**1-(Carbethoxymethyl)-1,2,3,4-tetrahydroisoquinoline (IIIa).**—A solution of 50 g. (0.23 mole) of Xa in a 150 ml. of 1:1 acetic acid–ethanol, containing 5 g. of 5% palladium on carbon, was hydrogenated at 4 atm. The hydrogen absorption was complete after 1 hr. The ethanol was evaporated and the acetic acid solution was neutralized with potassium carbonate. The oil which appeared was taken up in ether and dried over sodium sulfate. Concentration of the ether solution gave 50.2 g. of crude product. Distillation of the latter afforded 47.1 g. (93%) of the reduced product: b.p. 120° (0.4 mm.); $n^{25}D$ 1.5337; $\lambda^{film}$ 2.96, 5.80 $\mu$.

*Anal.* Calcd. for $C_{13}H_{17}NO_2$: C, 71.23; H, 7.76; N, 6.39. Found: C, 71.20; H, 7.93; N, 6.40.

**1-(Carboethoxyethyl)-3,4-dihydro-6-methoxyisoquinoline (Xb) and 1-(carboethoxyethyl)-1,2,3,4-tetrahydro-6-methoxyisoquinoline (IIIb)** were prepared by the method described by Nelson, *et al.*[21]

**Formation of Ia and V (Ethylene Glycol Procedure).**—A solution of 10.0 g. (0.05 mole) of IIIa, 8.4 g. (0.1 mole) of cyclopentanone, and 100 ml. of toluene was refluxed with azeotropic removal of water for 72 hr. Examination of an aliquot after 48 hr. indicated no further increase in the enamine band at 1642 cm.$^{-1}$. The toluene was removed under reduced pressure and 150 ml. of freshly distilled ethylene glycol was added to the residue. The dark solution was heated for 15 hr. at 170–180° and after cooling to room temperature was diluted with 400 ml. of chloroform. The homogeneous solution was washed five times with 200-ml. portions of water and the organic layer was dried over sodium sulfate. Removal of the chloroform left a waxlike mass (11.4 g.) which deposited a crystalline solid upon the addition of petroleum ether. The solid (3.1 g.) was collected by filtration and only partially dissolved in hot ethyl acetate. Filtration of the latter solution gave 0.45 g. of a high-melting solid, whereas the filtrate, upon cooling, deposited 1.9 g. (20%) of Ia. The ethyl acetate insoluble product, V, had m.p. 259–260° (from ethanol); $\lambda_{max}^{EtOH}$ 286 m$\mu$ (log $\epsilon$ 4.23), 256 (4.57); and a vinyl singlet ($CDCl_3$) at $\tau$ 3.19.

*Anal.* Calcd. for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90. Found: C, 80.99; H, 6.58; N, 5.87.

**Formation of Id and V (Ethylene Glycol Method).**—The isoquinoline ester IIIa and 4-methoxycyclohexanone were treated as above to yield 24% of Id and 7% of VI: m.p. 203–205°; $\lambda_{max}^{EtOH}$ 282 m$\mu$ (log $\epsilon$ 4.17), 256 (4.50); $\lambda^{CHCl_3}$ 6.1 $\mu$; vinyl singlet ($CDCl_3$) at $\tau$ 3.21.

*Anal.* Calcd. for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.66; H, 6.91; N, 5.02.

**Benzo[*a*]cycloalkano[*f*]quinolizinones (I). A.**—A solution of 0.1 mole of the appropriate isoquinoline ester, 0.20 mole of the ketone (IV), and 100 ml. of toluene was heated in the presence of a Dean–Stark trap for 5–7 days. Although water was observed in the trap during the initial period of the reaction, the solution gradually became homogeneous. At the end of the heating period the solvent was evaporated under aspirator pressure and subsequently under oil pump pressure. The viscous oil that remained was triturated with petroleum ether causing a crystalline solid to precipitate. The latter was collected by filtration and recrystallized from a minimum amount of ethyl acetate.

**B.**—The same ratio of reactants and solvents was employed and, in addition, 1–3 ml. of trifluoroacetic acid was added. The solution was refluxed with azeotropic water removal for 15–30 hr., cooled to room temperature, and washed first with bicarbonate and then with water. After drying over sodium sulfate, the toluene was evaporated as in part A. The residual oil in most cases solidified, but in those cases where it did not, the addition of petroleum ether caused immediate precipitation of the product. The latter was then purified by recrystallization from ethyl acetate.

Perchlorate salts were prepared by adding 1:1 perchloric acid–ether to an alcoholic solution of I. The salt crystallized on standing or with subsequent cooling. Purification was achieved by recrystallization from 1:1 acetonitrile–ether.

(21) N. A. Nelson, K. O. Gelotte, Y. Tamura, H. B. Sinclair, J. M. Schuck, V. J. Bauer, and R. W. White, *J. Org. Chem.*, **26**, 2599 (1961).

# The Methylation of Enamines of 1-Azabicycloalkanes[1]

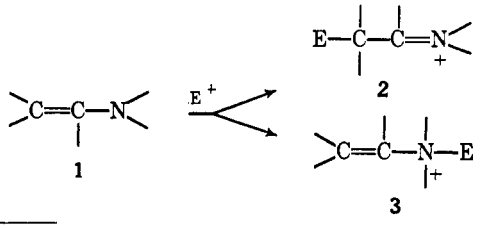
MANFRED G. REINECKE[2a] AND LOUIS R. KRAY[2b]

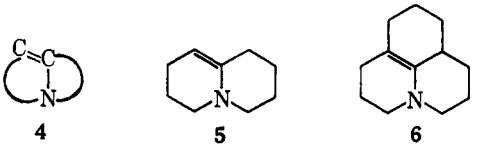
*Department of Chemistry, University of California, Riverside, California*

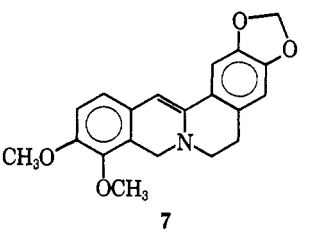
*Received May 25, 1965*

The methylations of several indolizidine and quinolizidine enamines with methyl iodide were studied. The major products were the N-monomethyl derivatives except in the case of the indolizidine enamine **9**, which underwent exclusive C-monomethylation as well as extensive dimethylation. The unique behavior of **9** is rationalized in terms of I strain in the transition state leading to N- but not to C-methylation.

Enamines (**1**) are ambident nucleophiles which may react with electrophilic reagents either at carbon or nitrogen to give **2** or **3**, respectively.[3] With simple alkyl halides the enamines of aldehydes appear to give only the vinyl quaternary ammonium salts[4] (**3**), while the enamines of cyclic ketones form both C- and N-alkylated products in varying proportions depending on, among other things, the structures of the starting enamines.[5] Much less is known about the position of alkylation of enamines of 1-azabicycloalkanes of the general structure **4**; $\Delta^{1(10)}$-dehydroquinolizidine[6] (**5**)




7

(1) Presented in part at the 146th National Meeting of the American Chemical Society, Denver, Colo., Jan. 1964; Abstracts, p. 27C.

(2) (a) Department of Chemistry, Texas Christian University, Fort Worth, Texas 76129. (b) National Science Foundation Summer Teaching Fellow, 1963; National Institute of Health Predoctoral Fellow in Chemistry, 1963–1965.

(3) J. Szmuszkovicz, *Advan. Org. Chem.*, **4**, 3 (1963).

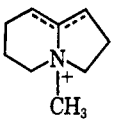
(4) (a) E. Elkik, *Bull. soc. chim. France*, 972 (1960); (b) G. Opitz and H. Mildenberger, *Ann.*, **649**, 26 (1961).

(5) (a) G. Opitz, H. Mildenberger, and H. Suhr, *ibid.*, **649**, 47 (1961); (b) G. Stork, XVIth National Organic Symposium Abstracts, Seattle, Wash., June 1959, p. 44.

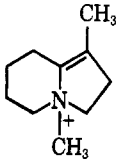
and $\Delta^5$-tetrahydrojulolidine[7] (6) apparently are methylated exclusively on nitrogen whereas dihydroberberine (7) undergoes predominant C-methylation.[8] In the course of studies in our laboratory on the synthesis of various alkaloids, the methylation of several additional enamines of 1-azabicycloalkanes have been investigated.

## Results

The structural similarity of $\Delta^8$-dehydroindolizidine (9) and the quinolizidine enamine 5 suggested that the former compound ought to undergo predominant N-methylation as well, and in fact a compound with the expected solubility properties and infrared spectral characteristics (no appreciable absorption in the 6-$\mu$ region)[4b,5a,6,7] for the quaternary ammonium salt 10 was isolated in about 50% yield. The elemental analysis of this compound as its crystalline 2,4,6-trinitrobenzenesulfonate indicated that two new methyl groups had been introduced, however. This conclusion was substantiated by the n.m.r. spectrum of the salt which displayed two sharp three-proton singlets at $\tau$ 6.78 and 8.14 indicative of quaternary N-methyl[7,9a] and vinyl C-methyl[9b] groups, respectively. Of the two reasonable structures which fit these data (11 and 12), the former was shown to be correct by methylation of 8-methyl-$\Delta^8$-dehydroindolizidine (13) to the same quaternary ammonium salt as was obtained from 9 (*vide infra*).



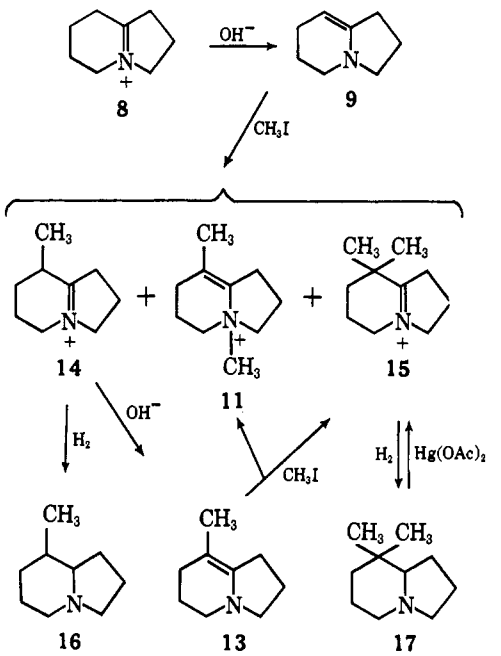
10



12

In addition to the ammonium salt 11, the methylation of the indolizidine enamine 9 produced a basic substance, also in about 50% yield,[10] which appeared homogeneous on vapor phase chromatography and which formed a sharp-melting perchlorate salt whose infrared spectrum displayed a sharp peak at 1685 cm.$^{-1}$ similar to those found for the C=N$^+$ group of many enamine salts.[11,12] Although these preliminary observations seemed to be consistent with the expected structures 13 and 14 for the base and its salt, respectively, neither elemental analyses nor infrared and n.m.r. spectra supported these formulations. Thus the characteristic shift of the 6-$\mu$ peak in the infrared to higher frequencies on converting an enamine to its salt[11,12] was not observed.[13] Furthermore, while the n.m.r. spectrum of the perchlorate salt was in many respects similar to that expected[14] for a structure such as 14, the presence of three sharp peaks in the C-methyl region could not be explained by any *single* reasonable structure. The n.m.r. spectrum of this salt could, in fact, be reconstructed by combining the n.m.r. spectra[14] of the mono- and di-C-methylated enamine salts 14 and 15, respectively in a ratio of approximately 2:1. The obvious conclusion that the salt of the basic methylation product of the indolizidine enamine 9 was actually a mixture of 14 and 15 was substantiated by catalytic reduction of this salt to a v.p.c. separable, 2:1 mixture of 8-methylindolizidine (16)[15] and 8,8-dimethylindolizidine (17) (*vide infra*).

Treatment of 8-methyl-$\Delta^8$-dehydroindolizidine (13) with methyl iodide led to a quaternary ammonium salt in 65% yield whose properties were identical with those of the quaternary salt 11 obtained from the indolizidine enamine 9. The basic substance from this methylation reaction was converted to a perchlorate salt which, on catalytic hydrogenation, led to 8,8-dimethylindolizidine (17) in an over-all yield of 22% from the enamine 13. The structure of 17 was assigned on the basis of its elemental analysis, origin, and mercuric acetate oxidation to a compound whose analytical, infrared, and n.m.r. properties[14] were consistent only with the iminium salt structure 15.

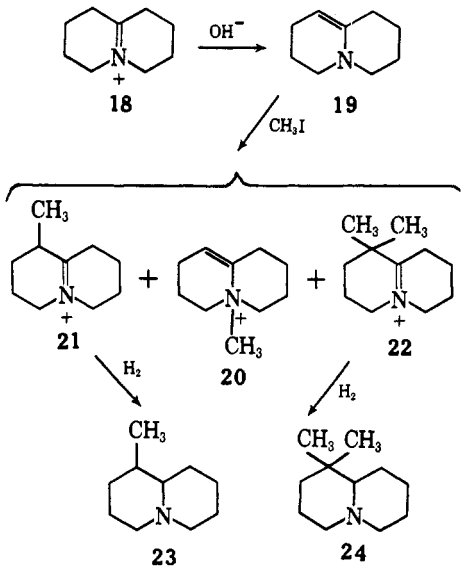



In agreement with the observation of Leonard, *et al.*,[6] the predominant product (83% yield) from the methylation of the quinolizidine enamine 19 was the N-quaternary salt 20. Although the melting point of this salt is considerably lower than that reported,[6] its elemental analysis and the presence in its n.m.r. spectrum of peaks attributable to one vinyl hydrogen[16] ($\tau$ 4.20) and to a quaternary N-methyl group[7,9a] ($\tau$ 6.73) are consistent with the structure 20.

An n.m.r. spectrum of the salts of the basic products from the methylation of the quinolizidine enamine 19 displayed three sharp peaks in the C-methyl region

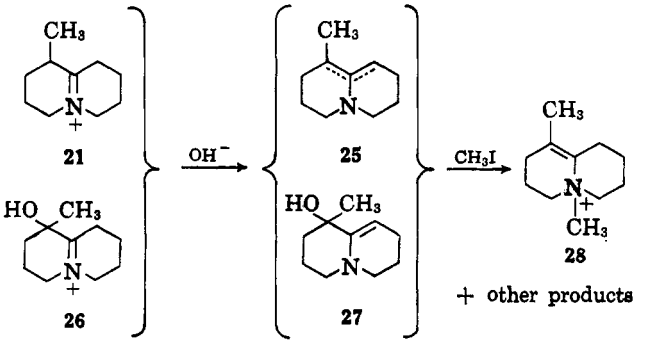
(6) N. J. Leonard, A. S. Hay, R. W. Fulmer, and V. W. Gash, *J. Am. Chem. Soc.*, **77**, 439 (1955).
(7) N. J. Leonard, C. K. Steinhardt, and C. Lee, *J. Org. Chem.*, **27**, 4027 (1962).
(8) M. Freund and K. Fleischer, *Ann.*, **409**, 188 (1915).
(9) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press Inc., New York, N. Y., 1959: (a) p. 56; (b) p. 58.
(10) Considerable unreacted enamine 9 was present in those methylations carried out with just methyl iodide and methanol. This is presumably due to a proton exchange with product (see Discussion) and could be virtually eliminated by carrying out the methylation in the presence of aqueous potassium carbonate (see Experimental Section).
(11) Reference 3, p. 96.
(12) N. J. Leonard and V. W. Gash, *J. Am. Chem. Soc.*, **76**, 2781 (1954).
(13) This point will be discussed in more detail in a forthcoming paper.[14]
(14) M. G. Reinecke and L. R. Kray, to be submitted.
(15) M. G. Reinecke and L. R. Kray, *J. Org. Chem.*, **29**, 1736 (1964).
(16) Reference 9, p. 61.

suggesting a mixture of the mono- and di-C-methylated iminium salts, **21** and **22**, respectively. This interpretation was substantiated by catalytic hydrogenation of this mixture to 1-methylquinolizidine (**23**) and a compound tentatively assigned structure **24** on the basis of its n.m.r. spectrum which suggests the presence of nonequivalent *gem*-methyl groups ($\tau$ 9.05 and 9.16, 3H each).




18 19 21 20 22 23 24

The methylation of the methylquinolizidine enamine **25** was confused by the fact that although the iminium salt from which **25** was generated had properties identical with those reported in the literature[17] for **21**, it was in fact a 2:1, apparently eutectic, mixture of **21** and the hydroxylated compound **26**, respectively.[14] Unfortunately, therefore, the only methylations of **25** which were investigated were actually carried out on a mixture of **25** and **27**. Although the basic fraction from the methylation was a complex mixture, the quaternary fraction surprisingly produced a single quaternary salt in *ca.* 70% yield based on the actual amount of **21** present in the starting salt. The elemental analysis of this salt as the 2,4,6-trinitrobenzenesulfonate and the presence of quaternary N-methyl[7,9a] and vinyl C-methyl[9b] peaks in its n.m.r. spectrum at $\tau$ 6.7 and 8.4, respectively, suggest it is probably the dimethyl compound **28**.

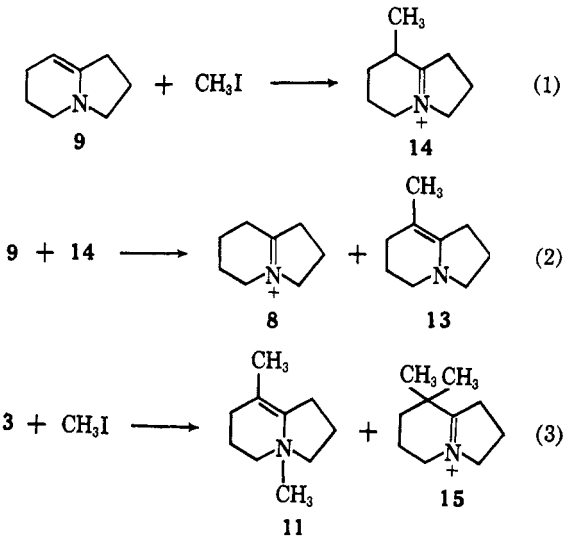



21 26 25 27 28

One last point, pertinent to the following discussion, is the possibility of migration of a methyl group from nitrogen to carbon[18] during the work-up of the methylation reaction. Under conditions actually more severe than those used in this work-up, the quaternary ammonium salt **11** produced no detectable amounts of either of the C-methylated compounds **14** or **15**, but only a mixture of what appeared to be products of Hofmann degradation.

## Discussion

A comparison of the methylation reactions described above with respect to the percentage of mono- *vs.* dimethylation and the percentage of the first methylation which goes on carbon and nitrogen (Table I) reveals that the behavior of the indolizidine enamine **9** is unique. While the major products from the other enamines are their respective N-monomethyl quaternary salts, *none* of the corresponding product **10** was found for the indolizidine enamine **9**. The products which were formed (**11**, **14**, **15**, and sometimes[10] **8**) can be rationalized by C-monomethylation (eq. 1) followed by deprotonation of the resulting iminium salt **14** by potassium carbonate or, where this reagent




9 14 8 13 11 15

was not present, the starting enamine **9** (eq. 2). The 8-methyl-$\Delta^8$-dehydroindolizidine (**13**) formed in this way is then methylated predominantly on nitrogen but also on carbon to give **11** and **15**, respectively (eq. 3). A detailed discussion of these reactions follows.

TABLE I

COMPARISON OF METHYLATION OF ENAMINES OF 1-AZABICYCLOALKANES

| Enamine | % Monomethylation | % Dimethylation | % First methylation on C | % First methylation on N |
|---|---|---|---|---|
| **9** | 35 | 65 | 100 | 0 |
| **13** | 87 | Trace | 25 | 75 |
| **19** | 89 | 6 | 13 | 87 |
| **25** | ≥70 | *a* | *a* | ≥70 |

[a] Isolation was not attempted.

The absence of the N-methylated enamine **10** in the *methylation* reaction (eq. 1) indicates that (i) it was not formed, (ii) it decomposed, or (iii) it rearranged to the

(17) N. J. Leonard, R. W. Fulmer, and A. S. Hay, *J. Am. Chem. Soc.*, **78**, 3457 (1956).

(18) (a) G. Opitz, H. Hellmann, H. Mildenberger, and H. Suhr, *Ann.*, **649**, 36 (1961); (b) K. C. Brannock and R. D. Burpitt, *J. Org. Chem.*, **26**, 3576 (1961).

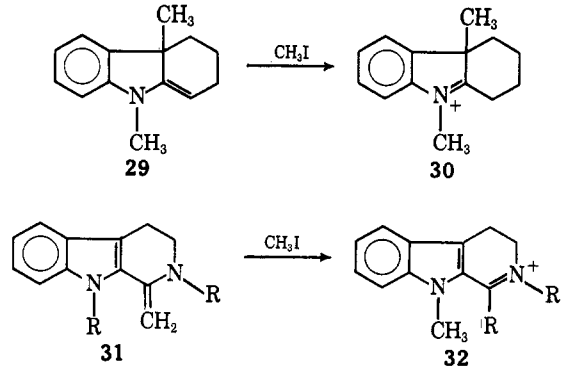
C-methylated enamine **14**. Since the ammonium salt **11** does not undergo N-to-C methyl migration (see Results) it is reasonable to assume that the N-methylammonium salt **10** would have behaved in an analogous fashion had it been formed during the methylation of the indolizidine enamine **9**. Therefore, the failure to find any of the ammonium salt **10** or its degradation products indicates that the enamine **9** is methylated exclusively on carbon as shown in eq. 1.

This striking selectivity can be rationalized in terms of differences in the energies of the transition states for N- and C-methylation. In the former transition state the nitrogen atom of the originally planar C=C—N system must rehybridize from a trigonal to a tetrahedral configuration, an unfavorable process since the nitrogen atom is in a five-membered ring (I strain).[19] The analogous rehybridization of the β-carbon atom of the C=C—N system in the transition state for C-methylation is more favorable, however, because this carbon is situated solely in the six-membered ring.[19]

The above hypothesis for the exclusive C-methylation of the enamine **9** is substantiated by the predominant N-methylation of the quinolizidine enamines **19** and **25**, since in these compounds the nitrogen atom is not part of a five-membered ring and therefore readily can adopt a tetrahedral configuration in the transition state for N-methylation. The exclusive C-methylation of dihydroberberine (**7**)[8] is not necessarily inconsistent with this picture since the flexibility of the quinolizidine moeity may be reduced by the rigid, planar aromatic rings thereby decreasing the ease with which the nitrogen atom can rehybridize.

The ratio of carbon to nitrogen methylation naturally will be affected by other factors besides I strain.[19b] Thus, the predominant N-methylation of the 8-methylindolizidine enamine **13** is probably due to unfavorable steric interactions in the transition state leading to the di-C-methyl derivative **15**. This is substantiated by an inspection of molecular models which indicate that one of the methyl groups must take up a pseudoaxial position.

The *exchange* reaction (eq. 2) explains the isolation of substantial quantities of the original enamine salt **8** from those methylation reactions carried out in the absence of potassium carbonate. The formation of the salts **30**[20] and **32**[21] by reaction of the enamines **29** and **31**, respectively, with methyl iodide may be due to a similar exchange reaction rather than to the hydrolysis of methyl iodide as has been suggested.[20,21]




The extensive *polymethylation* of the enamine **9** (eq. 3) is in direct contrast to observations with enamines of cyclic ketones.[22] This difference is not surprising since molecular models show that the steric factors which inhibit polyalkylation of the latter enamines[23,24] are absent in **13**.

The difference with respect to dimethylation between the indolizidine enamine **9** and the other enamines of 1-azabicycloalkanes examined in this study (Table I) is more apparent than real. Only a C-methylated enamine is capable of undergoing exchange (eq. 2) and thus a second methylation (eq. 3), and **9** is the only enamine which is appreciably C-methylated. Thus the amount of the C-methylated derivative of the quinolizidine enamine **19** which is methylated further (50%) is comparable to that (60–65%) observed for the indolizidine enamine **9**.

One last point of interest is that the di-C-methylation product of the enamine **9** is **15** rather than **33**. If the position of C-alkylation of enamines is assumed[22] to reflect the position of the double bond, then this result suggests that the intermediate enamine has the double bond in the most (**13**) rather than the least (**34**) substituted position as is the case for enamines of cyclic ketones.[22] This "normal" order of double bond stabilities has been observed for other enamines[7,14,25] and is substantiated for **13** by its n.m.r. spectrum.[14]


**33** **34**

## Experimental Section[26]

**Methylation of Δ⁸-Dehydroindolizidine (9).**—To a solution of 6.8 g. of Δ⁴⁽⁹⁾-dehydroindolizidinium perchlorate (**8**) in 25 ml. of absolute methanol was added dropwise 2 *M* methanolic potassium hydroxide until no more potassium perchlorate precipitated. The resulting mixture was centrifuged and the decantate was heated for 1 hr. under reflux with 25 g. of methyl iodide, 25 ml. of water, 25 ml. of methanol, and 5 g. of potassium carbonate. Removal of the methanol and excess methyl iodide by distillation through a small Vigreux column left a dark red, oily residue which was directly steam distilled under a nitrogen atmosphere from 100 ml. of 25% aqueous potassium hydroxide until the distillate was no longer basic to litmus (200 ml.). The volume of liquid in the distilling flask was held constant during the distillation by addition of water from a dropping funnel.

**A. Quaternary Fraction.**—The steam distilland was extracted with three 25-ml. portions of chloroform which were dried over anhydrous magnesium sulfate and evaporated under reduced pressure on a solvent stripper. The residue consisted of approximately 3 g. of a dark red hygroscopic oil which could not be induced to crystallize and whose infrared spectrum had no appreciable absorption in the 6-μ region.

(19) H. C. Brown, J. H. Brewster, and H. Shechter, *J. Am. Chem. Soc.*, **76**, 467 (1954); (b) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p. 265 ff.

(20) F. Berlage and P. Karrer, *Helv. Chim. Acta*, **40**, 736 (1957).

(21) R. Gupta and I. Spenser, *Can. J. Chem.*, **40**, 2041 (1962).

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

(23) W. R. N. Williamson, *Tetrahedron*, **3**, 314 (1958).

(24) F. Johnson and A. Whitehead, *Tetrahedron Letters*, 3825 (1964).

(25) S. Danishefsky and M. Feldman, *ibid.*, 1131 (1965).

(26) All melting points and boiling points are corrected; proton magnetic resonance spectra were recorded on a Varian A-60 instrument in deuteriochloroform solution with tetramethylsilane as an internal reference unless otherwise noted; v.p.c. analyses were carried out with a Wilkens Aerograph A-90-C on a 10-ft., 10% silicone on Fluoropack column; analyses were determined by Mr. C. F. Geiger, Ontario, Calif.

Upon addition of a methanol solution of this oil to a methanol solution of 2,4,6-trinitrobenzenesulfonic acid (TNBS) followed by a large excess of ether, 4,8-dimethyl-$\Delta^{8}$-dehydroindolizidinium 2,4,6-trinitrobenzenesulfonate (**11**·**TNBS**) was obtained as a pale yellow solid which, after five recrystallizations from methanol–ether with the aid of Norit, formed fine white needles, m.p. 190–191° dec.

*Anal.* Calcd. for $C_{16}H_{20}N_4O_9S$: C, 43.25; H, 4.54. Found: C, 43.82; H, 4.46.

An n.m.r. spectrum of this salt in trifluoroacetic acid displayed two peaks of equal area at $\tau$ 6.78 add 8.14.

**B. Basic Fraction.**—The steam distillate was saturated with potassium carbonate and extracted with three 75-ml. portions of ether. The combined ether extracts were dried over anhydrous potassium carbonate, concentrated to 50 ml. with a rotary evaporator, diluted with 25 ml. of absolute ethanol, and acidified to litmus with a 50% (v./v.) solution of 70% perchloric acid in absolute ethanol. Upon addition of a large excess of ether, light brown crystals precipitated.

In different experiments the quantity of this salt formed was always about 50–60 wt. % of the starting perchlorate. The composition of this salt, however, varied greatly depending on whether or not the original methylation reaction was carried out in the presence of potassium carbonate. Thus, v.p.c. analysis indicated that 10% of the free base obtained by basification and ether extraction of the salt prepared as above was starting enamine **9** as compared to as much as 80% from methylations carried out in the absence of water and potassium carbonate. With either procedure, isolation of the other major constituent of the basic fraction by preparative v.p.c. gave an oil which formed a perchlorate salt that melted sharply at 245–246° after several recrystallizations from ethanol–ether with the aid of some Norit. Satisfactory elemental analyses could not be obtained, however.

The infrared spectrum of this salt displayed a sharp peak at 1685 cm.$^{-1}$ (KBr or mull) which did not show any significant change in position or intensity in the corresponding free base ($CHCl_3$, ether, or film).[13]

The n.m.r. spectrum of this salt was very similar to that of the iminium perchlorate **8**[14] except that the peak assigned[14] to the six-membered ring $-CH_2-C{=}N^+$ was substantially modified and three sharp peaks ($\tau$ 8.58, 8.63, and 8.70) were present in the C-methyl region. A reasonable facsimile of this n.m.r. spectrum could be constructed by combining the n.m.r. spectra[14] of iminium salts **14** and **15** in a 2:1 ratio, respectively.

**Catalytic Reduction of the Perchlorate Salt of the Basic Methylation Product of $\Delta^{8}$-Dehydroindolizine (9).**—A solution of 1 g. of the above perchlorate salt (m.p. 245–246°) in 10 ml. of absolute methanol was hydrogenated at ambient pressure and temperature in the presence of about 10 mg. of platinum oxide catalyst. After absorption of hydrogen ceased (15 min., 0.96 equiv. based on a 2:1 mixture of **14** and **15**, respectively), the catalyst was removed by filtration and the methanol by evaporation on a rotary evaporator. The solid residue was dissolved in water, basified with 30% sodium hydroxide, and extracted with three 50-ml. portions of ether. The combined ether extracts were dried with anhydrous potassium carbonate, concentrated on a rotary evaporator, and fractionated by preparative v.p.c. Two peaks were observed, the one of lower retention time predominating by a ratio of 2:1.

The major product was identified as 8-methylindolizidine (**16**) by comparison of its infrared and n.m.r. spectra and v.p.c. retention time with those of an authentic sample.[15] In addition, a picrate, m.p. 204–205° (lit.[15] m.p. 203–204°), and a perchlorate, m.p. 153–154° (lit.[15] m.p. 154–155°), were prepared.

The infrared and n.m.r. spectra ($CCl_4$) of the minor product, 8,8-dimethylindolizine (**17**) (b.p. 189° at 738 mm.),[27] showed the absence of N–H absorption and the presence of nonequivalent *gem*-methyl groups ($\tau$ 9.14 and 9.08, 3H each), respectively. Treatment of **17** with picric acid in ethanol gave the picrate, m.p. 235–237° dec.

*Anal.* Calcd. for $C_{16}H_{22}N_4O_7$: C, 50.13; H, 5.75. Found: C, 50.07; H, 5.66.

**Methylation of 8-Methyl-$\Delta^{8}$-dehydroindolizidine (13).**—Treatment of 8-methyl-$\Delta^{4(9)}$-dehydroindolizidinium perchlorate (**14**)[15] according to the methylation procedure described above also led to a basic and a quaternary fraction. The former was converted to a perchlorate salt and catalytically hydrogenated to give, in 22% yield, 8,8-dimethylindolizidine (**17**) as determined by comparison of its boiling point, infrared and n.m.r. spectra, v.p.c. retention time, and the melting point of its picrate with those of the minor, hydrogenated, basic product from the methylation of the enamine **9** (see above). The noncrystalline quaternary fraction (65% yield) had the same infrared and n.m.r. spectra as the quaternary salt obtained from the methylation of the enamine **9** and formed a crystalline TNBS derivative, m.p. 189–191° dec. (undepressed on admixture with an authentic sample of **11**·**TNBS**).

**8,8-Dimethyl-$\Delta^{4(9)}$-dehydroindolizidinium Perchlorate (15).**—In a 50-ml., three-necked flask fitted with an efficient mechanical stirrer, gas-inlet valve, and a serum cap was placed 7 g. of mercuric acetate and 20 ml. of 5% aqueous acetic acid. After the apparatus had been evacuated and refilled with nitrogen several times, it was placed on a steam bath until all of the mercuric acetate had dissolved. Upon addition of 0.5 g. of 8,8-dimethylindolizidine (**17**) through the serum cap by means of a syringe, an immediate precipitate of mercurous acetate formed. The reaction mixture was stirred on the steam bath for 1 hr. and then cooled, and the mercurous acetate was removed by filtration. The filtrate was saturated with hydrogen sulfide, and the resulting black precipitate was removed by centrifugation. The resulting clear centrifugate was basified with 30% sodium hydroxide, saturated with potassium carbonate, and extracted with three 75-ml. portions of ether which were dried over anhydrous potassium carbonate. After the drying agent had been removed by filtration, the ether extracts were concentrated to 75 ml. on a rotary evaporator, diluted with 10 ml. of absolute ethanol, and acidified to litmus with a 50% (v./v.) solution of 70% perchloric acid in absolute ethanol. The precipitated iminium perchlorate salt was recrystallized from ethanol–ether with the aid of some Norit to give 0.50 g. (61% yield) of 8,8-dimethyl-$\Delta^{4(9)}$-dehydroindolizidinium perchlorate (**15**) as white needles, m.p. 235–237° dec.

*Anal.* Calcd. for $C_{10}H_{18}ClNO_4$: C, 47.72; H, 7.16; N, 5.57. Found: C, 47.37; H, 7.14; N, 5.86.

The infrared spectrum of **15** displayed a sharp peak at 1690 cm.$^{-1}$ ($C{=}N^+$), and the n.m.r. spectrum[14] was very similar to the indolizidinium perchlorate **8** except that the peak assigned[14] to the six-membered ring $CH_2-C{=}N^+$ group was missing and a sharp singlet ($\tau$ 8.63, 6H) was present in the C-methyl region.

**Methylation of $\Delta^{1(10)}$-Dehydroquinolizidine (19).**—The basic fraction obtained by methylating $\Delta^{5(10)}$-dehydroquinolizidinium perchlorate (**18**), according to the procedure described above, was converted to a crude perchlorate salt whose n.m.r. spectrum was very similar to that of **18**[14] except that the area of the $-CH_2-C{=}N^+$ peak was diminished and three new sharp peaks ($\tau$ 8.58, 8.63, and 8.71) were observed. Catalytic reduction of this crude salt led to a mixture of bases which was separated by preparative v.p.c. on a diisodecyl phthalate column into two fractions in 5–6% yield each, based on the amount of **18** actually reacted. The fraction of lower retention time was identified as a mixture of 1-methylquinolizidine diastereoisomers (**23**) by a comparison of its v.p.c. retention time with that of an authentic sample[15] and by its conversion to a picrate, m.p. 188–190° [lit.[17] m.p. 189–191°, for a sample prepared from the hydrogenation product of 1-methyl-$\Delta^{5(10)}$-dehydroquinolizidinium perchlorate (**18**)]. The n.m.r. spectrum of the fraction of higher retention time displayed two sharp peaks at $\tau$ 9.05 and 9.16 (3H each) as might be expected[14] for the nonequivalent *gem*-methyl groups of 1,1-dimethylquinolizidine (**24**). Insufficient material was available for the preparation of a crystalline derivative.

The quaternary fraction from the methylation of **18** was crystallized from methanol–ether with the aid of some Norit to give 5-methyl-$\Delta^{1(10)}$-dehydroquinolizidinium iodide (**20**) in 83% yield based on the amount of **18** which actually reacted. After several recrystallizations of **20** from methanol–ether, an analytical sample was obtained as a white, nonhygroscopic, microcrystalline solid, m.p. 250–252° dec. (evacuated capillary) (lit.[6] m.p. *ca.* 278° dec.).

*Anal.* Calcd. for $C_{10}H_{18}IN$: C, 43.02; H, 6.49. Found: C, 43.03; H, 7.05.

The infrared spectrum of **20** displayed a small but sharp peak at 3010 cm.$^{-1}$ ($C{=}C-H$) and a broad, weak absorption centered at 1640 cm.$^{-1}$ ($C{=}C$). A vinyl hydrogen absorption was also

(27) Micro boiling point determination according to R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 4th Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, p. 32.

observed in the n.m.r. spectrum of **20** ($\tau$ 4.20, 1H) as was a quaternary N-methyl peak ($\tau$ 6.73).

**Methylation of the Enamines from "1-Methyl-$\Delta^{4(9)}$-dehydroquinolizidinium Perchlorate" (21 and 26).**—A sample of the iminium salt **21** prepared[15] by the mercuric acetate oxidation of 1-methylquinolizidine (**23**) was recrystallized to a constant melting point of 253–255° which agreed well with that reported in the literature[17] (252–253°). After the methylation experiment described below had been carried out, this salt was shown[14] to consist of a 2:1 mixture of the iminium perchlorates **21** and **26**.

The basic fraction obtained by methylation of the above mixed salt according to the usual procedure was, according to its vapor phase chromatogram, a mixture of at least six components which were not readily separable. An n.m.r. spectrum ($D_2O$) of the noncrystalline quaternary fraction (**28**) (*ca.* 70% yield based on the amount of **21** actually present in the starting mixed salt) displayed sharp peaks at $\tau$ 6.7 and 8.4. After several recrystallizations from methanol–ether with the aid of some Norit, the white TNBS derivative of **28** melted at 185–187°.

*Anal.* Calcd. for $C_{17}H_{22}N_4O_9S$: C, 44.53; H, 4.83. Found: C, 44.75; H, 4.73.

**Reaction of Quaternary Salt 11 with Base.**—A mixture of 0.6 g. of the crude salt **11**, 2 ml. of water, and 10 ml. of a saturated solution of sodium hydroxide was directly steam distilled until the distillate was no longer basic. Approximately 0.15 g. of **11** was recovered from the distillate by extraction with chloroform. The distillate was worked up in the same way as the methylation reactions to give 0.4 g. of a crude perchlorate salt which was catalytically hydrogenated to give a basic substance whose v.p.c. indicated the presence of three compounds. The compound formed in highest yield had a v.p.c. retention time similar to 8-methylindolizidine (**16**), but its picrate melted at 105–107° as compared to 203–204° for that of **16**.[15] Furthermore, the infrared spectrum of this material was similar to that of N-methylpiperidine and not **16**.

The product of highest retention time had an infrared spectrum similar to that of N-methylpyrrolidine, while that of lowest retention time was not present in sufficient quantity for isolation.

**Acknowledgment.**—This research was supported in part by funds from the Research Committee of the University of California.

# The Reaction of Enamines with Activated Butadienes. A One-Step Synthesis of Benzenes[1]

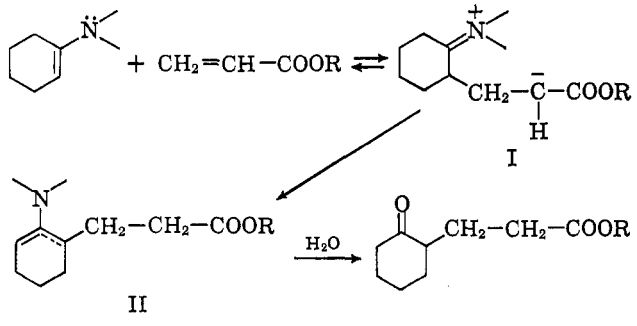
SAMUEL DANISHEFSKY AND ROBERT CUNNINGHAM

*Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15213*

*Received April 3, 1965*

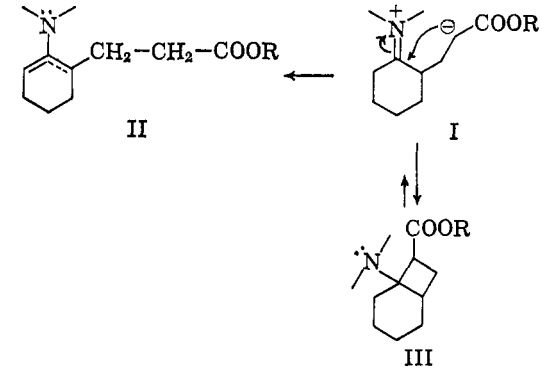
The reaction of enamines with ethyl sorbate and ethyl 2,4-pentadienoate was studied. Under appropriate conditions, cycloaddition, retro-Michael elimination, and aromatization were realized, thus affording a one-step synthesis of benzenes.

Stork and co-workers[2] demonstrated the ability of electrophilic olefins to undergo nucleophilic attack with enamines. A typical over-all process is shown below.

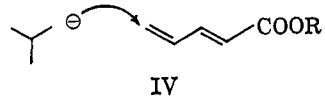



Brannock and co-workers[3] found that, under appropriate conditions, cyclobutane derivatives of the type III may be observed. It is not certain whether they arise from direct cycloaddition or *via* a two-step (Michael–Mannich) sequence. From the results of the Columbia workers,[1] it would appear that III could well be in equilibrium with I (Mannich–retro-Mannich), an equilibrium which is presumably irreversibly displaced toward II by proton transfer.

The purpose of this communication is to disclose preliminary results of a study of this type of reaction

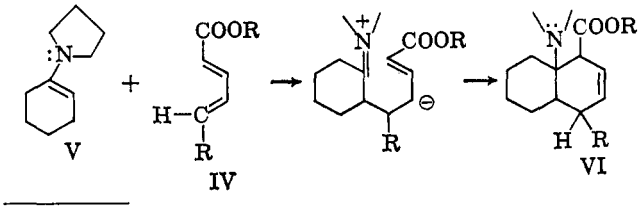



on a system vinylogously related to the one considered above. Derivatives of $\beta$-vinylacrylates are well known[4] to undergo 1,6 addition preferentially. We therefore




IV

felt it of interest to examine the enamine reaction on derivatives of IV with the hope of realizing terminal addition and attendant (or concurrent by a cycloaddition process) six-membered ring formation.




(1) This work was supported by a Grant from the National Institutes of Health, No. AM-08695-0. The efforts of Mrs. Celia B. Lerman are gratefully acknowledged.

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

(3) K. C. Brannock, R. D. Burpitt, V. M. Goodlett, and J. G. Thweatt, *J. Org. Chem.*, **29**, 813 (1964).

(4) E. P. Kohler and F. R. Butler, *J. Am. Chem. Soc.*, **48**, 1041 (1926).