TABLE II

POLARIMETRIC ANALYSIS OF REACTION PRODUCTS OF OPTICALLY ACTIVE ALCOHOLS

Source of product	Temp., °C.	Solvent	$[\alpha]^{45}D$, deg.	α (initial)	α (final)[a]	% (+)-*exo*-norbornyl bromide[b]	% (+)-*endo*-norbornyl bromide[b]
exo-Norbornanol (triglyme)	45.0	Aqueous acetic acid–sodium acetate	0.55	0.10 ± 0.02	0.09 ± 0.02	15 ± 20	85 ± 20
endo-Norbornanol (triglyme)	45.0	Aqueous acetic acid–sodium acetate	6.15	0.96 ± 0.02	0.00 ± 0.02	100 ± 2	0 ± 20

[a] The final rotation of the product derived from *exo*-norborneol was measured after two solvolytic half-lives of *exo*-norbornyl bromide. The rotation of the product from *endo*-norborneol was measured after ten half-lives. [b] This crude estimate is based on the assumption that the two isomers have equal maximum rotations and refers to the relative percentages of the two *optically active* isomers present in the reaction mixture.

TABLE III

CONDUCTOMETRIC SOLVOLYSIS OF THE MAJOR PRODUCT OF EACH REACTION[a]

Source of product	10^4k, sec.$^{-1}$
exo-Norbornanol (triglyme)	1.4
endo-Norbornanol (triglyme)	1.4
exo-Norbornanol (DMF)	1.4
endo-Norbornanol (DMF)	1.3
exo-Norbornyl bromide[b]	1.3

[a] Run in 50% aqueous triglyme at 35.1°. [b] This bromide was prepared according to the procedure given by Roberts.[21]

The major component of the reaction mixture was identified as *exo*-norbornyl bromide by a comparison of its retention time, infrared spectrum, and rate of solvolysis with those of an authentic sample. A slower solvolyzing component was also present in the alkyl halide fraction when triglyme was used as the solvent and it was identified as the *endo* isomer since it was optically active when optically active alcohol was used.

The relative amount of *exo*- and *endo*-norbornyl bromides was determined by selective solvolysis in 80% ethanol. It was found that at 90° solvolysis of the *exo* halide was complete in 1 hr. while the *endo* halide required 100 hr. for complete solvolysis and reacted to a negligible degree during the time required to solvolyze the *exo* isomer.[21] The halogen liberated was estimated by the Volhard method.

When reactions were carried out with optically active alcohols, the products were also analyzed by their polarimetric solvolysis rates in aqueous acetic acid containing sodium acetate. All of the results from the above determinations are summarized in Tables I–III.

Attempted Isolation of *exo*-Norbornoxytriphenylphosphonium Bromide.—The identical procedure described for the *endo* isomer was used.[3] Initially the yield of crude product was lower (19 g., 88.5%) and contained much triphenylphosphine oxide in addition to the intermediate. After a 2-hr. evacuation period at 0.5 mm. at room temperature, the residue which remained was primarily triphenylphosphine oxide, m.p. 130–156°, and no longer precipitated from chloroform upon the addition of ether (the intermediate is insoluble in this solvent combination whereas triphenylphosphine oxide is completely soluble); the ultraviolet spectrum was identical with that of triphenylphosphine oxide and markedly different from the *endo* and 7 intermediates. The rapid decomposition of the *exo*-norbornoxytriphenylphosphonium bromide at room temperature indicates that this isomer is much more reactive than the corresponding *endo* derivative.

(21) J. D. Roberts and W. Bennett, *J. Am. Chem. Soc.*, **76**, 4623 (1954)

The Reaction of Ketene with Enamines[1,2]

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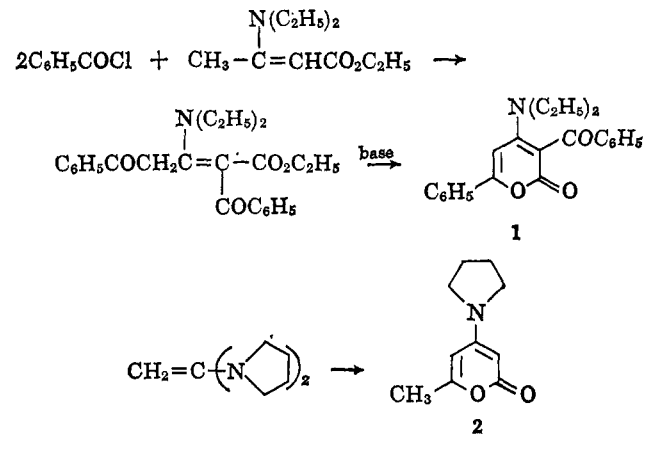
Received March 2, 1965

Several enamines derived from ketones have been found to react with excess ketene to yield 2H-pyran-2-ones containing substituents in the 4-, 5-, and 6-positions.

Although the cycloaddition reaction of enamines with 1 equiv. of a ketene or an acid chloride in excess base has received considerable attention as a synthetic route to cyclobutanones,[4,5] little attention has been given to the reaction of enamines with excess ketene to form 2H-pyran-2-ones.[2] Diketene has been observed to react with enamines derived from cyclic ketones to afford 4H-pyran-4-ones.[6,7] The 2H-pyran-2-one **1** has been prepared from ethyl β-diethylaminocrotonate by reaction with 2 equiv. of benzoyl chloride to give ethyl 2,4-dibenzoyl-3-diethylaminocrotonate which cyclized to **1** in base.[8]

This paper is concerned with a one-step preparation of 2H-pyran-2-ones substituted in the 4-, 5-, and 6-positions by reaction of enamines with excess ketene.



(1) This research has been supported by the National Science Foundation, Grant No. G-21443 and GP-1562.

(2) For a preliminary communication on this work, see G. A. Berchtold, G. R. Harvey, and G. E. Wilson, Jr., *J. Org. Chem.*, **26**, 4776 (1961).

(3) Alfred P. Sloan Research Fellow.

(4) G. Opitz and M. Kleemann, *Ann.*, **665**, 114 (1963), and previous papers in this series.

(5) R. H. Hasek and J. C. Martin, *J. Org. Chem.*, **28**, 1468 (1963); **26**, 4775 (1961).

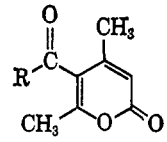
(6) B. B. Millward, *J. Chem. Soc.*, 26 (1960).

(7) S. Hünig, E. Benzing, and K. Hubner, *Chem. Ber.*, **94**, 486 (1961).

(8) W. M. Lauer and N. H. Cromwell, *J. Am. Chem. Soc.*, **64**, 612 (1942).

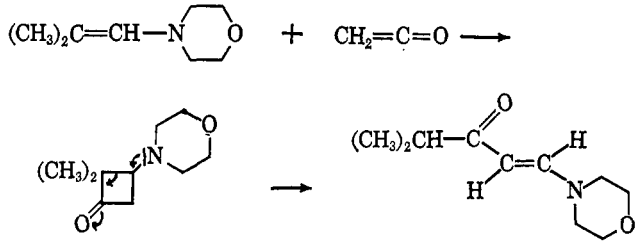
Opitz and Zimmermann[9] have recently reported the reaction of 1,1-bisdialkylaminoethylenes with excess ketene to produce 4-dialkylamino-2H-pyran-2-ones. 1,1-Dipyrrolidinoethylene, for example, was converted to 4-N-pyrrolidino-6-methyl-2H-pyran-2-one (**2**) in 58% yield. 1,1-Bisdialkylaminoethylenes containing a methyl or ethyl substituent in the 2-position also proceeded satisfactorily. Opitz and Tempel[10] have recently reported the preparation of β-amino δ-sultones from the cycloaddition of monoenamines of 1,3-dicarbonyl systems to sulfene generated from methanesulfonyl chloride in the presence of triethylamine.

Treatment of ethyl 3-pyrrolidinocrotonate with ketene produced the known ethyl isodehydroacetate (**3**) in 35% yield. In a similar manner 4-N-pyrrolidino-3-penten-2-one afforded 5-acetyl-4,6-dimethyl-2-H-pyran-2-one (**4**) in 52% yield. The mode of formation of **4** apparently involves initial acetylation at the β-carbon atom of the enamine. Whether this step proceeds by cycloaddition to the cyclobutanone followed by ring opening or by direct acetylation is open to question.



3, R = OC_2H_5
4, R = CH_3

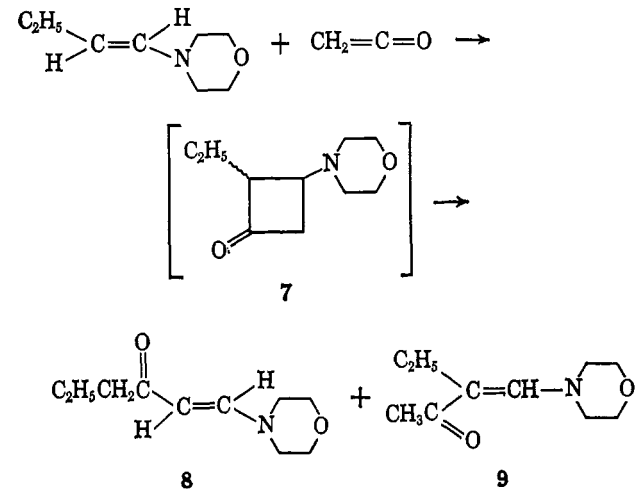
Simple enamines derived from aldehydes react with 1 equiv. of ketene to form a 3-aminocyclobutanone[2,4,5] which undergoes ring cleavage to the monoenamine of a β-dicarbonyl system. 4-Isobutenylmorpholine, for example, readily forms the cyclobutanone **5** which can be isolated as a stable crystalline product at room temperature but quantitatively rearranges to **6** at steam bath temperatures. The structure of **6** was established by preparation of an authentic sample from morpholine and ethynyl isopropyl ketone. 4-(1-Butenyl)morpholine reacted with 1 equiv. of ketene to produce the cyclobutanone **7** which could not be isolated prior to rearrangement to a 4:1 mixture of **8** and **9**, respectively.



5 **6**

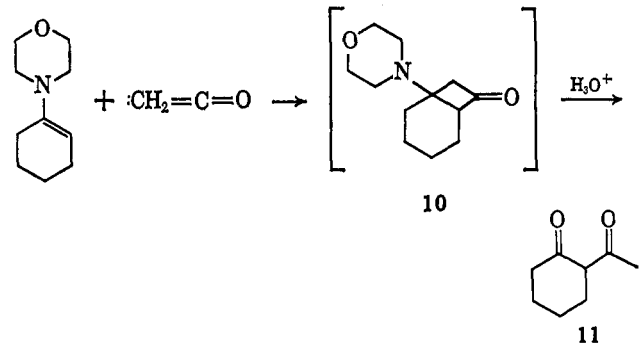
4-(1-Cyclohexenyl)morpholine and 4-(1-cyclopentenyl)morpholine also reacted smoothly with 1 equiv. of ketene or acid chloride and base to produce, after hydrolysis, the corresponding 2-acylcycloalkanone. The reaction apparently proceeds by cycloaddition in these cases also since a strong absorption band at 1776 cm.$^{-1}$ could be observed in the infrared spectrum of

(9) G. Opitz and F. Zimmermann, *Chem. Ber.*, **97**, 1266 (1964).
(10) G. Opitz and E. Tempel, *Angew. Chem.*, **76**, 922 (1964); *Angew. Chem., Intern. Ed. Engl.*, **3**, 754 (1964).



7 **8** **9**

the crude reaction mixture from 4-(1-cyclohexenyl)-morpholine, indicating the presence of **10**.[4] Hydrolysis of the reaction mixture yielded only **11** and no 1,3-cyclooctanedione. Presumably the steric strain in



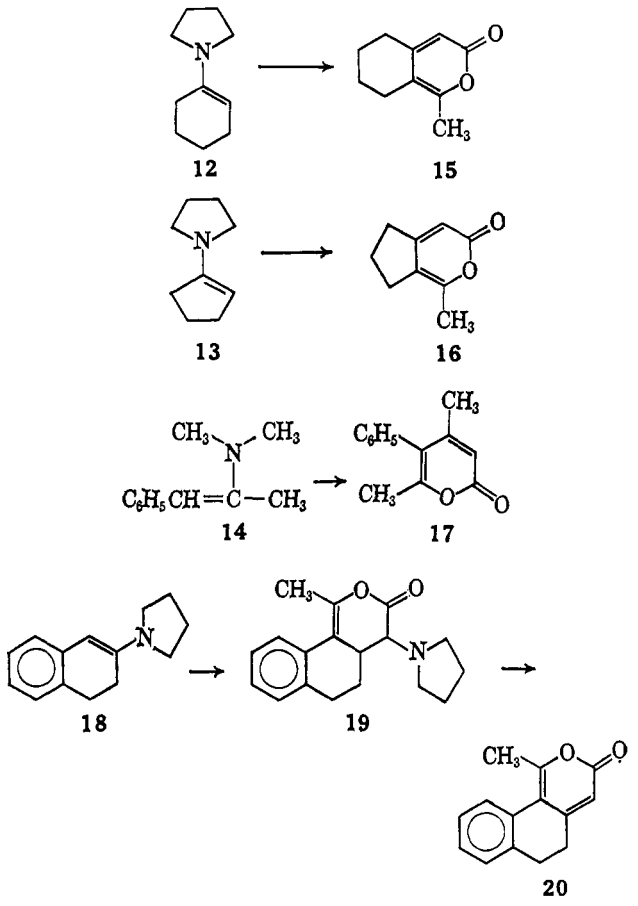
10 **11**

the cyclooctane ring system makes cleavage to the acetylcyclohexane derivative a more favorable rearrangement process. The reaction of acryloyl chloride with enamines yields a mixture of products.[11]

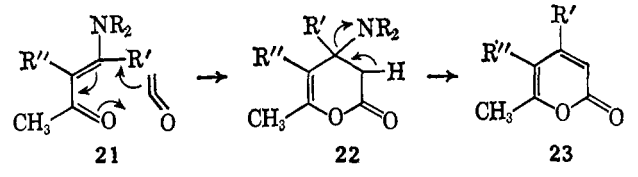
In view of this facile cleavage of the 3-aminocyclobutanone derivatives to the corresponding enamine derivative of the 1,3-diketone, it was presumed that the reaction of simple enamines with excess ketene should lead to the formation of 2H-pyran-2-ones by analogy with the above-described formation of **3** and **4**. The enamines **12**–**14**, on treatment with excess ketene, indeed formed the corresponding 2H-pyran-2-ones **15**–**17** in yields ranging from 20 to 35%. Of particular interest was the reaction of **18** with ketene in benzene which resulted in precipitation of the intermediate aminoenol lactone **19** as it was formed. Compound **19** slowly eliminated pyrrolidine at room temperature to form the 2H-pyran-2-one **20** and could be converted quantitatively to **20** by stirring with 17% aqueous hydrochloric acid.

In view of the above, it appears reasonable that the acetylated enamine **21** undergoes a 1,4 cycloaddition reaction with ketene to produce the intermediate 4-amino-3,4-dihydro-2H-pyran-2-one (**22**) which, on further reaction with ketene, eliminates secondary amine to form an N,N-dialkylacetamide and the corresponding 2H-pyran-2-one. The low yield of 2H-pyran-2-one in many of these reactions is apparently

(11) P. W. Hickmott, *Proc. Chem. Soc.*, 287 (1964).



due to polyacetylation by ketene to form polyketones and/or enol lactones. No 4H-pyran-4-one products were isolated from any of the reaction mixtures.



Experimental[12]

General Procedure for Pyrones. A.—Ketene (4 equiv.) was bubbled through a 10% solution of the enamine in dry ether or benzene. The solution was stoppered, kept at 25° for 4 hr., concentrated, and chromatographed on a column of alumina (50:1, Merck activity III). The 2H-pyran-2-one was eluted with ether–benzene (3:1) as the first yellow band. Purification was effected by recrystallization from tetrahydrofuran–pentane or by sublimation.

B.—After standing for 4 hr., the reaction solution was concentrated and taken up in 17% hydrochloric acid. The solution was boiled for 0.25 hr. and extracted with ethyl acetate until the extracts were colorless. The combined organic phase was washed with saturated sodium bicarbonate and then brine, dried, and concentrated. Distillation by a short-path method afforded the pure 2H-pyran-2-one.

(12) All melting points are corrected and all boiling points are uncorrected. The infrared spectra were determined with either a Perkin-Elmer Model 21, Model 237, or Infracord recording spectrophotometer fitted with a sodium chloride prism. The ultraviolet spectra were determined with a Cary recording spectrophotometer, Model 11 MS. The microanalyses were performed by Dr. S. M. Nagy and his associates and by the Scandinavian Microanalytical Laboratory. The n.m.r. spectra were determined with a Varian A-60 spectrometer. The values are reported in parts per million downfield from tetramethylsilane. Unless specified otherwise, calcium sulfate was used as the drying agent; infrared spectra were determined in chloroform, n.m.r. spectra in deuteriochloroform, and ultraviolet spectra in ethanol.

5-Acetyl-4,6-dimethyl-2H-pyran-2-one (**4**) was isolated in 52% yield and had m.p. 72.5–73°; λ_{max} 296 mμ (ε 6090); and $\bar{\nu}_{max}$ 1740, 1698, 1625, 1545, and 849 cm.$^{-1}$. The n.m.r. spectrum shows singlets at δ 2.08 (3H), 2.20 (3H), 2.45 (3H), and 6.06 (1H).

Anal. Calcd. for $C_9H_{10}O_3$: C, 65.05; H, 6.02. Found: C, 65.10; H, 6.01.

Ethyl isodehydroacetate (**3**) was isolated in 35% yield and had b.p. 60° (6 mm.). It was identical in all respects with a sample prepared by the method of Smith and Wiley[13] and had a microanalysis corresponding to $C_{10}H_{12}O_4$.

5-Phenyl-4,6-dimethyl-2H-pyran-2-one (**17**) was isolated in 34% yield and had m.p. 61–62°; λ_{max} 301 mμ (ε 6711) and 231 mμ (ε 7382); and $\bar{\nu}_{max}$ 1730, 1680, 1625, 870, 848, and 702 cm.$^{-1}$. The n.m.r. spectrum has methyl absorption at δ 1.85 (3H) and 2.80 (3H), olefinic proton absorption at 6.15 (1H), and the aromatic absorption centered at 7.3 (5H).

Anal. Calcd. for $C_{13}H_{12}O_2$: C, 77.97; H, 6.08. Found: C, 77.91; H, 6.00.

4,5-Tetramethylene-6-methyl-2H-pyran-2-one (**15**) was isolated in 35% yield and had m.p. 82–84.5°; λ_{max} 312 mμ (ε 6800); and $\bar{\nu}_{max}$ 1730, 1630, 1536, and 850 cm.$^{-1}$ The n.m.r. spectrum has a methylene envelope centered at δ 2.0 (8H), a methyl singlet at 2.18 (3H), and the vinyl proton at 5.88 (1H).

Anal. Calcd. for $C_{10}H_{12}O_2$: C, 73.14; H, 7.37. Found: C, 72.93; H, 7.21.

4,5-Trimethylene-6-methyl-2H-pyran-2-one (**16**) was isolated in 20% yield and had m.p. 61–63°; λ_{max} 304 mμ (ε 2050); and $\bar{\nu}_{max}$ 1730, 1655, 1580, and 850 cm.$^{-1}$. The n.m.r. spectrum has a methylene envelope centered at δ 2.0 (6H), a methyl singlet at 2.17 (3H), and the vinyl proton at 5.88 (1H).

Anal. Calcd. for $C_9H_{12}O_2$: C, 71.98; H, 6.71. Found: C, 71.60; H, 6.79.

Amino lactone 19 was isolated from the benzene solution in 31% yield and had m.p. 129–130° and $\bar{\nu}_{max}$ 1780 cm.$^{-1}$. The n.m.r. spectrum has vinyl methyl absorption at δ 2.1 (3H) and the methylene singlet at 2.8 (2H). It was not sufficiently stable to obtain an elemental analysis.

2-Oxa-3-oxo-1-methyl-2,3,5,6-tetrahydrophenanthrene (**20**) was isolated in 100% yield from the amino lactone **19**, by stirring with 17% hydrochloric acid followed by the usual work-up. Compound **20** had m.p. 109–110°; λ_{max} 318 mμ (ε 4100) and 250 mμ (ε 2180); and $\bar{\nu}_{max}$ 1740, 1650, 1550, and 880 cm.$^{-1}$. The n.m.r. spectrum has a vinyl methyl at δ 2.55 (3H), methylene multiplet at 2.7 (4H), olefinic proton at 6.10 (1H), and an aromatic sextet centered at 7.25 (4H).

Anal. Calcd. for $C_{14}H_{12}O_2$: C, 79.24; H, 5.66. Found: C, 79.00; H, 5.80.

Ethyl 3-Pyrrolidinocrotonate.—To 91.0 g. (0.7 mole) of ethyl acetoacetate was added dropwise with stirring 50 g. (0.7 mole) of pyrrolidine. The solution was stirred at 27° for 2 hr. Pentane (50 ml.) was added, decanted from the aqueous layer, and cooled. The crystals were washed several times with pentane at 0°. The yield was 73 g. (57%). The enamine had m.p. 25°, b.p. 200° (40 mm.), and $\bar{\nu}_{max}$ 1675 (unsaturated ester) and 1560 cm.$^{-1}$ (conjugated olefin). These data agree with the reported melting point (29–30°) and infrared spectrum of **11** as prepared by Postovskii.[14]

1-Phenyl-2-dimethylaminopropene.—Phenyl-2-propanone (75 g., 0.5 mole), 50 g. (1 mole) of dimethylamine, 60 g. of potassium carbonate, and 100 ml. of toluene were rocked in a stainless steel bomb at 100° for 16 hr. After cooling, the mixture was decanted, concentrated, and distilled on a 45 × 0.5 cm. spinning-band column at 0.2 mm. The fractions having b.p. 55–60° were combined and refractionated. The material which had b.p. 59.5–60° (0.2 mm.), $n^{25}D$ 1.5824, was 99% pure as determined by v.p.c. (11% XF1150 on Chromosorb W, 190°). The enamine had $\bar{\nu}_{max}$ 1640, 1610, 942, 910, 785, 730, and 695 cm.$^{-1}$, and n.m.r. absorption at δ 2.0 (3H, singlet due to vinyl methyl), 2.75 (6H, singlet of the N-methyls), 5.1 (1H, singlet of the vinyl proton), and aromatic absorption at 7.2 (5H).

Anal. Calcd. for $C_{11}H_{15}N$: C, 81.93; H, 9.38; N, 8.69. Found: C, 81.85; H, 9.44; N, 8.62.

2,2-Dimethyl-3-N-morpholinocyclobutanone (**5**).—Ketene (0.7 mole) was bubbled through a solution of 4-isobutenylmorpholine

(13) N. R. Smith and R. H. Wiley, *Org. Syn.*, **32**, 76 (1952).

(14) Y. Postovskii, E. I. Grinblat, and L. F. Trefilova, *Zh. Obshch. Khim.*, **31**, 400 (1961).

(103 g., 0.66 mole) in 200 ml. of pentane at 0°. The solution was stored in a freezer for 8 hr. The pentane was evaporated at 0° and the residue was crystallized by immersion in a Dry Ice–acetone bath. The solid was filtered and washed with cold pentane to leave pale yellow granules (90 g., 70%). The compound had m.p. 41–42° (sublimed) and $\bar{\nu}_{max}$ 1780 cm.$^{-1}$. The n.m.r. spectrum has a doublet at δ 1.18 (6H) due to the nonequivalent methyl groups, a morpholino pattern at 2.35 and 3.7, methylene protons at 2.5, and the proton under N at 3.1.

Anal. Calcd. for $C_{10}H_{17}NO_2$: C, 65.57; H, 9.29; N, 7.65. Found: C, 65.73; H, 9.38; N, 7.71.

Rearrangement of 5.—One gram of **5** was heated to 50° in a sealed tube for 10 min. The resulting oil (1 g.) had an infrared spectrum identical with that of 1-N-morpholino-4-methyl-1-penten-3-one.

Anal. Calcd. for $C_{10}H_{17}NO_2$: C, 65.54; H, 9.35; N, 7.64. Found: C, 65.78; H, 9.45; N, 7.64.

1-N-Morpholino-4-methyl-1-penten-3-one (6).—2-Methylpent-4-yn-3-one[15] (362 mg., 3.77 mmoles) was dissolved in 7 ml. of anhydrous ether, cooled to 0°, and treated with 324 mg. (3.77 mmoles) of morpholine in 4 ml. of ether. The solution was warmed to 25° over 8 hr. and concentrated to a pale yellow oil. This oil had λ_{max} 307 mμ (ϵ 7600) and $\bar{\nu}_{max}$ 1650, 1550, and 1120 cm.$^{-1}$.

Reaction of 4-(1-Butenyl)morpholine and Ketene.—The enamine (3.9 g., 0.03 mole) in 50 ml. of ether was treated with 0.1 mole of ketene at 20°. After standing for 2 hr., the solution was concentrated to a yellow oil which showed infrared absorption at 1780 and 1650 cm.$^{-1}$. Distillation through a semimicro column separated 4.0 g. (68%) of a straw yellow oil which had b.p. 144–145° (2 mm.) and $\bar{\nu}_{max}$ 1650, 1550, and 1120 cm.$^{-1}$. The n.m.r. spectrum has the vinyl proton doublet of **8** and the vinyl singlet of **9** at δ 7.4 and 7.05 in the ratio of 4:1.

Anal. Calcd. for $C_{10}H_{17}NO_2$: C, 65.52; H, 9.29; N, 7.65. Found: C, 65.17; H, 9.40; N, 7.66.

(15) We wish to thank Professor N. J. Leonard of the University of Illinois for a generous sample of this compound.

Sterically Crowded Amines. IV. Secondary and Tertiary Bispropargylic Amines and Their Hydrogenation Products[1]

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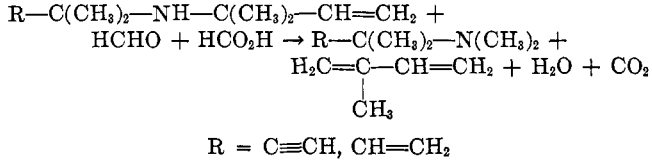
Received February 15, 1965

A series of sterically crowded amines of the type $R^1C(CH_3)_2N(R^2)C(CH_3)_2R^3$ in which R^1 and R^3 are C≡CH, CH=CH_2, and CH_2CH_3 *in all possible combinations* and R^2 = H or CH_3 has been prepared. The formation of pyrrolines and pyrrolidines *via* a new cyclization reaction of bispropargylic and propargylic–allylic amines with sodium in liquid ammonia is described. The basicities of some sterically crowded amines are reported.

The facile synthesis of some sterically crowded acetylenic amines $R^1R^2C(NR^3R^4)$—C≡CH described in earlier papers[3,4] and the finding[5] that many of these have notable hypotensive properties prompted a study of the preparation of other compounds of this type having enhanced steric crowding, varying degrees of unsaturation (both propargylic and allylic), and the relation of unsaturation to basicity in sterically crowded amines.

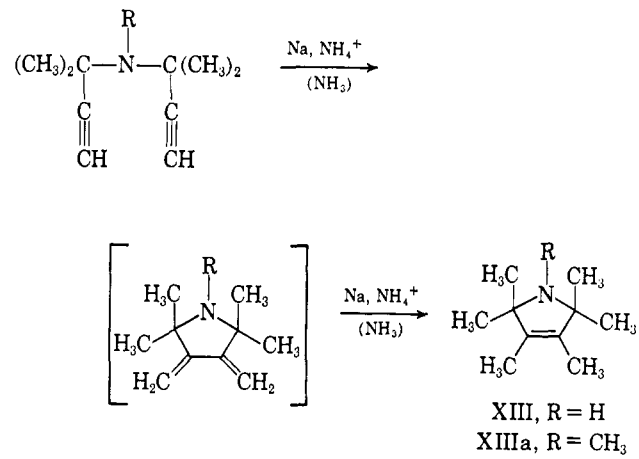
Primary and secondary amines of the type $(CH_3)_2C(NHR^1)R^2$ where R^1 = H or CH_3 and R^2 = C≡CH, CH=CH_2, and —CH_2CH_3 were alkylated with 3-chloro-3-methyl-1-butyne in a manner similar to that previously reported.[3] The products, obtained in good yield where R^1 = H, were subjected to selective catalytic hydrogenation which usually proceeded without extensive hydrogenolysis. Notable exceptions were the attempts to prepare di-*t*-amylamine hydrochloride from bis(1,1-dimethylpropargyl)amine and 3-*t*-amylamino-3-methyl-1-butyne hydrochlorides using platinum oxide catalyst. Di-*t*-amylamine (XII) was prepared, however, from the above amines in good yields using Raney nickel catalyst.

Some of the sterically crowded secondary amines were converted to tertiary amines *via* the previously described[4] Clarke–Eschweiler methylation. In cases of severe steric crowding this procedure either failed or led to extensive decomposition as shown.



R = C≡CH, CH=CH_2

Attempted semihydrogenation of the bispropargylic and propargylic–allylic amines with sodium in liquid ammonia led to the discovery of a new reaction, namely intramolecular C–C coupling across the two unsaturated centers. The presumed course of the reaction is as shown. Conjugated dienes are known[6] to undergo



XIII, R = H
XIIIa, R = CH_3

reduction with 1,4 addition of hydrogen under the reaction conditions.

In the two cases where propargylic–allylic amines (VIII and VIIIa) were treated with sodium in liquid ammonia, the isomeric 3-methylenepyrrolidines (XIV

(1) Paper No. 79 on substituted acetylenes. Previous paper: G. F. Hennion and P. E. Butler, *J. Org. Chem.*, **27**, 2088 (1962).

(2) Eli Lilly Co. Fellow, 1962–1964. Abstracted from a portion of the Ph.D. Dissertation of C. V. D.

(3) G. F. Hennion and R. S. Hanzel, *J. Am. Chem. Soc.*, **82**, 4908 (1960).

(4) C. Ainsworth and N. R. Easton, *J. Org. Chem.*, **26**, 3776 (1961).

(5) N. R. Easton, Abstracts of papers presented at the 138th National Meeting of the American Chemical Society, New York, N. Y., Sept. 1960, p. 46 O.

(6) N. L. Bauld, *J. Am. Chem. Soc.*, **84**, 4347 (1962).