

Metcalf Chemical Laboratories, Brown University

Oxazolidines Versus Schiff Bases (I)

R. M. Srivastava, Katherine Weissman and Leallyn B. Clapp

The formation of oxazolidines from propionaldehyde and aliphatic β -aminoalcohols is complicated by the appearance of appreciable amounts of unsaturated Schiff bases. The simple Schiff base, often the dominant species when aromatic aldehydes react with amines, could not be detected in the present aliphatic systems. We conclude that in aliphatic systems the order of stability is $C=C-C=N-C-C-OH > C=C-C \begin{matrix} O \\ \diagup \\ N \end{matrix}$ and $C-C-C \begin{matrix} O \\ \diagup \\ N \end{matrix} > C-C-C=N-C-C-OH$. The *gem*-dimethyl group α to nitrogen stabilizes the heterocyclic ring remarkably.

Aldehydes and some ketones condense with β -aminoalcohols containing primary amino groups to form oxazolidines (2). Using aromatic aldehydes and other ketones with ethanolamine, Daasch (3,4) showed by infrared spectra that the Schiff base formulation was the dominant structure for the reaction product. Bergmann in a review of the literature (5) and from his own work (6) concluded that a state of mobile equilibrium between oxazolidine and Schiff base existed in carbonyl-aminoalcohol systems.

We now report one more complication in the aldehyde - aminoalcohol system, the appearance of an unsaturated Schiff base.

Two isomeric oxazolidines, 2-ethyl-4,4-dimethyl-oxazolidine (III) and 2-ethyl-5,5-dimethyloxazolidine (IX), were synthesized in analytical purity by the method of Cope and Hancock (2) but the two differed rather markedly in stability.

The IR spectra of III showed the characteristic oxazolidine triplet (6) near 1150 cm^{-1} . Upon standing for 80 days at room temperature, three weak bands not in the analytical sample appeared at 1680 , 1652 , and 1640 cm^{-1} , suggesting that III eventually reverts to a mixture containing a small percentage of unsaturated compound, shown to be VI. The index of refraction rose from 1.4260 to 1.4295 during this time, a criterion which has also been used to designate a shift to a Schiff base (7).

Oxazolidine IX was also obtained in analytical purity but even this sample had a very weak band at 1675 cm^{-1} along with the triplet. After standing for one day the intensity of this band increased and after eight days additional bands at 1650 and 1638 cm^{-1} appeared. The observation suggests that this oxazolidine ring is much less stable than that in III. The ring opens to form a double bond and rapidly goes to the unsaturated Schiff base XI. The index of refraction of pure IX changed much more rapidly than that of III.

Compounds VI and XI were readily prepared in yields of 69% and 67%, respectively, from V and the corresponding aminoalcohol without any evidence in the fractional distillation for an unsaturated oxazolidine such as VII. Compounds VI and XI were also formed in small yields during the preparation of III and IX, respectively. Part of the destabilization of a system containing IX may be due to the removal of XI from the equilibria involving I, V, VIII, and IX through loss of a molecule of water, extending the conjugation to three π bonds. Compound VI, in the other equilibrium system, a primary alcohol with no α hydrogen, does not have this opportunity. Compound VI was, indeed, more stable on standing than XI.

We conclude that the *gem*-dimethyl group α to nitrogen (III) has a greater stabilizing effect on the oxazolidine ring than a *gem*-dimethyl group α to oxygen (IX). Preliminary experiments in this research were carried out on the isomeric oxazolidines, 2-ethyl-4-methyloxazolidine and 2-ethyl-5-methyloxazolidine. Neither could be obtained in pure form. A sharp band appears at 1675 cm^{-1} in the IR in the best samples that could be obtained. Estimated yields of 33% of 2-ethyl-4-methyloxazolidine accompanied by 44% of the corresponding unsaturated Schiff base were obtained from propionaldehyde and 2-amino-1-propanol. The index of refraction of the freshly distilled oxazolidine changed slowly while it was in the refractometer. Estimated yields of 38% of 2-ethyl-5-methyloxazolidine accompanied by 46% of the corresponding unsaturated Schiff base were obtained from propionaldehyde and 1-amino-2-propanol. The index of refraction of this freshly distilled oxazolidine changed rapidly in the refractometer. Due to the instability of these oxazolidines, this series was abandoned in favor of the *gem*-dimethyl aminoalcohols. From this preliminary work, however, it is clear that one methyl group α to the nitrogen has a greater stabi-

lizing effect on the oxazolidine than one methyl α to oxygen in the oxazolidine. The equilibrium between oxazolidine and unsaturated Schiff base is more labile in this system than the one involving *gem*-dimethyl groups.

When III was refluxed over sodium iodide in acetonitrile for an extended period, 70% of the starting compound was recovered and 2% of compound VI had been formed. Upon treatment of III with the strong base, sodium methoxide, and then with propionaldehyde, a small yield (8%) of compound VI was obtained and 24% of unchanged III was recovered. This experiment testifies that this oxazolidine does not deteriorate completely even in the presence of strong base.

We picture this last reaction as an aldol condensation, with the oxazolidine III acting as anion in the strong base, first forming VII which rapidly isomerizes to VI (7a). This pathway is favored rather than an equilibrium involving I, II, V, and VI since triethylamine would not effect the preparation of VI from III and I although it will catalyze the aldol condensation of propionaldehyde.

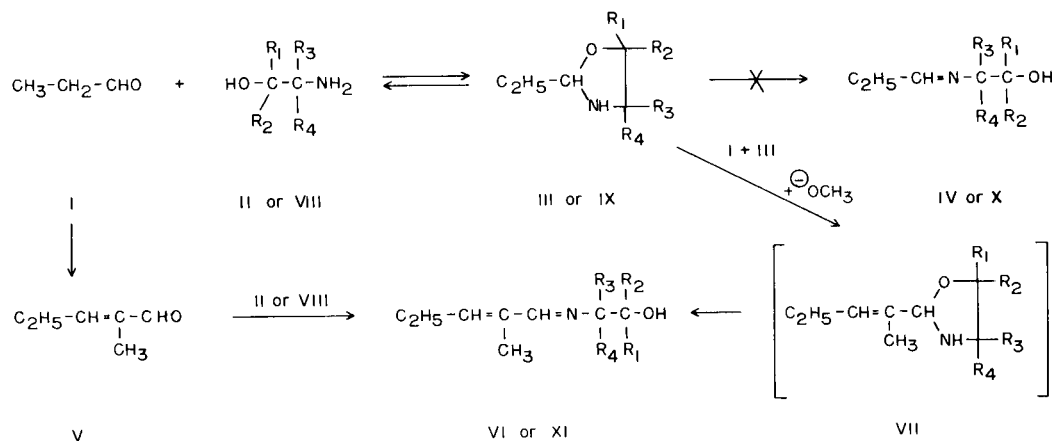
Since we were unable in the synthesis of III or IX to isolate any fraction containing type VII compounds, our results are in contrast to those of

Paquin (8). He claimed that butyraldehyde and ethanolamine react in a ratio of 2:1 to give three oxazolidines, 2-propyloxazolidine, and two unsaturated ones, 2-(1-ethyl-1-pentenyl)oxazolidine and 2-(1,3,5-triethyl-1,3,5-nonatrienyl)oxazolidine. The first compound, however, boils at least 50° (at 12 mm) higher than other reported isomeric oxazolidines (2) and 50-60° higher than III or IX.

We conclude that in aliphatic systems the order of stability is $C=C-C=N-C-C-OH > C=C-C \begin{matrix} O \\ \diagup \\ N \end{matrix}$ and $C-C-C \begin{matrix} O \\ \diagup \\ N \end{matrix} > C-C-C=N-C-C-OH$. The oxazolidine ring has more stabilizing effect than one double bond and the oxazolidine ring plus one double bond has less stabilizing effect than a 1,3-conjugated system.

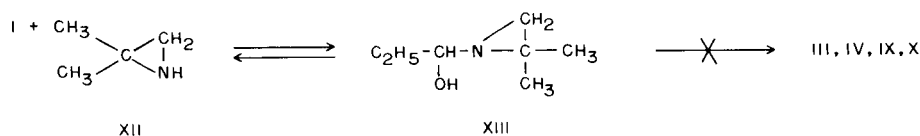
The original objective of the present research was to see if the iminohydrin XIII could be isomerized by Heine's (9) universal catalyst for aziridine isomerizations, sodium iodide, to an oxazolidine. The iminohydrin structure for the addition compounds of aziridines with aldehydes and ketones (10, 11, 12) was well established by infrared spectra (11) although earlier it was reported (13) that the initial product of the addition was an oxazolidine.

However, the equilibrium between iminohydrin XIII



II, III, IV, VI, VII, $R_1 = R_2 = H, R_3 = R_4 = CH_3$

VIII, IX, X, XI, $R_1 = R_2 = CH_3, R_3 = R_4 = H$



and the reactants I and XII is extremely sensitive. The iminohydrin XIII, acceptably pure by elemental analysis, still showed a weak carbonyl band at 1735 cm^{-1} in the IR spectrum. Sublimation of the pure compound at room temperature or even dissolution in dry hexane immediately produced a strong carbonyl band at 1735 cm^{-1} and the proton signal of an aldehyde group at low field ($0.27\ \tau$) by n.m.r.

The iminohydrin was subjected to isomerization by sodium iodide in dry acetonitrile. At room temperature, no change occurred except for the usual appearance of the carbonyl band in the IR to indicate some reversal to aldehyde I and ethylenimine XII. On refluxing 12 hours in acetonitrile, the iminohydrin does not isomerize to III but gives a viscous liquid which on distillation gave a mixture of products including compound VI (or XI) and a polymer of the aziridine in low yield. Evidence for compound VI (or XI) came from IR bands at 1635 and 1650 cm^{-1} and proton signals in the n.m.r. at 2.27 and $4.25\ \tau$, suggesting, respectively, $-\text{CH}=\text{N}$ and $-\text{CH}=\text{C}-$ functions. The boiling point of the mixture and nitrogen analysis suggested 60–70% unsaturated Schiff base (VI) or (XI) and 40–30% polymer, possibly a trimer of 2,2-dimethylaziridine.

When a shorter reflux time was employed for the attempted isomerization, 2-methyl-2-pentenal (V) was isolated which confirms the reversal of XIII to aldehyde and imine. The propionaldehyde apparently undergoes the aldol condensation and loss of water in the presence of the weak base to give compound V. The unsaturated Schiff base VI or XI is then formed.

EXPERIMENTAL (14)

2-Ethyl-4,4-dimethyloxazolidine (III).

Twenty grams (0.22 mole) of 2-methyl-2-amino-1-propanol was dissolved in 100 ml. of benzene and cooled. To this was added dropwise 13.0 g. (0.22 mole) of freshly distilled propionaldehyde. The flask was shaken during addition. The water formed was separated by azeotropic distillation (2) with benzene. The reaction mixture was cooled and 1.3 g. (0.022 mole) more of propionaldehyde was added. Azeotropic distillation gave 4 g. of water, the theoretical yield. Benzene was removed on a rotary evaporator and the remaining liquid was subjected to fractional distillation. Two distillations under nitrogen atmosphere gave 20.1 g. (71%) of 2-ethyl-4,4-dimethyloxazolidine, b.p. 52° (10 mm); $n_D^{25} = 1.4260$.

Anal. Calcd. for $\text{C}_7\text{H}_{15}\text{NO}$: C, 65.07; H, 11.70; N, 10.84. Found: C, 65.40; H, 11.73; N, 10.67.

The index of refraction did not change upon a second distillation. The IR spectra showed the characteristic triplet (6) of oxazolidines at 1080 – 1200 cm^{-1} . Found: 1100, 1122, and 1150 cm^{-1} ; 3280 cm^{-1} , weak (NH); 1036 cm^{-1} , strong (C–O stretching).

Upon standing for 80 days the index of refraction increased to 1.4295 (25°) and three very weak bands, not present in the analytical sample, appeared at 1640, 1652, and 1680 cm^{-1} , suggesting that the oxazolidine reverts to a mixture containing a small percent of compound VI (below).

The n.m.r. spectra (neat) of the pure oxazolidine gave the following proton signals: CH, $5.64\ \tau$ (triplet); ring CH_2 , $6.66\ \tau$ (quartet); CH_2 , 8.00 – $8.68\ \tau$; two ring CH_3 , 8.80, $8.90\ \tau$; CH_3 , $9.07\ \tau$. The NH proton signal could not be located even after adding a trace of pyridine.

In the original reaction mixture, a higher boiling fraction of 0.9 g. (2.5%) of colorless liquid (b.p., 57 – 58° (0.13 mm)) was identified as the unsaturated Schiff base, VI, by IR spectra, n.m.r. and analysis.

Anal. Calcd. for $\text{C}_{10}\text{H}_{19}\text{NO}$: C, 70.98; H, 11.30; N, 8.28. Found: C, 70.46; H, 11.12; N, 7.75.

2,2,5-Trimethyl-3-aza-3,5-octadien-1-ol (VI).

The aldol condensation of propionaldehyde gave 2-methylpentanal-3-ol and this was easily dehydrated to 2-methyl-2-pentenal (15) (V), and identified by I.R. spectra (16). Treatment with 2-amino-2-methyl-1-propanol and azeotropic removal of water gave the unsaturated Schiff base, VI in 69% yield; b.p., 65 – 66° (0.18 mm); $n_D^{25} = 1.4795$, $d_4^{25} = 0.9094\text{ MR}_D$. Calcd: 51.93. Found: 52.55.

Bands in the IR spectra were identified as follows: C=C, 1648 cm^{-1} ; C=N, 1632 cm^{-1} ; and OH (primary), 1058 cm^{-1} .

In the n.m.r. spectra ((20%) soln. in CCl_4 , W/V), the protons were identified as follows: $-\text{CH}=\text{N}$, $2.21\ \tau$; $\text{CH}=\text{C}$, $4.19\ \tau$ (triplet); CH_2O , $6.7\ \tau$; OH, $7.25\ \tau$; CH_2 , $7.74\ \tau$ (triplet); $\text{CH}_3\text{C}=\text{C}$, $8.21\ \tau$. The hydroxylic proton shifted 5 c.p.s. downfield by the addition of a trace of pyridine.

Anal. Calcd. for $\text{C}_{10}\text{H}_{19}\text{NO}$: C, 70.98; H, 11.30; N, 8.28. Found: C, 71.18; H, 11.53; N, 8.28.

2-Ethyl-5,5-dimethyloxazolidine (IX).

By the method just described for the isomer III, 2-ethyl-5,5-dimethyloxazolidine was prepared in 61% yield, b.p. 46° (10 mm), $n_D^{25} = 1.4290$.

The 1-amino-2-methyl-2-propanol used in the synthesis was prepared in low yield (20%) by reduction of acetone cyanohydrin with lithium aluminum hydride as described for another cyanohydrin by Nace and Smith (17). Due to instability of the oxazolidine IX, it was analysed on the same day after preparation.

Anal. Calcd. for $\text{C}_7\text{H}_{15}\text{NO}$: C, 65.07; H, 11.70; N, 10.84. Found: C, 65.07; H, 11.85; N, 11.00.

This oxazolidine gave the triplet at 1103 , 1134 and 1170 cm^{-1} and $-\text{NH}$ stretching band at 3275 cm^{-1} in the IR spectra.

The chemical shifts in the n.m.r. spectra (33% soln. in CCl_4 , V/V) for this oxazolidine were as follows: CH, $5.70\ \tau$ (triplet); ring CH_2 , $7.27\ \tau$ (quartet); CH_2 , 8.25 – $8.70\ \tau$; and NH, $7.82\ \tau$ (singlet). When a trace of pyridine was added, the band at $7.82\ \tau$ moved downfield 7 cps. A small unidentified band at $7.53\ \tau$ was present in the analytical sample.

2,6-Dimethyl-4-aza-4,6-nonadien-2-ol (XI).

Schiff base XI was prepared in the same way as described for VI by azeotropic removal of water from a mixture of 2-methyl-2-pentenal and 1-amino-2-methyl-2-propanol in 67% yield, b.p. 55° (0.15 mm), $n_D^{25} = 1.4753$, $d_4^{25} = 0.8853\text{ MR}_D$. Calcd, 51.93. Found, 53.86 (18).

Anal. Calcd. for $\text{C}_{10}\text{H}_{19}\text{NO}$: C, 70.98; H, 11.30; N, 8.28. Found: C, 71.15; H, 11.45; N, 8.53.

IR spectra: C=C, 1650 cm^{-1} ; C=N, 1638 cm^{-1} ; OH bonded, round band 3100 – 3625 cm^{-1} ; OH (tertiary), 1167 cm^{-1} .

In the n.m.r. spectra ((20%) soln. in carbon tetrachloride, W/V) the protons were identified as follows: HC=N, $2.24\ \tau$ (broad singlet); HC=C, $4.2\ \tau$ (triplet); C=N- CH_2 , $6.69\ \tau$ (singlet); OH, $7.35\ \tau$ (this proton moved 6 cps downfield by the addition of a trace of pyridine); CH_2 , $7.74\ \tau$ (triplet); $\text{CH}_3\text{C}=\text{C}$, $8.18\ \tau$ (singlet).

In the workup of the preparation of 2-ethyl-5,5-dimethyloxazolidine IX a higher boiling fraction remained after the distillation of the oxazolidine. This second fraction, b.p. 54 – 58° (0.5 mm.), $n_D^{25} = 1.4760$, proved to be an 8% yield of 2,6-dimethyl-4-aza-4,6-nonadien-2-ol (XI) by IR spectra, n.m.r. spectra, and elemental analysis.

Anal. Calcd. for $\text{C}_{10}\text{H}_{19}\text{NO}$: C, 70.98; H, 11.30; N, 8.28. Found: C, 70.72; H, 11.16; N, 8.23.

N-(1-Hydroxypropyl)-2,2-dimethylaziridine (XIII).

Ice cold 2,2-dimethylaziridine (18.4 g., 0.26 mole) was added dropwise during a period of 1.5 hours to an equimolar quantity (15 g.) of freshly distilled propionaldehyde which was also cooled to 0° . During the addition of the aziridine, the reaction mixture was stirred magnetically and the temperature was not allowed to rise above 5° . The product solidified in the flask and was allowed to stand overnight in the refrigerator. The yield of crude product was quantitative. The mass was washed with ice-cold ether and crystallized from pentane, m.p. 39 – 40° .

The analytical sample was recrystallized four times from pentane and dried over paraffin wax. The iminohydrin sublimed readily in air and was kept confined in a small space over paraffin wax. The compound could be collected on a cold finger by sublimation at 25° (55 mm).

Anal. Calcd. for C_7H_9NO : C, 65.07; H, 11.70; N, 10.84. Found: C, 64.85; H, 11.66; N, 10.51.

The IR spectra (Nujol) showed a strong band at 1735 cm^{-1} , characteristic of propionaldehyde, even on the analytically pure sample. The n.m.r. spectra (20% soln. in carbon tetrachloride W/V) showed the characteristic proton signal of propionaldehyde at 0.27τ . A broad band was also observed at 8.07τ which on addition of a trace of pyridine became sharp and moved 4 cps downfield. This observation suggests that this proton signal may either be due to NH proton of ethylenimine or due to OH proton of the iminohydrin. An attempt was made to locate the OH signal by taking the n.m.r. in benzene but only the proton signals corresponding to propionaldehyde and ethylenimine as such were obtained.

Attempted Isomerization of Iminohydrin (XIII) and Oxazolidine (III).

Ten grams (0.077 mole) of 2-ethyl-4,4-dimethyloxazolidine III dissolved in 200 ml. of dry acetonitrile was refluxed over 45 g. (0.3 mole) of sodium iodide for 12 hours under a nitrogen atmosphere after stirring for six hours at room temperature. Most of the sodium iodide was removed by filtration and the filtrate was reduced to a small volume. Addition of benzene precipitated the remainder of the sodium iodide. Solvent was removed on a rotary evaporator and the remaining liquid was fractionated in an atmosphere of nitrogen. The original 2-ethyl-4,4-dimethyloxazolidine was recovered to the extent of 70% along with 2% of the unsaturated Schiff base VI, b.p. 58° (0.1 mm). No evidence for the simpler Schiff base IV was obtained.

When isomerization was attempted on the iminohydrin XIII under the same conditions no oxazolidine (III or IX) was isolated but a high boiling fraction (19% by mass), b.p. $80-81^\circ$ (0.26 mm), $n_D^{25} = 1.4665$, containing both C=C (1650 cm^{-1}) and C=N (1635 cm^{-1}) linkages was obtained. This appears to be a mixture of (60-70%) unsaturated Schiff bases (VI and/or XI) and aziridine polymer (40-30%) from the elemental analysis. The Dumas nitrogen analysis suggests the lower figure for unsaturated Schiff base and a Van Slyke (19) method, the higher figure.

Anal. Calcd. for $C_{10}H_{13}NO$: C, 70.98; H, 11.30; N, 8.28. Calcd. for $(C_4H_5N)_x$: C, 67.55; H, 12.69; N, 19.70. Found: C, 70.59, 71.70; H, 11.55, 11.49; N, 13.23, 13.53 (Dumas), 14.55 (Van Slyke).

When a shorter time (7 hours) was used for the reflux in acetonitrile, 2-methyl-2-pentenal was identified in the reaction mixture.

Condensation of Oxazolidine (III) with Propionaldehyde.

Ten grams (0.077 mole) of 2-ethyl-4,4-dimethyloxazolidine in 50 ml. of anhydrous methanol was added to a freshly prepared solution of 0.35 g. (0.015 mole) of sodium in 150 ml. of anhydrous methanol using a nitrogen atmosphere. After stirring the solution one hour at room temperature, 4.5 g. (0.077 mole) of propionaldehyde in 50 ml. of anhydrous methanol was added dropwise during one hour. The mixture was stirred 2 hours more and then refluxed for two hours, cooled and left overnight. The solvent was removed at room temperature on a rotary evaporator and the remaining oil was extracted with 300 ml. of pentane and then with 50 ml. of benzene. Fractional distillation under nitrogen gave 2.4 g. (24%) of starting oxazolidine (b.p. $52-57^\circ$ (10 mm)) and 1.2 g. (8.5%) of 2,2,5-trimethyl-3-aza-3,5-octadien-1-ol (VI), b.p. 54° (0.12 mm). The unsaturated Schiff base was identified by comparison of refractive index, IR, and n.m.r. spectra of an authentic sample of VI.

REFERENCES

- (1) Supported in part by Public Health Service Grant CA-07521 and in part by an Academic Year Institute grant from the National Science Foundation (for K.W.).
- (2) A. C. Cope and E. M. Hancock, *J. Am. Chem. Soc.*, **64**, 1503 (1942); **66**, 1453, 1738, 1747 (1944).
- (3) L. W. Daasch, *ibid.*, **73**, 4523 (1951).
- (4) L. W. Daasch and U. E. Hanninen, *ibid.*, **72**, 3673 (1950).
- (5) E. D. Bergmann, *Chem. Rev.*, **53**, 309 (1953).
- (6) E. D. Bergmann, E. Gil-Av, and S. Pinchas, *J. Am. Chem. Soc.*, **75**, 358 (1953); E. D. Bergmann, E. Zimkin, and S. Pinchas, *Rec. trav. chim.*, **71**, 168 (1952).
- (7) J. Metzger, *ibid.*, **71**, 243 (1952).
- (7a) A referee suggested that the Schiff base (IV) may be the initial key intermediate in the following pathway: IV, A, B, C to VI. An enamine A is, indeed, a more popular precursor for the aldol $HOCH_2C(CH_3)_2NH-CH=CH-CH_3 \longrightarrow HOCH_2C(CH_3)_2N^{\ominus}-CH=CH-CH_3$ $\xrightarrow{O-CH-C_2H_5}$ $HOCH_2C(CH_3)_2N^{\ominus}-CH(O-CH-C_2H_5)-CH-CH_3$ \longrightarrow $HOCH_2C(CH_3)_2N=CH-CH-CH_3$ \longrightarrow VI $\xrightarrow{HO-CH-C_2H_5}$ VI
- type condensation than the anion of III but no evidence for enamine formation was found. We doubt that the hydrogen α to the function $-CH^{\ominus}N^{\ominus}$ in III is any less acidic than the hydrogen α to the function, $-CH=N$, which would be required for the rearrangement of IV to A as the first step in the suggested pathway. No information on this point has appeared in the literature. We cannot exclude the suggested mechanism, however.
- (8) A. M. Paquin, *Chem. Ber.*, **82**, 316 (1949).
- (9) H. W. Heine, *Angew. Chem.*, **74**, 772 (1962).
- (10) A. Dornow and W. Schacht, *Chem. Ber.*, **82**, 464 (1949).
- (11) W. J. Rouborn and W. L. Howard, *J. Org. Chem.*, **27**, 1039 (1962).
- (12) M. Lidak and S. Hiller, *Latvijas PSR Zinatnu Akad. Vestis*, No. 5, 99 (1961).
- (13) J. B. Doughty, C. L. Lazzell, and A. R. Collett, *J. Am. Chem. Soc.*, **72**, 2866 (1950).
- (14) Analyses were performed by S. M. Nagy, Microchemical Laboratory, M.I.T., Cambridge, Mass. Boiling points are uncorrected. The IR spectra were obtained with a Perkin-Elmer model 337-Spectrometer. The n.m.r. spectra were determined with a Varian Associates model HA-60 Spectrometer and the peak positions are reported in τ values relative to TMS as internal standard.
- (15) M. Hausermann, *Helv. Chim. Acta*, **34**, 1482 (1951).
- (16) R. Mecke and K. Noack, *Chem. Ber.*, **93**, 210 (1960).
- (17) H. R. Nace and B. B. Smith, *J. Am. Chem. Soc.*, **74**, 1861 (1952).
- (18) Bergmann, ref. 6, has reported an exaltation in the molar refraction of unsaturated Schiff bases over the calculated value.
- (19) D. D. Van Slyke, *J. Biol. Chem.*, **9**, 188 (1911).

Received October 3, 1966

Providence, Rhode Island 02912