phosphate used in each of reactions I–III was prepared from 11.2 g. (0.038 mole) of a sample of freshly prepared but undistilled enol phosphate and 10.7 g. (0.038 mole) of oleic acid. Reaction IV employed 44.4 g. (0.15 mole) of distilled enol phosphate and 42.3 g. (0.15 mole) of oleic acid. The following experimental conditions were used for the acyl phosphate–dipalmitin reactions.

Reaction I.—1,3-Dipalmitin (14.2 g., 0.025 mole) and 300 ml. of water-washed, dried, and distilled (alcohol-free) chloroform were added to the acyl phosphate, and this mixture was stirred overnight under argon at room temperature.

Reaction II.—To a solution of 300 ml. of alcohol-free chloroform, the acyl phosphate, and 14.2 g. (0.025 mole) of 1,3-dipalmitin was added 0.050 ml. of 70% perchloric acid. The reaction mixture was stirred in an argon atmosphere for 3.5 hr. at room temperature.

Reaction III.—A solution of the acyl phosphate in 300 ml. of alcohol-free chloroform was preheated to 50°, and then 14.2 g. (0.025 mole) of 1,3-dipalmitin and, finally, 0.050 ml. of 70% perchloric acid were added. This solution was kept under argon for 3.5 hr. at 50°.

Reaction IV.—A solution of the acyl phosphate, 56.9 g. (0.10 mole) of 1,3-dipalmitin, and 0.257 ml. of 70% perchloric acid in 500 ml. of alcohol-free chloroform was stirred at room temperature for 4 hr. under argon.

All of the products were isolated in the same manner. The chloroform solution was poured into an equal volume of water in a separatory funnel. Enough ether was added to give a lighter-than-water organic layer which was then water washed three times. The organic layer was dried over anhydrous magnesium sulfate and filtered, and most of the solvent was evaporated. The residual solid was dissolved in approximately 10 vol. of acetone and recrystallized at −7° to give the products whose analyses are listed in Table II.

These triglycerides were then freed of fatty acid and diglyceride by column chromatography (4-g. sample on a 40-g. silica gel with 5% water column eluted with 500 ml. of benzene), and the 2-position fatty acids of the pure triglycerides were determined by the lipase hydrolysis method of Mattson and Volpenhein.[9] The results are shown in Table I.

Acknowledgment.—The author wishes to express his appreciation to Dr. T. J. Flautt for considerable assistance in interpreting the n.m.r. data.

Reaction of Enamines with Nitro Olefins[1]

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The morpholine enamines of cyclohexanone, cyclopentanone, desoxybenzoin, and 2-methylcyclohexanone reacted with nitroethylene and 2-acetoxynitroethane to give aminocyclobutanes or alkylated enamines. The corresponding nitroethyl ketones were formed on acid hydrolysis. Reactions of the first three enamines and of the pyrrolidine enamine of butyraldehyde with nitrostyrene gave similar condensation products. Factors affecting the course of these reactions are discussed.

Ketones bearing a γ-nitrogen substituent are of interest as synthetic intermediates for hydroindoles and thus are useful in synthetic schemes leading to many structurally diverse natural products such as alkaloids of the aspidosperma, amaryllidacea, and erythrina classes. One approach to their preparation has been the substitution of ketones with a β-nitroethyl group, using the Mannich condensation. Although 2-dimethylaminomethylcyclohexanone was reported to react with nitromethane and sodium methoxide to give nitroethylcyclohexanone in 72% yield,[3] the sequence appeared to be of limited use in the hands of other investigators who found that this reaction furnished only 15% of the pure product.[4] Through a more extensive route using nitrodiethyl malonate in the Mannich condensation, followed by ester hydrolysis and decarboxylation, the over-all yield of nitroethylcyclohexanone could be raised to 40%.[4a]

The present report describes the direct nitroethylation of ketones and aldehydes in form of their enamine derivatives with nitroethylene, β-acetoxynitroethane, and nitrostyrene as alkylating agents.

A vigorous exothermic reaction was seen on addition of nitroethylene to morpholinocyclohexene (Ia). The course of this reaction was found to depend upon the polarity of the solvent. In acetonitrile, at −20°, the main product was an alkylated enamine IIa, whereas in a hydrocarbon solvent the reaction led primarily to an aminocyclobutane IIIa. Storage of either product at room temperature for a few hours in the original solvents or in the interchanged solvents did not result in noticeable interconversion of the aminocyclobutane and alkylated enamine. Even in refluxing acetonitrile the aminocyclobutane product did not undergo ring cleavage to the alkylated enamine. These results indicate that the two products do not arise from equilibration and that their formation must be considered to be kinetically controlled. In accord with these observations, one can postulate a zwitterionic reaction stage IV which collapses rapidly to the aminocyclobutane III in a nonpolar solvent but in polar solvents has an expected increased lifetime and selectivity for further transformations. This selectivity is expressed in the proton transfer which leads to an enamine product II. Abstraction of a proton from the α′ side of the α-substituted cycloheximmonium intermediate through a six-membered transition state is preferred[5] and could be established by showing the presence of a vinyl enamine hydrogen in the n.m.r. spectrum of the product.

Hydrolysis of the aminocyclobutane IIIa or the alkylated enamine IIa with acid (through protonated IV) gave nitroethylcyclohexanone Va in 80% yield.

The enamine alkylation method[6,7] is particularly

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(1) This research was supported by Grant G. P. 225 of the National Science Foundation.

(2) National Science Foundation undergraduate research participant.

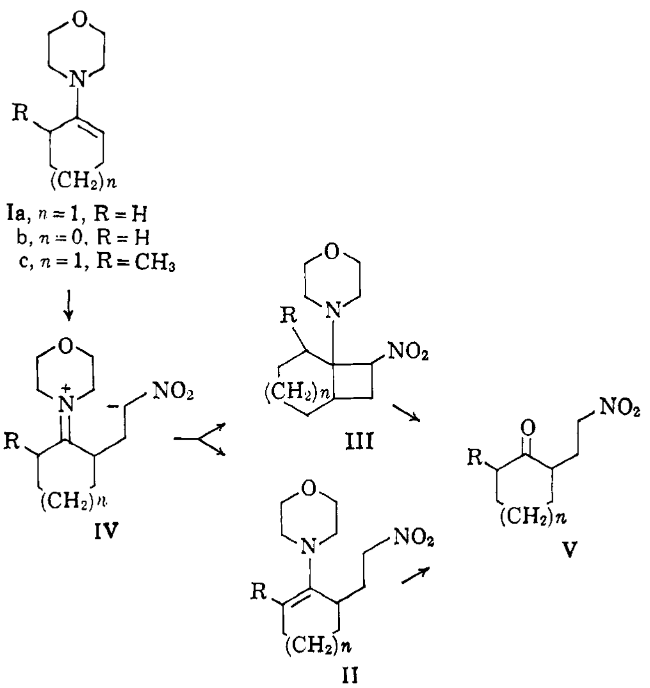
(3) J. H. Brewster and E. L. Eliel, *Org. Reactions*, **7**, 99 (1953).

(4) (a) V. Boekelheide, M. Müller, J. Jack, T. T. Grossnickle, and M. Chang, *J. Org. Chem.*, **81**, 3955 (1959); (b) B. Belleau, *Can. J. Chem.*, **35**, 651 (1957); (c) F. E. King, D. M. Bovey, K. G. Mason, and St. D. Whitehead, *J. Chem. Soc.*, 250 (1953); (d) B. Reichert and H. Posemann, *Arch. Pharm.*, **275**, 65 (1937).

(5) The assignment of this reaction pathway is also in accord with other reactions of enamines with electrophiles which lead to dipolar intermediates where selectivity in further transformations could be demonstrated and controlled by structural variations. To be published.

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

(7) J. Smuszkovicz, *Advan. Org. Chem.*, **4**, 1 (1963).



Ia, $n = 1$, R = H
b, $n = 0$, R = H
c, $n = 1$, R = CH_3

IV

III

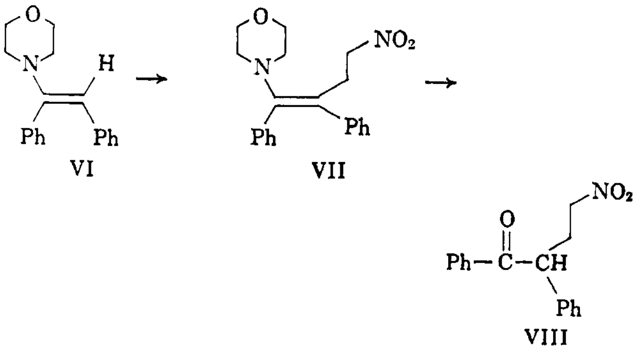
V

II

valuable in nitroethylation reactions because nitro olefins are extremely sensitive to attack and destruction by bases, and even the desired reaction products are not completely stable under the usual base-catalyzed Michael condensation conditions. Presumably because of this base sensitivity, better yields of nitroethyl ketones were obtained with morpholine enamines ($pK_a = 7$) than with pyrrolidine enamines ($pK_a = 10$) when nonconjugated enamines were used.

Since the preparation of nitroethylene[8-10] is not as facile as the formation of enamines of commercially available ketones and thus constitutes the greatest obstacle in the new alkylation sequence, its generation and reaction *in situ* from 2-acetoxynitroethane was studied.[11] With equivalent amounts of morpholinocyclohexene (Ia) and the readily available 2-acetoxynitroethane, a 64% yield of 2-nitroethylcyclohexanone (Va) was obtained. Addition of N-ethylmorpholine for neutralization of the generated acetic acid did not increase the yield. The slow formation of nitro olefin in the presence of enamine was particularly valuable in the reactions of 6-methylmorpholinocyclohexene (Ic) and morpholinocyclopentene (Ib), where considerably higher yields were thus obtained, perhaps because nitro olefin polymerization competes more strongly with the enamine carbon alkylation in these cases.

Nitroethylene was also condensed with the morpholine enamine of benzylphenyl ketone (VI). In this example the alkylated enamine VII was obtained even when the reaction was carried out in petroleum ether. Abstraction of an α-hydrogen from the immonium intermediate is facilitated here by an adjacent phenyl substituent. Deactivation of the starting enamine by conjugation caused a 50% recovery from the reaction when an equivalent amount of nitroethylene was used and extensive polymerization of the nitroethylene. However, with β-acetoxynitroethane, the alkylated enamine was again obtained in good yield. In this reaction the use of N-ethylmorpholine as an auxiliary base was required, apparently because the starting enamine VI is much less basic than the unconjugated enamines Ia, b, and c considered above and thus does not generate nitroethylene from 2-acetoxynitroethane. Acid hydrolysis of the alkylated enamine VII gave the nitroethyl ketone VIII.

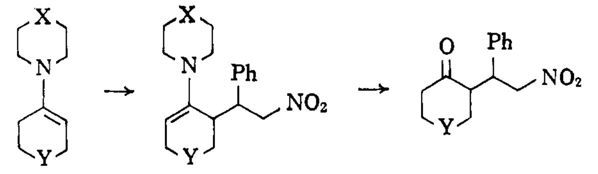


VI

VII

VIII

In addition to the electronic effect described above, steric compression may also prevent cyclobutane formation from dipolar immonium intermediates. Thus, the reaction of nitrostyrene with the morpholine or pyrrolidine enamines of cyclohexanone or cyclopentanone gave the crystalline alkylated enamines IXa and b at 0° in petroleum ether. The position of the enamine double bond in the alkylated morpholinocyclohexene IXa was again defined by the enamine vinyl hydrogen n.m.r. absorption. Acid hydrolyses of the alkylated enamines gave the corresponding β-nitro-α-phenethyl ketones Xa and b.



Ia, Y = CH_2; X = O or —
b, Y = —; X = O or —

IXa, b

Xa, b

All attempts to effect a condensation of the nitrophenethylmorpholinocyclohexene IXa with a second equivalent of nitrostyrene were unsuccessful. Similarly, no clean condensation product could be obtained from 6-methylmorpholinocyclohexene Ic and nitrostyrene. In these cases one encounters the familiar decreased reactivity of α′-substituted cyclohexenamines, which arises from the preferred axial orientation of the substituent and axial approach of the electrophile in the transition state of alkylation.[6,12] A further example of steric hindrance in these reactions was seen in the failure of nitroisobutene to condense with morpholinocyclohexene.

In the condensation of nitrostyrene with the morpholine and pyrrolidine enamines of desoxybenzoin, VI, both the alkylated enamine XI and the aminocyclobutane XII were formed, again with dependence on the solvent polarity. Hydrolysis produced the nitrophenethyl ketone XIII.

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[8] I. M. Gorski and S. P. Makarow, *Ber.*, **B67**, 996 (1934).

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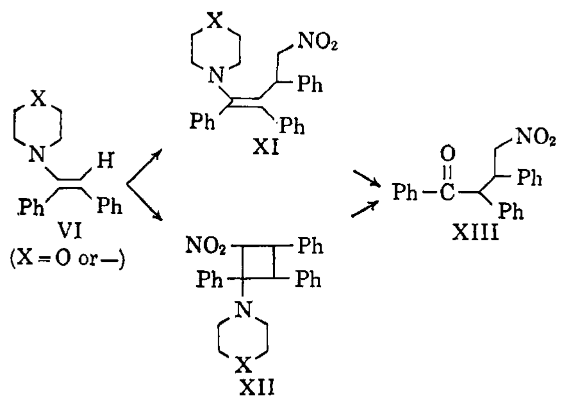
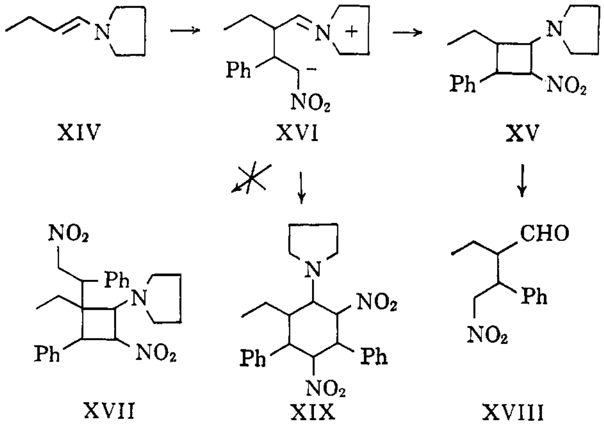
[10] N. Levy, C. W. Scaife, and A. E. Wilder Smith, *ibid.*, 1096 (1946).

[11] The formation and reactions of secondary nitro olefins from acetoxynitroalkanes and sodium acetate was studied by (a) H. Feuer and R. Miller, *J. Org. Chem.*, **26**, 1348 (1961); (b) H. Feuer, R. Miller, and C. B. Lawyer, *ibid.*, **26**, 1357 (1961).

[12] W. R. W. Williamson, *Tetrahedron*, **3**, 314 (1958).



Finally, the reaction of the pyrrolidine enamine of butyraldehyde[13] XIV with nitrostyrene was examined. Only the aminocyclobutane XV was obtained in quantitative yield, with petroleum ether or acetonitrile as solvents. An attempt to direct the reaction course from collapse of the dipolar immonium intermediate XVI and cyclobutane formation to generation of the alkylated enamine gave an unexpected result. Ethanol was chosen as a solvent to ensure protonation of the dipolar intermediate XVI and thus facilitate the generation of a new enamine, and 2 equiv. of nitrostyrene was used in order to trap the new enamine as a second condensation product, the nitrophenethylaminocyclobutane XVII. This method for double condensation had been successful in the closely analogous condensation of methyl acrylate with the same enamine.[14,15] A 2:1 condensation product was indeed obtained, but its resistance to acid hydrolysis, which was quite facile for the 1:1 condensation product XV, leading to the aldehyde XVIII, precluded an aminocyclobutane structure and indicated that the isomeric aminocyclohexane XIX had formed by reaction of the dipolar intermediate with the second equivalent of nitrostyrene.



Experimental Section[16]

2-(2-Nitroethyl)cyclohexanone (Va). A.—A solution of 1.5 g. (9.0 mmoles) of morpholinocyclohexene[17] in 5 ml. of dry acetonitrile was cooled to −20° and 0.50 ml. (0.68 g., 9.7 mmoles) of nitroethylene[9] was added with rapid stirring under an atmosphere of nitrogen. A white crystalline precipitate, which formed rapidly, became soluble in the acetonitrile at room temperature. Infrared spectra (liquid films) of the crystalline material and a small portion of the concentrated acetonitrile solution, separated at −20°, showed strong absorption at 1640 (C=C—N, cyclohexene) and 1545 cm.$^{-1}$ (NO_2), some carbonyl absorption at 1710 cm.$^{-1}$, and definite differences in the 750–1000-cm.$^{-1}$ region when compared with the starting enamine or nitroethylene. A sample of the reaction mixture, concentrated under vacuum, showed the integrated approximate one enamine vinyl hydrogen triplet at τ 5.3, and the α-nitromethylene two-proton triplet at τ 5.7. After standing at room temperature for 1 hr., an excess of 10% hydrochloric acid was added to the reaction mixture; the solution was stirred for 12 hr. at room temperature. Addition of water, extraction with ether, and distillation gave 1.24 g. of product (80% yield), b.p. 88–89° (0.2 mm.). A dinitrophenylhydrazone derivative, recrystallized from ethanol, showed m.p. 142–143°.

Anal. Calcd. for $C_{14}H_{17}N_5O_6$: C, 47.86; H, 4.88; N, 19.94. Found: C, 47.70; H, 4.70; N, 19.66.

B.—The same reaction in petroleum ether (b.p. 60–90°) produced the aminocyclobutane (infrared absorption bands in the 1600–1700-cm.$^{-1}$ region missing). Concentration under vacuum, addition of acetonitrile, and prolonged standing at room temperature or refluxing of the acetonitrile solution did not generate the characteristic enamine absorption at 1640 cm.$^{-1}$. Addition of methanol and excess aqueous hydrochloric acid and the same work-up as given above again produced nitroethylcyclohexanone, identified as its dinitrophenylhydrazone.

C.—Addition of 1.3 g. (10.0 mmoles) of 2-acetoxynitroethane to 1.5 g. (9.0 mmoles) of morpholinocyclohexene in 5 ml. of dry acetonitrile, at −20°, under an atmosphere of nitrogen, and subsequent stirring for 15 hr. at room temperature produced a red solution which on hydrolysis and work-up as used in A above, gave 0.98 g. (64% yield) of nitroethylcyclohexanone. The same reaction run with the addition of 1.0 g. (8.7 mmoles) of N-ethylmorpholine and prolongation of the reaction time to 40 hr. did not alter the yield. An infrared spectrum (liquid film) of this reaction mixture showed a relatively small absorption band at 1640 cm.$^{-1}$ (C=C—N).

2-(2-Nitroethyl)cyclopentanone (Vb). A.—A reaction of 1.3 g. (8.4 mmoles) of morpholinocyclopentene[17] and 0.50 ml. (9.7 mmoles) of nitroethylene in 5 ml. of acetonitrile, as described for morpholinocyclohexene under A, produced after hydrolysis 0.19 g. (14% yield) of nitroethylcyclopentanone, b.p. 80–90° (0.2 mm.).

B.—An analogous reaction in petroleum ether gave 0.15 g. (11% yield) of product. An infrared spectrum (liquid film) of the initial reaction mixture showed a pronounced absorption band at 1625 cm.$^{-1}$ (C=C—N, cyclopentene).

C.—A reaction mixture of 1.3 g. (8.4 mmoles) of morpholinocyclopentene and 1.3 g. (10.0 mmoles) of 2-acetoxynitroethane in 5 ml. of dry acetonitrile, under an atmosphere of nitrogen, was cooled to −23° during combination of the reagents and stirred at 25° for 18 hr. Addition of excess 10% hydrochloric acid, continued stirring for 20 hr., extraction with dichloromethane, and distillation at 83–84° (0.2 mm.) gave 0.86 g. (65% yield) of product.

Anal. Calcd. for $C_{13}H_{15}N_5O_6$: C, 46.29; H, 4.48; N, 20.76. Found: C, 45.92; H, 4.46; N, 21.25.

6-Methyl-2-(2-nitroethyl)cyclohexanone (Vc).—Analogous reactions of 1.6 g. (8.8 mmoles) of 6-methylmorpholinocyclohexene[17] and 0.68 g. (9.7 mmoles) of nitroethylene, gave on hydrolysis: (A) 0.58 g. (36% yield) of the nitroethyl ketone, b.p. 81–84° (0.2 mm.), with acetonitrile as the solvent; and (B) 0.17 g. (10% yield) with petroleum ether as the reaction solvent. An infrared spectrum of the reaction mixture in petroleum ether showed a 1635-cm.$^{-1}$ (C=C—N, cyclohexene) absorption band of moderate intensity, possibly owing to either unreacted starting material or newly formed alkylated enamine.

C.—A similar reaction of 1.6 g. (8.8 mmoles) of 6-methylmorpholinocyclohexene and 1.3 g. (10.0 mmoles) of 2-acetoxynitroethane in acetonitrile gave 1.1 g. (67% yield) of the nitroethyl ketone, which was converted to the dinitrophenylhydrazone with m.p. 122–124° after recrystallization from ethanol.

Anal. Calcd. for $C_{15}H_{19}N_5O_6$: C, 49.32; H, 5.24; N, 19.18. Found: C, 48.93; H, 5.33; N, 19.34.

1,2-Diphenyl-2-(2-nitroethyl)morpholinoethylene (VII). A.—Nitroethylene (0.5 ml., 9.7 mmoles) was added to a stirred solu-

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[13] The formation of cycloaddition products from the reactions of nitrostyrene with enamines of isobutyraldehyde was recently described by K. C. Brannock, A. Bell, R. D. Burpitt, and C. A. Kelly, *J. Org. Chem.*, **29**, 801 (1964).

[14] M. E. Kuehne, *J. Am. Chem. Soc.*, **86**, 2946 (1964).

[15] M. E. Kuehne, *Lloydia*, **27**, 435 (1964).

[16] All melting points were corrected.

[17] M. E. Kuehne, *J. Am. Chem. Soc.*, **81**, 5400 (1959).

tion of 2.5 g. (9.4 mmoles) of 1,2-diphenylmorpholinoethylene[18] in 25 ml. of petroleum ether, under an atmosphere of nitrogen, with cooling in an ice bath. The reaction temperature was raised to 25° after 1 hr. and the reaction mixture was concentrated to dryness after 16 hr. Recrystallization from cyclohexane and petroleum ether (b.p. 30–60°) gave 1.2 g. (38% yield) of the alkylated enamine, m.p. 144–147°, raised to 147–148° after repeated recrystallization: infrared absorption at 1590, 1610 (conjugated enamine and aromatic systems), and 1545 cm.$^{-1}$ (NO_2).

Anal. Calcd. for $C_{20}H_{22}N_2O_3$: C, 70.98; H, 6.55; N, 8.28. Found: C, 70.83; H, 6.74; N, 8.39.

From the mother liquor material 1.3 g. of crystalline starting enamine was recovered.

B.—Alternatively, 1.3 g. (9.8 mmoles) of 2-acetoxynitroethane was added to a solution of 2.5 g. (9.4 mmoles) of 1,2-diphenylmorpholinoethylene and 1.0 g. (6.7 mmoles) of N-ethylmorpholine in 5 ml. of acetonitrile, cooled to 0° under an atmosphere of nitrogen. After 32 hr. at 25°, 1.6 g. of product was removed by filtration, the solvent was concentrated under vacuum, and the residue was triturated with a small amount of methanol to give an additional 0.48 g. of product. The nitroalkylenamine, 2.1 g. (65% yield), was recrystallized from cyclohexane and petroleum ether (b.p. 30–60°). In the absence of N-ethylmorpholine, the starting enamine did not react and was recovered.

3-Benzoyl-3-phenylnitropropane (VIII).—A solution of 0.35 g. of 1,2-diphenyl-2-(2-nitroethyl)morpholinoethylene in 5 ml. of methanol, acidified with aqueous hydrochloric acid, was refluxed for 30 min., and cooled, a small amount of water was added, and 0.25 g. of the ketone, m.p. 44–45°, was collected by filtration. The product was recrystallized from cyclohexane and petroleum ether (b.p. 30–60°), using a small amount of alumina (Woelm, acid, activity I) for decolorization. Two interconvertible crystalline forms, m.p. 48–49° and 58–59°, were obtained.

Anal. Calcd. for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.20; H, 5.44; N, 5.14.

2-(2-Nitro-1-phenethyl)morpholinocyclohexene (IXa). A.—A solution of 2.0 g. (13.4 mmoles) of nitrostyrene in 3 ml. of acetonitrile under an atmosphere of nitrogen was cooled to −10°. To this 2.0 g. (12.0 mmoles) of morpholinocyclohexene[17] was added. The bright orange color which developed initially quickly faded to produce a yellow solution. The temperature of the reaction mixture was raised to 25° over a 1-hr. period, the solvent was evaporated under vacuum, and the residual material was crystallized from 5 ml. of methanol to give 3.8 g. (100% yield) of product, m.p. 79–86°, recrystallized from methanol to m.p. 86–87°: infrared absorption (KBr) at 1650 (C=C—N, cyclohexene) and 1560 cm.$^{-1}$. (NO_2). The n.m.r. spectrum in deuteriochloroform shows the vinyl proton around τ 5 as a multiplet superimposed on the α-nitromethylene proton multiplet.

Anal. Calcd. for $C_{18}H_{24}N_2O_3$: C, 68.33; H, 7.65; N, 8.86. Found: C, 68.54; H, 7.73; N, 8.61.

B.—An analogous reaction with 20 ml. of petroleum ether (b.p. 60–90°) as the solvent gave direct formation of 2.4 g. (63% yield) of crystalline product, filtered from the reaction mixture.

2-(2-Nitro-1-phenethyl)cyclohexanone (Xa). A.—A solution of 1.0 g. (3.2 mmoles) of 2-(2-nitro-1-phenethyl)morpholinocyclohexene in 25 ml. of methanol, acidified to pH 4, was refluxed gently for 15 min., cooled, and concentrated under vacuum, and 0.78 g. (100% yield) of nitrophenethyl ketone, m.p. 106–109°, was collected by filtration. Recrystallization from methanol gave the pure product, m.p. 111–112°.

Anal. Calcd. for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 67.71; H, 7.00; N, 5.67.

B.—A reaction of 2.0 g. (13.0 mmoles) of pyrrolidinocyclohexene[17] and 2.0 g. (13.0 mmoles) of nitrostyrene in petroleum ether (b.p. 60–90°) at 0° under an atmosphere of nitrogen gave 3.3 g. (85% yield) of crystalline condensation product, m.p. 92–94°, within 2 min. Attempted recrystallizations led only to lower melting material. Hydrolysis with aqueous hydrochloric acid, analogous to that described under A for the morpholine enamine, produced the nitrophenethyl ketone in quantitative yield.

2-(2-Nitro-1-phenethyl)cyclopentanone (Xb).—A suspension of 1.0 g. (7.7 mmoles) of nitrostyrene in 10 ml. of petroleum ether (b.p. 60–90°) was stirred under a nitrogen atmosphere at 0° and 1.0 g. (6.6 mmoles) of morpholinocyclopentene[17] was added at once. A gummy solid, which formed rapidly, showed infrared absorption at 1630 (C=C—N, cyclopentene) and 1550 cm.$^{-1}$ (NO_2). Recrystallization from methanol gave 0.62 g. (33% yield), m.p. 145–146°, of the alkylated enamine. Further recrystallizations led to successively decreasing melting points around 135–138°. Hydrolysis of the total reaction mixture with aqueous methanol, acidified with hydrochloric acid to pH 4, for 20 hr. at 25°, concentration under vacuum, and crystallization from petroleum ether (b.p. 60–90°) gave 0.60 g. (40% yield) of ketone, m.p. 82–83°.

Anal. Calcd. for $C_{13}H_{15}NO_3$: C, 66.92; H, 6.48; N, 6.00. Found: C, 66.83; H, 6.75; N, 5.84.

3-Benzoyl-2,3-diphenylnitropropane (XIII). A.—A solution of 1.6 g. (6.0 mmoles) of 1,2-diphenylmorpholinoethylene[18] in 10 ml. of dry ethanol under nitrogen was cooled to 0°, 0.90 g. (6.0 mmoles) of nitrostyrene was added, and the reaction mixture was refluxed for 4 hr. After cooling, 0.63 g. of nitrostyrene was filtered from the reaction mixture and an excess of aqueous hydrochloric acid and some methanol was added to the concentrated filtrate. After stirring for 2 days at 25°, 0.6 g. (29% yield) of crude product was collected, m.p. 185–195°. Recrystallization from dichloromethane and methanol and from dichloromethane and petroleum ether (b.p. 60–90°) gave a pure sample with m.p. 212–213°. Attempted reactions in petroleum ether at 25° or at reflux did not yield any product.

Anal. Calcd. for $C_{22}H_{19}NO_3$: C, 76.52; H, 5.55; N, 4.06. Found: C, 76.26; H, 5.41; N, 4.17.

B.—Alternatively, 1.0 g. (4.0 mmoles) of 1,2-diphenylpyrrolidinoethylene[19] in 10 ml. of petroleum ether (b.p. 60–90°) on reaction with 0.60 g. (4.0 mmoles) of nitrostyrene at 0° for 1 hr. and at 25° for 4 hr., following concentration and hydrolysis with methanol and hydrochloric acid, produced 0.43 g. (27% yield) of the alkylated ketone.

An analogous reaction in acetonitrile gave 0.35 g. (22% yield) of product.

C.—Repeating these experiments, it was noted that the characteristic conjugated enamine absorption at 1585 cm.$^{-1}$ decreases markedly in petroleum ether but not in acetonitrile.

Ethyl-3-nitro-2-phenyl-4-pyrrolidinocyclobutane (XV) and 2-Ethyl-4-nitro-3-phenylbutanal (XVIII).—To 2.0 g. (13.4 mmoles) of nitrostyrene in 20 ml. of petroleum ether (b.p. 60–90°), under an atmosphere of nitrogen and cooled to 0°, was added 1.9 ml. (1.7 g., 13.5 mmoles) of pyrrolidinobutene.[19] After 30 min. the solvent was evaporated under vacuum, leaving the aminocyclobutane as a clear oil without infrared absorption in the 1610–2000-cm.$^{-1}$ region (no enamine) but with absorption at 1550 (NO_2) and 1600 cm.$^{-1}$ (phenyl). The compound readily formed a crystalline hydrochloride, m.p. 140–142°, on addition of cold 10% hydrochloric acid. An infrared spectrum of this hygroscopic salt showed a lack of enimmonium or carbonyl absorption. Warming of the hydrochloride salt in methanol containing a small amount of water and concentration produced the alkylated butyraldehyde as a clear oil, characterized as the dinitrophenylhydrazone, m.p. 185–186° after recrystallization from dichloromethane and methanol. The same dinitrophenylhydrazone could be obtained by reaction of the aminocyclobutane with dinitrophenylhydrazine reagent.

Anal. Calcd. for $C_{18}H_{19}N_5O_6$: C, 53.86; H, 4.77; N, 17.45. Found: C, 54.02; H, 4.72; N, 17.37.

Formation of the aminocyclobutane and its hydrolysis were found to take place in quantitative yields, as judged from infrared spectra and yields of dinitrophenylhydrazone derivatives. A reaction of nitrostyrene with the enamine in acetonitrile gave analogous results. A reaction in methanol gave a crude product with infrared absorption at 1650 cm.$^{-1}$ (C=C—N) which gave a poor yield of the alkylated butyraldehyde dinitrophenylhydrazone.

2,4-Dinitro-3,5-diphenyl-6-ethylpyrrolinocyclohexane (XIX).—The combination of 2.0 g. (13.4 mmoles) of nitrostyrene and 0.95 ml. (6.7 mmoles) of pyrrolidinobutene in 10 ml. of methanol at 0° under an atmosphere of nitrogen led to rapid solution of the nitrostyrene and, after 5 min., a copious deposition of crystalline material. After 12 hr. at −10°, 2.2 g. (78% yield) of product was collected by filtration and recrystallized from dichlorometh-

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[18] Prepared according to procedure of Kuehne, *et al.* [19]: m.p. 84–85°.

[19] M. E. Kuehne, S. J. Weaver, and P. Franz, *J. Org. Chem.*, **29**, 1582 (1964).

ane and methanol. A pure sample, m.p. 257–258°, which was about 20% of the total initial material and may represent one of several stereoisomers, showed an infrared spectrum essentially identical with that of the initial product. The compound did not undergo acid hydrolysis or reaction with dinitrophenylhydrazine reagent.

Anal. Calcd. for $C_{24}H_{29}N_3O_4$: C, 68.06; H, 6.90; N, 9.92. Found: C, 67.99; H, 6.79; N, 9.93.

Acetal Formation for Ketones and Aromatic Aldehydes with Methanol[1]

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Equilibrium constants for acetal formation in methanol have been calculated for eight aromatic aldehydes, nine acyclic ketones, and seven cyclic ketones from spectrophotometric data at 10 and 25°. The values of ΔH, ΔG, and ΔS have also been calculated for these reactions. The method involves the determination of the absorbance of the carbonyl compound in neutral methanol and those in acidic methanol–water mixtures with the differences in absorbances representing the extent of acetal formation. The hemiacetal form does not interfere with acetal determination since when hemiacetal formation occurs, it does so in the neutral and acidic solutions. On the basis of the absorbance change with temperature in neutral methanol, hemiacetal formation has been detected for a few of the carbonyl compounds, but in general most of the compounds used in this study do not form hemiacetals in significant amounts in methanol. The data have been treated by a Taft linear free-energy correlation, but the results were not overly successful. It is suggested that for either equilibrium studies or for kinetic studies for the acetal reaction that a Taft treatment should not correlate the data on a single line for all types of carbonyl compounds because of ΔS (or ΔS^*) effects. Our data suggest that the equilibrium for acetal formation is controlled by the nucleophilic addition of methanol to the carbonyl group and not by the conversion of the hemiacetal to acetal stage. We find that rates parallel equilibria for acetal hydrolysis but bear an inverse relationship for acetal formation.

The equilibrium formation of acetals[3] from aldehydes has been the subject of numerous studies. The classical work of Adkins and his co-workers[4] has served to define the broad relationship between the structures of carbonyl compounds and of alcohols for the extent of formation of acetals. Generally, the reaction is believed to proceed through the formation of the corresponding hemiacetal.[4,5] While the equilibrium conversion of saturated aliphatic aldehydes with primary alcohols is quite good, the equilibrium for α,β-unsaturated aldehydes and aromatic aldehydes are less favorable. Ketones, in general, are not sufficiently converted to acetals to make the equilibrium technique useful to prepare acetals. Under proper operating conditions (low temperature and using an ion-exchange resin catalyst) certain ketones, such as acetone and cyclohexanone, are efficiently converted to acetals.[6,7] Many acetals of ketones can be made in good yields by acetal exchange.[8] The alcohol structure also has a marked influence on the equilibrium of acetals with the extent of conversion markedly decreasing in the order primary > secondary > tertiary.[4]

Much less is known about the relationship between the structures of carbonyl compounds and alcohols and the extent of hemiacetal formation. In part, the problem is complicated by the fact that hemiacetals cannot be isolated in general.[9] There is, however, a great deal of physical evidence which demonstrates the existence of simple hemiacetals in alcohol solutions, including studies by refractive indices,[10,11] by heats of solution,[12] and by the loss of carbonyl absorption in the ultraviolet[5,13,14] and infrared[5,15] regions of the spectrum.

While it is often assumed that all aldehydes and ketones form hemiacetals, Melchior apparently was the first to suggest that aromatic aldehydes do not form significant amounts of hemiacetals in the acetal equilibrium with methanol.[16] Wheeler suggested on the basis of an ultraviolet absorption study that cyclic ketones, such as cyclohexanone, form hemiacetals but not acetals in methanol and ethanol.[17] Subsequently it was demonstrated by a combination of chemical analyses and spectroscopic analyses that cyclohexanone in acidified methanol forms acetal predominantly and that Wheeler's erroneous conclusions were probably due to water as an impurity in the reaction mixtures.[18] The formation of the acetal is adequately confirmed by its isolation in significant yields.[6,7,18]

While thorough kinetic studies have been made for acetal hydrolysis,[19–21] only limited studies have been made for the kinetics of acetal formation.[22–24] Complications due to various extents and rates of formation

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[3] In this paper we refer to *gem*-dialkoxy compounds as acetals regardless of the carbonyl or alcohol structures.

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