4-Methyl-2-methoxypropiophenone had ir (CH_2Cl_2, 5%) 1669 (C=O), 1610, 1570, 1495, 1460 (aryl C=C), and 1209 cm^{-1} (CO).

Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.58; H, 7.80.

2,5-Dimethyl-4-methoxypropiophenone had ir (CH_2Cl_2, 5%) 1672 (C=O), 1610, 1560, 1508, 1462 (aryl C=C), and 1231 cm^{-1} (CO).

Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.94; H, 8.39. Found: C, 74.34; H, 8.42.

4-Chloro-2-methoxypropiophenone had ir (CH_2Cl_2, 5%) 1673 (C=O), 1590, 1568, 1480, 1460 (aryl C=C), and 1241 cm^{-1} (CO).

Anal. Calcd for $C_{10}H_{11}O_2Cl$: C, 60.46; H, 5.58; Cl, 17.85. Found: C, 60.11; H, 5.56; Cl, 17.74.

All inorganic compounds used (perchloric acid, sodium perchlorate, sodium bromide, bromine) were reagent grade. Water used as solvent was distilled twice over alkaline potassium permanganate.

Kinetic Measurements.—All kinetic measurements were performed by the automatic method of couloamperometry as previously described.[2,3]

Synthesis of Reaction Products.—The same method was used for the preparation of the three bromo ketones (3-bromo-4-methoxyacetophenone, 5-bromo-2-methoxyacetophenone, 3-bromo-2,4-dimethyl-6-methoxypropiophenone).

To a mechanically stirred solution of 4.5–4.9 g (0.025 mol) of methoxyaromatic ketone in 250 ml of acetic acid, a solution of 4.0 g (0.025 mol) of bromine in 50 ml of acetic acid was added in small portions. After complete addition of bromine (40 min), about 50 ml of water was added to accelerate the reaction; the mixture was stirred for 2 hr. It was extracted three times with carbon tetrachloride and dried over sodium carbonate. Most of the CCl_4 was evaporated. The CCl_4 concentrated layer was analyzed and its components were separated by preparative gas chromatography. The following columns were used: 20% XF-1150 and 10% UCON Polar on Chromosorb W (Aerograph Co.). Vpc analysis showed traces of the starting methoxy aromatic ketone and in each case only one brominated compound, identified by nmr as the nuclear bromo ketone (see Table I). The retention times of these synthesized bromo ketones were found to be identical with those of the bromo ketones obtained under kinetic conditions.

Registry No.—**1**, 579-74-8; **2**, 100-06-1; **3**, 5561-92-2; **4**, 121-97-1; **5**, 13404-83-6; **6**, 4160-51-4; **7**, 36871-54-2; **8**, 36871-55-3; **9**, 36871-56-4; **10**, 5384-14-5; **11**, 36871-58-6.

Cyclopropylamines as Intermediates in a New Method for Alkylation of Aldehydes and Ketones

MARTIN E. KUEHNE* AND JAMES C. KING

Department of Chemistry, University of Vermont, Burlington, Vermont 05401

Received June 27, 1972

A series of 1-(N,N-disubstituted amino)bicyclo[*n*.1.0]alkanes was prepared from cyclic ketone enamine derivatives and methylene or ethylene iodide and diethylzinc or diazomethane or diazoethane and cuprous chloride. Thermal opening in aqueous methanol furnished the α-alkylated and ring-expanded ketones. Similarly, propionaldehyde was converted to isobutyraldehyde (49%), cholestenone to 4-methylcholestenone (76%), and 17-β-hydroxy-5-α-androstan-3-one to 2β-methyl-17β-hydroxy-5α-androstan-3-one (67%) through cyclopropylamine intermediates. The thermolysis is accelerated by surface-active agents, *i.e.*, 10% Pd/C. Opening of the cyclopropylamines in the presence of acrylonitrile gave products corresponding to those obtained with the alkylated enamines. Hydrogenolyses of some bicyclic cyclopropylamines furnished *N*-(2-methylcycloalkyl)amines.

In syntheses of aliphatic compounds, the α-alkylation of ketones and aldehydes is the most widely used reaction principle for carbon to carbon bond formation. Classically, such alkylations are accomplished by formation of enolate anions or enols and reactions of these with electrophilic alkylating agents. In order to overcome some of the difficulties inherent in enolate anion generation and alkylation and to achieve controlled monoalkylation, regiospecificity, and stereospecificity, considerable effort has been spent during the past decades on the development of new alkylation methods. The Stork enamine alkylation principle[1] was notably most stimulating[2] and useful[3] to synthetic chemists.

Our present report describes the formation and use of cyclopropylamines as intermediates in the α-alkylation of ketones and aldehydes. The advantages of this new synthetic principle are (a) selective formation and isolation of pure monoalkylation products; (b) regiospecificity in positioning of new substituents; (c) improved alkylation yields in some of the studied examples where reported yields obtained by other methods were found to be low.

This new alkylation route formally parallels the recently developed use of cyclopropyl ethers as alkylation intermediates.[4,5] However, in contrast to that reaction sequence it is now possible to avoid drastic acidic treatment and to achieve cleavage of the cyclopropane intermediates under neutral conditions.

Formation of Cyclopropylamines.—The most practical method for large-scale preparations of tertiary cyclopropylamines from carbonyl compound precursors was found to be the reaction of diethylzinc and diiodomethane[6,7] with enamines. For small-scale preparations the alternative method of diazomethane–cuprous chloride[8] induced addition of methylene to enamine double bonds was more satisfactory. Analo-

(1) G. Stork, R. Terrell, and J. Szmuszkovics, *J. Amer. Chem. Soc.*, **76**, 2029 (1954).

(2) For a summary of enamine chemistry with 731 references see M. E. Kuehne in "Enamines: Their Synthesis, Structure an Reactions," A. G. Cook, Ed., Marcel Dekker, New York, N. Y., 1969.

(3) A summary of enamine applications to syntheses of natural products is M. E. Kuehne, *Synthesis*, 510 (1970).

(4) E. Wenkert and D. A. Benges, *J. Amer. Chem. Soc.*, **89**, 2507 (1967).

(5) E. Wenkert, R. A. Mueller, E. J. Reardon, Jr., S. S. Sathe, D. J. Scharf, and G. Tosi, *ibid.*, **92**, 7428 (1970).

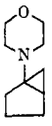
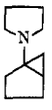
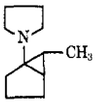
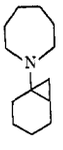
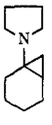
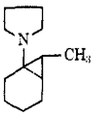
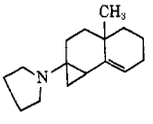
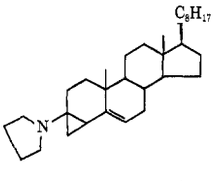
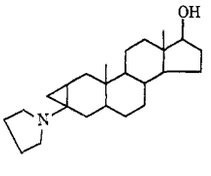
(6) J. Furukawa, N. Kawabata, and J. Nishimura, *Tetrahedron*, **24**, 53 (1968).

(7) J. Nishimura, J. Furukawa, N. Kawabata, and M. Kitayama, *ibid.*, **27**, 1799 (1971).

(8) D. L. Muck and E. R. Wilson, *J. Org. Chem.*, **33**, 419 (1968).

TABLE I

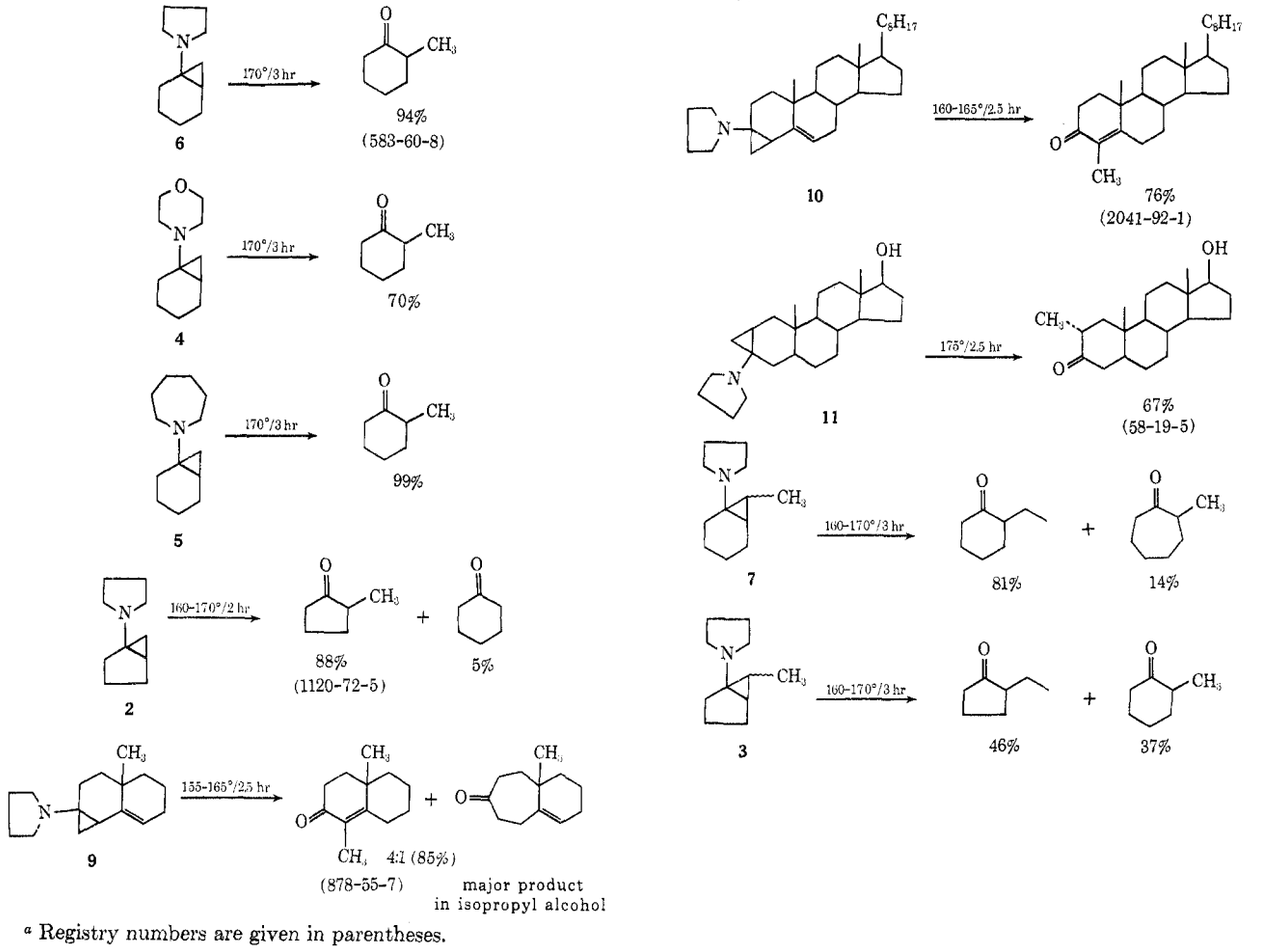
CONVERSION OF ENAMINES TO CYCLOPROPYLAMINES

	Cyclopropylamine	Yield, %	Method	Bp, °C (mm)	Salt, mp, °C	Anal., % Calcd for salt (top) Found (bottom) C	H	N[j]
1		68	*a*	72–75	HCl: 167–168	59.0	8.9	6.9
		86	*b*	(2.5)		59.1	8.8	6.9
2		71	*a*	114–117	HCl: 124–125	64.0	9.7	7.5
		(75)[g]	*b*	(53)		63.6	9.9	7.2
3		58	*c*	89–91 (10)	Methiodide: 228–230 dec	46.9	7.2	4.7
						46.8	7.4	4.6
4		32	*a*	144–146 (26)	HCl: 178–180	60.7	9.3	6.4
						60.5	9.6	6.7
		87	*b*					
5		67	*a*	156–158 (30)	HCl: 202–203	67.9	10.5	6.1
						67.9	10.6	5.9
6		48	*a*	128–132	HCl: 147–149	65.5	10.0	6.9
		61	*b*	(48)		65.2	10.1	6.7
		(72)[g]	*b*					
7		54	*d*	95–105 (7)	Picrate: 154–155	52.9	5.9	13.7
						52.9	5.9	13.8
8		57	*b*	68–69 (55)		76.7	12.1	11.2
						76.7	12.2 (for amine)	11.0
9		67	*b*	70–82 (0.06)	Methiodide: 196–197	54.6	7.6	3.8
						54.8	7.7	3.7
10		82	*b*	mp 132–142		Converted to methyl ketone		
11		>67	*b*	mp 82–87		Converted to methyl ketone		

[a] Diiodomethane–diethylzinc method. [b] Diazomethane–cuprous chloride method. [c] Diiodoethane–diethylzinc method. [d] Diazoethane–cuprous chloride method.

TABLE II

THERMOLYSIS–HYDROLYSIS REACTION IN 90% AQUEOUS METHANOL[a]



[a] Registry numbers are given in parentheses.

gous results were achieved with ethylene iodide or diazoethane.

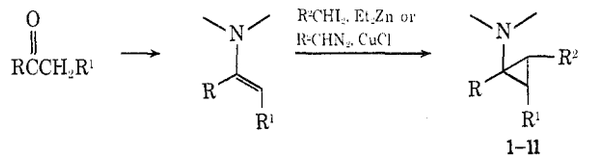


Table I indicates the cyclopropylamines obtained from corresponding cyclic ketone derived enamines and dienamines and from 1-pyrrolidinopropene. A stereoselective (α?) introduction of the cyclopropane methylene group in formation of compounds **9**, **10**, and **11** is suggested by the observation of one major rather than two C-10 or C-18 methyl signals in 100-MHz nmr spectra of crude product **9**.

Cyclopropylamine Ring-Opening Reactions.—The exploration of aminocyclopropanes as synthetic intermediates experienced setbacks with their failure to react as homologous enamines with electrophiles[9] and with the observation of their resistance to opening by acids.[4,10] Accordingly, we have found that the pyrrolidino[3.1.0]bicyclohexane **2** was largely recovered from a solution in acetic and sulfuric acids, at reflux for 3 days, while a similar alkyl-substituted bicyclic compound[11] and alkoxycyclopropanes[4] are readily cleaved under these strongly acidic conditions. Protonation of the nitrogen in acid thus prevents its assistance in ring opening and leads instead to inhibition of the cyclopropane fission.

Cyclopropylamines were also found to be resistant to treatment with base. They could be recovered from a methanol solution containing sodium methoxide after 2 days.

However, we have found that heating of bicyclic [n.1.0]aminocyclopropanes in aqueous alcohols gave ketones. Best yields from such thermolyses were obtained by heating the compounds at 150–170° in aqueous methanol in a sealed tube.[12] The results are shown in Table II.

In order to lower the activation temperature required for the cyclopropylamine ring cleavage, the effect of adsorbing surface agents was studied. Addition of 10% palladium on charcoal allowed good cyclopropane cleavage in refluxing aqueous methanol in 1–2 days (Table III). With various activated charcoal preparations the cleavage rate under these conditions was reduced to one half and without an additive to

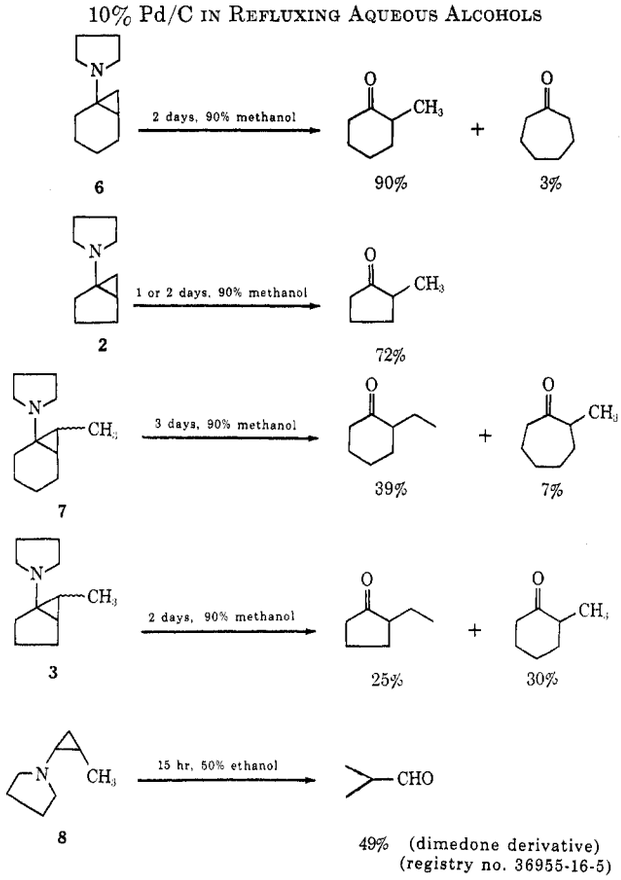
(9) R. A. Fouty, "Reactions of Cyclopropylamine and *N*,*N*-Dimethylcyclopropylamine," Ph.D. Dissertation, University of Pennsylvania, 1962.

(10) (a) J. Weinstock, *J. Org. Chem.*, **26**, 3511 (1961); (b) C. Kaiser, B. M. Lester, C. L. Zirkle, A. Burger, C. S. Davis, T. J. Delia, and L. Zirngible, *J. Med. Chem.*, **5**, 1243 (1962); (c) J. E. Hodgkins and R. J. Flores, *J. Org. Chem.*, **28**, 3356 (1963).

(11) R. T. LaLonde and A. D. Debboli, Jr., *ibid.*, **35**, 2657 (1970).

(12) I. G. Bolesov, S. A. Gladyr', A. S. Koz'min and R. Y. Levina, *J. Org. Chem. USSR*, **6**, 2443 (1970). Concurrently it was found that heating of 1-morpholino-6,6-diphenylbicyclo[3.1.0]hexane and its next higher homolog at 185–195° in ethylene glycol gave 2-benzhydrylcyclopentanone and 2-benzhydrylcyclohexanone, respectively.

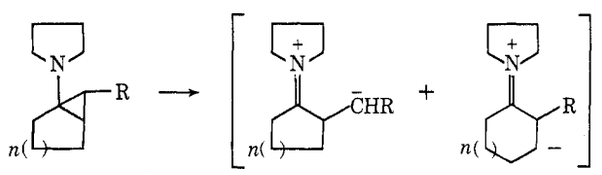
TABLE III
THERMOLYSIS–HYDROLYSIS REACTION
10% Pd/C IN REFLUXING AQUEOUS ALCOHOLS



6 2 7 3 8

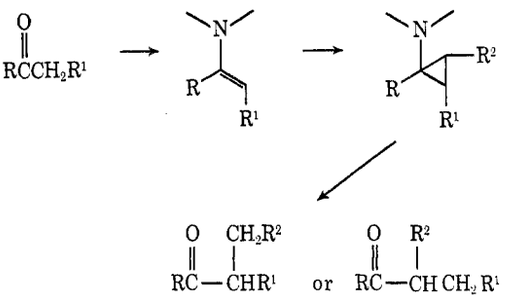
one quarter of the rate found with 10% palladium on charcoal.

The direction of cyclopropane ring cleavage was found to favor protonation at the carbon with the smallest number of alkyl substituents, thus resulting predominantly in methylation rather than ring expansion from the bicyclic [*n*.1.0] compounds and formation of isobutyraldehyde rather than *n*-butyraldehyde in the linear example. These observations are consistent with a transfer of negative charge from nitrogen to a β carbon atom in the transition state of the cyclopropane cleavage reaction. Accordingly, increased ring expansion was found for the two methyl-substituted cyclopropane examples **3** and **7** with the extent of this reaction pathway determined by the respective release of ring strain. Increased ring expansion was also found by allylic stabilization of nega-



tive charge in opening of the tricyclic skeleton **9**. When aqueous isopropyl alcohol rather than aqueous methanol was used as protonating solvent, ring expansion predominated with this last system.

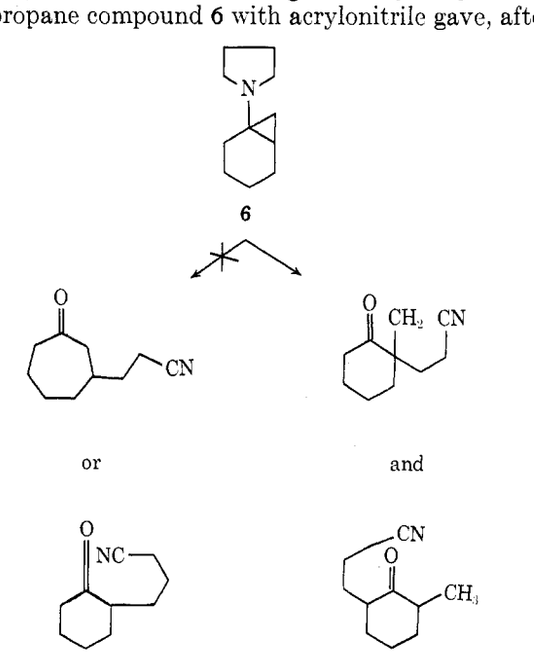
These results establish a new route for aldehyde and ketone alkylations.



Its usefulness is seen by contrasting the C-2 methylation of a 3-keto steroid in 69% yield by this new method with the corresponding enamine alkylation with methyl iodide, which gives a 14% yield.[13] The methylation of propionaldehyde to isobutyraldehyde serves as a model for aldehyde methylations which may otherwise be difficult because of aldehyde aldol condensation in base and alternatively because of extensive N-methylation of aldehyde enamine derivatives with methyl iodide.

Two other advantages of this alkylation sequence are apparent. (a) The aminocyclopropane intermediates can be easily separated from unreacted starting materials because of their basicity and acid stability. In the process of acid extraction unreacted starting aldehyde or ketone can be recovered through enamine hydrolysis. Since di- or polyalkylations are not possible, *pure monoalkylation products* are obtained. (b) Because of its resistance to acid and base treatment, the aminocyclopropane group can also be a *protective function for carbonyl groups*, allowing chemical transformations at other functional groups before liberation of the α-alkylated carbonyl function.

While thermal opening of aminocyclopropanes in the presence of water led to ketones and aldehydes, through formation and hydrolysis of imonium intermediates, their opening in the absence of water gave enamines. These could be demonstrated spectroscopically and by their reactions with acrylonitrile. Thus it was found that heating of the [4.1.0] aminocyclopropane compound **6** with acrylonitrile gave, after



6 or and

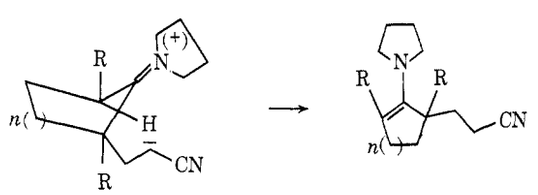
(13) U. S. Patent 3,098,850 (1957); J. C. Babcock, J. A. Campbell, and R. L. Pederson (Upjohn Co.), *Chem. Abstr.*, **59**, 14067 (1963).

hydrolysis, the same product ratio of 2-cyanoethyl-2-methylcyclohexanone and 2-cyanoethyl-6-methylcyclohexanone as the pyrrolidine enamine derivative of 2-methylcyclohexanone when it was heated with acrylonitrile in dioxane.[14,15] Interception of a zwitterionic intermediate or direct electrophilic attack by acrylonitrile on the aminocyclopropane, with formation of alternative ketone products, was not found.

When the [4.1.0]cyclopropylamine **6** was heated with acrylonitrile in methanol, only the 2,6-substituted cyclohexanone was obtained, again in agreement with the corresponding reaction of the enamine derivative of 2-methylcyclohexanone in ethanol.[16]

Heating of the [3.1.0]aminocyclopropane compound **2** with acrylonitrile led only to the 2,2-disubstituted cyclopentanone and some 2-cyanoethylcyclohexanone. Analogously, the methylcyclopentanone enamine derivative gave only the 2,2-disubstituted cyclopentanone when heated in dioxane with acrylonitrile.[17] When either the aminocyclopropane or the enamine was heated in methanol with acrylonitrile, the same mixture of 2,2- and 2,5-disubstituted cyclopentanone products was obtained (Table IV).

The opposite solvent effects found with the above five- and six-membered ring enamine derivatives are remarkable. They can be understood if one postulates a kinetically favored reaction of the predominant less substituted enamine double bond isomer to give a zwitterionic 2,6- (or 2,5-) substituted imonium intermediate which can undergo protonation by solvent or intramolecular proton transfer to yield the 2,6- (or 2,5-) substituted products. Alternatively, reversion of the 2,6- (or 2,5-) substituted zwitterionic intermediate to starting materials and slower formation of 2,2-substituted imonium intermediates provide a route to the less substituted enamine double bond isomers.[14] The latter pathway may be favored more in the five- relative to the six-membered ring enamine reaction by the smaller eclipsing interaction of the α,α substituents with the pyrrolidine ring system as well as by decreased intramolecular bridged proton transfer at the zwitterionic stage.



Hydrogenolyses of the pyrrolidino- and hexamethyleneimino[4.1.0]bicycloheptanes **6** and **5** and the pyrrolidino[3.1.0]bicyclohexane **2** gave *N*-(2-methylcycloalkyl)amines in 98, 96, and 84% yields, respectively. The *N*-(2-methylcyclohexyl)pyrrolidine obtained in this way appeared to be a mixture of cis and trans stereoisomers. Thus Cope pyrolysis of the *N*-oxide furnished 82% of 3-methylcyclohexene and 18% of 1-methylcyclohexene, indicating the presence of the trans isomer. The crude amine also furnished a crystalline methiodide which was matched with the methiodide of the cis isomer, obtained from pyrrolidine and *trans*-2-methylcyclohexanol tosylate.[18] The trans isomer, obtained from *cis*-2-methylcyclohexanol tosylate,[19] did not form a crystalline methiodide. A close similarity of nmr and ir spectra and vpc or tlc retention times of the amines obtained by these routes, or from the catalytic reduction of the pyrrolidine enamine derivative of 2-methylcyclohexanone, did not allow a quantitative stereochemical assignment to the aminocyclopropane hydrogenolysis product.

Experimental Section

Preparation of Cyclopropylamines Using Diethylzinc and Methylene Iodide.—The following procedure for the preparation of 1-(*N*-morpholino)bicyclo[3.1.0]hexane (**1**) is representative. To a three-neck flask equipped with a magnetic stirrer, thermometer, pressure-equalized addition funnel, and nitrogen inlet were added under a nitrogen atmosphere 50 ml of dry benzene, 7.0 g (0.045 mol) of 1-morpholinocyclopentene, and 5.2 ml (0.050 mol) of diethylzinc. The reaction vessel was cooled in an ice bath to 5° and stirred while 12.1 g (0.045 mol) of methylene iodide was added slowly *via* the addition funnel at such a rate that a temperature of less than 10° was maintained. The addition normally took about 1.5 hr. After addition the reaction mixture was allowed to warm to room temperature and stirred for an additional 0.5 hr. The mixture was then poured slowly onto 100 ml of 10% ammonium hydroxide–ice mixture. The mixture was stirred well, then shaken. The benzene was separated and the aqueous portion was extracted with a small amount of benzene. The benzene was combined, dried over magnesium sulfate, filtered, and distilled at approximately 110 mm, leaving a light brown oil which upon distillation through a 12-in. Vigreux column gave 5.1 g (68%) of clear, colorless liquid: bp 72–75° (2.5 mm); ir 3020 cm^{-1}; nmr δ 0.55 (m, 2 H), 1.5 (m, 7 H), 2.6 (t, 4 H), 3.6 (t, 4 H).

Anal. Calcd for $C_{10}H_{17}NO$: C, 71.8; H, 10.3; N, 8.4. Found: C, 72.0; H, 10.0; N, 8.6.

The methiodide derivative was formed by heating the amine in a sealed tube with excess methyl iodide at 85° for 3 hr. Recrystallization from ethanol gave white needles, mp 177–178°.

Anal. Calcd for $C_{11}H_{20}NOI$: C, 42.8; H, 6.5; N, 4.5. Found: C, 42.7; H, 6.3; N, 4.3.

Preparation of Cyclopropylamines Using Diazomethane and Cuprous Chloride.—The following preparation of 7-methyl-4-*N*-pyrrolidinotricyclo[5.4.0.$0^{2,4}$]undec-11-ene (**9**) is representative. To 0.952 g (4.37 mmol) of the pyrrolidine dienamine of 10-methyl-1(9)-octalone-2 in 20 ml of dry ether was added 0.7 g of finely powdered cuprous chloride. While the solution was stirred magnetically, approximately 0.5 g of ethereal diazomethane was slowly added, and 15 min after completion of the addition the solution was filtered and the ether was evaporated at reduced pressure leaving a light brown oil which was distilled at 70–82° (0.06 mm) to give 0.680 g (2.94 mmol) of product: yield 67.5%; ir 1650 cm^{-1} (very weak); nmr δ 0.3–0.8 (m, 2 H), 1.0 (s, 3H), 2.3 (m, 17 H), 2.7 (m, 4 H). The methiodide of the cyclopropylamine was formed in methanol and recrystallized from acetone–ether, mp 196–197° dec.

Anal. Calcd for $C_{17}H_{28}NI$: C, 54.6; H, 7.6; N, 3.8; I, 34.0. Found: C, 54.8; H, 7.7; N, 3.7; I, 34.2.

Thermolysis of 1-Pyrrolidinobicyclo[4.1.0]heptane.—The following procedure is representative of the thermolysis reaction of cyclopropylamines in aqueous methanol solution. 1-Pyrrolidinobicyclo[4.1.0]heptane (76 mg, 0.461 mmol) was sealed in a glass tube under a nitrogen atmosphere with 0.7 ml of methanol and 0.08 ml of water and heated for 3 hr at 170–175°. The tube was cooled and opened, and the contents were analyzed by glc (5 ft × 0.125 in. 10% FFAP column at 105°) using cycloheptanone as an

(14) N. F. Firrell and P. W. Hickmott, *Chem. Commun.*, 544 (1969).

(15) H. O. House, W. L. Roelofs, and B. M. Trost, *J. Org. Chem.*, **31**, 646 (1966).

(16) G. Stork, A. Brizzolara, H. K. Landesman, J. Szmuszkovics, and R. Terrell, *J. Amer. Chem. Soc.*, **85**, 207 (1963).

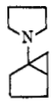
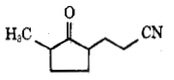
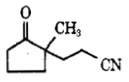
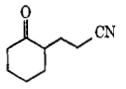
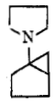
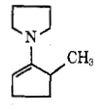
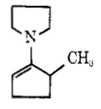
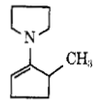
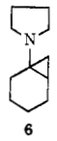
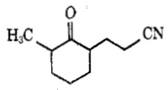
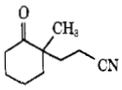
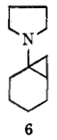
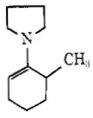
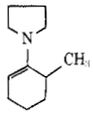
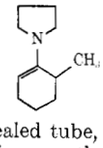
(17) In contrast to the 2,2 disubstitution obtained with the enamine of 2-methylcyclopentanone and acrylonitrile in dioxane, 2,5 disubstitution was found on reaction of the enamine of 2-ethylcyclopentanone with methyl vinyl ketone in dioxane: Ph.D. dissertation of Charles E. Bayha, University of Vermont, 1966. In this instance the kinetic alkylation product undergoes cyclization to a hydrindanone.

(18) W. G. Dauben, G. J. Fonken, and D. S. Noyce, *J. Amer. Chem. Soc.*, **78**, 2579 (1956).

(19) W. Hückel and A. Hubele, *Justus Liebigs Ann. Chem.*, **613**, 27 (1958).

TABLE IV

THERMOLYSIS REACTIONS WITH ONE EQUIVALENT OF ACRYLONITRILE AND COMPARATIVE ENAMINE ALKYLATIONS

Amine	Temp, °C (time, hr)	Solvent	Yield, %	Products after hydrolysis, %[f]		
 2	165–175[a] (3)	None	67[d]	 0 (36955-18-7)	 80 (36955-19-8)	 20 (4594-78-9)
 2	170–180[a] (4)	Methanol	40[d]	100[b]		0
 1	165–175[a] (6)	None	58[d]	85[b]		15
	Reflux (16)	Methanol	50[d]	100[b]		0
	Reflux (16)	Dioxane	52[d]		100	0
	150–155[a] (3)	None	62[d]		100	0
 6	170–180[a] (4)	None	56[c]	 58 (16488-85-0)	 42 (21197-29-5)	
 6	170–180[a] (4)	Methanol	41[c]	100		0
	Reflux (16)	Dioxane	65[d]	57		43
	150–155[a] (1.5)	None	90[c]	78		22
	Reflux (4)	Ethanol	55[e]	100[e]		0

[a] Sealed tube, nitrogen atmosphere. [b] Not separable. [c] Crude yield. [d] Distilled yield. [e] Reference 16. [f] Registry numbers are given in parentheses.

internal standard. The analysis indicated 48.3 mg (94%) of 2-methylcyclohexanone present. The identity of 2-methylcyclohexanone was established in another similar run by formation of a 2,4-dinitrophenylhydrazone derivative directly from the methanol solution. The derivative was recrystallized from ethanol, mp 128–129.5°. The melting point was not depressed when the derivative was mixed with the 2,4-dinitrophenylhydrazone derivative of authentic 2-methylcyclohexanone. In another similar run the glc analysis was performed without addition of cycloheptanone. The analysis indicated only a trace amount of cycloheptanone present (≪1%).

Thermolysis of 7-Methyl-4-pyrrolidinotricyclo[5.4.0.0^{2,4}]-undec-11-ene.—A solution of 0.538 g (2.33 mmol) of 7-methyl-4-pyrrolidinotricyclo[5.4.0.0^{2,4}]undec-11-ene in 2.0 ml of methanol

and 0.3 ml of water was heated in a sealed glass tube under a nitrogen atmosphere for 2.5 hr at 155–165°. The tube was opened and its contents were diluted with 3 ml of water and made acidic with 10% hydrochloric acid. The resulting mixture was shaken and then extracted with several portions of ether. The combined ether extracts were dried over magnesium sulfate, filtered, and evaporated to yield 0.421 g of a yellow oil which was distilled up a glass tube (55–70°, 0.03 mm) to yield 0.352 g (1.98 mmol) of clear, colorless liquid: yield 85%; ir 1605, 1665, and 1700 cm^{-1}; nmr δ 1.1 (s, ~0.2 H), 1.2 (s, ~2.8 H), 1.4–2.6 (m, ~15 H), 5.5 (m, ~0.1 H). Tlc (silica gel, 5% methanol–methylene chloride, methylene chloride, ether, 4% methanol–ether, benzene, and ethyl acetate; alumina, ether, and ether–benzene) showed one spot. Glc (10% Carbowax, 150°, 10% Apiezon L, 130°, 10% SE-30, 115°) did not resolve the mixture consisting of a 4:1 ratio of α,β-unsaturated to saturated ketone component according to the ir spectrum. Column chromatography employing silver nitrate impregnated alumina (pentane–benzene and pentane–cyclohexene) also did not separate the mixture. A Girard Reagent T procedure also failed to separate the mixture. Refluxing the mixture in methanolic potassium hydroxide or sulfuric acid solutions did not alter the relative intensities of the carbonyl absorptions.

A brick red 2,4-dinitrophenylhydrazone derivative was formed from the mixture and recrystallized from ethanol, mp 195–197°. The mixture melting point of this derivative with the 2,4-dinitrophenylhydrazone derivative of 1,10-dimethyl-1(9)-octalone-2[20] was 195–196°.

Conversion of the Pyrrolidine Dienamine of Δ^4-Cholesten-3-one to 4-Methyl-Δ^4-cholesten-3-one.—To 380 mg (0.902 mmol) of the pyrrolidine dienamine of Δ^4-cholesten-3-one in 40 ml of dry ether was added 0.6 g of finely divided cuprous chloride. While the solution was stirred magnetically, approximately 0.2 g of ethereal diazomethane was added slowly at room temperature. The addition was completed and 15 min later the solution was filtered and the ether was evaporated, yielding a yellowish, solid residue. The residue was dissolved in boiling ethanol and crystallized, yielding 280 mg of solid material, mp 132–142°. Concentration of the mother liquor yielded an additional 35 mg, mp 131–142°. The nmr spectrum (100 MHz) of this material exhibited absorptions at δ 0.3 (cyclopropane), 0.68, 0.82, 0.88, and 0.95 (methyl singlets), 2.71 (NCH_2), and 5.40 (vinyl H). A solution of 75 mg of the cyclopropylamine, 1.5 ml of methanol, and 0.1 ml of water was sealed in a glass tube and heated at 160–165° for 2.5 hr. The tube was cooled and opened. The contents were diluted with water, acidified with hydrochloric acid, and extracted with ether. The ether was dried over magnesium sulfate, filtered, and evaporated, yielding a brownish solid residue. The residue was chromatographed on 6.0 g of neutral alumina with acetone–benzene, yielding 50 mg of white solid which was recrystallized from methanol: mp 101–102° (lit. mp 102–103°,[20] 101–103°[21]); 76% from the enamine; ir 1665, 1600 cm^{-1} (Nujol mull).

Conversion of the Pyrrolidine Enamine of Androstanolone to 2-Methylandrostanolone.—To 629 mg (1.83 mmol) of the pyrrolidine enamine of androstanolone in 30 ml of dry ether was added 431 mg of finely powdered cuprous chloride. While the solution was stirred magnetically, approximately 0.3 g of ethereal diazomethane was added slowly at room temperature. The addition was completed and 15 min later the solution was filtered and the ether was evaporated, yielding 679 mg of a white, fluffy solid, mp 82–87°. The nmr spectrum of this material showed characteristic cyclopropane absorptions at δ 0.1 and 0.5 and the ir spectrum (Nujol mull) showed the absence of the 1645-cm^{-1} enamine band. A solution of 88 mg (0.246 mmol) of the crude steroidal cyclopropylamine, 2.0 ml of methanol, and 0.1 ml of water sealed in a glass tube under a nitrogen atmosphere. The tube was heated at 175° for 2.5 hr, cooled, and opened, and the contents were diluted with water, acidified with hydrochloric acid, and extracted with ether. The ether was dried over magnesium sulfate, filtered, and evaporated to yield 73.9 mg of semisolid material which was chromatographed on 6.0 g of Florisil with petroleum ether (bp 60–75°)–acetone. The chromatography yielded 50.4 mg of white solid material: mp 151–152.5° (lit.[13] mp 174–176 or 151–153°); 67% from the enamine; ir (CCl_4) 1710 cm^{-1}.

Reaction of 1-(*N*-Pyrrolidino)bicyclo[3.1.0]hexane in the Presence of Palladium on Charcoal.—The following procedure is representative. A solution composed of 112 mg of 1-(*N*-pyrrolidino)bicyclo[3.1.0]hexane, 1.0 ml of 90% aqueous methanol, and 15 mg of 10% palladium on charcoal was refluxed for 24 hr. Glc analysis (6 ft × 0.125 in. 10% UC-W98 80–1005 operated at 140°) showed pyrrolidine and 2-methylcyclopentanone present. The yield, determined by the use of cycloheptanone as an internal standard, was 72%.

Reaction of 1-(*N*-Pyrrolidino)-2-methylcyclopropane in the Presence of Palladium on Charcoal and 5,5-Dimethyl-1,3-cyclohexanedione.—A solution composed of 128 mg (1.02 mmol) of 1-(*N*-pyrrolidino)-2-methylcyclopropane, 15 mg of 10% palladium on charcoal, and 429 mg (3.06 mmol) of 5,5-dimethyl-1,3-cyclohexanedione was refluxed for 19 hr in 3.0 ml of 50% aqueous ethanol. After cooling, sufficient hot ethanol was then added to dissolve in solid product. The solution was filtered and the volume was reduced to approximately 3 ml by evaporation at reduced pressure. The solution was cooled and the crystals were collected, 155 mg, mp 138–145°. Concentration of the mother liquor yielded additional crystalline material, 25 mg, mp 138–145°, which was combined with the first crop and recrystallized from aqueous ethanol to yield 168 mg of white solid, mp 151.5–152.0°. The mixture melting point determination of this material and the di 5,5-dimethyl-1,3-cyclohexanedione adduct of authentic isobutyraldehyde was 151.5–152.0° (lit.[22] mp 153–154.5°). The yield of adduct based on the cyclopropylamine was 49%.

Reaction of 1-(*N*-Pyrrolidino)bicyclo[4.1.0]heptane in the Presence of Different Catalysts.—In all cases 40 mg of the cyclopropylamine, 1.50 ml of 90% aqueous methanol, and 20 mg of catalyst were refluxed for 2.5 hr and cooled, and the mixture was then analyzed by glc (6 ft × 0.125 in. 10% UC-W98 80–1005 operated at 140°) using 2-methylcyclopentanone as an internal standard. The corrected peak heights of 2-methylcyclohexanone and the catalyst employed are shown below.

Catalyst[23]	Peak height, mm
Nuchar B-100-N	34
Nuchar C-190-N	30
Nuchar C-N	39
Nuchar CEE-N	36
10% Pd/C	61
None	17

Hydrogenolysis of Cyclopropylamines.—A solution of 371 mg (2.25 mmol) of 1-(*N*-pyrrolidino)bicyclo[4.1.0]heptane in 2.5 ml of dry methanol was stirred with 60 mg of 10% palladium on charcoal for 3 days at room temperature under a hydrogen atmosphere. The solution was then filtered, yielding 367 mg (2.20 mmol) of clear, colorless liquid which was homogeneous on glc (5 ft × 0.125 in. 10% SE-30 operated at 105°): yield 98%; nmr δ 0.9 (d, 3 H), 1.7 (m, 14 H), 2.5 (m, 4 H). The methiodide of this amine was formed in methanol and recrystallized from methanol–ether, mp 210–212° dec.

Anal. Calcd for $C_{12}H_{24}NI$: C, 46.6; H, 7.8; N, 4.5. Found: C, 46.5; H, 8.1; N, 4.7.

1-(*N*-Pyrrolidino)bicyclo[3.1.0]hexane was treated as above and produced 84% of *N*-(2-methylcyclopentyl)pyrrolidine. The methiodide of this amine was formed in methanol and recrystallized from methanol–ether, mp 220–221° dec.

Anal. Calcd for $C_{11}H_{22}NI$: C, 44.8; H, 7.5; N, 4.8. Found: C, 44.5; H, 7.7; N, 4.7.

1-(*N*-Hexamethylenimino)bicyclo[4.1.0]heptane was treated as above and produced 96% of *N*-(2-methylcyclohexyl)hexamethylenimine. The methiodide of this amine was formed in methanol and recrystallized from methanol–ether, mp 237–238° dec.

Anal. Calcd for $C_{14}H_{28}NI$: C, 49.9; H, 8.4; N, 4.2. Found: C, 50.1; H, 8.6; N, 4.3.

Hydrogenation of the Pyrrolidine Enamine of 2-Methylcyclohexanone.—A solution composed of 861 mg of the pyrrolidine enamine of 2-methylcyclohexanone, 0.2 g of 10% palladium on charcoal, and 3.0 ml of dry methanol was stirred under a hydrogen atmosphere at room temperature. After 5 hr the solution was filtered and the methanol was evaporated, yielding 852 mg of a very slightly amber liquid. Glc analysis (5 ft × 0.125 in. 10% SE-30 operated at 105°) showed this material to be

(20) J. A. Marshall and A. R. Hochstetler, *J. Org. Chem.*, **31**, 1020 (1966).
(21) F. Sondheimer and Y. Mazur, *J. Amer. Chem. Soc.*, **79**, 2906 (1957).
(22) E. C. Horning and M. G. Horning, *J. Org. Chem.*, **11**, 95 (1946).
(23) Westvaco Chemical Division, Covington, Va.

95% pure, nmr δ 0.9 (d, 3 H), 1.7 (m, 14 H), 2.5 (m, 4 H). This spectrum was superimposable on that of the material obtained from the hyrogenolysis of 1-(*N*-pyrrolidino)bicyclo[4.1.0]-heptane. The methiodide derivative of this amine was formed in ethanol and recrystallized from ethanol–ether, mp 210–212°. The mixture melting point with the methiodide of the amine of cyclopropylamine origin was 209–211°.

Alternative Preparation of *N*-(2-Methylcyclohexyl)pyrrolidine.—An ethereal solution of 2.5 g of 2-methylcyclohexanone was reduced with 0.40 g of lithium aluminum hydride to yield 2.1 g of 1-hydroxy-2-methylcyclohexane. Dauben[18] has shown this reduction to produce 82% trans and 18% cis isomer. The tosylate of the alcohol mixture was formed by treatment in dry pyridine with *p*-toluenesulfonyl chloride at 0°. The crude tosylate mixture, which existed as a yellow oil, was then refluxed in dry pyrrolidine for 16 hr. The solution was cooled, diluted with water, and separated from 0.5 g of amber oil. This oil was shown by glc analysis to consist of olefin and amine in the ratio of 3:7, respectively. The nmr spectrum of this mixture exhibited a sharp methyl doublet at δ 0.9 which was superimposable on those obtained from the hydrogenolysis of 1-(*N*-pyrrolidino)-bicyclo[4.1.0]heptane and the hydrogenation of the pyrrolidine enamine of 2-methylcyclohexanone. The methiodide of the amine produced by this reduction had mp 210–212° and mixture melting point with the methiodide of the amine of cyclopropylamine origin 209–211°.

Preparation of *trans*-*N*-(2-Methylcyclohexyl)pyrrolidine.—The procedure of Hückel[19] was followed with the exception that extensive esterification of the *cis*-2-methylcyclohexanol had taken place. Therefore, the product after hydrogenation was refluxed for 10 hr in 20% aqueous sodium hydroxide to hydrolyze the acetate. The tosylate was obtained in 85% yield, mp 49–52° (lit.[19] mp 56–57°). The tosylate, 1.1 g (4.0 mmol), was refluxed for 16 hr in 5 ml of pyrrolidine. The solution was cooled and 20 ml of water was added. The mixture was extracted with several portions of ether. The ether was extracted twice with 5 ml of water, dried over magnesium sulfate, filtered, and evaporated, leaving a slightly yellow oil. The oil was distilled up a glass tube (86–89°, 15 mm) to yield 0.054 g of clear oil (8%). The presence of a large quantity of olefin in the crude oil was shown by the presence of an ir absorption at 1665 cm^{-1}. The distilled oil was homogeneous on tlc (silica gel, methylene chloride) and the nmr spectrum exhibited a methyl doublet at δ 0.9 which was superimposable on those of the amines prepared by other methods. This material would not form a crystalline methiodide derivative.

Preparation of the Amine Oxide of *N*-(2-Methylcyclohexyl)-pyrrolidine.—To 367 mg of *N*-(2-methylcyclohexyl)pyrrolidine was added 1 ml of 30% hydrogen peroxide and 1.3 ml of methanol. After standing at room temperature for 1.5 days, amine was still present (positive phenolphthalein test), and an additional 1 ml of hydrogen peroxide was added. After standing for one additional day no free amine was present. The excess hydrogen peroxide was destroyed with metallic platinum. The solution was filtered and the solvent was evaporated at reduced pressure. The residue was dried by evacuation to 0.03 mm overnight. After drying, the viscous yellow oil weighed 405 mg.

Pyrolysis of the Amine Oxide of *N*-(2-Methylcyclohexyl)-pyrrolidine.—The amine oxide from above was heated to 140°, and the pyrolysis products were distilled at 93–98°, yielding 101 mg: ir 1665 cm^{-1}; nmr δ 1.0 (d), 1.7 (m), 5.6 (m). Glc analysis (6 ft × 0.125 in. 10% UC-W98 80–1005 operated at 80°) showed two components present with retention times of 1.6 (82%) and 2.2 min (18%). The smaller component was shown to be 1-methylcyclohexene by peak enrichment techniques. The larger component was identified as 3-methylcyclohexene by the nmr spectra of the mixture.

Reaction of 1-(*N*-Pyrrolidino)bicyclo[4.1.0]heptane with Acrylonitrile.—A mixture of 0.804 g (4.87 mmol) of 1-(*N*-pyrrolidino)-bicyclo[4.1.0]heptane and 0.258 g (4.87 mmol) of acrylonitrile was sealed in a glass tube under nitrogen and heated for 4 hr at 170–180°. The tube was opened and the contents were refluxed in 2.5 ml of water for 1 hr. The solution was cooled, acidified with hydrochloric acid, and extracted with several portions of ether. The ether was dried over magnesium sulfate, filtered, and evaporated, leaving 0.449 g (56%) of a clear liquid which was analyzed directly by glc (10 ft × 0.375 in. 10% Versamide column at 145°) to find two components present with retention times of 15 (58%) and 21.5 min (42%). The components were separated by preparative glc (same conditions as above). The component of shorter retention time had ir 2240, 1705 cm^{-1}; nmr δ 1.0 (d, 3 H), 2.0 (m, 12 H). This material was assigned the structure 2-β-cyanoethyl-6-methylcyclohexanone. The component with the longer retention time had ir 2240, 1710 cm^{-1}; nmr δ 1.2 (s, 3 H), 2.1 (m, 12 H); it was assigned the structure 2-β-cyanoethyl-2-methylcyclohexanone.

Reaction of 1-(*N*-Pyrrolidino)bicyclo[3.1.0]hexane with Acrylonitrile.—1-(*N*-Pyrrolidino)bicyclo[3.1.0]hexane (1.53 g, 10.1 mmol) and 0.53 g (10.1 mmol) of acrylonitrile were sealed in a glass tube under a nitrogen atmosphere and heated to 165–170° for 3 hr. After cooling, the contents of the tube were poured into 5 ml of water, made acidic with hydrochloric acid, and heated to 80° for 1 hr. The aqueous solution was extracted with several portions of ether. The ether was dried over magnesium sulfate, filtered, and evaporated at reduced pressure, yielding 1.13 g of slightly yellow oil, 74% crude yield. The oil was distilled at 70–75° (0.15 mm), yielding 1.01 g (67%) of clear, colorless liquid. The liquid was analyzed by glc (10 ft × 0.375 in. 10% Versamide column operated at 143°) and shown to consist of two components with retention times of 19.4 (80%) and 25.5 min (20%). The mixture was separated by preparative glc (same conditions as above). The larger component had ir 2245, 1735 cm^{-1}; nmr δ 1.1 (s, 3 H), 2.1 (m, 10 H).

Anal. Calcd for $C_9H_{13}NO$: C, 71.5; H, 8.7; N, 9.3. Found: C, 71.5; H, 8.9; N, 9.3.

This material was identified as 2-β-cyanoethyl-2-methylcyclopentanone by comparison with the authentic compound using glc peak enrichment techniques and by comparison of spectroscopic properties.

The smaller component had ir 2245, 1705 cm^{-1}; nmr center δ 2.2 (m). A 2,4-dinitrophenylhydrazone derivative was formed and recrystallized from ethanol yielding the analytical sample, mp 150–151°.

Anal. Calcd for $C_{15}H_{17}O_4N_5$: C, 54.4; H, 5.2; N, 21.1. Found: C, 54.1; H, 5.5; N, 21.4.

This derivative had mp 149.0–150.5° upon mixture with the 2,4-dinitrophenylhydrazone derivative of authentic 2-β-cyanoethylcyclohexanone.[16]

Preparation of 2-β-Cyanoethyl-2-methylcyclopentanone.—The procedure used was patterned after that of House.[15] To 2.00 g (18.5 mmol) of 2-methylcyclopentanone was added 89 mg of potassium in 20 ml of dry *tert*-butyl alcohol. The potassium was dissolved and 0.98 g (19.0 mmol) of acrylonitrile was added slowly at 25–30°. The mixture was stirred overnight and then poured onto 3% sulfuric acid and extracted with several portions of ether. The ether was rinsed with saturated sodium chloride, dried over magnesium sulfate, filtered, and evaporated, leaving a liquid which was distilled at 75–95° (0.15 mm), 0.53 g. A large amount of residue remained which was not distillable up to 115° (0.15 mm). The volatile material was analyzed by glc and found to consist of three components with retention times of 9.4 (20%), 12.3 (14%), and 19.4 min (66%). The 19.4-min component was separated by preparative glc and its nmr and ir spectra were identical with those of the larger component from the reaction of 1-(*N*-pyrrolidino)bicyclo[3.1.0]hexane with acrylonitrile. These compounds were also shown to be identical by peak enrichment glc techniques.

Registry No.—**1**, 36955-07-4; **1** (HCl), 36955-08-5; **1** (MeI), 36955-09-6; **2**, 15043-70-6; **2** (HCl), 36955-11-0; **3**, 36955-12-1; **3** (MeI), 36955-13-2; **4**, 36994-07-7; **4** (HCl), 36994-08-8; **5**, 36994-09-9; **5** (HCl), 36994-10-2; **6**, 4668-96-6; **6** (HCl), 36994-12-4; **7**, 36994-13-5; **7** (picrate), 36994-14-6; **8**, 36955-14-3; **9**, 36955-15-4; **9** (MeI), 36994-15-7; **10**, 36949-91-4; **11**, 36994-16-8; *cis*-*N*-(2-methylcyclohexyl)pyrrolidine, 36949-94-7; *trans*-*N*-(2-methylcyclohexyl)pyrrolidine, 36949-95-8; *cis*-*N*-(2-methylcyclohexyl)pyrrolidine (MeI), 36949-96-9; *N*-(2-methylcyclopentyl)pyrrolidine (MeI), 36994-17-9; *N*-(2-methylcyclohexyl)hexamethylenimine (MeI), 36994-18-0; amine oxide of *N*-(2-methylcyclohexyl)pyrrolidine, 36955-17-6; acrylonitrile, 107-13-1.

Acknowledgment.—This work was supported in part by a National Institutes of Health Grant: USPHS Grant No. 5 RO1 CA 12010-10.