[CONTRIBUTION FROM AVERY LABORATORY, UNIVERSITY OF NEBRASKA]

Ethylene Imine Ketones. VIII.[1] Stereochemical Configurations and Reactions with Organometallic Compounds[2]

BY NORMAN H. CROMWELL, J. HILL ANGLIN, JR.,[3] FRANK W. OLSEN[3] AND NORVAL G. BARKER[3]

The reactions of the geometrically isomeric tri-substituted ethylene imine ketones with organometallic compounds have been contrasted. It has been found that the geometrical isomers which had been assigned a *trans* structure on the basis of spectral evidence, form the more stable complex with one equivalent of arylmagnesium bromide. Excess Grignard reagent is necessary to convert these ketones into tertiary carbinols. It was found that the ketone which forms the more stable complex with the Grignard reagent (the *trans* geometrical isomer), reacts in competition less readily than the *cis* isomer with phenyllithium. When the aryl group introduced by the organometallic reagent is different than that attached to the carbonyl group, the *trans* ethylene imine ketones produce the two possible racemic tertiary carbinols, while the *cis* form gives only one product. When the aryl group being introduced is the same as that present in the ketone both isomeric ethylene imine ketones give only one racemic tertiary carbinol.

In an earlier investigation[4] it was shown that ethylene imine ketones react readily with excess amounts of Grignard reagents to produce the expected ethylene imine tertiary carbinols in excellent yields. Recently it has been found that *cis* and *trans* configurations may be assigned to isomeric pairs of the ethylene imine ketones on the basis of absorption spectral differences as well as because of differences in their behavior with phenylhydrazine.[1]

It was of interest to carry out comparable studies of the various available isomeric pairs of ethylene imine ketones with both Grignard reagents and phenyllithium. It has been found that the results of such experiments add to the total evidence for the assigned configurations of these ethylene imines.

The various new ethylene imine tertiary carbinols obtained during the course of this work are described in Table I and by the formulas below. Several of these are being studied by others for various pharmacological properties[5] including inhibition of tumor growth in mice.[6] The ethylene imine ketone precursors of the carbinols are mentioned in the experimental section.

In the general formulas given for the *cis* and *trans* structures of these ethylene imines, AR′ represents the aryl group present in the ethylene imine ketone precursor while AR″ stands for the group introduced by the organometallic reagent. Carbinols III and IV of course do not exist as geometrical isomers since only one asymmetric carbon atom is present in the ethylenimine ring.

With excess amounts of aryl Grignard reagents the *cis*-1-substituted-2-phenyl-3-aroylethylenimines gave only one racemic tertiary carbinol whether or not the aryl group being introduced was the same or different from that present in the aroyl group. The other *cis* racemate resulted when the order of introduction of the aryl groups on —C(OH)— was reversed by using the other aryl Grignard reagent and the corresponding *cis* ethylene imine ketone.[7]

If the aryl group being introduced by the Grignard reagent differed from that present in the aroyl group of the *trans*-1-substituted-2-phenyl-3-aroylethylenimine then the two possible *trans* racemic tertiary carbinols resulted, although in unequal amounts. When the order of introduction of the aryl groups to form the tertiary carbinol group was reversed the same two products again resulted but this time the previously minor product now became the major one. Thus, it is seen that while the *cis* ethylene imine ketones give the stereochemical results which would be predicted from the work of Tiffeneau and Levy[8] the *trans* isomers show less stereochemical specificity toward the Grignard reagent. The *trans* ethylene imine ketones gave only one racemic compound when the aryl group being introduced was identical with that present in the aroyl group of the starting material.

The reactions of the individual ethylene imine ketones with one equivalent of phenyllithium gave the same results as the studies with excess amounts of Grignard reagents but the yields were slightly higher in some cases. Although the general structures of analogous ethylene imine carbinols had been rather well demonstrated in the earlier work,[4] carbinols VA and VIA were oxidized to give the expected phenyl *p*-tolyl ketone. The ultraviolet absorption spectra studies of carbinols I, IV, VA, VIA, VIB, XIA, XB, XII, XIII and XV showed them to have only one low maximum at 260–266 mμ (*E*, 370–450); see Fig. 1. A molecular weight determination for XIVA indicated that dimerization through ring cleavage had not occurred during this reaction with organometallic compounds.

It was found that both the *cis* and *trans* forms of the ethylene imine ketones react rapidly with one equivalent of aryl Grignard reagent to precipitate insoluble and rather stable complexes from ether–benzene solutions. The fact that carbonation or benzoylation was impossible with these precipitates indicated them to be true Grignard reagent complexes. In all cases decomposition of the precipitate regenerated the corresponding ethylene imine ketone in a very pure state.

It was interesting to learn that addition of one

(1) Paper VII, Cromwell, *et al.*, THIS JOURNAL, **73**, 1044 (1951).

(2) This material was a part of a paper presented in the Chemistry of Small-ring Compounds Symposium, 117th Meeting of the American Chemical Society, April 11, 1950, Philadelphia, Pa.

(3) Master of Science Theses, University of Nebraska, April, 1950, May, 1950, and May, 1949, respectively.

(4) Cromwell, THIS JOURNAL, **69**, 258 (1947).

(5) By Smith, Kline and French Laboratories, Philadelphia, Pa.

(6) By the Sloan–Kettering Institute for Cancer Research, New York, N. Y.

(7) This stereochemical result is similar to that experienced in adding Grignard reagents to α,β-diamino ketones, see Cromwell and Cram, THIS JOURNAL, **71**, 2579 (1949).

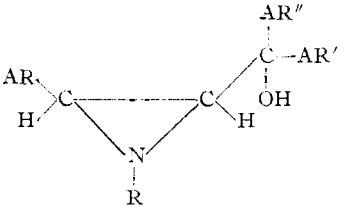
(8) Tiffeneau and Levy, *Bull. soc. chim. France*, [5] **2**, 1848 (1935).

TABLE I

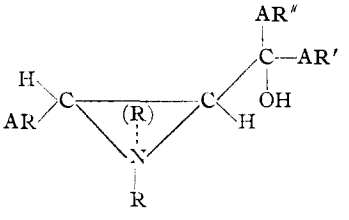
PHYSICAL AND ANALYTICAL DATA FOR ETHYLENE IMINE CARBINOLS

Ethylene imines	No.	Yield, %	M.p., °C.	Recrystn. solvent[a]	Formula	Percentage composition Calcd. C	Calcd. H	Found C	Found H
1-Methyl-2-phenyl-3-(α-phenyl-α-hydroxyethyl) *trans*[b]	I	60	72–73	A	$C_{17}H_{19}NO$	80.59	7.56	80.73	7.31
3-(α-*p*-Tolyl-α-hydroxyethyl) *trans*	II	73	129–130	A	$C_{24}H_{25}NO$	83.96	7.29	83.83	7.41
1-Cyclohexyl-2-(α-phenyl-α-hydroxyethyl)[c]	III	82	87–88	B	$C_{16}H_{23}NO$	78.32	9.49	78.10	9.42
2-(Diphenyl-hydroxymethyl)[d]	IV	80	88–89	B	$C_{21}H_{25}NO$	82.04	8.20	82.18	8.16
1-Cyclohexyl-2-phenyl-3-(phenyl-*p*-tolyl-hydroxymethyl) *cis*	VA	80	151–152	C	$C_{28}H_{31}NO$	84.59	7.86	84.65	7.79
	VB	98	145–147[e]	C, D				84.85	8.08
trans	VIA	50	163–165	D				84.87	7.84
	VIB	25	145–148[f]	D				84.71	7.77[g]
3-(Di-*p*-tolyl-hydroxymethyl) *cis*	VII	75	149–150	E	$C_{29}H_{33}NO$	84.67	8.03	84.42	8.22
trans	VIII	85	145–147[h]	D				84.75	8.16
3-(Diphenyl-hydroxymethyl) *cis*	IX	73	146–148	D	$C_{27}H_{29}NO$	84.60	7.57	84.80	7.68
trans	X	98	166–167[i]	D				84.35	7.72
1-Benzyl-2-phenyl-3-(phenyl-*p*-tolyl-hydroxymethyl) *trans*	XIA	65	158–160	D	$C_{29}H_{27}NO$	85.89	6.71	85.94	6.85
	XIB	70	115–117[k]	D				85.87	7.12
3-(Di-*p*-tolyl-hydroxymethyl) *cis*	XII	80	111–112	D	$C_{30}H_{29}NO$	85.81	6.97	85.80	7.12
trans	XIII	71	94–96[m]	D				85.96	6.47
3-(Diphenyl-hydroxymethyl) *trans*	XV	75	110–112	D	$C_{28}H_{25}NO$	85.90	6.44	86.26	6.72

[a] Recrystallizing solvents: 95% ethanol, A; ethanol–H_2O, B; petroleum ether–benzene, C; methanol, D; petroleum ether, E. [b] Calcd.: N, 5.53. Found: N, 5.62. [c] Calcd.: N, 5.71. Found: N, 5.49. [d] Calcd.: N, 4.56. Found: N, 4.64. [e] Mixed with VA, m.p. 125–135°. [f] Mixed with VB, m.p. 122–132°. [g] Calcd.: N, 3.52. Found: N, 3.55. [h] Mixed with VII, m.p. 130–140°. [i] Mixed with VIA, m.p. 134–144°. [k] Mixed with XIVA, m.p. 95–104°. [m] Mixed with XII, m.p. 80–88°.



cis-series



trans-series

No.	R	AR	AR′	AR″
III	C_6H_{11}	H	C_6H_5	CH_3
IV	C_6H_{11}	H	C_6H_5	C_6H_5
VA	C_6H_{11}	C_6H_5	*p*-$CH_3C_6H_4$	C_6H_5
VB	C_6H_{11}	C_6H_5	C_6H_5	*p*-$CH_3C_6H_4$
VII	C_6H_{11}	C_6H_5	*p*-$CH_3C_6H_4$	*p*-$CH_3C_6H_4$
IX	C_6H_{11}	C_6H_5	C_6H_5	C_6H_5
XII	$C_6H_5CH_2$	C_6H_5	*p*-$CH_3C_6H_4$	*p*-$CH_3C_6H_4$
XIVA	$C_6H_5CH_2$	C_6H_5	*p*-$CH_3C_6H_4$	C_6H_5
XIVB[9]	$C_6H_5CH_2$	C_6H_5	C_6H_5	*p*-$CH_3C_6H_4$
XVI[10]	$C_6H_5CH_2$	C_6H_5	C_6H_5	C_6H_5

No.	R	AR	AR′	AR″
I	CH_3	C_6H_5	C_6H_5	CH_3
II	CH_3	C_6H_5	*p*-$CH_3C_6H_4$	CH_3
VIA	C_6H_{11}	C_6H_5	*p*-$CH_3C_6H_4$	C_6H_5
VIB	C_6H_{11}	C_6H_5	C_6H_5	*p*-$CH_3C_6H_4$
VIII	C_6H_{11}	C_6H_5	*p*-$CH_3C_6H_4$	*p*-$CH_3C_6H_4$
X	C_6H_{11}	C_6H_5	C_6H_5	C_6H_5
XIA	$C_6H_5CH_2$	C_6H_5	*p*-$CH_3C_6H_4$	C_6H_5
XIB	$C_6H_5CH_2$	C_6H_5	C_6H_5	*p*-$CH_3C_6H_4$
XIII	$C_6H_5CH_2$	C_6H_5	*p*-$CH_3C_6H_4$	*p*-$CH_3C_6H_4$
XV	$C_6H_5CH_2$	C_6H_5	C_6H_5	C_6H_5

one molar equivalent of Grignard reagent to a mixture of one equivalent of each of the *cis* and *trans* forms always formed the complex with the *trans* isomer. The unchanged *cis* form was also recovered from the filtrate. In an experiment designed to investigate the equilibrium situation in these competitive reactions it was found that the *cis* form complex readily gives up the Grignard reagent when an ether suspension of it is stirred for one hour with a solution of the *trans* ethylene imine ketone. Decomposition of the final precipitate again produced the pure *trans* isomer while the *cis* isomer was recovered from the filtrate. This may be interpreted as evidence that the *trans* ethylene imine ketones contain a more polar (more nucleophilic) carbonyl group than the *cis* isomers.[11]

It was also interesting and significant to learn that those ethylene imine ketones (the *cis* isomers) which complex the least readily with Grignard reagents turn out to react the most readily with phenyllithium in the competitive experiments. If the analogy may be drawn this is the very result which would be expected in view of the important recent

(9) M.p. 138°, ref. 4, Table I, compd. VI

(10) M.p. 137°, ref. 4, Table I, compd. V.

(11) The available evidence does not allow one to decide whether the imino group or the carbonyl group function separately or jointly as donors in the magnesium complex. If the imino groups were actually engaged in such activity one might have expected the increased polarization and strain of the endocyclic carbon to nitrogen bonds to have resulted in ring opening in the presence of excess Grignard reagent. Moreover, it is to be expected that these *cis* ethylene imine ketone structures would have the more hindered approach to the unshared electrons of both their nitrogen and oxygen atoms.

findings of Swain[12] concerning the mechanism of the reaction of phenyllithium with ketones. Swain has shown that those ketones (the most nucleophilic) which complex the most readily with Grignard reagents also react the least readily with phenyllithium. In these competitive experiments with the ethylene imine ketones both the *cis* and *trans* isomers are undergoing rapid but reversible formation of the ketone–phenyllithium complexes. However, the *cis* isomer is able to give the necessary intramolecular rearrangement to form the lithium salt of the carbinol the more readily since the electron density at the carbonyl carbon is less here than in the *trans* structure.[1,12] The configurations of these geometrical isomers have been assigned previously by concluding that the *trans* isomers would be expected to have the more polar carbonyl group because of greater electron interaction with the three-ring as indicated by spectral studies.[1]

It is unfortunate that an absolute assignment of geometrical configurations to at least one pair of these isomeric ethylene imine ketones seems remote at the moment.[1] Nevertheless, it is apparent that the combination of consistent chemical and spectral evidence now available makes the present geometrical assignments seem entirely plausible.

It should be emphasized that in none of our studies have we found evidence of the presence of more than two isomers with any of the ethylene imine ketones we have investigated.

Experimental[13]

Ethylene Imine Ketones and Excess Grignard Reagent.—In general these reactions were carried out according to the previously published[4] conditions. The individual compounds are described in Table I.

The addition of methylmagnesium iodide to 1-methyl-2-phenyl-3-benzoylethylenimine (*trans*?),[14] *trans* 1-methyl-2-phenyl-3-*p*-toluylethylenimine[1] and 1-cyclohexyl-2-benzoylethylenimine[1] gave I, II and III, respectively. Addition of phenylmagnesium bromide to the latter ketone produced IV.

Phenylmagnesium bromide was added to the *cis* form of 1-cyclohexyl-2-phenyl-3-*p*-toluylethylenimine[1] to give VA, and to the *trans* form to produce a mixture of VIA and VIB which was separated by fractional recrystallization. With *p*-tolylmagnesium bromide the *cis* form of this ketone gave VII while the *trans* isomer resulted in VIII.

The reaction of *cis*-1-cyclohexyl-2-phenyl-3-benzoylethylenimine[1] with *p*-tolylmagnesium bromide gave VB. With phenylmagnesium bromide the *cis* and *trans* forms of this ketone produced IX and X, respectively.

The *trans*-1-benzyl-2-phenyl-3-*p*-toluylethylenimine[1] reacted with excess phenylmagnesium bromide to give a good yield (65%) of XIA along with a 16% yield of XIB; the *trans*-1-benzyl-2-phenyl-3-benzoylethylenimine[1] produced a 70% yield of XIB and a 5% yield of XIA on treatment with excess *p*-tolylmagnesium bromide.

The *cis* and *trans* isomers of 1-benzyl-2-phenyl-3-*p*-toluylethylenimine[1] reacted with *p*-tolylmagnesium bromide to give XII and XIII, respectively.

Reaction of Ethylene Imine Ketones with Phenyllithium.—The ethylene imine ketones in dry benzene solutions were treated with one molar equivalent of phenyllithium[15,16] in ether solution. The reaction mixtures were decomposed by iced ammonium chloride.

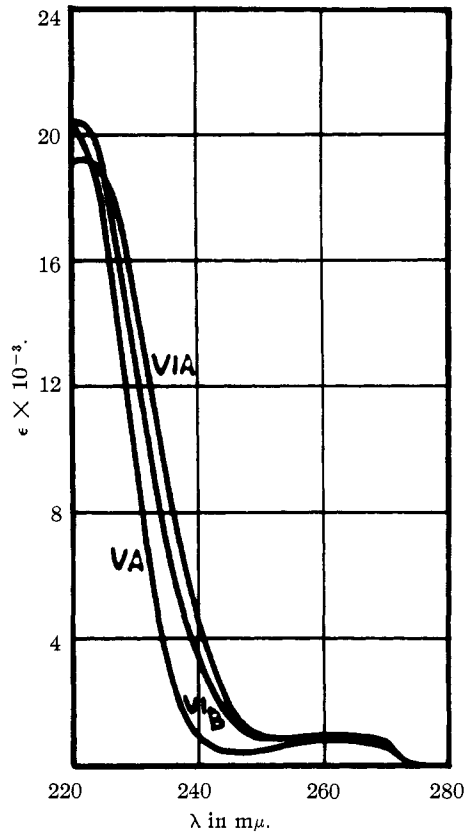


Fig. 1.—Typical ultraviolet absorption spectra curves determined in heptane solution using a Beckman model DU spectrophotometer; *i.e.*, for VA, VIA and VIB.

cis-1-Benzyl-2-phenyl-3-*p*-toluylethylenimine gave a 95% yield of the known[4] *cis*-1-benzyl-2-phenyl-3-(phenyl-*p*-tolylhydoxymethyl)-ethylenimine, (XIVA), m.p. 117–119°; mol. wt., calcd., 419.5, found, 415. The *trans* form of this ketone gave an 80% yield of XIA along with a 15% yield of XIB. The reaction of *trans*-1-benzyl-2-phenyl-3-benzoylethylenimine[1] with excess phenyllithium in ether solution produced XV, see Table I.

Competitive Complexing with Arylmagnesium Bromides.—The Grignard reagents were formed from 0.011 mole of magnesium and 0.012 mole of the aryl bromide in ether solution in a small flask equipped with a reflux condenser and closed at the top with a calcium chloride tube. When the reaction was complete the solution was quickly transferred to a dry separatory funnel and added dropwise, with rapid stirring, to dry 50% ether–benzene solutions, of the ethylene imine ketones over a period of 30 minutes. The flocculent gray or yellow precipitates were filtered from the solutions after either 5 or 60 minutes stirring and decomposed with iced ammonium chloride. The filtrates were separately treated in the same manner and the organic materials isolated in both cases and purified by recrystallization from methanol or petroleum ether.

Using this technique it was found that phenylmagnesium bromide gave a complex with either the pure *cis* or pure *trans* form of 1-benzyl-2-phenyl-3-*p*-toluylethlenimine which readily regenerated the corresponding unchanged ketone on decomposition. Treatment of these phenylmagnesium bromide ketone complexes with either carbon dioxide or benzoyl chloride in dry ether solution with subsequent decomposition with iced ammonium chloride also regenerated only the original ethylene imine ketone.

A mixture of *cis* and *trans*-1-benzyl-2-phenyl-3-*p*-toluylethylenimines[1] (0.01 mole each) on treatment with 0.011 mole of phenylmagnesium bromide produced a complex which was decomposed to give an 80% recovery of the *trans* ketone, m.p. 74–76°. The unchanged *cis* form was re-

(12) Swain, THIS JOURNAL, **72**, 518 (1950).

(13) Several of the microanalyses for carbon, hydrogen and nitrogen are by the Clark Microanalytical Laboratory, Urbana, Illinois, arranged for through the courtesy of the Smith, Kline and French Laboratories, Philadelphia, Pa.

(14) Cromwell and Caughlan, THIS JOURNAL, **67**, 2235 (1945).

(15) Prepared by the "A" conditions of Gilman, Zoellner and Selby, *ibid.*, **55**, 1252 (1933).

(16) Standardized according to the method of Gilman, Zoellner and Selby, *ibid.*, **54**, 1957 (1932).

covered from the reaction filtrate in 75% yield, m.p. 116–118°.

In another experiment one molar equivalent of phenylmagnesium bromide was added to an ether–benzene solution containing 2.0 g. of the *cis* isomer to give an immediate heavy precipitate. To this solution was then added 2.0 g. of the *trans* isomer and the mixture stirred at 20° for one hour. Decomposition of the precipitated complex produced 1.55 g. of the *trans* isomer, m.p. 74–76°, and 1.9 g. of the *cis* isomer, m.p. 117–118°, was recovered from the filtrate.

A mixture of the *cis*- and *trans*-1-cyclohexyl-2-phenyl-3-*p*-toluylethylenimines[1] (0.01 mole each) on treatment with 0.011 mole of *p*-tolylmagnesium bromide gave a yellow precipitate which decomposed to regenerate a 20% yield of the *trans* ketone, m.p. 89–90°. From the filtrate 95% of the unchanged *cis*-ethylene imine ketone, m.p. 110–112°, was recovered.

Competitive Addition of Phenyllithium.—An apparatus was constructed so that the phenyllithium could be prepared in ether solution under nitrogen,[15] a portion removed and titrated[16] and other portions transferred to measuring burets and then added to reaction flasks without opening the system to the air.

A mixture of *cis*- and *trans*-1-benzyl-2-phenyl-3-*p*-toluylethylenimine (3.0 g., 0.0092 mole of each) dissolved in 50% ether–benzene was cooled to 0° and treated dropwise with stirring over a period of one hour with 31 ml. (0.0092 mole) of the phenyllithium solution. The reaction mixture was stirred an additional hour at room temperature and decomposed with iced ammonium chloride. Careful fractional recrystallizations from benzene and petroleum ether mixtures separated 2.2 g. of XIVA, m.p. 115–117° from 2.1 g. of unchanged *trans*-1-benzyl-2-phenyl-3-*p*-toluylethylenimine. A mixture of this sample of XIVA with XIB showed m.p. 95–108°.

In a similar manner a mixture (3.0 g. each) of *cis*- and *trans*-1-benzyl-2-phenyl-3-benzoylethylenimine[1] resulted in 2.0 g. of the known[4] *cis*-1-benzyl-2-phenyl-3-(diphenylhydroxymethyl)-ethylenimine (XVI), m.p. 134–136°; a mixed m.p. with an authentic sample showed no depression. From the reaction mixture 2.3 g. of the *cis* ketone was recovered.

A mixture of 2.0 g. each of the *cis* and *trans* forms of 1-cyclohexyl-2-phenyl-3-benzoylethylenimine gave 0.60 g. of carbinol IX and a trace of carbinol X. From the reaction mixture filtrate was also recovered 0.82 g. of the unchanged *trans* ketone.

Oxidation of Ethylene Imine Carbinols.—Oxidation[4] of VA and VIA gave phenyl *p*-tolyl ketone in both cases.

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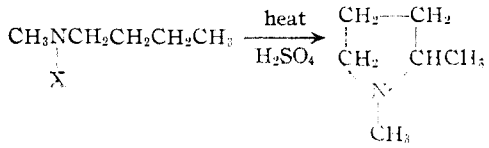
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, STATE UNIVERSITY OF IOWA]

Preparation of Quinuclidines[1]

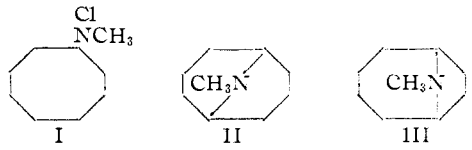
BY S. WAWZONEK, M. F. NELSON JR., AND P. J. THELEN

N-Bromo- and N-chloro-4-alkylpiperidines are converted into quinuclidines by irradiating first with ultraviolet light in 85% sulfuric acid at temperatures ranging from 0 to 23° and then treating with alkali. Comparable yields are obtained with both the bromoamine and the chloroamine. Evidence is presented that the β-bromoalkylpiperidine is an intermediate in the reaction.

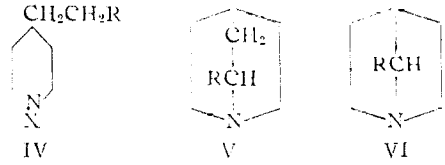
N-Haloalkylamines are converted in sulfuric acid by heat into substituted pyrrolidines.[2]



N-Halocycloalkylamines when treated in a similar manner, differ in their behavior and give bicyclic compounds which vary in the size of the rings formed. N-Chloro-N-methylcycloheptylamine, for example, behaves normally and gives tropane which involves a pyrrolidine ring.[3] N-Chloro-N-methylcycloöctylamine (I) behaves differently because of steric factors and gives N-methylgranatanine (II) in which two piperidine rings are present rather than the substituted pyrrolidine, 9-azabicyclo[4,2,1]nonane[4] (III)



The present paper reports a new variation in this ring closure with N-halo-4-alkylpiperidines (IV) which gives quinuclidines (V) rather than 1-azabicyclo[2,2,1]heptane (VI).



The ring closure was carried out in 85% sulfuric acid with both the N-chloro- and the N-bromoamines. Best yields were obtained if the solution was irradiated with ultraviolet light at room temperature or lower for twenty-four hours. A summary of the results obtained is given in Table I.

The results indicate that comparable yields are obtained with both the bromoamines and the chloroamines in all cases except one. N-Bromo-4-*n*-propylpiperidine gives a better yield than the corresponding chloro compound. The behavior of the N-bromo compounds is opposite to that observed when cyclization is brought about by heat[2b] and is probably due to the milder cyclization conditions used.

The quinuclidines were isolated in the customary manner by treating the sulfuric acid solution with excess alkali, steam distilling and removing the secondary amines as benzenesulfonamides. When the irradiated sulfuric acid solution of N-bromo-4-ethylpiperidine (IX) was adjusted quickly to *p*H 9 with dilute alkali and then warmed to 40°, the solution became acidic (*p*H 5). This phenomenon

(1) Abstracted in part from the Ph.D. thesis (1948) of P. J. Thelen and the Ph.D. thesis (1949) of M. F. Nelson, Jr. Presented before the Division of Organic Chemistry at the Chicago meeting of the American Chemical Society, September, 1950.

(2) (a) E. C. Britton, U. S. Patent 1,607,605; *C. A.*, **21**, 249 (1927); (b) G. H. Coleman and G. E. Goheen, THIS JOURNAL, **60**, 730 (1938); (c) G. H. Coleman, G. Nichols and T. F. Martens, *Org. Syn.*, **25**, 14 (1945).

(3) G. H. Coleman and J. J. Carnes, *Proc. Iowa Acad. Sci.*, **49**, 288 (1942) (abstract).

(4) S. Wawzonek and P. J. Thelen, THIS JOURNAL, **72**, 2118 (1950).