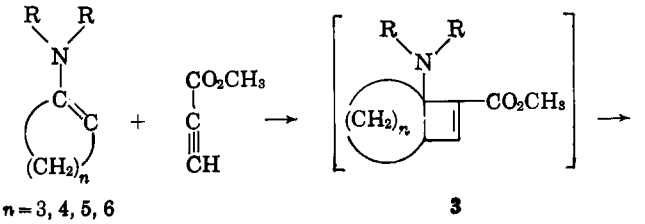
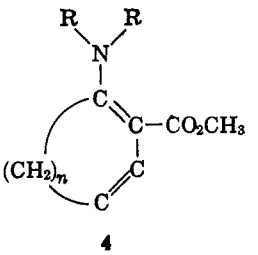
The extension of the enamine–propiolate reaction to enamines derived from cyclic ketones was studied then. Reactions of such cyclic enamines with methyl propiolate might be expected by analogy to yield cyclic products with the ring enlarged by two carbon atoms. Ring enlargement products of the type shown were actually obtained in most cases. However, the conditions, yields, and number and types of by-products varied greatly with the ring size of the enamine.



n = 3, 4, 5, 6 **3**



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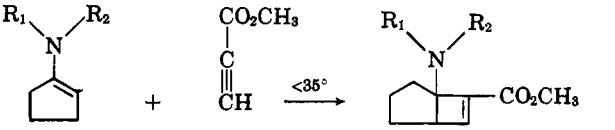
When enamines derived from cyclopentanone were allowed to react with methyl propiolate at temperatures below 35°, the products were bicycloheptene derivatives (**5**). The bicycloheptenes were found to undergo rearrangements which depended on the nature of the groups attached to the enamine nitrogen atom.



5a, $R_1 = R_2 = CH_3$
b, $R_1 + R_2 = -(CH_2)_4-$
c, $R_1 + R_2 = -(CH_2)_5-$
d, $R_1 + R_2 = -CH_2CH_2OCH_2CH_2-$

On standing at room temperature, **5a** isomerized to methyl 2-dimethylamino-1-cyclopentene-1-acrylate (**6**), analogous to the products obtained by Stork and coworkers from cyclopentenylamines and acrylic esters.[5] The structure of **6** was established by hydrolysis and hydrogenation to methyl 2-oxocyclopentanepropio-

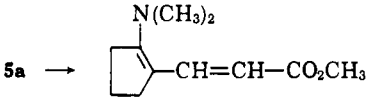
(1) A portion of the material in this paper was presented at the Enamine Chemistry Symposium, 140th National Meeting of the American Chemical Society, Chicago, Ill., Sept., 1961.

(2) K. C. Brannock, A. Bell, R. D. Burpitt, and C. A. Kelly, *J. Org. Chem.*, **26**, 625 (1961).

(3) K. C. Brannock, R. D. Burpitt, V. W. Goodlett, and J. G. Thweatt, *ibid.*, **28**, 1464 (1963).

(4) G. A. Berchtold and G. F. Uhlig, *ibid.*, **28**, 1459 (1963).

(5) G. Stork and H. K. Landesman, *J. Am. Chem. Soc.*, **78**, 5128 (1956).



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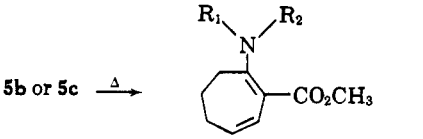
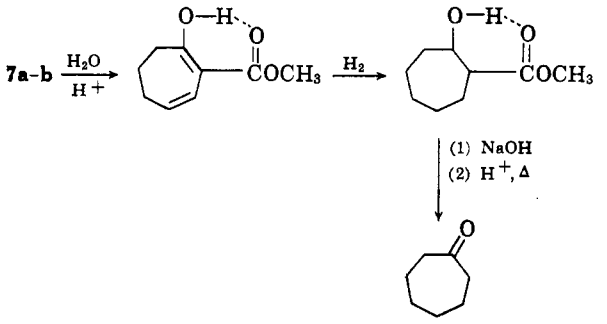
nate. The presence of a small amount of an analogous rearrangement product from **5b** was indicated by the n.m.r. spectra of the crude bicycloheptene and of its crude thermal rearrangement product. It is not clear how the Stork products are formed from the bicycloheptenes. The most plausible explanation is that the initial cycloaddition is reversible and that it competes with a slower but irreversible reaction which leads to the Stork addition product (**6**).

The rearrangement of **5b** and **c** proceeded exothermically when they were heated to about 90°. The products were cycloheptadiene derivatives (**7a** and **b**)

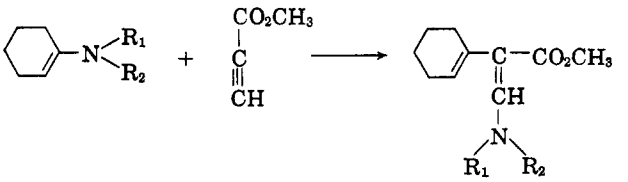


7a, $R_1 + R_2 = -(CH_2)_4-$
b, $R_1 + R_2 = -(CH_2)_5-$

apparently formed by cyclobutene rearrangement. The structure of **7** was established by degradation to cycloheptanone.

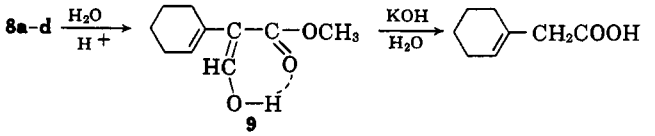


Enamines derived from cyclohexanone reacted with methyl propiolate to form unexpected products.



8a, $R_1 = R_2 = CH_3$
b, $R_1 + R_2 = -(CH_2)_4-$
c, $R_1 + R_2 = -(CH_2)_5-$
d, $R_1 + R_2 = -CH_2CH_2OCH_2CH_2-$

Assignment of structures **8a–d** was based initially on the infrared and n.m.r. spectra of the products. It was supported by acid hydrolysis of the various compounds to a common hydrolysis product (**9**), which could in turn be hydrolyzed by base to 1-cyclohexene-1-acetic acid.



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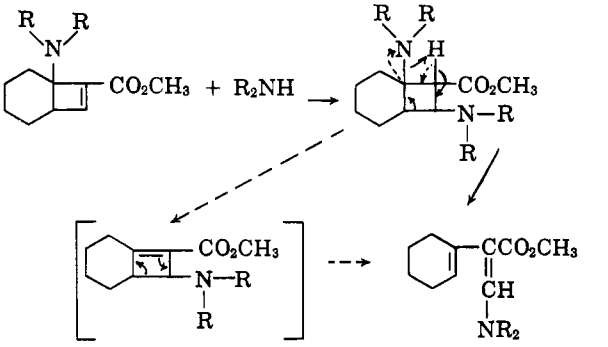
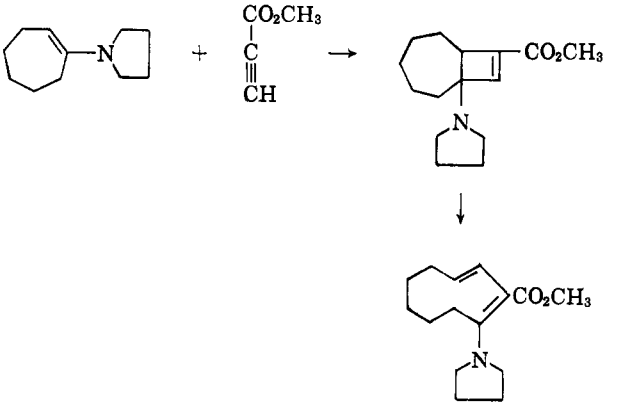
It was not possible to detect any products analogous to **6** or **7** in the reaction mixtures of cyclohexanone enamines with methyl propiolate, nor could any bicyclooctene derivatives analogous to **5** be isolated. Apparently the geometry of the bicyclooct-7-ene system is such that cyclobutene rearrangement is not favored, and other reactions occur.[6]

It is possible to rationalize the formation of **8** by assuming the addition of a secondary amine (which would have to be present in only trace amounts) to the intermediate bicyclooctene, followed by loss of the bridgehead amine group with simultaneous or subsequent rearrangement to **8** and regeneration of the secondary amine.



The reaction of 1-(1-cyclohepten-1-yl)pyrrolidine with methyl propiolate proceeded readily. The intermediate bicyclononene rearranged too rapidly for it to be detected, and the product of ring enlargement (**10**) could be isolated in good yield by chilling the reaction mixture. The structure assignment of **10** was based on its infrared and n.m.r. spectra. The compound was quite unstable and rearranged on standing overnight at room temperature or rapidly when it was treated with dilute acid. The product of this rearrangement was a



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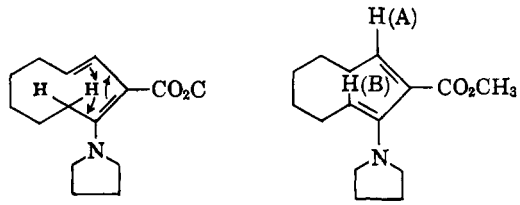
basic liquid which no longer showed the characteristic infrared absorptions of the $-C(NR_2)=C(CO_2R)-CH=CH-$ system (maxima at 5.97–6.02 and 6.45–6.6 μ) but showed strong maxima at 5.88 and 6.2 μ. In addition, the n.m.r. spectrum showed a triplet centered at 6.95 p.p.m. (relative to tetramethylsilane) due to one olefinic proton, and an overlapping pair of doublets centered at 4.17 p.p.m. due to one proton. In the light of these spectral data and the chemical transformations to be

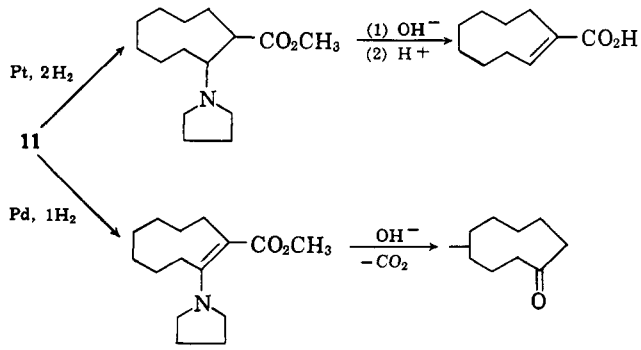
(6) *Cf.* ref. 3.



10 11

described, we are assigning structure **11** to the rearrangement product derived from **10**. In **11** the 5.88-μ absorption is due to the α,β-unsaturated ester and the 6.2-μ absorption is due to the enamine C=C. The 6.95-p.p.m. triplet is due to proton A and the 4.17-p.p.m. absorption is due to proton B.[4]

On hydrogenation over platinum in acetic acid, **11** absorbed two equivalents of hydrogen, and the reduction product on digestion with aqueous base gave 1-cyclononene-1-carboxylic acid. Reduction of **11** over palladium in acetic acid gave a break in the rate of hydrogen absorption when one equivalent of hydrogen had been absorbed. Interruption of the hydrogenation at this stage gave **12**, which like **11** did not undergo hydrolysis of the enamine function in dilute acid. Treatment of **12** with dilute base did, however, give cyclononanone in good yield.



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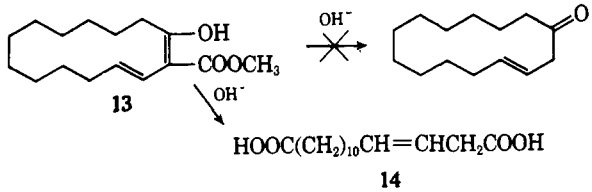
We can offer no explanation for the failure of **11** and **12** to undergo acid-catalyzed hydrolysis of the enamine function, but can find no other structures which satisfy the available data. Support for the idea that rearrangement of **10** to **11** involves a proton transfer also is found in the fact that the reaction appears to be acid-catalyzed.

Reaction of the pyrrolidine enamines of cyclooctanone and cyclododecanone with methyl propiolate gave products of ring enlargement which were much more stable than the corresponding cyclononadiene. Both the cyclodecadiene and cyclotetradecadiene derivatives underwent acid hydyrolysis of the enamine function. The hydrolysis products on hydrogenation, saponification, and decarboxylation gave cyclodecanone and cyclotetradecanone, respectively, in satisfactory yield. Several attempts to convert the cyclotetradecene keto ester or its enol (**13**) to cyclotetradecenone by basic hydrolysis led only to the ring-opened acid (**14**).



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Experimental[7]

Materials.—The pyrrolidine enamines of cyclopentanone, cyclohexanone, cycloheptanone, and cyclooctanone were prepared as described by Kuehne.[8] The morpholine and piperidine enamines of cyclopentanone[9] and cyclohexanone[10] were prepared also by essentially this same method. 1-(1-Cyclododecen-1-yl)-pyrrolidine was prepared as described in a previous paper.[3] The dimethylamine enamine of cyclopentanone was prepared by a modification of the method of Mannich and Davidsen.[11] Linde 13X Molecular Sieve was used as the drying agent instead of potassium carbonate. N,N-Dimethyl-1-cyclopenten-1-ylamine, b.p. 59–60° at 30 mm., $n^{20}D$ 1.4810, was obtained in 63% yield.

Anal. Calcd. for $C_7H_{13}N$: N, 12.6. Found: N, 11.7.

Many of the enamines prepared during this investigation failed to give good analytical results, presumably because of reaction with air and/or atmospheric moisture. Kuehne[8] noted that the refractive indices of enamines which he prepared dropped rapidly on exposure to air, probably for the same reason.

Ethyl 2-(Dimethylaminomethylene)-4-methyl-3-pentenoate (1b).—N,N-Dimethylisobutenylamine (50 g., 0.5 mole) was added over a 15-min. period to ethyl propiolate (50 g., 0.5 mole) with cooling to keep the temperature below 50°. The mixture was allowed to stand for 3 hr. Heat was evolved slowly throughout this period, and the temperature was maintained at 30–45° by cooling the mixture occasionally. After 3 hr. no more heat was evolved, and the mixture was allowed to stand overnight at room temperature. Distillation gave 47 g. (47%) of ethyl 2-(dimethylaminomethylene)-4-methyl-3-pentenoate (**1b**), b.p. 92–95° at *ca.* 1 mm., a 7.5-g. intermediate cut; and 21.5 g. (29%) of an adduct from 1 mole of N,N-dimethylisobutenylamine and 2 moles of ethyl propiolate, b.p. 135–137° at *ca.* 1 mm., $n^{20}D$ 1.4949.

Anal. Calcd. for **1b**, $C_{11}H_{19}NO_2$: C, 67.0; H, 9.7. Found: C, 66.7; H, 9.7.

Anal. Calcd. for 2:1 adduct, $C_{16}H_{25}NO_4$: C, 65.1; H, 8.5. Found: C, 64.8; H, 8.2.

With 2,4-dinitrophenylhydrazine, **1b** gave the 2,4-dinitrophenylhydrazone of ethyl 2-formyl-4-methyl-3-pentenoate, m.p. 108–109°.

Anal. Calcd. for $C_{15}H_{18}N_4O_6$: C, 51.4; H, 5.2. Found: C, 51.6; H, 5.2.

Methyl 2-(Dimethylaminomethylene)-4-methyl-3-pentenoate (1a).—Methyl propiolate (55 g., 0.65 mole) was added dropwise to N,N-dimethylisobutenylamine (80 g., 0.8 mole) in 50 ml. of ether. The temperature of the reaction mixture rose to 50° after 0.5 hr. and decreased to room temperature over the next 3 hr. Distillation gave, after removal of ether and excess N,N-dimethylisobutenylamine, 61 g. (50%) of methyl 2-(dimethylaminomethylene)-4-methyl-3-pentenoate (**1a**), b.p. 88–95° at 1–1.5 mm., $n^{20}D$ 1.5297, and 24 g. of higher-boiling material which was not further investigated.

Anal. Calcd. for $C_{10}H_{17}NO_2$: C, 65.6; H, 9.4; N, 7.6. Found: C, 65.4; H, 9.3; N, 7.8.

With 2,4-dinitrophenylhydrazine, **1a** gave the 2,4-dinitrophenylhydrazone of methyl 2-formyl-4-methyl-3-pentenoate, m.p. 126–127°.

Anal. Calcd. for $C_{14}H_{16}N_4O_6$: C, 50.0; H, 4.8. Found: C, 49.8; H, 4.9.

Methyl 2-Formyl-4-methyl-3-pentenoate.—Methyl 2-(dimethylaminomethylene)-4-methyl-3-pentenoate (56 g., 0.31 mole) was dissolved in a solution of concentrated hydrochloric acid (130 ml.) in water (700 ml.). The mixture was allowed to stand with occasional shaking for 3 hr., and an oily layer gradually separated.

The mixture was extracted with ether and the ether layer was distilled to give, after removal of ether, 40 g. (84%) of methyl 2-formyl-4-methyl-3-pentenoate, b.p. 50–53° at 2 mm., $n^{20}D$

(7) 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. All structure assignments were supported by infrared and n.m.r. spectra. Spectral data for specific compounds are included when pertinent.

(8) M. E. Kuehne, *J. Am. Chem. Soc.*, **81**, 5400 (1959).

(9) A. Rieche, E. Schmitz, and E. Beyer, *Chem. Ber.*, **92**, 1212 (1959).

(10) S. Hünig, E. Benzing, and E. Lücke, *ibid.*, **90**, 2833 (1957).

(11) C. Mannich and H. Davidsen, *Ber.*, **69**, 2106 (1936).

1.4808. This product gave an intense violet color with iron(III) chloride solution, and its infrared spectrum indicated that it exists largely in the enolic or hydroxymethylene form. This spectrum was compared with those of similar compounds.

Anal. Calcd. for $C_8H_{12}O_3$: C, 61.5; H, 7.7. Found: C, 61.9; H, 8.0.

4-Methyl-3-pentenoic Acid.—Methyl 2-formyl-4-methyl-3-pentenoate (37 g., 0.24 mole) was refluxed with a solution of potassium hydroxide (40 g., 1 mole) in water (150 ml.) for 4 hr. The solution was acidified with concentrated hydrochloric acid and extracted with ether. Distillation of the ether layer gave, after removal of ether, 20 g. (74%) of 4-methyl-3-pentenoic acid, b.p. 85–90° at 4 mm., $n^{20}D$ 1.4464; lit.[12] b.p. 83–84° at 4 mm., $n^{20}D$ 1.4457.

4-Methylvaleric Acid.—4-Methyl-3-pentenoic acid (5 g., 0.044 mole) in 50 ml. of pentane was hydrogenated over 0.5 g. of 5% palladium on alumina at room temperature and 3-atm. pressure. Distillation gave, after removal of pentane, 4.1 g. (80%) of 4-methylvaleric acid, b.p. 69° at 2.5 mm., $n^{20}D$ 1.4144; lit.[13] b.p. 199° at 752 mm., $n^{20}D$ 1.4144. The infrared spectrum was identical with that of authentic 4-methylvaleric acid.

Methyl 5-Piperidinobicyclo[3.2.0]hept-6-ene-6-carboxylate (5c).—Methyl propiolate (57 g., 0.68 mole) was added slowly to 1-(1-cyclopenten-1-yl)piperidine (103 g., 0.68 mole) in ether (200 ml.) over a period of 2 hr. The temperature was maintained below 35° during the addition. The ether was removed by distillation under reduced pressure while the temperature was maintained below 35°. The residue crystallized to give 145 g. (91%) of methyl 5-piperidinobicyclo[3.2.0]hept-6-ene-6-carboxylate, m.p. 41–43°.

Anal. Calcd. for $C_{14}H_{21}NO_2$: C, 71.5; H, 9.0. Found: C, 71.0; H, 9.1.

The n.m.r. spectrum of this compound showed a single peak at 6.59 p.p.m. assignable to the olefinic proton, and a broad unresolved peak in the region associated with tertiary protons. The failure to observe resolvable splitting between the tertiary and olefinic protons is in agreement with the observed absence of spin–spin splitting in cyclobutene.[14] The infrared spectrum contained a strong absorption at 5.8 and a sharp absorption of medium intensity at 6.1 μ.

When the enamines prepared from cyclopentanone and dimethylamine, pyrrolidine, and morpholine were allowed to react with methyl propiolate under conditions similar to those described for formation of **5c**, the similarity of the infrared and n.m.r. spectra to those of **5c** indicated that the major part of the crude product in each case was the bicycloheptene derivative. Failure to obtain these products as solids, and their thermal instability, precluded complete characterization.

Methyl 2-Dimethylamino-1-cyclopenten-1-acrylate (6).—To N,N-dimethyl-1-cyclopenten-1-ylamine (5.55 g., 0.05 mole) in ether (15 ml.) was added portionwise methyl propiolate (4.2 g., 0.05 mole) over 5 min. with cooling to keep the temperature below 30°. The solvent was distilled under reduced pressure after the mixture had stood at room temperature for 1 hr. The crude product, upon continued standing at room temperature, slowly crystallized. After standing for 11 days, the crystalline mass was triturated with cold ether and filtered to give 7 g. (72%) of methyl 2-dimethylamino-1-cyclopentene-1-acrylate, m.p. 74–75°. The infrared and n.m.r. spectra were different from the spectra of the initial crude product and were consistent with the assigned structure. Characteristics of the spectra were infrared absorptions at 5.95, 6.45, and 8.70 μ and n.m.r. doublets (one proton each) at 7.9 and 5.1 p.p.m.

Anal. Calcd. for $C_{11}H_{17}NO_2$: C, 67.7; H, 8.8; N, 7.2; neut. equiv., 195. Found: C, 67.9; H, 8.8; N, 7.2; neut. equiv., 201.

Methyl 2-Oxocyclopentaneacrylate.—Methyl 2-dimethylamino-1-cyclopentene-1-acrylate (12.5 g., 0.064 mole) was mixed with methanol (50 ml.) and concentrated hydrochloric acid (6.5 ml.), and the mixture was allowed to stand at room temperature for 4 days. Water (40 ml.) was added and the methanol was evaporated on the steam bath until an oil began to separate. Extraction with ether and distillation of the ether extracts gave 4.1 g. (38%) of methyl 2-oxocyclopentaneacrylate, b.p. 104–107° at 1.2 mm., $n^{20}D$ 1.4895.

Anal. Calcd. for $C_9H_{12}O_3$: C, 64.3; H, 7.2. Found: C, 64.1; H, 7.2.

Methyl 2-Oxocyclopentanepropionate.—Methyl 2-oxocyclopentaneacrylate (3.3 g., 0.0196 mole) was hydrogenated in 50 ml. of pentane and 20 ml. of methanol at room temperature and 40 p.s.i. over 0.25 g. of 5% palladium on alumina. The catalyst was removed by filtration and the solvent was removed by distillation *in vacuo* to leave 3.3 g. of residue, $n^{20}D$ 1.4606. An infrared spectrum of this material was identical with that of methyl 2-oxocyclopentanepropionate reported by Terrell.[15] The 2,4-dinitrophenylhydrazone melted at 86.5–87.5°, lit.[16] m.p. 87–88°.

Methyl 2-(1-Pyrrolidinyl)-1,6-cycloheptadiene-1-carboxylate (7a).—To a solution of 34.3 g. (0.25 mole) of 1-(1-cyclopenten-1-yl)pyrrolidine in 75 ml. of dry ether was added dropwise 21.0 g. (0.25 mole) of methyl propiolate. The temperature of the mixture was maintained at 10–20° during the addition and for 1.5 hr. thereafter by periodic cooling in an ice bath. The solvent was distilled at reduced pressure while the base temperature was kept below 35°. The residue was distilled through an 8-cm. Vigreux column at 0.5-mm. pressure to yield 35.5 g. (65%) of methyl 2-(1-pyrrolidinyl)-1,6-cycloheptadiene-1-carboxylate (**7a**), b.p. 122–140° (mostly 126–130°), which solidified on cooling. After one recrystallization from hexane, the product melted at 117–119°.

Anal. Calcd. for $C_{13}H_{19}NO_2$: C, 70.6; H, 8.7; N, 6.3. Found: C, 70.4; H, 8.7; N, 6.8.

The product had infrared maxima at 6.0, 6.25, and 6.60 μ. The n.m.r. spectrum showed olefinic proton resonance at 6.4 (doublet) and 5.6 p.p.m. (multiplet).

In subsequent preparations it was found that **7a** could be obtained without distillation by carrying out the reaction of the enamine and methyl propiolate in ether and evaporating the ether on a steam bath. When the temperature of the residue reached 85–90°, an exothermic reaction occurred. The temperature reached a maximum of about 130° in preparations on a 0.1–0.2-mole scale. The mixture solidified on cooling to about 50°. The cycloheptadiene (**7a**) could be isolated in an average yield of 63% by trituration of the solid residue with ether and filtration to remove the product.

Methyl 2-Oxo-6-cycloheptene-1-carboxylate.—Methyl 2-(1-pyrrolidinyl)-1,6-cycloheptadiene-1-carboxylate (39 g., 0.18 mole) was dissolved in a mixture of 20 ml. of concentrated hydrochloric acid and 100 ml. of water. After the solution had stood at room temperature for 5 hr., it was extracted with ether to remove an oil which had separated. Evaporation of ether and distillation of the residue yielded 8 g. (27%) of methyl 2-oxo-6-cycloheptene-1-carboxylate, b.p. 71–76° at 1.5 mm., $n^{20}D$ 1.5236.

Anal. Calcd. for $C_9H_{12}O_3$: C, 64.3; H, 7.2. Found: C, 65.2; H, 7.4.

Similar results were obtained when the oily crude product from thermal rearrangement of the analogous piperidine compound (**5c**) was hydrolyzed under the same conditions.

Cycloheptanone from Methyl 2-Oxo-6-cycloheptene-1-carboxylate.—Methyl 2-oxo-6-cycloheptene-1-carboxylate (8 g., 0.048 mole) was dissolved in pentane (100 ml.) and hydrogenated at room temperature and 30 p.s.i. over 0.5 g. of 5% palladium-on-alumina catalyst. The mixture absorbed 0.05 mole of hydrogen in 1 hr.

The catalyst was removed by filtration. The filtrate was evaporated on a steam bath to leave 7.5 g. of residue which gave a deep blue color when a small sample was added to alcoholic iron(III) chloride.

Potassium hydroxide (5 g., 0.089 mole) in water (25 ml.) and methanol (10 ml.) was added to the 7.5 g. of residue, and the resulting mixture was heated on the steam bath for 0.5 hr., during which time an oil separated. The solution then was acidified with concentrated hydrochloric acid (gas evolved) and extracted with ether. The ether was evaporated on the steam bath, and 4 g. (74%) of crude cycloheptanone was obtained. The infrared spectrum of this product was identical with that of an authentic sample of cycloheptanone.

The 2,4-dinitrophenylhydrazone, yellow crystals from an ethyl alcohol–ethyl acetate mixture, melted at 147–148°, lit.[17] m.p. 148°.

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Cycloheptanone from Methyl 2-(1-Pyrrolidinyl)-1,6-cycloheptadiene-1-carboxylate (7a).—A solution of 22 g. (0.10 mole) of methyl 2-(1-pyrrolidinyl)-1,6-cycloheptadiene-1-carboxylate in 100 ml. of acetic acid was hydrogenated over 1.5 g. of 5% palladium on carbon at 40 p.s.i. and room temperature until 0.10 mole of hydrogen had been absorbed. The reaction mixture was filtered, and most of the acetic acid was removed by distillation under reduced pressure. The mixture was then heated with excess sodium hydroxide in 80% aqueous methanol. After most of the methanol had been distilled, the mixture was extracted with ether. The ether solution was washed with dilute hydrochloric acid, and the ether was evaporated to yield 6.0 g. (54%) of cycloheptanone, which was identified by its infrared spectrum.

Methyl α-(Hydroxymethylene)-1-cyclohexene-1-acetate (9).—Methyl propiolate (16.8 g., 0.20 mole) dissolved in 15 ml. of ether was added over a period of 50 min. to a solution of 25 g. (0.20 mole) of N,N-dimethyl-1-cyclohexen-1-ylamine in 50 ml. of ether. The temperature of the reaction mixture was maintained at 25–35° by means of intermittent cooling. The mixture was allowed to stand overnight at room temperature, after which the ether was evaporated on a steam bath. The infrared spectrum of the residue showed a strong absorption at 5.95 and a strong doublet at 6.20–6.26 μ; the n.m.r. spectrum contained a single peak at 7.28 (olefinic proton adjacent to nitrogen) and a closely spaced triplet at 5.28 p.p.m. (cyclohexene olefinic proton). The residue was cooled and added to 100 ml. of 10% hydrochloric acid. An oil began separating almost immediately. After 3 hr., the oil was removed by extraction with ether. Distillation of the ether extract yielded 20.2 g. (55%) of methyl α-(hydroxymethylene)-1-cyclohexene-1-acetate, b.p. 80–82° at 1.5 mm., $n^{20}D$ 1.5003. This compound gave an intense purple color with iron(III) chloride and a positive Fuchsin aldehyde test. Its infrared spectrum had maxima at 5.65, 5.92, and 6.16 μ; its n.m.r. spectrum showed absorptions at 11.3 (bonded O–H, doublet), 6.94 (>C=C(O)–H), doublet), and 5.28 p.p.m. (ring olefinic proton, unresolved).

Anal. Calcd. for $C_{10}H_{14}O_3$: C, 65.9; H, 7.7. Found: C, 65.4; H, 7.8.

This same product was obtained in approximately the same yield when enamines prepared from cyclohexanone and pyrrolidine, piperidine, and morpholine were treated with methyl propiolate. The nature of the product and the yield were not affected appreciably by the temperature at which the reaction was carried out or by the nature of the solvent. The intermediate aminomethylene esters were all obtained as oils. When attempts were made to purify these compounds by distillation, small amounts of distillates were obtained along with large amounts of tarry residues. The distillates were mixtures in all cases.

1-Cyclohexene-1-acetic Acid.—Methyl α-(hydroxymethylene)-1-cyclohexene-1-acetate (9, 2 g., 0.011 mole) was added to a solution of potassium hydroxide (1 g.) in water (5 ml.). The resulting clear yellow solution was heated on a steam bath for 15 min., cooled, and diluted with 10 ml. of water. This solution was extracted once with 10 ml. of ether and the ether extract was discarded.

Acidification of the aqueous layer with concentrated hydrochloric acid gave an oil which was extracted with ether. Evaporation of the ether on the steam bath gave 1.5 g. of oil, which crystallized on cooling. This solid was recrystallized with considerable loss from pentane to yield 1-cyclohexene-1-acetic acid, m.p. 33–35°. The infrared spectrum was identical with that of a sample of authentic 1-cyclohexene-1-acetic acid obtained from Aldrich Chemical Co.

Anal. Calcd. for $C_8H_{12}O_2$: neut. equiv., 140.2. Found: neut. equiv., 141.8.

Methyl 2-(1-Pyrrolidinyl)-1,8-cyclononadiene-1-carboxylate (10).—To a solution of 49.5 g. (0.30 mole) of 1-(1-cyclohepten-1-yl)pyrrolidine in 100 ml. of ether was added dropwise with stirring 25.2 g. (0.30 mole) of methyl propiolate over a period of 15 min. The temperature of the mixture was maintained at 5–15° during the addition and for 30 min. longer. After part of the solvent was removed at reduced pressure, a white solid separated and was removed by filtration. After being dried in a vacuum oven, the solid weighed 45.5 g. Concentration of the filtrates yielded 5.0 g. of additional solid. The infrared spectrum showed the absorption pattern characteristic of the $-C(NR_2)=C(CO_2R)-CH=CH-$ structure (strong maxima at 5.98 and 6.56 μ). The n.m.r. spectrum showed resonance for single olefinic protons at 6.13 (doublet) and 5.23 p.p.m. (pair of triplets). This solid rearranged on standing overnight at room temperature or immediately on treatment with acid to form an oil, $n^{20}D$ 1.5320, which had strong infrared maxima at 5.88 and 6.2 μ and showed n.m.r. absorption at 6.95 (triplet) and 4.17 p.p.m. (unresolved pair of doublets). Both the infrared and n.m.r. spectra indicated that the oil was a single compound.

Anal. Calcd. for $C_{15}H_{23}NO_2$: C, 72.3; H, 9.3. Found: C, 72.3; H, 9.5.

1-Cyclononene-1-carboxylic Acid.—A solution of 24.9 g. (0.10 mole) of the oil (11) in 100 ml. of acetic acid was hydrogenated at 40 p.s.i. and room temperature over 0.25 g. of platinum oxide with absorption of 0.20 mole of hydrogen. After the catalyst and most of the acetic acid were removed, the residue was treated with 200 ml. of 10% sodium hydroxide and 200 ml. of methanol. The basic mixture was heated overnight on a steam bath in an open beaker. The concentrated solution was diluted to 250 ml. to dissolve the solids and was acidified to precipitate a gummy material. Addition of 150 ml. of ethyl alcohol, warming to 40°, and cooling to 0° precipitated 9.5 g. (57%) of 1-cyclononene-1-carboxylic acid, m.p. 72–77°. An analytical sample, m.p. 77–78°, was prepared by recrystallization from pentane.

Anal. Calcd. for $C_{10}H_{16}O_2$: C, 71.3; H, 9.5. Found: C, 71.5; H, 9.7.

Cyclononanecarboxylic Acid.—1-Cyclononene-1-carboxylic acid (500 mg., 3 mmoles) dissolved in 25 ml. of hexane was hydrogenated at 40 p.s.i. and room temperature over 0.5 g. of 5% palladium on alumina. Removal of catalyst and evaporation of solvent yielded an oil which was treated with excess thionyl chloride. The residue, after evaporation of excess thionyl chloride, was divided into two portions and was converted to the amide, m.p. 175.5–177° (lit.[18] m.p. 175–177°), and the anilide, m.p. 140.5–142.5° (lit.[18] m.p. 140.4–141.6°).

Methyl 2-(1-Pyrrolidinyl)-1-cyclononene-1-carboxylate (12).—A solution of 20.0 g. (0.080 mole) of the oil (11) in 90 ml. of acetic acid was hydrogenated at 40 p.s.i. over 3 g. of 5% palladium on carbon until a definite decrease in the rate of hydrogen absorption was observed; 0.076 mole of hydrogen had been absorbed. The mixture was filtered to remove the catalyst, and most of the solvent was removed under reduced pressure. An aqueous solution of the residue was extracted with ether, made basic, and then extracted again with ether. The ether extract from the basic solution was evaporated to yield 13.5 g. of tan solid, m.p. 75–81°. An analytical sample, m.p. 84–85.5°, was prepared by one recrystallization from methanol.

Anal. Calcd. for $C_{15}H_{25}NO_2$: C, 71.7; H, 10.0; N, 5.6. Found: C, 71.8; H, 9.7; N, 5.6.

When this compound was dissolved in dilute acid, hydrolysis to the keto ester did not take place to any appreciable extent.

Cyclononanone. A.—Methyl 2-(1-pyrrolidinyl)-1-cyclononene-1-carboxylate (12, 6.0 g., 0.024 mole) dissolved in 25 ml. of methanol was treated with 8 ml. of 25% aqueous sodium hydroxide solution. The methanol was distilled and gradually replaced with water. The resulting two-phase mixture was extracted with ether, and the ether extract was washed with dilute hydrochloric acid. Evaporation of the ether yielded 3.2 g. (95%) of cyclononanone, which was pure according to vapor phase chromatography and which had an infrared spectrum identical with a published spectrum.[19] The 2,4-dinitrophenylhydrazone, m.p. 142–143° (lit. m.p. 139–140°,[20] 146°[21]), and the semicarbazone, m.p. 182–185° (lit.[22] m.p. 183°) were prepared by standard methods.

B.—To a solution of 27 g. (0.16 mole) of 1-(1-cyclohepten-1-yl)-pyrrolidine in 50 ml. of ether was added 14 g. (0.165 mole) of methyl propiolate. The reaction was carried out at 20–28°. The solvent was removed *in vacuo*, and the residue (46 g.) was dissolved in 165 ml. of acetic acid. The acetic acid solution was hydrogenated over 8 g. of 5% palladium on carbon at 40 p.s.i. until 0.16 mole of hydrogen had been absorbed. The mixture was filtered to remove catalyst, and the acetic acid was removed by distillation under reduced pressure until the base temperature reached 50° at 1 mm. The residue (56 g.) was dissolved in 100 ml. of methanol and was treated with 80 g. of 25% aqueous

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(20) K. Schenker and V. Prelog, *Helv. Chim. Acta*, **36**, 896 (1953).
(21) V. Prelog, K. Schenker, and W. Küng, *ibid.*, **36**, 471 (1953).
(22) L. Ruzicka, Pl. A. Plattner, and H. Wild, *ibid.*, **26**, 1637 (1943).

sodium hydroxide solution. The methanol was distilled over a period of 2 hr., after which the two-phase mixture was cooled and extracted twice with ether. The ether solution was washed with dilute hydrochloric acid and dried over magnesium sulfate. After evaporation of the ether, the residue was distilled to yield 12.5 g. (54% from enamine) of cyclononanone, b.p. 91–95° at 12 mm. Vapor phase chromatography of this material indicated it to be about 91% cyclononanone, with one major and one minor impurity. The infrared spectrum was identical with that of pure cyclononanone except for a weak absorption at 6.06 μ.

Methyl 2-(1-Pyrrolidinyl)-1,9-cyclodecadiene-1-carboxylate.—To a solution of 52.0 g. (0.29 mole) of 1-(1-cycloocten-1-yl)pyrrolidine in 150 ml. of ether was added dropwise a solution of 24.9 g. (0.29 mole) of methyl propiolate in 50 ml. of ether. During the addition, the temperature was maintained at 28–32° by cooling. When most of the methyl propiolate had been added, a white solid began to separate. The mixture was stirred at 25–27° for 1.0 hr., cooled to 0°, and filtered to remove 61.5 g. (80%) of a white solid, m.p. 102–105°. An analytical sample, m.p. 103–105°, was prepared by recrystallization from acetone–ether.

Anal. Calcd. for $C_{16}H_{25}NO_2$: C, 73.0; H, 9.6. Found: C, 72.9; H, 9.4.

Although this compound was hydrolyzed normally in dilute acid and appeared stable at room temperature, it deteriorated on prolonged storage. The n.m.r. spectrum of a sample which had stood for 40 days at room temperature indicated that only about 20% of the sample had the original structure. When this 40-day-old sample was dissolved in dilute acid and allowed to stand for several hours, only a part of it hydrolyzed. An oil was recovered from the acid solution by making it basic, extracting with ether, and evaporating the ether. This oil appeared to be mainly one component, which had infrared maxima at 5.82 and 6.18 μ and single olefinic proton resonance at 6.80 (pair of doublets) and at 3.90 p.p.m. (triplet) in the n.m.r. spectrum. Thus, this oil appeared to have a structure analogous to that of oil 11 obtained so readily from the cyclononadiene derivative previously described.

Methyl 2-Oxo-9-Cyclodecene-1-carboxylate.—Methyl 2-(1-pyrrolidinyl)-1,9-cyclodecadiene-1-carboxylate, 32.0 g. (0.12 mole), was dissolved in a mixture of 60 ml. of 10% hydrochloric acid and 40 ml. of water; the mixture was warmed at 55–60° on a steam bath. After 0.5 hr. and 1.0 hr., the mixture was cooled and extracted with ether to yield 12.5 g. and 10.5 g., respectively, of colorless oil. Additional heating yielded no more product. The oil was distilled to yield 19.0 g. (74%) of methyl 2-oxo-9-cyclodecene-1-carboxylate, b.p. 109–111° at 0.9 mm., $n^{20}D$ 1.4950.

Anal. Calcd. for $C_{12}H_{18}O_3$: C, 68.4; H, 8.6. Found: C, 68.5; H, 8.7.

Cyclodecanone.—A solution of 18.5 g. (0.088 mole) of methyl 2-oxo-9-cyclodecene-1-carboxylate in 50 ml. of cyclohexane was hydrogenated at 40 p.s.i. over 0.5 g. of 5% palladium on alumina until 0.09 mole of hydrogen had been absorbed. Filtration of the hydrogenation mixture, followed by removal of solvent, yielded 17 g. of residue which was dissolved in 50 ml. of methanol. The methanol solution was treated with 18 g. of 50% aqueous potassium hydroxide solution, and the resulting two-phase mixture was heated at reflux for 0.8 hr. The cooled mixture was extracted with 100 ml. of ether, and the extract was washed with 15 ml. of water. The combined aqueous solutions were extracted with 50 ml. of ether. The combined ether solutions were distilled to remove low-boiling materials, first at atmospheric pressure and finally by heating to a base temperature of 105° at 14 mm. The residue of cyclodecanone weighed 10.0 g. (87%) and contained less than 3% impurities according to vapor phase chromatography. The infrared spectrum was essentially the same as a published spectrum[19] and as a spectrum of commercial cyclodecanone. The 2,4-dinitrophenylhydrazone, m.p. 166° (lit.[23] m.p. 167°), and the semicarbazone, m.p. 205–206° (lit.[19] m.p. 203.5–205.5°), were prepared by standard methods.

Methyl 2-(1-Pyrrolidinyl)-1,13-cyclotetradecadiene-1-carboxylate.—To a solution of 7.33 g. (0.031 mole) of 1-(1-cyclododecen-1-yl)pyrrolidine in 20 ml. of refluxing hexane was added 2.62 g. (0.031 mole) of methyl propiolate. The heat of the reaction maintained the temperature at reflux during the addition although the heating mantle was removed. After addition of the propiolate was complete, heating was resumed for 5 min. The chilled reaction mixture yielded 8.0 g. (81%) of methyl 2-(1-pyrrolidinyl)-1,13-cyclotetradecadiene-1-carboxylate, m.p. 59.5–62°. Attempts to recrystallize this product from several solvents were unsuccessful. In those cases when the material separated from the solvent, the melting point was lowered, sometimes to the extent that only an oil was obtained. Accordingly, an analysis was obtained from the crude product.

Anal. Calcd. for $C_{20}H_{33}NO_2$: C, 75.2; H, 10.4; N, 4.4. Found: C, 75.7; H, 10.8; N, 4.4.

Methyl 2-Oxo-13-cyclotetradecene-1-carboxylate.—Methyl propiolate (136 g., 1.62 moles) was added as rapidly as possible (*ca.* 15 min.) to a refluxing solution of 348 g. (1.63 moles) of 1-(1-cyclododecen-1-yl)pyrrolidine in 500 ml. of hexane. Immediately after the addition was complete, the solvent was removed at reduced pressure, and the residue was added to a well-stirred solution of 200 ml. of concentrated hydrochloric acid in 400 ml. of water. After it was warmed on the steam bath for 30 min., the hydrolysis mixture was cooled and extracted with two 200-ml. portions of ether. Evaporation of the ether yielded an oil, which soon began to crystallize. After being dried overnight *in vacuo*, a small fraction of the product had a melting point of 49–51°. An analytical sample, m.p. 51.5–53.5°, was recrystallized from methanol and from hexane.

Anal. Calcd. for $C_{16}H_{26}O_3$: C, 72.1; H, 9.8. Found: C, 71.3; H, 9.8.

Cyclotetradecanone.—The crude methyl 2-oxo-13-cyclotetradecene-1-carboxylate (see above) in 2 l. of methanol was passed through a 3-cm. bed of activated alumina and then was treated with decolorizing charcoal. The filtered solution was hydrogenated at room temperature and 40 p.s.i. over 10 g. of 5% palladium on alumina. After filtration to remove catalyst, the methanol solution was treated with 348 g. of 50% sodium hydroxide solution and 2.5 l. of water. The resulting mixture was stirred at room temperature for 11 days and the product which separated was removed by filtration every 2–3 days. There was obtained a total of 253 g. (67%) of cyclotetradecanone, m.p. 49–51°, lit.[24] m.p. 52°. The semicarbazone had a melting point of 198.5–199.5°, lit.[24] m.p. 197–198°.

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(24) L. Ruzicka, M. Stoll, and H. Schinz, *ibid.*, **9**, 249 (1926).