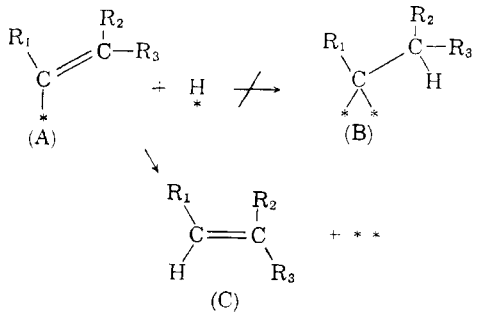
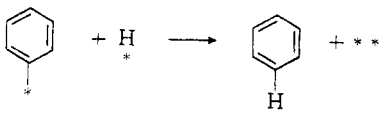
which requires the desorption of a cycloalkene, it might be formed *via* some surface complex (A) such as one postulated by Burwell[19] to explain the racemization of an optically active alkane while undergoing exchange with deuterium atoms on the catalytically active surfaces of noble metals. However, as discussed elsewhere,[3] the most probable reaction of this intermediate with hydrogen is one yielding an alkene (C) rather than another surface complex (B).

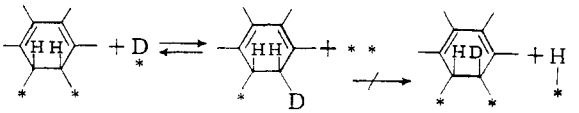


Further, the experiments of Anderson and Kemball on the deuteration of benzene[20] indicated that the exchange with benzene involved chemisorbed phenyl and phenylene radicals while the addition proceeded in a parallel reaction which involved little or no additional exchange with deuterium. Such a mechanism was first postulated by Farkas and Farkas.[21] The geometrical relationship of the phenyl radical to the surface atoms should be analogous to the intermediate A and apparently the preferred reaction path with hydrogen is the abstraction of hydrogen from the surface to release a molecule of benzene.



(19) R. L. Burwell, Jr., *Chem. Revs.*, **57**, 895 (1957).
(20) J. R. Anderson and C. Kemball, in ref. 7, p. 51.
(21) A. Farkas and L. Farkas, *Trans. Faraday Soc.*, **33**, 827 (1937).

Stereochemical arguments support the view that the exchange of hydrogen in benzene proceeds *via* the dissociative mechanism. The rival associative mechanism[18] fails for the reasons cited by Burwell in explaining why neither dissociative adsorption of an alkane nor the migration of the point of attachment to the surface of the half-hydrogenated state could account for the racemization of an optically active saturated hydrocarbon.[19] The replacement of a carbon to surface bond by a carbon to hydrogen bond occurs with retention of configuration at the carbon atom, and the reverse process must do likewise to be consistent with the principle of microscopic reversibility. Indeed, if the associative mechanism were operative for the exchange, then either di- or tetradeuteriobenzene should be more abundant than monodeuteriobenzene[21] because only *via* the desorption and readsorption, on its opposite face, of either cyclohexadiene or cyclohexene followed by dehydrogenation to benzene could the hydrogen be exchanged for deuterium in accord with the stereochemical restrictions of the postulated scheme.[22]



The associative mechanism for the *addition* of hydrogen to the benzene ring is supported by the observed stereochemistry of the hydrogenation of aromatic compounds and related cyclohexenes. It is not certain that every molecule of the cycloalkane which is formed passes through a desorbed cycloalkene, although a considerable portion must. But the fraction which does so is apparently a function of the pressure of hydrogen.

Acknowledgment.—The support by a grant from the National Science Foundation is gratefully acknowledged. This research was also supported in part by a grant from the Petroleum Research Fund administered by the American Chemical Society. Grateful acknowledgment is hereby made to the donors of this fund.

(22) R. L. Burwell, Jr., in ref. 7, p. 87.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY, CAMBRIDGE 39, MASS.]

The Synthesis of Certain Azabicyclic Ketones[1a]

BY HERBERT O. HOUSE, PETER P. WICKHAM[1b] AND HANSPETER C. MÜLLER

RECEIVED MARCH 15, 1962

The N-methyl derivatives of 3-azabicyclo[3.2.1]octan-8-one, 3-azabicyclo[3.3.1]nonan 9-one and 8-azabicyclo[4.3.1]-decan-10-one have been prepared by the direct reaction of methylamine and formaldehyde with cyclopentanone, cyclohexanone and cycloheptanone, respectively. The azabicycloöctanone also was obtained by a multi-step reaction sequence.

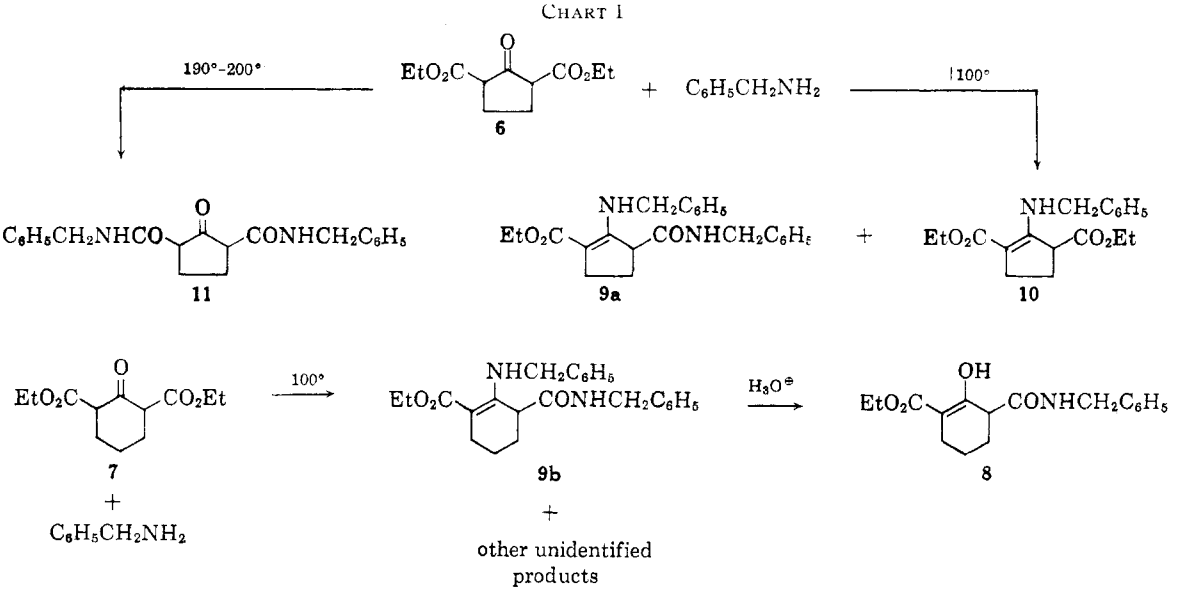
As substrates for a study of conformation, the stereodirective influence of an amine function on addition reactions and the stereochemistry of N-alkylation, we desired synthetic routes to the azabicyclic ketones **1**, **2** and **3**. Although the derivative **4** had been described[2] previously and the derivative **5** was described[3] during the course of

(1) (a) This research is supported by grants from the Alfred P. Sloan Foundation, the National Institutes of Health (RG-8761) and the McNeil Laboratories, Inc. (b) National Institutes of Health Predoctoral Fellow, 1958–1960.

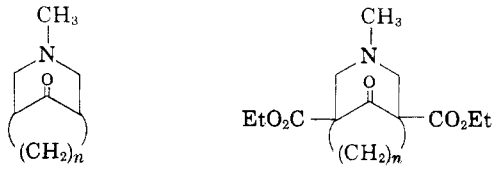
(2) E. F. L. J. Anet, G. K. Hughes, D. Marmion and E. Ritchie, *Austral. J. Sci. Research*, **3A**, 330 (1950).

(3) F. F. Blicke and F. J. McCarty, *J. Org. Chem.*, **24**, 1379 (1959).

CHART I

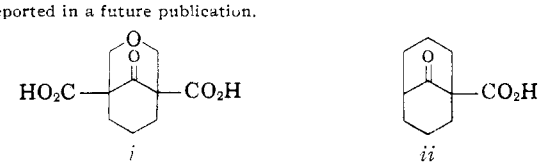


this work, only recently[4] has the unsubstituted amino ketone **2** been described as the product of decarboxylation[5] of the keto diester **5** in boiling, 20% hydrochloric acid.



1, $n = 2$; **2**, $n = 3$; **3**, $n = 4$ **4**, $n = 2$; **5**, $n = 3$

Our initial experiments were directed toward the synthesis of the keto amide **8** and its homologs with the thought that these products, after reduction of the enolic keto function to a hydroxyl group, could be cyclized to imides which could be reduced with lithium aluminum hydride.[6] A summary of the reaction of the keto diesters **6** and **7** with benzylamine[7] is presented in Chart I. The poor yields and complex product mixtures obtained prompted us to turn our attention to the reaction sequences summarized in Chart II. While this sequence provided one of the desired ketones **1** as well as one of its reduction products **28**,[8] it was clearly not a desirable preparative route to the bicyclic ketone **1**. We were stimulated to reinvestigate the claim[9] that reaction of cyclohexanone with formaldehyde and methylamine afforded the diketo amine **30** but not the bicyclic amino ketone **2** by the reported[10] isolation of the hydrochloride of the bicyclic amino ketone **3** from the reaction of cycloheptanone with formaldehyde and methylamine in acetic acid. We found that each of the three desired amino ketones **1–3** could be isolated from reaction of the monocyclic ketone **31** with formaldehyde and methylamine in acetic acid. Although the isolated yields of the desired bicyclic amino ketones are low and our attempts to improve them have thus far been unrewarding, the procedure is none-the-less rapid and makes the bicyclic ketones readily available in useful quantities. The formation and certain of the transformations of these bicyclic ketones are summarized in Chart III. The azabicycloöctanone **1** is unstable on storage and its salts exist as stable hydrates **32** and **33**. However, heating the quaternary salt hydrate **33** under reduced pressure did serve to form the keto ammonium salt **34a**.[11] The absence of ir-



(4) W. Schneider and H. Götz, *Naturwiss.*, **47**, 397 (1960); *Arch. Pharm.*, **294**, 506 (1961).

(5) This successful decarboxylation is to be contrasted with the thermal stability of the keto acids i [C. Mannich and W. Brose, *Ber.*, **56B**, 833 (1923)] and ii [A. C. Cope and M. E. Synerholm, *J. Am. Chem. Soc.*, **72**, 5228 (1950)]. We have established that the reaction conditions (ref. 4) which effect the conversion of **5** to **2** in 67% yield fail to cause the decarboxylation of the keto acid ii, more than 98% of the starting keto acid being recovered. However, our temptation to ascribe this apparent violation of Bredt's rule [F. S. Fawcett, *Chem. Revs.*, **47**, 219 (1950)] to the formation of monocyclic intermediates during the decarboxylation of the keto diacid derived from **5** was mitigated when we found that the same reaction conditions failed to convert the diester **4** to the ketone **1**. Our studies of this reaction will be reported in a future publication.

(6) For comparable syntheses, see (a) R. A. Barnes and H. M. Fales, *J. Am. Chem. Soc.*, **75**, 975 (1953); (b) L. M. Rice and C. H. Grogan, *J. Org. Chem.*, **22**, 1100, 1223 (1957); (c) L. M. Rice and C. H. Grogan, *ibid.*, **23**, 844 (1958); (d) L. M. Rice and C. H. Grogan, *ibid.*, **24**, 7 (1959); (e) L. M. Rice, *ibid.*, **24**, 1520 (1959); (f) S. Rossi, C. Valvo and W. Butta, *Gazz. chim. ital.*, **89**, 1164 (1959); (g) G. Cignarella, G. Nathansohn and E. Occelli, *J. Org. Chem.*, **26**, 2747 (1961); (h) S. W. Blackman and R. Baltzly, *ibid.*, **26**, 2750 (1961).

(7) For previous studies of the reaction of β-keto esters with primary amines, see (a) J. K. Thomson and F. J. Wilson, *J. Chem. Soc.*, 1262 (1933); (b) J. K. Thomson and F. J. Wilson, *ibid.*, 111 (1935); (c) S. Coffey, J. K. Thomson and F. J. Wilson, *ibid.*, 356 (1936); (d) C. J. Kibler and A. Weissberger, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 108; (e) R. J. Brown, F. W. S. Carver and B. L. Hollingsworth, *J. Chem. Soc.*, 4295 (1961).

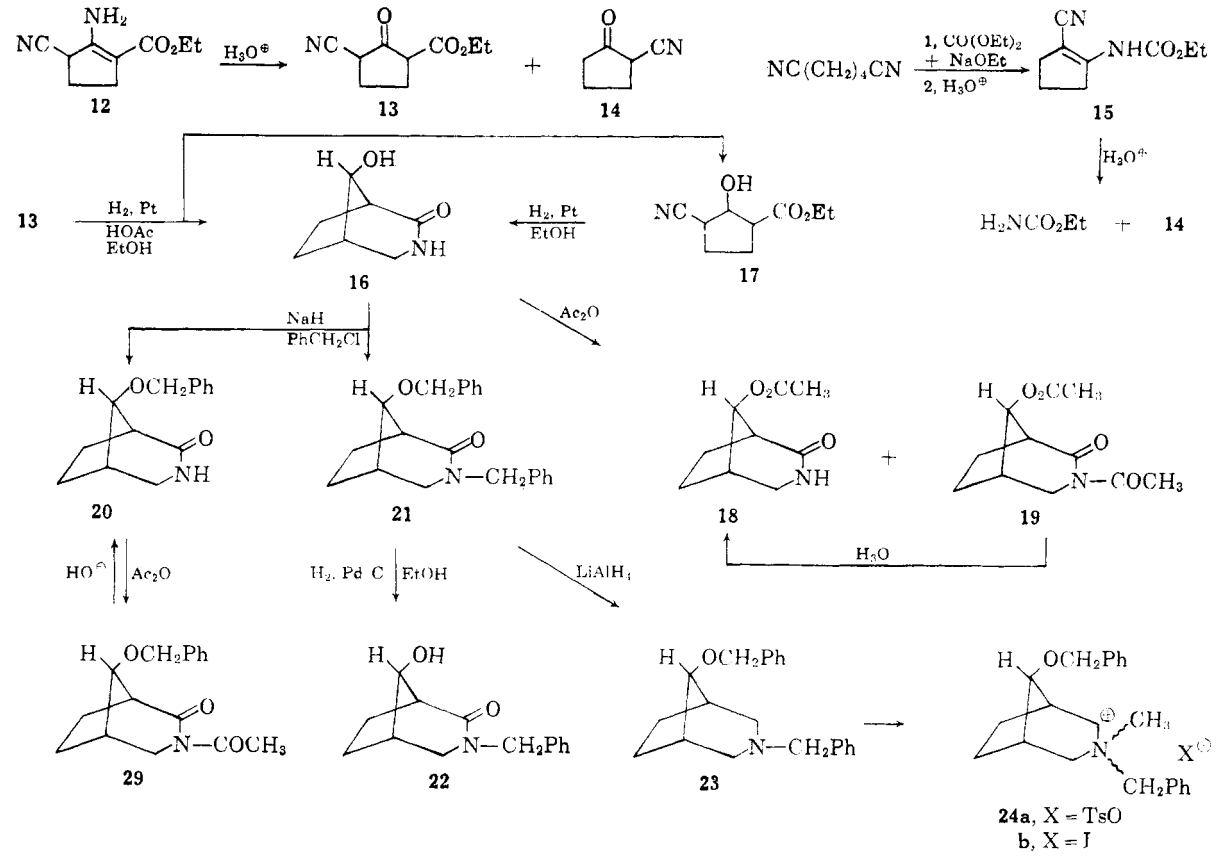
(8) This alcohol, and hence its precursors **16**, **21**, **23**, **24** and **26**, has been tentatively assigned the stereochemistry indicated in structure **28** for reasons to be discussed in a subsequent paper.

(9) C. Weatherbee, W. E. Adcock and D. Winter, *J. Org. Chem.*, **22**, 465 (1957).

(10) R. A. Covey, Ph.D. Dissertation, University of Michigan, 1957.

(11) For analogous cases, see (a) J. G. Murphy, J. H. Ager and E. L.

CHART II



regularities in the infrared and ultraviolet spectra of the ketones 1–3 suggests that there is no appreciable interaction between the amine and carbonyl functions (*i.e.*, 1 ⇄ 36). The physical properties of the amino ketones and their salts, discussed in the Experimental section of this paper, suggest that the preferred conformation of these substances is that illustrated in formula 37.

May, *J. Org. Chem.*, **25**, 1386 (1960); (b) E. L. May, H. Kugita and J. H. Ager, *ibid.*, **26**, 1621 (1961); (c) D. E. Applequist and J. P. Klieman, *ibid.*, **26**, 2178 (1961).

Acknowledgment.—We are indebted to Professor Norman A. LeBel for the dipole moment data recorded in this paper.

Experimental[12]

Reaction of 2,5-Dicarbethoxycyclopentanone (6) with Benzylamine. A.—A mixture of 4.84 g. (0.021 mole) of the diester 6, b.p. 116–123° (1.4 mm.), $n^{25}D$ 1.4551 [lit.[13] b.p. 88° (0.1 mm.), $n^{20}D$ 1.4568], and 2.28 g. (0.021 mole) of benzylamine was heated on a steam-bath for 18 hr. and then diluted with ether and filtered. The residual white solid (1.00 g., m.p. 175–181°) was recrystallized from aqueous ethanol to separate the pure amino amide **9a** as white needles, m.p. 181.5–183.5°. The material, which gives no immediate color with ethanolic ferric chloride but develops a violet color on standing, exhibits infrared absorption[14] at 3300 (assoc. N–H stretching), 1650 (amide C=O), 1630 and 1590 (β-amino-α,β-unsaturated ester)[15] and at 1555 cm.$^{-1}$ (N–H bending) with an ultraviolet maximum[16] at 298 mμ (ε 21,000).

Anal. Calcd. for $C_{23}H_{26}N_2O_3$: C, 72.99; H, 6.93; N, 7.40. Found: C, 73.03; H, 6.60; N, 7.26.

(12) All melting points are corrected and all boiling points are uncorrected. The infrared spectra were determined with either a Baird, model B, or a Perkin–Elmer, model 21, infrared recording spectrophotometer fitted with a sodium chloride prism. The ultraviolet spectra were determined with a Cary recording spectrophotometer, model 11MS. The microanalyses were performed by Dr. S. M. Nagy and his associates and by the Scandinavian Microanalytical Laboratory.

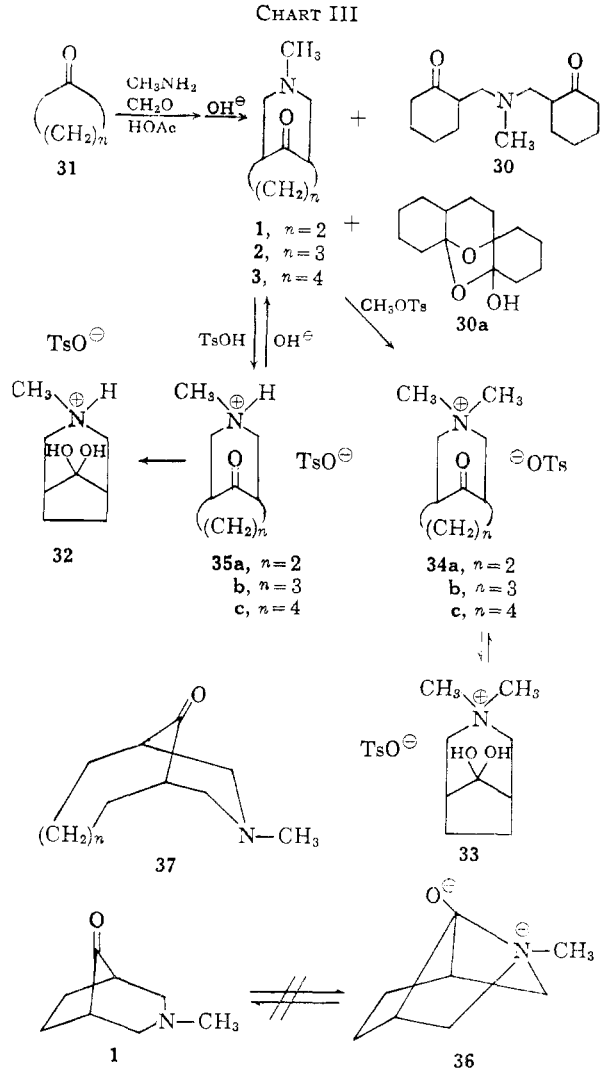
(13) R. W. Kierstead, R. P. Linstead and B. C. L. Weedon, *J. Chem. Soc.*, 3616 (1952).

(14) Determined as a suspension in a potassium bromide pellet.

(15) (a) For the infrared and ultraviolet spectra of β-amino-α,β-unsaturated esters, see B. Witkop, *J. Am. Chem. Soc.*, **78**, 2873 (1956), and H. P. Schad, *Helv. Chim. Acta*, **38**, 1117 (1955). (b) For the infrared and ultraviolet spectra of β-amino-α,β-unsaturated nitriles, see C. F. Hammer and R. A. Hines, *J. Am. Chem. Soc.*, **77**, 3649 (1955).

(16) Determined as a solution in 95% ethanol.

CHART III



The ethereal filtrate was washed with dilute, aqueous hydrochloric acid and with 5% aqueous sodium hydroxide and then dried over magnesium sulfate and concentrated. Several recrystallizations of the residue from pentane–ether mixtures separated 2.25 g. of the amino ester **10** as white needles, m.p. 37–38°. The product, which gave no color with ethanolic ferric chloride, has infrared absorption[17] at 3200 (assoc. NH), 1710 (ester C=O) and at 1640 and 1600 cm.$^{-1}$ (β-amino-α,β-unsaturated ester)[15] with an ultraviolet maximum[16] at 299 mμ (ε 18,900).

Anal. Calcd. for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.31; N, 4.41. Found: C, 68.32; H, 7.19; N, 4.45.

B.—A mixture of 6.84 g. (0.03 mole) of the diester **6** and 3.21 g. (0.03 mole) of benzylamine was heated to 190–200° for 1.5 hr. and then cooled, diluted with ether and washed successively with dilute, aqueous hydrochloric acid and water. The ethereal solution was dried over magnesium sulfate, concentrated and the residue partially crystallized from a benzene–hexane mixture to separate 0.55 g. of white plates, m.p. 161–178°. Recrystallization from the same solvent mixture separated the pure diamide **11**, as white plates, m.p. 176–177°. The sample, which gives an immediate violet color with ethanolic ferric chloride, has infrared absorption[18] at 3250 (assoc. O—H), 1710 (C=O), 1655 (amide C=O) and at 1530 cm.$^{-1}$ (N—H bending).

Anal. Calcd. for $C_{21}H_{22}N_2O_3$: C, 71.98; H, 6.33; N, 8.00. Found: C, 72.23; H, 6.22; N, 7.98.

(17) Determined as a solution in carbon tetrachloride.

(18) Determined as a solution in chloroform.

Reaction of 2,6-Dicarbethoxycyclohexanone (7) with Benzylamine.—A mixture of 3.00 g. (0.0124 mole) of the diester **7**, b.p. 120–125° (0.9 mm.), $n^{26}D$ 1.4631 [lit.[19] 165–165.5° (2 mm.)], and 2.70 g. (0.0248 mole) of benzylamine was heated to 135° for 2.5 hr. and then cooled and allowed to stand overnight. Recrystallization of the solid which separated from ethanol afforded 1.146 g. (23.6%) of fractions of the crude amino compound **9b** melting within the range 132–139°. Two additional crystallizations from ethanol separated the pure amino compound **9b** as white needles, m.p. 136.5–137.5°, with infrared absorption[18] at 3420 and 3300 (N—H) 1655 and 1600 (amide C=O and β-amino-α,β-unsaturated ester)[15] and at 1520 cm.$^{-1}$ (N—H bending) with an ultraviolet maximum[16] at 305 mμ (ε 18,200).

Anal. Calcd. for $C_{24}H_{28}N_2O_3$: C, 73.44; H, 7.19; N, 7.14. Found: C, 73.61; H, 7.31; N, 7.44.

To a suspension of 0.85 g. (2.17 mmoles) of the amino compound **9b** in 9 ml. of ethanol and 1 ml. of water was added 0.25 ml. (3 mmoles) of concentrated hydrochloric acid.[20] The resulting solution was allowed to stand for 2 hr. and then diluted with 25 ml. of water and extracted with ether. After the ethereal extract had been dried over magnesium sulfate and concentrated, crystallization of the residue from an ether–petroleum ether mixture separated 0.132 g. (20%) of the crude amide **8**, m.p. 99–102°. The recrystallizations from ether–petroleum ether mixtures afforded one form of the amide **8** as white prisms, m.p. 98–99°, with infrared absorption[18] at 3400 (N–H and OH), 1660 and 1615 (amide C=O and enolic β-keto ester) and at 1520 cm.$^{-1}$ (N—H bending) and an ultraviolet maximum[16] at 257 mμ (ε 12,100). The material gave an immediate red-brown color with ethanolic ferric chloride.

Anal. Calcd. for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.28; H, 7.10; N, 4.91.

In a comparable experiment employing 5.0 g. of the amino compound **9b**, the crude fractions isolated were (a) 0.352 g., m.p. 115–117°; (b) 0.703 g., m.p. 99.8–104.7°; (c) 0.305 g., m.p. 105–115°; and (d) 0.52 g., m.p. 98–102°. Two recrystallizations of the higher-melting fraction (m.p. 115–117°) from ethanol afforded a second tautomer or crystalline form of the amide **8** as white needles, m.p. 116.3–117.6°. Solutions of this sample exhibit the same infrared[18] and ultraviolet[16] absorption observed with the sample of m.p. 98–99°.

Anal. Calcd. for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.09; H, 6.82; N, 4.70.

Ethyl 3-Cyano-2-ketocyclopentanecarboxylate (13).—From the previously described[21] reaction of 342 g. (1.82 moles) of 1,2-dibromoethane and 418 g. (3.70 moles) of ethyl cyanoacetate with the sodium ethoxide prepared from 84 g. (3.7 g.-atoms) of sodium and 1.4 l. of ethanol was isolated 115.2 g. (35.1%) of the crude amino ester **12**, m.p. 106.5–11.2.°, as white prisms from ethanol. Recrystallization, sublimation (100° at 0.25 mm.) and a final recrystallization from hexane afforded the pure amino ester as white prisms, m.p. 115.5–116.6° (lit.[21] 119.5°). The material exhibits infrared absorption[14] at 3450 and 3375 (NH_2), 2250 (C≡N) and at 1660 and 1570 cm.$^{-1}$ (β-amino-α,β-unsaturated ester)[15] with an ultraviolet maximum[16] at 279 mμ (ε 15,200).

Anal. Calcd. for $C_9H_{12}N_2O_2$: C, 59.98; H, 6.71; N, 15.55. Found: C, 59.95; H, 6.67; N, 15.35.

After a solution of 5.0 g. (0.028 mole) of the amino ester **12** and 2.3 ml. (0.028 mole) of concentrated hydrochloric acid in 30 ml. of ethanol and 5 ml. of water had been allowed to stand 2.5 hr., 50 ml. of water was added and the mixture was extracted with ether. The ethereal extract was dried over magnesium sulfate, concentrated and distilled to separate 3.33 g. (66.6%) of the keto ester **13** as a colorless liquid, b.p. 118–123° (0.25 mm.), $n^{26}D$ 1.4678 [lit.[21] 172–174° (18 mm.)], with infrared absorption[17] at 2250 (C≡N), 1765 (cyclopentanone C=O), 1730 (ester C=O) and weaker bands at 2200 (shoulder), 1670 and 1630 cm.$^{-1}$ suggesting the presence of some of the enolic β-keto nitrile tautomer; ultra-

(19) M. I. Ushakov, *J. Russ. Phys. Chem. Soc.*, **61**, 795 (1929); *C. A.*, **23**, 4678 (1929).

(20) *Cf.* S. A. Glickman and A. C. Cope, *J. Am. Chem. Soc.*, **67**, 1012, 1017 (1945).

(21) (a) S. R. Best and J. F. Thorpe, *J. Chem. Soc.*, **95**, 685 (1909); (b) H. C. H. Carpenter and W. H. Perkin, Jr., *ibid.*, **75**, 921 (1899).

violet maximum at 240 mμ (ε 5,290). Attempts to effect the hydrolysis of **12** with excess acid[20,21] produced samples of the keto ester **13** contaminated with the lower boiling keto nitrile **14**. An authentic sample of the keto nitrile **14**, prepared by acidic hydrolysis of the ester **13** as previously described,[21] $n^{25.7}$D 1.4668 (lit.[22] n^{14}D 1.4701), has infrared absorption[17] at 2250 (C≡N) and 1760 cm.$^{-1}$ (cyclopentanone (C=O)). The keto nitrile **14** formed a semicarbazone, m.p. 188–189° (lit.[21] 190°), in 56% yield.

Reaction of Adiponitrile and Diethyl Carbonate with Sodium Ethoxide.[23]—A solution of sodium ethoxide, prepared from 11.5 g. (0.50 g.-atom) of sodium and excess ethanol, in 293 g. (2.48 moles) of diethyl carbonate was refluxed under a fractionating column with removal of the excess ethanol present. Then 27.04 g. (0.25 mole) of adiponitrile was added, dropwise and with stirring, and refluxing was continued until no more ethanol was evolved (about 2 hr.). The reaction mixture was cooled, diluted with 25 ml. of acetic acid and 200 ml. of water and then extracted with ether. The ethereal extract was concentrated and distilled to remove the excess diethyl carbonate [b.p. 42–50° (24 mm.)]. Crystallization of the semi-solid residue from ether–petroleum ether mixtures separated 24.07 g. (53.1%) of the crude amide **15**, m.p. 67–69°. Repeated recrystallization from petroleum ether followed by sublimation (100° at 0.1 mm.) afforded the pure amide **15** as white needles, m.p. 68.7–69.1°, with infrared absorption[17] at 3450 and 3350 (NH), 2225 (conj. C≡N), 1755 (ester C=O) and 1645 cm.$^{-1}$ (C=C) with an ultraviolet maximum[16] at 256 mμ (ε 16,400).[16]

Anal. Calcd. for $C_9H_{12}N_2O_2$: C, 59.98; H, 6.71; N, 15.55. Found: C, 60.18; H, 6.82; N, 15.63.

A solution of 2.0 g. (0.011 mole) of the amide **15** and 1.4 ml. (0.017 mole) of concentrated hydrochloric acid in 25 ml. of ethanol was allowed to stand 24 hr. and then diluted with 50 ml. of water and extracted with ether. After the ethereal extract had been washed with water, dried over magnesium sulfate and concentrated, distillation separated a lower-boiling fraction, b.p. 99–103° (24 mm.), which solidified on cooling and 0.596 g. of a higher-boiling (0.04 mm. in a short-path still), liquid fraction. Recrystallization of the lower-boiling fraction from an ether–petroleum ether mixture separated ethyl urethan as colorless plates, m.p. 48–49.2°, identified with an authentic sample by a mixed melting-point determination and comparison of the infrared spectra of the samples. Reaction of the higher-boiling fraction, whose infrared spectrum was consistent with the presence of the keto nitrile **14**, with semicarbazide yielded the semicarbazone of the keto nitrile **14**, m.p. 188–189°, identified with the previously described sample by a mixed melting point determination and a comparison of the infrared spectra of the samples.

Hydrogenation of the Keto Ester 13. A.—A mixture of 180 ml. of an ethanol solution containing 13.3 g. (0.0734 mole) of the keto ester, 0.4007 g. of platinum oxide catalyst and 20 ml. of acetic acid[24] was subjected to an initial hydrogen pressure of 1000 p.s.i. in a glass-lined autoclave and heated, with shaking, to 80° overnight at which time 0.199 mole (90%) of hydrogen had been absorbed. After the resulting reaction mixture had been filtered and concentrated under reduced pressure, 300 ml. of benzene was added and 200 ml. was distilled from the reaction mixture to remove the residual acetic acid. The amide **16** separated from the residual benzene solution as white prisms, m.p. 216.4–218.8° dec., yield 4.29 g. (41.4%). Several additional recrystallizations from ethyl acetate raised the decomposition point of the amide to 223–224°. The material exhibits infrared absorption[14] at 3200–3300 (broad, intense, N-H) and at 1645 cm.$^{-1}$ (amide C=O) with only weak end absorption in the ultraviolet.[16]

Anal. Calcd. for $C_7H_{11}NO_2$: C, 59.55; H, 7.85; N, 9.92. Found: C, 59.68; H, 8.04; N, 9.60.

Although a variety of hydrogenation conditions was explored, the procedure just described, which could be applied to the crude, undistilled keto ester **13**, proved to be most reproducible and satisfactory.

B.—A solution of 14.39 g. (0.0794 mole) of the keto ester in 200 ml. of ethanol was hydrogenated at atmospheric pressure and room temperature over the catalyst obtained from 0.200 g. of platinum oxide. After 24 hr. the hydrogen uptake (0.118 mole or 1.49 equiv.) ceased. After the solution had been filtered and concentrated, addition of a mixture of ethyl acetate and petroleum ether precipitated 0.4097 g. (3.7%) of the crude amide, m.p. 213.5–215°. Distillation of the residue from the mother liquor separated 5.94 g. of fractions, b.p. 110–143° (0.28 mm.), n^{25}D 1.4704–1.4677, from which 1.28 g. of white solid, m.p. 74.2–76°, separated. Several recrystallizations from carbon tetrachloride afforded the pure hydroxy ester **17** as white needles, m.p. 78.4–78.7°, with infrared absorption[18] at 3500 (O—H), 2250 (C≡N) and 1720 cm.$^{-1}$ (ester C=O) and an ultraviolet maximum[16] at 220 mμ (ε 47).

Anal. Calcd. for $C_9H_{13}NO_3$: C, 59.00; H, 7.15; N, 7.65. Found: C, 58.94; H, 7.23; N, 7.63.

The liquid fractions from the mother liquors had infrared spectra very similar to the spectrum of this crystalline product and were presumably various mixtures of stereoisomers of the hydroxy ester structure **17**. A 0.2719-g. (0.00148 mole) sample of the crystalline alcohol **17** in 25 ml. of ethanol was hydrogenated at room temperature and atmospheric pressure over the catalyst obtained from 23.5 mg. of platinum oxide. After 20 hr. the hydrogen uptake (0.00311 mole or 2.1 equiv.) ceased. After the reaction mixture had been filtered and concentrated, crystallization of the residue from ethyl acetate separated 0.0828 g. (39.9%) of the amide **16**, m.p. 223.4–226° dec. A similar hydrogenation of 0.2943 g. of the crude liquid from the mother liquors produced 0.0408 g. (13.9%) of the amide **16**.

Acetylation of the Hydroxy Amide 16.—A solution of 0.9077 g. (0.00642 mole) of the hydroxy amide in 20 ml. of boiling acetic anhydride was refluxed for 2 hr. After 4 ml. of water had been added to this boiling mixture, the solvents were removed under reduced pressure. A solution of the oily residue in petroleum ether deposited 0.1332 g. (9.2%) of the crude acetoxy amide **18**, m.p. 153–162°. Recrystallization from ether afforded the pure acetoxy amide as white plates, m.p. 165–166°, with infrared absorption[18] at 3400 and 3200 (N—H), 1735 (ester C=O) and 1665 cm.$^{-1}$ (amide C=O) and only weak end absorption in the ultraviolet.[16]

Anal. Calcd. for $C_9H_{13}NO_3$: C, 59.00; H, 7.15; N, 7.65. Found: C, 59.25; H, 7.30; N, 7.86.

A solution of the mother liquors from the above crystallization in an ether–petroleum ether mixture deposited 1.002 g. (85%) of the crude diacetyl compound **19** as a tan solid, m.p. 59.5–63.5°. After sublimation (100° at 0.15 mm.) and recrystallization from petroleum ether, the pure diacetyl compound **19** was obtained as white rosettes, m.p. 67.4–68.6°, with infrared absorption[18] at 1745 cm.$^{-1}$ (ester C=O) and a broad band (presumably an unresolved doublet) in the range 1715 to 1690 cm.$^{-1}$ (C=O of an imide)[25] with an ultraviolet maximum[16] at 216 mμ (ε 7,700).

Anal. Calcd. for $C_{11}H_{15}NO_4$: C, 58.65; H, 6.71; N, 6.22. Found: C, 58.49; H, 6.69; N, 5.94.

A solution of 150 mg. of the diacetyl compound **19** in a mixture of 1.5 ml. of acetic acid and 20 ml. of water was refluxed for 1 hr. and then concentrated under reduced pressure. A solution of the residue in an ether–petroleum ether mixture deposited 47.4 mg. (38.8%) of the acetoxy amide **18**, m.p. 164.8–165.8°, identified with the previously described sample by comparison of the infrared spectra of the two samples.

Benzylation of the Amide 16.—After a mixture of 25.00 g. (0.175 mole) of the amide, 19.34 g. (10.52 g., 0.438 mole of pure NaH) of a 54.5% sodium hydride suspension in mineral oil and 400 ml. of dimethylformamide had been stirred for 15 min., 50 ml. (55.4 g., 0.438 mole) of benzyl chloride was added and the resulting mixture was heated at reflux for 3

(22) O. Riobe and L. Gouin, *Compt. rend.*, **234**, 1889 (1952).

(23) This reaction, run with the hope of carbethoxylating [V. H. Wallingford, D. M. Jones and A. H. Homeyer, *J. Am. Chem. Soc.*, **64**, 576 (1942)] adiponitrile prior to cyclization and thus produce the nitrile ester **12**, apparently proceeded by cyclization [*cf.* Q. E. Thompson, *ibid.*, **80**, 5483 (1958)] and subsequent carbethoxylation of the 2-amino-1-cyanocyclopentene.

(24) The advantageous use of platinum and acetic acid for the reduction of polyfunctional nitriles has been noted previously. For example, see (a) C. D. Gutsche, *J. Am. Chem. Soc.*, **71**, 3513 (1949); (b) A. F. Ferris, G. S. Johnson, F. E. Gould and H. K. Latourette, *J. Org. Chem.*, **25**, 492 (1960).

(25) The absence of absorption in the region 1660–1600 cm.$^{-1}$ serves to exclude the isomeric *O*-acetyl lactim structure. See W. Z. Heldt [*J. Am. Chem. Soc.*, **80**, 5880 (1958)], who reports bands at 1722–1742 and 1642–1645 cm.$^{-1}$ for *O*-acylated lactims.

hr. Then an additional 50 ml. (55.4 g., 0.438 mole) of benzyl chloride was added and the mixture was refluxed for an additional 10 hr. After the bulk of the dimethylformamide had been distilled from the mixture under reduced pressure, methylene chloride and water were added and the methylene chloride extract was dried over magnesium sulfate and concentrated. Recrystallization of the residual crude solid (41.3 g., m.p. 99–126°) from an ethanol–water mixture separated 25.56 g. (45.4%) of the dibenzyl amide **21** as white prisms, m.p. 111.2–113.6°. The material exhibits infrared absorption[15] at 1645 cm.$^{-1}$ (amide C=O) with a series of low intensity (ϵ 300-384) ultraviolet maxima[16] in the region 250–270 mμ.

Anal. Calcd. for $C_{21}H_{23}NO_2$: C, 78.47; H, 7.21; N, 4.36. Found: C, 78.36; H, 7.11; N, 4.43.

The solvent was removed from the mother liquors of the above crystallization and the residue, when treated with ethyl acetate, deposited 6.15 g. (15.2%) of the crude monobenzyl amide **20**, m.p. 134–138°. Recrystallization from ethyl acetate afforded the pure amide **20** as white plates, m.p. 139.3–139.6°, with infrared absorption[15] at 3420 and 3220 (N—H) and 1665 cm.$^{-1}$ (amide C=O) and a series of low intensity ultraviolet maxima[16] in the region 250–270 mμ.

Anal. Calcd. for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.64; H, 7.20; N, 5.98.

A solution of 0.407 g. (1.76 mmoles) of the monobenzyl amide **20** and 9 ml. of pyridine in 21 ml. of acetic anhydride was heated to 60° for 9 hr. and then poured into 50 ml. of ice-water, acidified to *p*H 2 with hydrochloric acid and extracted with methylene chloride. After the extracts had been washed with sodium bicarbonate, dried over magnesium sulfate and concentrated, distillation of the residue in a short-path still separated 0.331 g. (68.8%) of the imide **29**, b.p. 155–156° (0.7 mm.), which crystallized on standing. Recrystallization from ethanol afforded the pure imide as white prisms, m.p. 72–73°, with infrared absorption[17] at 1710 and 1700 (shoulder) cm.$^{-1}$ (imide C=O)[25,26] with end absorption in the ultraviolet[16] as well as maxima at 258 mμ (ϵ 450) and 264 mμ (ϵ 328).

Anal. Calcd. for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.13. Found: C, 70.60; H, 7.15; N, 5.25.

After a solution of 150.5 mg. (0.55 mmole) of the imide in 20 ml. of methanol containing 2 ml. of 3 *M* aqueous sodium hydroxide had been stirred at room temperature for 14 hr., the mixture was concentrated, diluted with water and extracted with methylene chloride. The residue, obtained by drying over magnesium sulfate and concentrating the extract, crystallized from methylene chloride as white crystals, m.p. 137.5–139.5°, of the monobenzyl amide **20** (yield 87 mg. or 68%) identified by a mixed melting point determination.

Chromatography on alumina of the mother liquors from comparable benzylations of the amide **16**, separated additional quantities of the dibenzylamide **21** as well as *trans*-stilbene as colorless needles, m.p. 123.4–124°, identified by comparison with an authentic sample.

Reduction of the Amide 21. A. Hydrogenolysis.—Hydrogenation of a solution of 7.20 g. (0.0217 mole) of the amide in 50 ml. of ethanol over 400 mg. of a 10% palladium-on-carbon catalyst at room temperature and atmospheric pressure resulted in the absorption of 585 ml. (1.08 equiv.) of hydrogen. After the mixture had been filtered and concentrated under reduced pressure, recrystallization of the residue from ethyl acetate afforded 3.90 g. (77.8%) of the monobenzyl amide **22** as white plates, m.p. 140.1–142.1°, with infrared absorption[15] at 3350 (OH) and 1630 cm.$^{-1}$ (amide C=O) and a series of low intensity (ϵ 158–258) ultraviolet maxima[16] in the region 250–270 mμ.

Anal. Calcd. for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.50; H, 7.40; N, 5.91.

B. With Lithium Aluminum Hydride.—To a solution of 0.62 g. (0.0163 mole) of lithium aluminum hydride in 200 ml. of anhydrous ether was added, dropwise and with stirring, a solution of 5.24 g. (0.0163 mole) of the amide in 50 ml. of tetrahydrofuran. After the resulting mixture had been refluxed with stirring for 2 hr., 0.6 ml. of water, 0.6 ml. of 15% aqueous sodium hydroxide solution and 1.8 ml. of water were added successively to the mixture and the precipitated aluminum salts were separated and washed with three 100-ml. portions of ether. After the combined organic solutions had been dried over magnesium sulfate and concentrated, crystallization of the residue from aqueous ethanol separated 3.73 g. (74.5%) of the amine **23** as white prisms, m.p. 54.5–55.4°, whose melting point was raised to 55.3–56° by recrystallization from ethanol. The material exhibits no infrared absorption[17] in the 3 and 6μ regions attributable to N—H, O—H or C=O functions and has a series of low intensity (ϵ 346–478) ultraviolet maxima[16] in the region 250–270 mμ.

Anal. Calcd. for $C_{21}H_{25}NO$: C, 82.04; H, 8.20; N, 4.56. Found: C, 82.06; H, 8.21; N, 4.59.

After a solution of 1.0303 g. (3.35 mmoles) of the amine **23** in 10 ml. of methyl iodide had been allowed to stand at room temperature for 70 hr., the precipitate was collected and washed with an ethanol–ether mixture to leave 1.12 g. (74.4%) of the methiodide **24b** as white needles, m.p. 165.7–167.7°. Recrystallization from ethanol[27] afforded the pure salt, m.p. 169.4–169.8°.

Anal. Calcd. for $C_{22}H_{28}NOI$: C, 58.80; H, 6.28; N, 3.12; I, 28.24. Found: C, 58.65; H, 6.26; N, 3.14; I, 28.08.

A mixture of 1.721 g. (5.60 mmoles) of the amine **23** and 1.250 g. (6.72 mmoles) of methyl *p*-toluenesulfonate was heated to 65° for 100 hr. and then diluted with ethyl acetate. The metho-*p*-toluenesulfate **24a** which separated was recrystallized from a large volume of ethyl acetate to afford 2.11 g. (76.5%) of the salt as white needles, m.p. 105.5–106.5°, which melted at 106.4–106.8° after further recrystallization.[27]

Anal. Calcd. for $C_{29}H_{35}NO_4S$: C, 70.56; H, 7.15; N, 2.84; S, 6.48. Found: C, 70.43; H, 7.15; N, 3.01; S, 6.59.

Hydrogenolysis of the Amine Salt 24a. A.—A solution of 342 mg. (0.692 mmole) of the amine salt in 25 ml. of ethanol was hydrogenated at room temperature and atmospheric pressure over 39.4 mg. of a 10% palladium-on-carbon catalyst. After the hydrogen uptake (15.4 ml. or 0.92 equiv.) ceased, the mixture was filtered and concentrated. Recrystallization of the residue from an ether–ethyl acetate mixture afforded 173.4 mg. (62.2%) of the amine salt **25** as white plates, m.p. 158.1–159.4°, which melted at 159.8–160.4° after recrystallization from ethyl acetate.

Anal. Calcd. for $C_{22}H_{29}NO_4S$: C, 65.48; H, 7.24; N, 3.47. Found: C, 65.18; H, 7.21; N, 3.30.

A mixture of 989 mg. (2.46 mmoles) of the amine salt **25**, a solution of 1.10 g. (0.0275 mole) of sodium hydroxide in 10 ml. of water and 25 ml. of ether was shaken vigorously and then the ether layer was separated and the aqueous phase was extracted with ether. After the combined ethereal extracts had been dried over magnesium sulfate and concentrated, distillation of the residue at 0.1 mm. in a short-path still afforded 406.8 mg. (71.6%) of the amine **27** which was redistilled to afford fractions, b.p. 70–87° (0.15 mm.), $n^{25}D$ 1.5303, with no infrared absorption[17] in the 3 and 6μ regions attributable to O—H, N—H or C=O functions and a series of low intensity (ϵ 115–146) ultraviolet maxima[16] in the region 250–270 mμ.

Anal. Calcd. for $C_{15}H_{21}NO$: C, 77.88; H, 9.15; N, 6.05. Found: C, 77.83; H, 9.23; N, 6.37.

B.—A solution of 3.1067 g. (0.00629 mole) of the amine salt **24a** in 20 ml. of acetic acid was hydrogenated at room temperature and atmospheric pressure over 283 mg. of a 5% palladium-on-carbon catalyst. The absorption of the first equivalent of hydrogen was relatively rapid, 156.9 ml. (1.02 equiv.), 330.8 ml. (2.15 equiv.) and 344.6 ml. (2.24 equiv.) of hydrogen having been absorbed after 1 hr., 10 hr. and 22 hr., respectively. After filtration and concentration of the mixture, crystallization of the residue from an ethanol–ethyl acetate mixture afforded the amine salt **26** as 1.213 g. (61.5%) of white crystals, m.p. 165.2–167.0°.

Anal. Calcd. for $C_{15}H_{23}NO_4S$: C, 57.49; H, 7.40; N, 4.47; S, 10.21. Found: C, 57.58; H, 7.37; N, 4.42; S, 10.02.

A solution of 1.00 g. (3.20 mmoles) of the amine salt **26** in 5 ml. of an aqueous solution containing 0.50 g. (0.013 mole)

(26) The absence of absorption in the 6μ region attributable to an ester function excludes the alternative formulation **22** (rather than **29**) for the monobenzyl amide.

(27) The stereochemistry of this salt has not yet been established.

of sodium hydroxide was extracted with seven 20-ml. portions of methylene chloride. After the combined extracts had been dried over magnesium sulfate and concentrated by distillation through a 75-cm. Vigreux column, sublimation (0.1 mm.) of the residual solid afforded 222 mg. (49%) of the amino alcohol **28** as white prisms, m.p. 81.7–82.8°, which melted at 82–83° after an additional sublimation. The material has infrared absorption[17] at 3620 (unassoc. O–H) and 3350 cm.$^{-1}$ (broad, associated O–H).[28,29] In chloroform solution[28] the bands are found at 3600 (unassociated O–H), 3400 (intermolecularly associated O–H) and 3180 cm.$^{-1}$ (intramolecularly associated O–H). In either solvent the bands below 3600 cm.$^{-1}$ attributable to an associated hydroxyl function disappear as the solutions are diluted.

Anal. Calcd. for $C_8H_{15}NO$: C, 68.04; H, 10.71; N, 9.92. Found: C, 67.90; H, 10.77; N, 10.15.

3-Methyl-3-azabicyclo[3.2.1]octan-8-one (1). A. Oxidation.—A solution of 3.512 g. (0.0112 mole) of the amino alcohol tosylate **26**, 0.9195 g. (0.00919 mole) of chromium trioxide and 5.15 g. (0.0525 mole) of sulfuric acid in 22 ml. of water was allowed to stand at room temperature for 12 hr. and then made basic with sodium hydroxide and extracted with methylene chloride. The methylene chloride solution, which contained a mixture of 77% of the ketone **1** and 23% of the alcohol **28**,[30] was washed with an aqueous buffer at *p*H 7 to remove the amino alcohol **28**. After the organic layer had been dried over magnesium sulfate and concentrated, distillation of the residue in a short-path still (100° at 0.1–0.2 mm.) afforded 0.399 g. (25.7%) of the amino ketone **1** identified by comparison of its infrared spectrum and gas chromatographic retention time with those of the subsequently described sample. After the above-mentioned buffered extracts had been made basic (*p*H 11) and extracted with methylene chloride, removal of the solvent from the extract left 0.438 g. of the crude amino alcohol **28**. The procedure described represents the most satisfactory of a variety of oxidizing conditions explored. Since the amino ketone was attacked by the oxidant, use of sufficient chromium trioxide to oxidize all of the starting amino alcohol **28** was a less satisfactory procedure.

B. Mannich Condensation.—A solution of 168 g. (2.0 moles) of cyclopentanone, 135 g. (2.0 moles) of methylamine hydrochloride and 450 ml. (6.0 moles) of a 40% aqueous formaldehyde solution in 4 l. of acetic acid was heated on a steam-bath for 2 hr. and then treated with 100 ml. of concentrated hydrochloric acid and concentrated under reduced pressure until as much acetic acid had been removed as was practical. After the viscous residue had been extracted with chloroform, the aqueous layer was made basic with cold, concentrated aqueous sodium hydroxide and extracted with chloroform. After this chloroform extract had been dried over magnesium sulfate and concentrated under reduced pressure, distillation of the residue in a short-path still (at 0.25 mm. with the pot temperature being raised to 180°) afforded a mixture of the desired amino ketone and other low-boiling components.[31] The distillate, collected in a receiver cooled in a Dry Ice–acetone-bath, was taken up in concentrated hydrochloric acid and the resulting mixture was extracted with chloroform and then made basic with cold, concentrated aqueous sodium hydroxide and again extracted with chloroform. After the chloroform extract had been dried over magnesium sulfate and concentrated, distillation through a Holtzman column afforded 17.88 g. (6.4%) of the crude amino ketone, b.p. 75–89° (14 mm.), $n^{25}D$ 1.4862–1.4891, as well as 2.95 g. of a fraction, b.p. 89–100° (14 mm.), $n^{25}D$ 1.4962, which was not investigated further. A solution of the crude amino ketone in acetone was treated with an acetone solution of 24.2 g. of *p*-toluenesulfonic acid and then concentrated under reduced pressure. Recrystallization of the residue from an acetone–isopropyl alcohol mixture afforded 21.21 g. (3.3%) of the hydrated *p*-toluenesulfonate salt **32** as white prisms, m.p. 178–181° dec. A solution of 8.02 g. (24.4 mmoles) of this salt in water was made basic with aqueous sodium hydroxide and then extracted with chloroform. After the extract had been dried over magnesium sulfate and concentrated, distillation of the residue through a Holtzman column afforded 2.624 g. (77.5% from the salt) of the pure amino ketone **1** as a colorless liquid, b.p. 66° (5 mm.), $n^{25}D$ 1.4839. A variety of attempts to modify and shorten the isolation procedure described proved unsatisfactory and usually resulted in the isolation of no pure amino ketone.

Although the free amino ketone **1** can be stored for several days under nitrogen at 0°, it rapidly turns yellow on exposure to air at room temperature. The hydrated *p*-toluenesulfonate salt is stable to storage. The amino ketone exhibits infrared absorption[18] at 1745 cm.$^{-1}$ with a shoulder at 1720 cm.$^{-1}$ (1750 and 1720 cm.$^{-1}$ in carbon tetrachloride solution, C=O in a five-membered ring)[32] with weak end absorption and a broad maximum centered at 295 mμ (ε 23.6) in the ultraviolet.[33]

Anal. Calcd. for $C_8H_{13}NO$: C, 69.03; H, 9.41; N, 10.06; mol. wt., 139. Found: C, 68.77; H, 9.50; N, 9.95; mol. wt. (mass spectrum), 139.

A sample of the pure amine ketone **1** was converted as previously described to its hydrated *p*-toluenesulfonate salt **32**, m.p. 177–182° dec., in 57.2% yield. Recrystallization from an acetone–isopropyl alcohol mixture raised the melting point to 182–183.7° with sintering (presumably dehydration) at 131–134°. The hydrate salt exhibits no infrared absorption[14] in the 6μ region attributable to a carbonyl function and has ultraviolet maxima[16] at 222 mμ (ε 10,900), 256 mμ (ε 223), 263 mμ (ε 263) and 268 mμ (ε 198).

Anal. Calcd. for $C_{15}H_{23}NO_5S$: C, 54.70; H, 7.04; N, 4.25. Found: C, 54.86; H, 7.20; N, 4.37.

A mixture of 0.2991 g. (2.15 mmoles) of the amino ketone **1** and 0.4192 g. (2.25 mmoles) of methyl *p*-toluenesulfonate was heated to 70–75° under nitrogen for 14 hr. The salt, which separated from the cold reaction mixture, was washed with ethyl acetate to leave 0.6505 g. (90.6%) of the crude hydrated quaternary ammonium salt **33**. Recrystallization from an acetone–isopropyl alcohol mixture afforded the pure hydrated salt **33**, m.p. 232–233° (presumably dehydration has occurred during the heating), which exhibits little or no infrared absorption[14] in the 6μ region attributable to a carbonyl function and has an ultraviolet maximum[16] at 222 mμ (ε 11,400).

Anal. Calcd. for $C_{16}H_{25}NO_5S$: C, 55.96; H, 7.34; N, 4.08. Found: C, 55.88; H, 7.19; N, 3.98.

After the hydrate salt **33** had been dried at 145° under 0.01 mm. pressure for 3 days, the free keto quaternary salt **34a** was obtained (m.p. 232–233°) which now exhibited infrared absorption[14,34] at 1764 cm.$^{-1}$ with no absorption in the 3μ region attributable to an N–H or O–H function.

Anal. Calcd. for $C_{16}H_{23}NO_4S$: C, 59.06; H, 7.13; N, 4.31. Found: C, 58.95; H, 7.22; N, 4.16.

3-Methyl-3-azabicyclo[3.3.1]nonan-9-one (2).—After a solution of 49 g. (0.50 mole) of cyclohexanone, 33.8 g. (0.50 mole) of methylamine hydrochloride 112.5 ml. (1.5 moles) of 40% aqueous formaldehyde in 2.5 l. of acetic acid had been heated on a steam-bath for 3.5 hr., application of the previously described isolation procedure afforded 10.2 g. (13.3%) of the crude amino ketone **2**, b.p. 108–113° (18 mm.), after the second distillation of the volatile basic product. A 6.8-g. portion of this distillate was treated with 8.5 g. of *p*-toluenesulfonic acid in acetone to yield, after recrystallization of the crude salt from a methanol–acetone mixture, 10.02 g. (9.25% over-all) of the *p*-toluenesulfonate salt **35b**, m.p. 182–184°. A 7.53-g. (23.2 mmoles) sample of the salt **35b** was reconverted to the free amino ketone **2** as previously described yielding 2.02 g. (57%) of the ketone as a colorless liquid, b.p. 88° (7 mm.), $n^{25}D$ 1.4898, which solidifies when cooled below room temperature. The product exhibits infrared absorption[18] at 1710 cm.$^{-1}$ (in carbon tet-

(28) Calcium fluoride optics were employed for these measurements.

(29) The position of absorption for an intramolecularly bonded hydroxyl function to an amino group has been found at 3500 cm.$^{-1}$ when the hydrogen bonded system forms a five-membered ring and at 3295 cm.$^{-1}$ when the hydrogen bonded system forms a six-membered ring: H. H. Freedman, *J. Am. Chem. Soc.*, **83**, 2900 (1961).

(30) A gas chromatography column packed with either 1540 Carbowax or Silicone Fluid No. 710 on base-washed ground firebrick was employed for this analysis.

(31) The infrared spectrum of this crude product had bands not attributable to the amino ketone **1** at 1690, 1645 and 1620 cm.$^{-1}$ suggesting the presence of α-methylenecyclopentanone in the mixture.

(32) The carbonyl stretching frequencies in carbon tetrachloride solution for bicyclo[3.2.1]octan-8-one and bicyclo[3.3.1]nonan-9-one are 1746 (with a shoulder at 1773 cm.$^{-1}$) and 1725 cm.$^{-1}$, respectively, C. S. Foote, Ph.D. Dissertation, Harvard University, 1961.

(33) Determined in heptane solution.

(34) Determined as a Nujol mull.

rachloride solution the value is 1730 cm.$^{-1}$ with a shoulder at 1710 cm.$^{-1}$) (C=O)[32] with ultraviolet maxima[33] at 288 mμ (ε 29.5) and 363 mμ (ε 24.6).

Anal. Calcd. for $C_9H_{15}NO$: C, 70.55; H, 9.87; N, 9.14; mol. wt., 153. Found: C, 70.36; H, 9.62; N, 8.97; mol. wt. (mass spectrum), 153.

Reaction of 101.2 mg. (0.66 mole) of the amino ketone **2** with 137.2 mg. (0.72 mmole) of *p*-toluenesulfonic acid in acetone followed by recrystallization of the crude salt from ethyl acetate afforded 181 mg. (84.2%) of the *p*-toluenesulfonate salt **35b**, m.p. 183–185°. This salt, whose melting point was sharpened to 184–184.7° by an additional crystallization, has infrared absorption[18] at 1740 cm.$^{-1}$ with a shoulder at 1710 cm.$^{-1}$ (C=O) with ultraviolet maxima at 222 mμ (ε 11,600), 256 mμ (ε 254), 262 mμ (ε 293) and 269 mμ (ε 226).

Anal. Calcd. for $C_{16}H_{23}NO_4S$: C, 59.06; H, 7.13; N, 4.31. Found: C, 58.92; H, 7.16; N, 4.11.

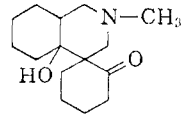
Reaction of the amino ketone **2** with excess perchloric acid in acetone afforded the perchlorate salt which crystallized from acetone as fine, colorless prisms, m.p. 224.8–225.2° dec. (lit.[4] 222° dec.), yield 32.6%, with infrared absorption[14] at 1735 and 1710 cm.$^{-1}$ (C=O).

After a mixture of 3.06 g. (20 mmoles) of the amino ketone **2** and 4.1 g. (22 mmoles) of methyl *p*-toluenesulfonate had been heated to 65° for 18 hr., the crude salt which crystallized from the reaction mixture was washed with ether and recrystallized from a methanol–ethyl acetate mixture. The pure quaternary salt **34b** separated as white needles, m.p. 163.5–164°, yield 4.85 g. (71.5%), after the sample had been dried for 3 days at 100° and at 0.01 mm. pressure. The salt has infrared absorption[15] at 1735 and 1720 cm.$^{-1}$ (C=O) with an ultraviolet maximum[16] at 222 mμ (ε 11,900).

Anal. Calcd. for $C_{17}H_{25}NO_4S$: C, 60.16; H, 7.43; N, 4.13. Found: C, 60.25; H, 7.46; N, 4.20.

Of a variety of reaction conditions explored for the preparation of the amino ketone **2**, the procedure described was most satisfactory. In one preparation, employing 24.7 g. (0.25 mole) of cyclohexanone, where the amino ketone **2** was isolated in 9% yield, the neutral fraction separated after the first distillation was crystallized from ethanol to separate 500 mg. of the hydroxy ketal **30a** as white prisms, m.p. 143–144°. Sublimation afforded a second crystalline form of the material, m.p. 155–156°.[35] The solution infrared spectra[18] of the two crystalline forms are identical and the spectrum[14] of the higher-melting form is identical with the published spectrum.[35a] This by-product presumably arises[35] from the dimer[36] of α-methylenecyclohexanone which is formed by the thermal decomposition of the diketo amine **30** during the isolation.

From a comparable preparation, employing 24.7 g. (0.25 mole) of cyclohexanone, an ethereal solution of the basic fraction separated after the first distillation deposited crystalline material which was collected and recrystallized from ethyl acetate to separate 2.7 g. (8.6%) of the diketo amine **30** as white needles, m.p. 162.5–163° dec. (lit.[9] 163.5–164° dec.). The material has infrared absorption[18] at 1702 cm.$^{-1}$ (C=O) with weak absorption at 3620 and 3500 cm.$^{-1}$ (unassoc. and assoc. O–H).[37] It is probable that appreci-



able quantities of this base are present in the high-boiling residue from the first distillation in each preparation.

8-Methyl-8-azabicyclo[4.3.1]decan-10-one (3).—After a solution of 44.8 g. (0.40 mole) of cycloheptanone, 27 g. (0.40 mole) of methylamine hydrochloride and 90 ml. (1.2 moles) of 40% aqueous formaldehyde in 2 l. of acetic acid had been heated for 2.5 hr. on a steam-bath, application of the previously described isolation procedure afforded 10.1 g. (7.4%) of the *p*-toluenesulfonate salt **35c** as white prisms, m.p. 175–176°, from a mixture of methanol and ethyl acetate. The sample for spectra and analysis was dried for 3 days at 100° and 0.01 mm. pressure. The salt exhibits infrared absorption[18] at 1722 cm.$^{-1}$ (C=O).

Anal. Calcd. for $C_{17}H_{25}NO_4S$: C, 60.16; H, 7.43; N, 4.13. Found: C, 59.97; H, 7.45; N, 4.02.

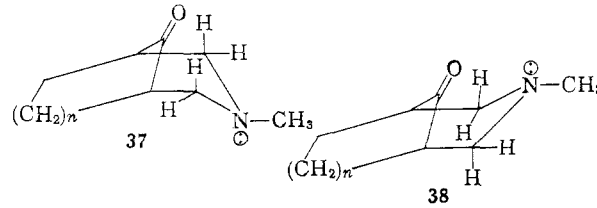
Conversion of a 4.3-g. (13.0 mmoles) sample of the salt **35c** to the free base as previously described afforded 1.72 g. (79%) of the amino ketone **3** as a colorless liquid, b.p. 106° (7 mm.), $n^{25}D$ 1.4938. The material has infrared absorption[18] at 1695 cm.$^{-1}$ with a shoulder at 1685 cm.$^{-1}$ (C=O; the values in carbon tetrachloride solution at 1708 and 1690 cm.$^{-1}$) with ultraviolet maxima[33] at 313 mμ (ε 38.7) and 366 mμ (ε 20.3).

Anal. Calcd. for $C_{10}H_{17}NO$: C, 71.81; H, 10.25; N, 8.38; mol. wt., 167. Found: C, 71.91; H, 10.52; N, 8.41; mol. wt. (mass spectrum), 167.

The undistilled amino ketone **3** obtained from 2.1 g. (6.2 mmoles) of the *p*-toluenesulfonate salt **35c** was mixed with 1.27 g. (6.8 mmoles) of methyl *p*-toluenesulfonate and heated to 65° for 14 hr. After trituration of the crude reaction mixture with ether, recrystallization of the crude salt which separated from a methanol–ethyl acetate mixture afforded 1.35 g. (62%) of the quaternary ammonium salt **34c** as white needles, m.p. 158–159.5°. An additional crystallization followed by drying at 100° and 0.002 mm. pressure for 2 days afforded the analytically pure salt, m.p. 159–160°. The material has infrared absorption[14] at 1710 cm.$^{-1}$ with an ultraviolet maximum[16] at 222 mμ (ε 12,300).

Anal. Calcd. for $C_{18}H_{27}NO_4S$: C, 61.17; H, 7.70; N, 3.96. Found: C, 61.19; H, 7.93; N, 4.01.

Physical Properties of the Azabicyclic Ketones 1, 2 and 3 and Their Derivatives.—Table I presents a number of the physical measurements made on the azabicyclic ketones. The series of three peaks in the 2600–2800 cm.$^{-1}$ region of the infrared in the three ketones indicates that the favored conformation of each of the three compounds has at least two hydrogen atoms *trans* and coplanar with the unshared electron pair on the nitrogen atom.[38] In other words the N-methyl group must be equatorial as in conformations **37** and **38**. The dipole moments[39] of the ketones are in accord with the expected value[40] (~2.7 D.) for conformation **37** and differ substantially from the expected value[40] (~3.8 D.) for conformation **38**.



It will be noted from the pK_{MCS}*[41] values that the basicity of the amino ketones decreases as the length of the methylene bridge increases (*i.e.* as the value of *n* in structure **37** increases). This observation is in accord with the idea that amines and their protonated salts have the same conformation[42]; in other words the nitrogen atom is protonated from

(35) (a) H. Böhme, H. J. Bohn, I. Henning and A. Scharf [*Ann.*, **642**, 49 (1961)] report m.p. 154–155°; (b) E. W. Warnhoff and W. S. Johnson, *J. Am. Chem. Soc.*, **75**, 496 (1953)] report melting points of 141–142° and 146–147°.

(36) C. Mannich, *Ber.*, **74**, 557 (1941).

(37) The absorption attributable to a hydroxyl function suggests that the diketo amine **30** is in equilibrium with the intramolecular aldol condensation product illustrated.

(38) F. Bohlman, *Chem. Ber.*, **91**, 2157 (1958); see also T. M. Moynehan, K. Schofield, R. A. Y. Jones and A. R. Katritzky, *Proc. Chem. Soc.*, 218 (1961).

(39) Determined as described by N. L. Allinger, H. M. Blatter, M. A. DaRooge and L. A. Freiberg, *J. Org. Chem.*, **26**, 2550 (1961); N. L. Allinger and J. Allinger, *ibid.*, **24**, 1613 (1959).

(40) N. J. Leonard, D. F. Marrow and M. T. Rogers, *J. Am. Chem. Soc.*, **79**, 5476 (1957).

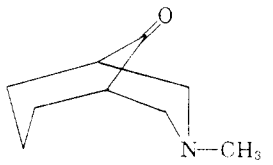
(41) The values pK_{MCS}* are the apparent pK_a values in a mixture of 80% methyl Cellosolve and 20% water. (a) W. Simon, G. H. Lyssy, A. Mörikofer and E. Heilbronner, "Zusammenstellung von scheinbaren Dissoziationkonstanten im Lösungsmittelsystem Methylcellosolve/Wasser," Jurluis-Verlag, Zurich, 1959; (b) W. Simon, *Helv. Chim. Acta*, **41**, 1835 (1958). For tropinone the pK_{MCS}* value is reported to be 6.49.

(42) For a discussion see G. L. Closs, *J. Am. Chem. Soc.*, **81**, 5456 (1959).

TABLE I

Compound	1	2	3
Infrared absorption,[17] cm.$^{-1}$			
C=O	1750, 1720 (sh)	1730, 1710 (sh)	1708, 1690 (sh)
CH adjacent to nitrogen	2760, 2730 (sh) 2690	2800, 2750 (sh) 2700 (sh)	2770, 2720 (sh) 2670
Ultraviolet absorption[33]			
Maxima, mμ (ϵ)	295 (23.6)	288 (29.5) 363 (24.6)	313 (38.7) 366 (20.3)
End absorption, ϵ at 220 mμ	1960	1090	490
Dipole moment, benzene soln. at 25°, D.	2.66 ± 0.02	2.89 ± 0.03	2.91 ± 0.03
pK_{MCS}*	7.59	6.56	5.03

the bottom side in conformation **37**. Thus, steric hindrance to protonation should increase with an increasing number of carbon atoms in the methylene bridge especially if the favored conformations of ketones **2** and **3** are those illustrated in structures **39** and **40**.



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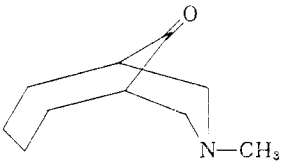

40

Although our present data suggest the importance of conformations **39** and **40**, no firm conclusion can be drawn from the results available.

As mentioned previously, the more intense infrared peak, attributable to a carbonyl stretching vibration, in the spectrum of each of the amino ketones is comparable in location to the carbonyl stretching frequency of the corresponding carbocyclic ketones.[32] In all cases the frequency of carbonyl absorption is appreciably greater than the value expected (*ca.* 1660 cm.$^{-1}$)[10] if an appreciable interaction (*e.g.* structure **36**) existed between the amine and carbonyl functions. Also, the absence of ultraviolet maxima in the region 220–230 mμ[10] of the amino ketone spectra suggests the absence of interactions of the type **36**.

Of interest is the presence of two carbonyl bands in the infrared spectrum of each of the amino ketones. Although this phenomenon, which is also observed with certain carbocyclic ketones,[32] could be attributed to the presence of two conformations in solution, we regarded the possibility that this double carbonyl peak resulted from Fermi resonance as a more probable explanation.[43]

The salient features of the n.m.r. spectra, determined at 60 mc. with a Varian A-60 n.m.r. spectrometer, are summarized in Table II. In each case the n.m.r. curve and its integral were not in disagreement with the structure assigned. As with previously examined tropine derivatives,[42] the two N-methyl groups of the quaternary salts **34** are not equivalent. Unfortunately, our present data do not allow us to decide which N-methyl group is responsible for the peak at higher field and this assignment must await completion of our work on the stereochemistry of N-alkylation. Although we were able to reproduce the previously reported[42] spectrum of pseudotropine hydrochloride (N-methyl peaks at 7.01 and 7.21τ), solutions of the amino ketone salts **35** in deuterium oxide containing excess deuterium chloride exhibited only one N-methyl peak corresponding in position to the higher-field N-methyl peak in the spectra of the quaternary salts **34**. As noted previously, it is probable that the protonated salts **35** have the conformation corresponding to structure **37**. Our data are consistent with the idea that the quaternary salts **34** also exist in a conformation corresponding to **37** with the equatorial N-methyl group being assigned to N-methyl peak in the n.m.r. spectra which is found at higher field. However, this interpretation is by no means certain since the quaternary salts may be exist in a boat conformation corresponding to **38** in order to avoid a serious steric repulsion between the polymethylene bridge and one of the N-methyl groups. We hope to resolve this question as part of our further studies of the stereochemistry of N-alkylation.

TABLE II

Compound	N–CH_3 resonance	–CH_2–N resonance	CH_3 resonance of *p*-$CH_3C_6H_4SO_4^-$
1[a]	7.66	...[b]	
2[a]	7.76	...[b]	
3[a]	7.70	...[b]	
34a[c]	6.73 and 6.92	6.00, 6.23, 6.40, 6.63 (quadruplet, J = 14 c.p.s.)	7.62[d]
34b[c,e]	6.69 and 6.97 (6.42 and 6.78)	6.01, 6.12 (5.70, 5.82)[i]	7.60 (7.68)[d]
34c[c,e]	6.72 and 7.00 (6.46 and 6.80)	6.10, 6.23 (5.81, 5.95)[i]	7.62 (7.68)[d]
35a[f,h]	7.22 (7.08)	6.78[g] (6.52)[g]	7.67 (7.60)
35b[f,h]	7.18 (7.04)	6.54[g] (6.32)[g]	7.67 (7.60)
35c[f,h]	7.18 (6.92)	6.55[g] (6.25)[g]	7.67 (7.59)

[a] Determined in deuteriochloroform. [b] Resolution was inadequate for unambiguous assignment. [c] Determined in deuterium oxide. [d] This assignment was verified by determining the peak position for the N–CH_3 group of the methiodides and metho-*p*-toluenesulfonates of several tertiary amines. In these cases the N–CH_3 group was in the region of 7.0τ and the CH_3 group of the *p*-toluenesulfonate anion was found in the region of 7.7τ. [e] The values in parentheses were determined in perdeuteriodimethylformamide solution. [f] Determined in deuterium oxide containing 20% of monodeuterio-*p*-toluenesulfonic acid. [g] Although the width and shape of this band suggests that it is not a singlet, the resolution is insufficient to reveal the splitting pattern. [h] The values in parentheses refer to spectra determined in deuterium oxide containing approximately 15% of deuterium chloride. [i] Remainder of quartet not discernible.

(43) For other examples see (a) P. Yates and L. L. Williams, *J. Am. Chem. Soc.*, **80**, 5896 (1958); (b) R. N. Jones, C. L. Angell, T. Ito and R. J. D. Smith, *Can. J. Chem.*, **37**, 2007 (1959). We are currently attempting to prepare the appropriate deuterated ketones to test this hypothesis.