Anal. Calcd for $C_{26}H_{35}NO_5$: C, 70.71; H, 7.99; N, 3.17. Found: C, 70.69; H, 7.98; N, 3.29.

Conversion of Aldol XIa into Quinoline XIIIa.—The transformation of XIa (160 mg) into XIIIa (100 mg) was carried out in acetic acid (4 ml) with reduced iron (200 mg) as described for the conversion of XIb into XIIIb. The intermediate (3β-acetate of XIIIa) was hydrolyzed in 4% methanolic sodium hydroxide (5 ml) for 12 hr at room temperature. Evaporation of the methanol left 100 mg of crude air-dried XIIIa as a yellowish solid. The product was recrystallized from ethanol–water to furnish white needles, mp 232–234°. A mixture melting point with authentic[2] XIIIa showed no depression. The infrared spectra of the product and that of authentic XIIIa were superimposable.

16-(o-Nitro-α-hydroxybenzyl)androstan-17-one (XIc).—A one-tenth aliquot of a phenylmagnesium bromide solution (prepared from 0.48 g of magnesium and 3.5 g of bromobenzene in 25 ml of dry ether) was added to a solution of 0.54 g of androstan-17-one in 12 ml of dry ether. The addition was accompanied by boiling. The slightly turbid solution was heated under reflux for 1.5 hr on a steam bath. o-Nitrobenzaldehyde (300 mg) in dry ether (10 ml) was added and heating was continued for 5 hr. The mixture was treated with dilute hydrochloric acid and the ether layer was washed with water, dried over anhydrous magnesium sulfate, filtered, and evaporated to give a yellow oil (470 mg) that solidified partially on standing. The product could not be recrystallized. It had ν_{max} 3450 (OH), 1725, 1650, 1630, 1530 (NO_2), and 1340 (NO_2) cm^{-1}.

16-o-Nitrobenzalandrostan-17-one (Vc).—The alcohol XIc (300 mg) was warmed with 6 ml of pyridine–acetic anhydride (1:2) for 6 hr. The solution was cooled and poured into ice to give the acetate Vc as a yellow sticky oil (300 mg): ν_{max} 1730 (b, s), 1600, 1525 (NO_2), and 1340 (NO_2) cm^{-1}. This crude material (290 mg) was dissolved in benzene (1 ml) and chromatographed over 10 g of alumina. The product, Vc (173 mg), was eluted with 100-ml portions of Skellysolve F (bp 40–55°)–benzene (8:2, 7:3, 6:4). It was recrystallized from methanol to give long yellowish prisms, melting at 175–177°. An analytical sample of Vc melted at 176–177°: ν_{max} 1720, 1640 (conjugated C=O), 1530 (NO_2), and 1340 (NO_2) cm^{-1}; λ_{max} 260 mμ (ϵ 17,350).

Anal. Calcd for $C_{26}H_{33}NO_3$: C, 76.62; H, 8.16; N, 3.44. Found: C, 76.74; H, 8.18; N, 3.63.

A Novel Reaction of Diketene with Water

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The reaction of diketene with water in the presence of a tertiary amine catalyst is described. Under carefully controlled conditions the major products of the reaction are 2,6-dimethyl-4H-pyran-4-one and 2,4,6-heptanetrione. An nmr spectrum of the latter compound is also discussed.

In the absence of a catalyst diketene does not appear to react readily with water to form acetoacetic acid; it may even be distilled in the presence of water with little decomposition.[1] However, in the presence of acidic and basic catalysts diketene is hydrolyzed easily to give acetoacetic acid (I) (Scheme I) which in turn decomposes to acetone and carbon dioxide.[1-3] We have now found that I in the presence of tertiary amines can react further with diketene to produce 2,4,6-heptanetrione (II) and 2,6-dimethyl-4H-pyran-4-one (III) in good yields.[4]

SCHEME I
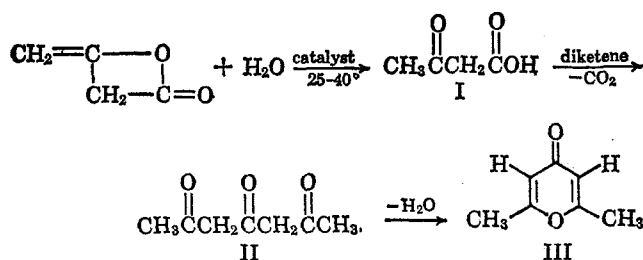
The best catalyst for the reaction was found to be 1,4-diazabicyclo[2.2.2]octane (DABCO). Under the mildest conditions the reaction proceeded smoothly in the absence of a solvent. A less effective catalyst was pyridine. With triethylamine the yield of the two products was very poor. The desired reaction did not occur at all when a catalytic amount of concentrated sulfuric acid was used. With hydrochloric acid a reaction appeared to occur initially, *but then the reaction proceeded so violently that the reaction vessel disintegrated.*

In order to obtain good yields of II and III, it was necessary to add 2 moles of diketene to 1 mole of water containing a catalytic amount of DABCO. When the molar amount of diketene with respect to water was increased to 2.5, the yield of the two products decreased. The reaction was exothermic and required a slow rate of addition or external cooling to maintain the temperature range. After the addition was complete the reaction mixture was kept at 30–40° for several hours until carbon dioxide ceased to evolve. Any low-boiling products (mainly acetone) formed during the reaction were removed on a rotary evaporator at 25° under reduced pressure. II and III were obtained as a mixture in ratios varying from 3:1 to 2:3 depending on the reaction conditions, and the combined yield was 60–78% according to vapor phase chromatographic analyses. Separation of the two products could be accomplished by fractional recrystallization.
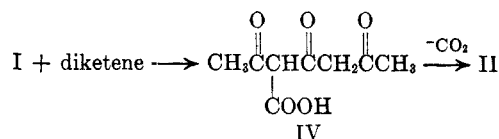
The yields of the desired products were also influenced by the reaction temperature. The best temperature range was 25–40°. At lower temperatures the reaction was very slow; at higher temperatures than 60° the reaction became difficult to control.

Although the detailed mechanism for the reaction is not known, a speculation concerning the possible intermediates is of interest. In an attempt to identify the intermediates, the reaction between diketene and water was followed by infrared and nmr spectroscopy. When 1 mole of diketene was allowed to react with 1 mole of water in the presence of DABCO, the product was definitely acetoacetic acid (I) which decomposed gradually into carbon dioxide and acetone. With 2

(1) A. B. Boese, *Ind. Eng. Chem.*, **32**, 16 (1940).
(2) J. M. Briody and D. P. N. Satchell, *J. Chem. Soc.*, 3778 (1965).
(3) N. T. M. Wilsmore and F. Chick, *ibid.*, **93**, 946 (1908).
(4) For interconversions of II and III see ref 5–7.
(5) F. Feist and H. Belert, *Ber.*, **28**, 1817 (1895).
(6) J. N. Collie and A. A. B. Reilly, *J. Chem. Soc.*, **119**, 1550 (1921).
(7) A. Feist, *Ann.*, **257**, 253 (1890).

moles of diketene and 1 mole of water, very weak bands caused by an intermediate of unknown structure were formed at some time during the reaction. Apparently the unknown intermediate had only a short lifetime.
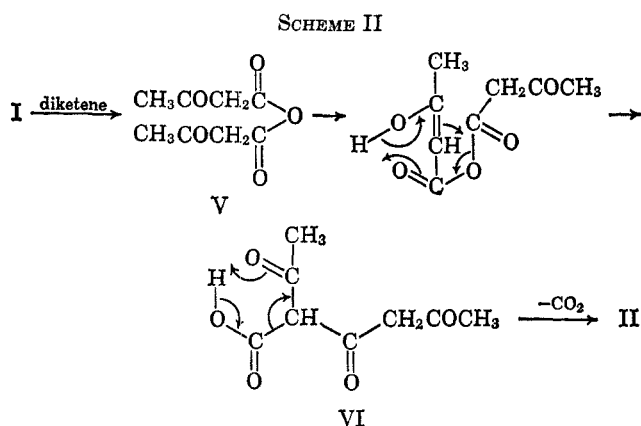
If acetoacetylation occurred at the active methylene group of I, the explanation would be very simple. The loss of carbon dioxide from the unstable acetoacetyl-acetoacetic acid (IV) would lead to II.

$$I + diketene \longrightarrow CH_3\overset{O}{\underset{}{C}}CH\overset{O}{\underset{\underset{COOH}{|}}{C}}CH_2\overset{O}{\underset{}{C}}CH_3 \xrightarrow{-CO_2} II$$
$$IV$$

However, acetoacetylation might also take place at the carboxyl group of I forming the unknown acetoacetic anhydride (V) as an intermediate. It has been reported that aromatic and aliphatic acids react with diketene to form mixed anhydrides of acetoacetic acids which decompose to the anhydride of the initial acid.[8]
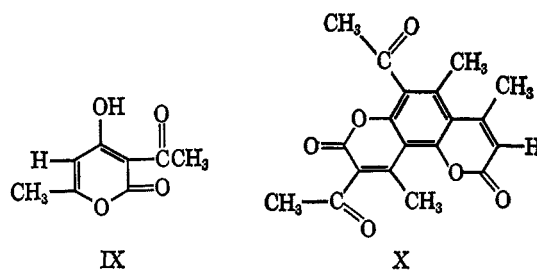
$$RCOOH \xrightarrow{diketene} RCO_2COCH_2COCH_3 \xrightarrow{RCOOH}$$

$$(RCO)_2O + (CH_3)_2CO + CO_2$$
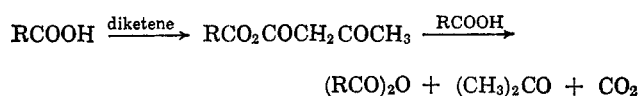
Similarly, diketene could react with I to give V. V could rearrange to VI which in turn would decarboxylate to produce II (Scheme II).

SCHEME II

V

VI

In a further attempt to shed light on the mechanism, diketene was allowed to react with ethyl acetoacetate in the presence of DABCO. Should a reaction occur at the active methylene group of ethyl acetoacetate, VII and VIII might be expected as products.

$$CH_3COCH_2CO_2C_2H_5 \xrightarrow{diketene}$$

VII   VIII
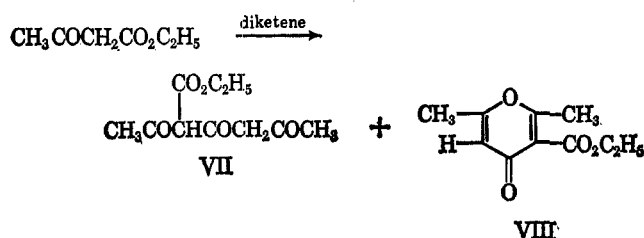
However, only dehydroacetic acid (IX) and a small

(8) H. J. Hagemeyer, U. S. Patent 2,476,859 (July 19, 1949).

IX   X

amount of a high-melting compound tentatively identified as X[9] could be isolated. Since IX could also be formed from the initial ethyl acetoacetate–diketene adduct, these results did not prove whether a reaction did or did not occur at the methylene group of ethyl acetoacetate.


$$\xrightarrow{-C_2H_5OH} IX$$
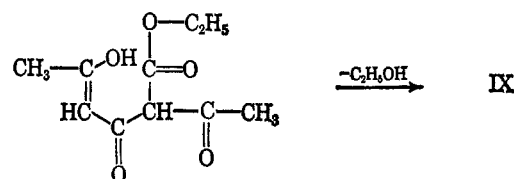
We have also investigated the reaction of diketene with acetic acid in the presence of DABCO at several temperatures (20–70°). The products formed were acetic anhydride (XII), IX, II, and III. Again, II and III could have been formed in two different ways: (a) the mixed anhydride (XI) could react with itself to

$$2CH_3CO_2COCH_2COCH_3 \longrightarrow CH_3CO_2COCH_3 + V$$
$$XI \qquad\qquad\qquad\qquad XII$$
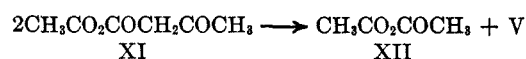
give XII and acetoacetic anhydride (V), which in turn would produce II and III, or (b) XI could react with another mole of acetic acid to form XII and acetoacetic acid (I); I could then react further with diketene to give II and III.

$$XI + CH_3COOH \longrightarrow XII + I$$

II and III have been reported by Feist and Belert,[5] and later by Collie and Reilly.[6] Both compounds were synthesized from dehydroacetic acid (IX) by the following reactions.

$$IX + HCl \xrightarrow[\Delta\Delta]{H_2O} III$$

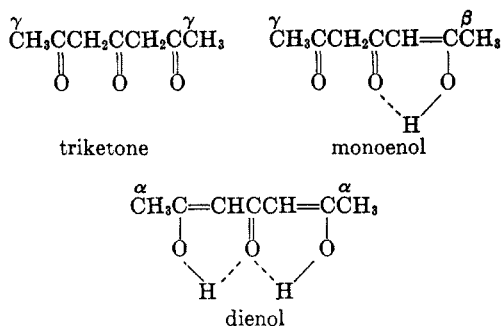$$III \xrightarrow[H_2O]{Ba(OH)_2} \xrightarrow[-BaCl_2]{HCl} II$$
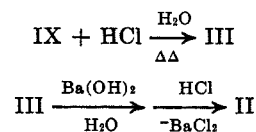
A comparison of the products obtained by the reaction of diketene and water with those obtained by Feist's method shows no difference in properties.

The nmr spectrum of II is of particular interest.[10] A solution of II in deuterated chloroform gives rise to a spectrum that shows II to be a mixture of 7% triketone, 68% monoenol, and 25% dienol. Three singlets at 1.95, 2.05, and 2.22 ppm can be assigned to two methyl groups in the dienol $(CH_3)_\alpha$, one group in the monoenol $(CH_3)_\beta$, and the two groups in the triketone as well as one group in the monoenol $(CH_3)_\gamma$. Two singlets at 3.40 and 3.68 ppm are produced by one methylene group in the monoenol and two methylene groups in the

(9) A report of this work will be published in a subsequent paper.

(10) The nmr spectrum of the related 2,4-pentanedione has been studied previously by other investigators: H. S. Jarrett, M. S. Sadler, and J. N. Shoolery, J. Chem. Phys., 21, 2092 (1953); L. W. Reeves, Can. J. Chem., 35, 1351 (1957).

$$\overset{\gamma}{CH_3}CCH_2CCH_2\overset{\gamma}{C}CH_3 \qquad \overset{\gamma}{CH_3}CCH_2CCH\!=\!\overset{\beta}{C}CH_3$$

triketone   monoenol

$$\overset{\alpha}{CH_3}C\!=\!CHCCH\!=\!\overset{\alpha}{C}CH_3$$

dienol

triketone, respectively. Two olefinic hydrogens of the dienol and one olefinic hydrogen of the monoenol show up as singlets at 5.16 and 5.60 ppm, respectively. Two broad resonance signals at 14.1 and 14.8 ppm are caused by the hydrogen of the hydroxyl group of the monoenol and the hydrogens of the two hydroxyl groups of the dienol, respectively. A comparison of the actual number of hydrogens corresponding to each peak with the calculated number based on the assumed enol distribution shows very close correlation (see Table I).

TABLE I
NMR DATA OF 2,4,6-HEPTANETRIONE

Hydrogen type	Position, ppm	No. of hydrogens Theoretical	Actual
$(CH_3)_\alpha$ in dienol	1.95	1.50	1.51
$(CH_3)_\beta$ in monoenol	2.05	2.04	2.12
$(CH_3)_\gamma$ in monoenol and triketone	2.22	2.46	2.54
CH_2 in monoenol	3.40	1.36	1.37
CH_2 in triketone	3.68	0.28	0.29
CH= in dienol	5.16	0.50	0.53
CH= in monoenol	5 60	0.68	0.65
OH in monoenol	14.1	0.68	0.57
OH in dienol	14.8	0.50	0.42

The ultraviolet spectrum of II in methanol shows 2 peaks, at 272 mμ (ϵ_{max} 8774) and at 317 mμ (ϵ_{max} 4627). The more intense peak at shorter wavelength is assigned to the conjugated carbonyl group of the monoenol, while the less intense peak at longer wavelength is attributed to the doubly conjugated carbonyl groups of the dienol.

Another reaction that is of interest is the conversion of II and III into 2,6-dimethyl-4-pyridinol (XIII), a compound originally reported by Feist.[7] It was found that by heating the crude reaction mixture obtained by the reaction of diketene and water with ammonium hydroxide under pressure, XIII was obtained in quantitative yields.

II + III $\xrightarrow[100°]{NH_4OH}$ XIII
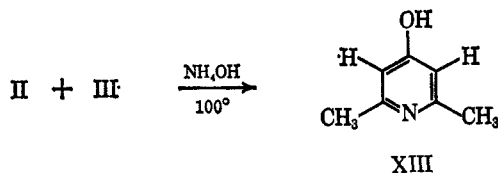
We have also investigated the reaction of diketene with hydrogen sulfide in the presence of DABCO. The gas evolved during the reaction was identified by mass spectroscopy as carbonyl sulfide. Other products obtained from the reaction were mainly IX and small amounts of II and III.

Experimental Section

All melting points are uncorrected. The nmr spectra were obtained from a Varian A-60 spectrometer with tetramethylsilane as an internal standard. The infrared spectra were taken on Baird-Atomic Models 4–55 and AB-2, the ultraviolet spectra on a Cary Model 14. The mass spectrometer used was a Consolidated Electrodynamics Corporation Model 21–130 instrument. Microanalyses were performed by Union Carbide European Research Associates, Brussels, Belgium. Vapor phase chromatograms were taken on an F and M Model 720 chromatograph.

Apparatus.—The reactions of diketene with water were conducted in a 500-ml four-necked flask equipped with a stirrer, dropping funnel, thermometer, and condenser; the condenser was connected to a gas trap for detection of carbon dioxide. A cooling bath maintained the reaction temperature at 25–40°. For the reaction of II and III with ammonium hydroxide, a 500-ml Parr bomb was used.

Reaction of Diketene with Water Using DABCO as Catalyst.—DABCO (0.5 g) was dissolved in water (18.0 g, 1.0 mole). Diketene (168 g, 2.0 moles) was added slowly at 25–30° over a period of 1.5 hr. After the addition the reaction mixture was kept at 30–40° several hours longer until carbon dioxide ceased to evolve. Any low-boiling products formed during the reaction were removed on a rotatory evaporator under reduced pressure. Gas chromatographic analyses taken by comparison with solutions containing known amounts of II and III indicated that a yield of 59% of II and 19% of III was obtained.

In a similar experiment, after the low-boiling products had been removed, the solid which precipitated was filtered off; it was mainly compound III, mp 124–130°. A mixture of this sample and a pure sample of III prepared by the method of Collie and Reilly[6] showed no depression in melting point. Further cooling of the mother liquor gave a mixture of II and III. The two products were separated by fractional recrystallization from cyclohexane. The trione (II) obtained melted at 45–47° (lit.[5] mp 49°).

Anal. Calcd for $C_7H_{10}O_3$: C, 59.10; H, 7.05. Found: C, 58.81; H, 7.10.

Its infrared spectrum (KBr pellet) was very similar to that of 2,4-pentanedione except in the fingerprint region, 10–14 μ, where it was more complex.

The nmr spectrum was taken at 36° in a concentration of approximately 35% by weight in deuterated chloroform. For nmr data see Table I.

Use of Pyridine and Triethylamine as Catalysts. A.—The reaction conditions in this experiment were the same as described in the previous experiment except that 1.0 g of pyridine instead of DABCO was used. The combined yield of II and III was 41%.

B.—Under the same conditions when 0.5 g of triethylamine was used in place of DABCO, the combined yield was only 16%.

2,6-Dimethyl-4-pyridinol (XII).—Ammonium hydroxide (30%) (350 ml) was added to 128.4 g of the crude reaction mixture which had been prepared by treating 2.5 moles of diketene with 1.0 mole of water using DABCO as catalyst. The crude mixture contained 26% by weight of II and 28% by weight of III according to gas chromatographic analyses. The mixture was heated to 100° in a rocker bomb for 18 hr. Excess ammonium hydroxide was then removed by distillation under reduced pressure. The solid was filtered and recrystallized from ethanol to give 63.5 g of XII, mp 227–229° (lit.[7] mp 225°).

Concentration of the mother liquor afforded another 3.5 g of product, mp 223–225°. The total yield was 99%. A mixture of the product and that obtained by Feist's method[7] showed no depression in melting point.

Reaction of Diketene with Ethyl Acetoacetate.—DABCO (1.0 g) was dissolved in ethyl acetoacetate (130.1 g, 1.0 mole). Diketene (84 g, 1.0 mole) was added at 27–34° over a period of about 1 hr. After the addition the mixture was stirred for 2.5 hr at room temperature. It was then cooled to 0° and filtered to give 36 g of solid, which was a mixture of IX and X.[9] The two compounds were separated by washing the mixture with acetone and then by fractional recrystallization from methanol. IX was recovered from the acetone and methanol, mp 104–107°. Its infrared spectrum indicated that it was dehydroacetic acid. The relatively insoluble residue believed to be X, melted at 228–230°.

Anal. Calcd for $C_{19}H_{16}O_6$ (X): C, 67.00; H, 4.71. Found: C, 66.81; H, 4.85.

The original mother liquor consisted mainly of ethyl aceto-acetate and some IX according to gas chromatography.

Reaction of Diketene with Acetic Acid.—DABCO (1.0 g) was added to glacial acetic acid (60 g, 1.0 mole). Diketene (84 g, 1.0 mole) was added slowly at 25–50° over a period of 1 hr. After the addition the mixture was kept at 45–50° until carbon dioxide stopped evolving. The mixture was cooled to 0° and filtered to give 8.6 g of IX, mp 102–105° (mixture melting point with a pure sample of IX showed no depression). The filtrate was then fractionally distilled. The first fraction of the distillate was identified by infrared spectroscopy as acetone, while the later fractions were a mixture of unchanged acetic acid and acetic anhydride. On filtering the residue, 14.4 g of a solid identified

as III was obtained, mp 128–132°. Gas chromatographic analyses indicated that the filtrate also contained about 7 g of II.

Reaction of Diketene with Hydrogen Sulfide.—DABCO (0.5 g) was dissolved in benzene (200 ml) containing about 2 g of hydrogen sulfide. Diketene (84 g, 1.0 mole) was added over a period of 2 hr at 18–20° while hydrogen sulfide (17 g) was also bubbled through. After the addition the mixture was kept at 20° for 2 hr and then at 40° for a few hours longer until gas ceased to evolve. The gas was identified by mass spectroscopy as carbonyl sulfide. Gas chromatographic analyses indicated that the reaction mixture contained mainly IX, and small amounts of II and III. The combined yield of II and III was approximately 10%.

Synthesis of cis- and trans-7-Azabicyclo[4.2.0]octanes[1-3]

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Base treatment of N,O-ditosyl-*trans*-2-aminomethylcyclohexanol (8) and N,O-ditosyl-*cis*-2-aminocyclohexane-methanol (12) led to the identical fused-ring azacyclobutane derivative, 7-tosyl-*cis*-7-azabicyclo[4.2.0]octane (1a). Similar treatment of N,O-ditosyl-*trans*-2-aminocyclohexanemethanol (16) converted it to 7-tosyl-*trans*-7-azabicyclo[4.2.0]octane (2a). Reductive detosylation of 1a and 2a with sodium in isoamyl alcohol led, respectively, to the previously unreported parent heterocycles, *cis*- (1b) and *trans*-7-azabicyclo[4.2.0]octane (2b). The adduct, 7-chlorosulfonyl-8-ketobenzo[d]-*cis*-7-azabicyclo[4.2.0]octane (17), prepared by chlorosulfonyl isocyanate addition to 1,2-dihydronaphthalene, was reduced with lithium aluminum hydride to benzo[d]-*cis*-7-azabicyclo[4.2.0]octane (3a). Unstable 1b, 2b, and 3a were converted to their equally unstable N-methyl derivatives *via* the Eschweiler–Clarke procedure.

We have applied an interest in both strained bicyclic compounds[4] and ring-fused azacyclobutanes[5] to the successful synthesis of the previously unreported parent heterocycles, *cis*- (1b) and *trans*-7-azabicyclo[4.2.0]-octane (2b),[7,8] and benzo[d]-*cis*-7-azabicyclo[4.2.0]-octane (3a).

(1) This research was supported by the Directorate of Chemical Sciences, Air Force Office of Scientific Research under Grant AF-AFOSR-488-64.

(2) Taken entirely from the Ph.D. Thesis of P. H. M., Fordham University, 1966.

(3) Presented, in part, at the 4th Annual Metropolitan Regional Meeting of the American Chemical Society, Hoboken, N. J., Feb 1, 1965, and before the Organic Division at the 150th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 14, 1965; Abstracts, p 18S.

(4) See J. Meinwald, J. T. Tufariello, and J. J. Hurst, *J. Org. Chem.*, **29**, 2914 (1964), for leading references and a discussion of highly strained *trans*-fused bicyclic compounds.

(5) Aside from the penicillins which contain a fused β-lactam system, authentic examples of fused azacyclobutanes include: 2,2-dimethyl-4-isopropylidene-1-azabicyclo[3.2.0]heptane (i),[5a] 6-azabicyclo[3.1.1]heptane (ii),[5b] 1-azabicyclo[2.2.0]hexane (iii),[5c] two diastereoisomers of 8-methyl-1-azabicyclo[4.2.0]octanes (iv),[5d] N,N-dimethyl-6-azabicyclo[3.2.0]heptane tosylate (v),[5e] and 6-azabicyclo[3.2.0]heptane (vi).[5f] The so-called acylanthranils (vii)[5g] have been shown to have the isomeric benzoxazine structure (viii).[5h]

1a, R = Ts   2a, R = Ts   3a, R = H
b, R = H   b, R = H   b, R = CH₃
c, R = CH₃   c, R = CH₃
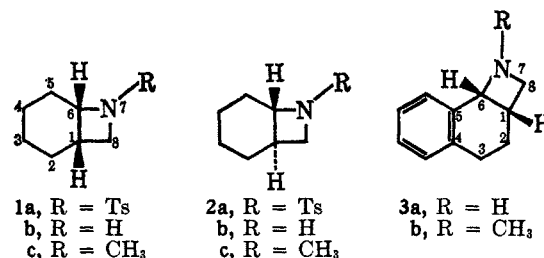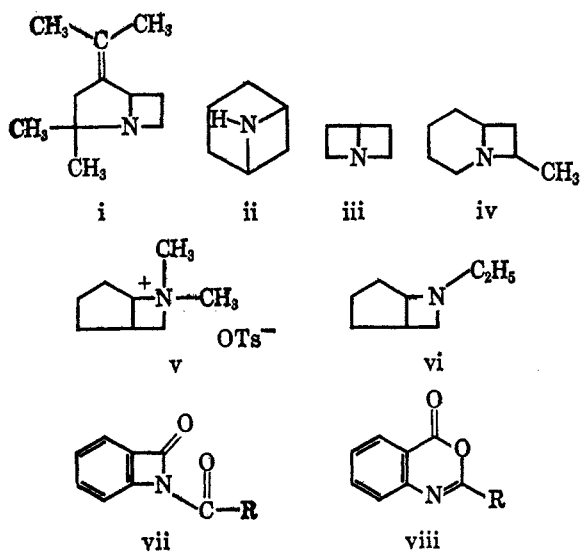
In the reaction sequence summarized in Chart I, the key compound required was the N,O-ditosylate (8) of the known *trans*-2-aminomethylcyclohexanol (7).[10] The less stable conformer of 8 would have the two *trans*-axial tosyl-substituted groups most favorably situated for ring closure to a *cis*-fused azacyclobutane.

(6) (a) A. I. Meyers and W. Y. Libano, *ibid.*, **26**, 1682 (1961); (b) J. V. Braun, W. Haensel, and F. Zobel, *Ann.*, **462**, 283 (1928); (c) C. A. Grob, *Helv. Chim. Acta*, **47**, 2145 (1964); (d) K. Löffler, *Ber.*, **37**, 1879 (1904); K. Löffler and A. Grosse, *ibid.*, **40**, 1325 (1907); K. Löffler and H. Remmler, *ibid.*, **43**, 2048 (1910); (e) C. A. Grob, *Bull. Soc. Chim. France*, 1360 (1960); (f) P. G. Gassman and D. C. Heckert, *Tetrahedron*, **21**, 2725 (1965); (g) P. R. Levy and H. Stephen, *J. Chem. Soc.*, 1588 (1938); (h) D. T. Zentmyer and E. C. Wagner, *J. Org. Chem.*, **14**, 967 (1949).

(7) J. A. Moore ["Heterocyclic Compounds with Three- and Four-Membered Rings," Vol. XIX, Part 2, A. Weissberger, Ed., Interscience Publishers, Inc., New York, N. Y., 1964, p 914] has noted "no authentic members have been recorded" containing the 7-azabicyclo[4.2.0]octane framework.

(8) Oxygen and sulfur analogs of 1b and/or 2b recently reported include *cis*- and *trans*-7-oxabicyclo[4.2.0]octanes[9a] and 7-thiabicyclo[4.2.0]octane[9b] of unspecified stereochemistry.

(9) (a) Ö. Kovács, Z. Tuba, I. Weisz, and Gy. Schneider, *Chem. Ind.* (London), 1222 (1961); A. Rosowsky and D. S. Tarbell, *J. Org. Chem.*, **26**, 2255 (1961); (b) D. C. Dittmer and F. A. Davis, *ibid.*, **29**, 3131 (1964); D. C. Dittmer and F. A. Davis, *J. Am. Chem. Soc.*, **87**, 2064 (1965).

(10) M. Mousseron, J. Jullien, and F. Winternitz, *Bull Soc. Chim. France*, **15**, 878 (1948).

i   ii   iii   iv

v   vi

vii   viii