firebrick; helium flow 80 cc/min] of 2-methylcyclohexanone and (+)-3-methylcyclohexanone showed minor impurities for these substances as starting materials. These impurities were no longer present in the final product.

It is recommended that the product be distilled to remove the yellow color introduced by traces of 2,4-dinitrophenylhydrazine carried over during steam distillation. In each case, gas chromatography of the crude reaction product showed the ketone to be purer than the starting material and to exhibit only a single peak.

Experimental Section

The 2,4-dinitrophenylhydrazones were prepared[11] and purified by recrystallization from ethyl acetate and mixtures of ethyl acetate and methanol.

General Procedure.—A 0.01-mole sample of 2,4-dinitrophenylhydrazone and 1.61 g (0.011 mole) of α-ketoglutaric acid[12] were added to a 1-l. two-necked flask containing 500 ml of warm 35% sulfuric acid[13] and equipped with steam inlet tube and a 12-in. Vigreux column fitted with a splash bulb. An efficient condenser mounted for downward distillation was attached to the splash bulb. The reaction flask was heated with a mantle, and steam[13] was introduced until the condensate no longer gave a positive reaction with 2,4-dinitrophenylhydrazine reagent.[14] The steam distillate was saturated with salt and extracted with 200 ml of ethyl ether in two portions; the ether was washed twice with small portions of water, dried over anhydrous magnesium sulfate, filtered, and concentrated by distillation. The concentrate was diluted to 20.0 ml with ether.

Standard solutions of ketone in ether (1, 2, and 4%) were prepared and the gas chromatographic curves (PDEAS column) of the solutions were obtained. The peak areas of these curves were plotted *vs.* concentrations of the standard ether–ketone solutions. The resulting straight-line plot was used to obtain the concentration of the steam-distilled ketone by interpolating from the peak area. The yield was calculated from these data.

Acknowledgment.—We are grateful to the Aldrich Chemical Company, Milwaukee, Wisconsin, for their contribution to this work, and to the American Petroleum Institute for some financial support. We wish to thank Dr. O. C. Dermer for having read the manuscript.

(11) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 5th ed, John Wiley and Sons, Inc., New York, N. Y., 1964.

(12) γ-Ketopimelic acid was also tried and is an excellent substitute.

(13) An earlier experiment using 20% sulfuric acid was not successful since the 2,4-dinitrophenylhydrazone was not completely cleaved. Steam distillation times varied from 20 (300 ml of condensate) to 90 min (1100 ml of condensate). The exchange rate is dependent upon the solubility of the 2,4-dinitrophenylhydrazone in the reaction mixture.

(14) A. L. Wilds, *Org. Reactions*, **2**, 200 (1944).

Ten π Electron Nitrogen Heterocyclic Compounds. V. The Site of Protonation and N-Methylation of Imidazo[1,2-*a*]pyridines and the Planarity of the Ring System

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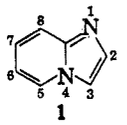
Recent publications from this laboratory have described some aspects of the chemistry of imidazo[1,2-*a*]pyridines.[1,2a] We now wish to report some studies of the protonation of this ring system and to discuss the question of planarity of the imidazo[1,2-*a*]pyridines (**1**).



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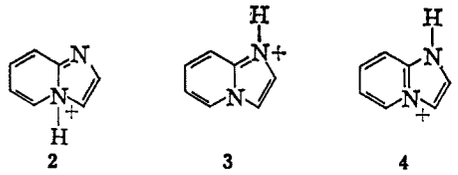
Analysis of the Nmr Spectra.—The nmr spectra of the hydrohalides and of the N-methyl derivatives of the imidazo[1,2-*a*]pyridines are considerably different from those of the free bases[1] and their analyses require some detailed discussion.

The assignment of the chemical shifts of H-2 and H-3 was made by comparing the spectra of 7-methylimidazo[1,2-*a*]pyridine hydrochloride with the 7-methyl-3-deuterioimidazo[1,2-*a*]pyridine hydrochloride (Table I).[2b] From this data it is clear that H-3 (H_E in Table I) is more deshielded than H-2 (H_F in Table I) in these compounds, while the reverse is true in the free bases.[1,2a,3–5] The assignment of the chemical shifts and coupling constants of the remaining protons now becomes relatively straightforward. It is of some interest to note the chemical shift differences between H-7 and H-8. The differences of these protons are of the same order of magnitude as the coupling constants; consequently they no longer appear as an AB pattern since the low-intensity transitions are not visible over the noise level of the instrument. It is, therefore, not possible to assign the chemical shifts of H-7 and H-8 precisely. The value reported for H-7 and H-8 in Table I is simply the center position of the apparent "doublet."

The Site of Protonation and N-Methylation in Imidazo[1,2-*a*]pyridines.—The protonation of these compounds can conceivably occur at either N-1 or N-4 to form salts of structures **2**, **3**, or **4**, or a resonance hybrid of **3** and **4**.[6]



2 **3** **4**

The most facile way of establishing the position of protonation involves the study of the nmr spectra of the salts and a comparison of these spectra with the corresponding mono-N-methyl derivatives.[7]

The imidazo[1,2-*a*]pyridines can readily be converted to their mono-N-methyl derivatives (**5** or **6**) with methyl iodide. Some studies are reported which favor methylation of N-1 for these compounds.[8]

(1) W. W. Paudler and H. L. Blewitt, *Tetrahedron*, **21**, 353 (1965).

(2) (a) W. W. Paudler and H. L. Blewitt, *J. Org. Chem.*, **30**, 4081 (1965). (b) This compound was prepared by reduction of the corresponding 3-bromo compound by the method previously described.[2a]

(3) P. J. Black, M. L. Heffernan, L. M. Jackman, Q. N. Porter, and G. R. Underwood, *Australian J. Chem.*, **17**, 1128 (1964).

(4) J. G. Lombardino, *J. Org. Chem.*, **30**, 403 (1965).

(5) J. P. Paolini and R. K. Robbins, *J. Heterocyclic Chem.*, **21**, 53 (1965).

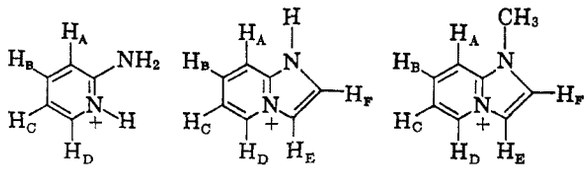
(6) Ultraviolet spectral data suggest that protonation occurs on N-1: W. L. F. Armarego, *J. Chem. Soc.*, 4226 (1964); 2778 (1965).

(7) The nmr spectra of the salts were obtained under conditions (approximately 1 *M* solutions) where the concentration of the nonprotonated species is essentially nil; thus, the comparison of the spectra of an equilibrium controlled process (hydrohalide salts in D_2O) with a nonequilibrium process (N-methylated compounds in D_2O) is tenable.

(8) A. E. Tschitschibabin, *Ber.*, **59**, 2048 (1926); *J. Russ. Phys. Chem. Soc.*, **58**, 1159 (1926).

TABLE I

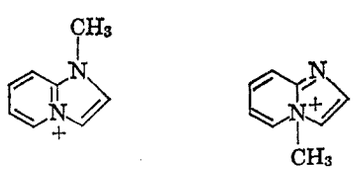
NMR SPECTRA OF THE HYDROCHLORIDES AND METHIODIDES OF SOME 2-AMINOPYRIDINES AND IMIDAZO[1,2-*a*]PYRIDINES



III IV V

Compd[a] No.	Substituent	H_A	H_B	H_C	H_D	H_E	H_F	Substituent
III	5-Methyl	2.34	3.10	...	2.22	...	...	7.78
IV	6-Methyl	2.13[b]	2.13[b]	...	1.38	1.78	1.89	7.44
V	6-Methyl	2.07[b]	2.07[b]	...	1.44	1.85	2.00	7.31 (C-CH_3)
								5.85 (N-CH_3)
III	4-Methyl	3.18	...	3.20	2.28	...	...	7.59
IV	7-Methyl[c]	2.32	...	2.67	1.42	1.93	2.10	7.38
IV	7-Methyl-3-deuterio	2.32	...	2.67	1.42	...	2.10	
V	7-Methyl	2.16	...	2.60	1.38	1.84	2.04	7.32 (7-CH_3)
								5.91 (N-CH_3)
III	4,6-Dimethyl	3.28	...	3.28	...	...	...	7.57 (4-CH_3)
								7.61 (6-CH_3)
IV	5,7-Dimethyl	2.74	...	3.02	...	2.14	2.14	7.62 (5-CH_3)
								7.44 (7-CH_3)
IV	8-Methyl	...	2.10	2.47	1.27	1.68	1.89	7.28 (8-CH_3)
V	8-Methyl	...	2.17	2.54	1.33	1.76	1.98	7.04 (8-CH_3)
								5.58 (N-CH_3)

[a] All spectra are in D_2O at 1.0 *M* concentration. The *J* values of compounds of type IV and V are essentially the same as those previously reported[1,2a] for the free bases except for $J_{2,3}$, which is 2.2 cps in these compounds. All chemical shifts are reported in τ units. [b] See text for explanation. [c] The corresponding τ values for B·HI are 2.24, 2.62, 1.38, 1.88, 2.04, and 7.35.



5 6

The proton on C-8 (H_A in Table I) in all the N-methyl compounds studied are more deshielded than in the corresponding hydrochlorides (*cf.* Table I). This is to be expected if there is *peri* interaction of the methyl group on the nitrogen atom with the proton on C-8. If the methyl group were on N-4, it would be H-5 (H_D in Table I) that is more deshielded in the methiodides, while in fact H-5 has essentially the same chemical shift in the hydrochlorides as in the methiodides.

Finally, a comparison of the nmr spectrum of the hydrochloride with that of the methiodide of 8-methylimidazo[1,2-*a*]pyridine (Table I) further confirms and strengthens the argument that methylation (and consequently protonation) occurs at N-1.

The 8-methyl group in the methiodide is considerably more deshielded in the methiodide than in the hydrochloride. This *peri* interaction is also evident in the more deshielded position of the N-methyl group in the methiodide of the 8-methylimidazo[1,2-*a*]-pyridines as compared to the other methiodides studied. We can consequently conclude that protonation and N-methylation occur at N-1.

We can now write structure **4** or a resonance hybrid of **3** and **4** for the hydrohalide salts of imidazo[1,2-*a*]-pyridines. These results are in agreement with the frontier-electron density calculations,[2] which ascribe a higher electron density to N-1 than to N-4.

The Planarity of Imidazo[1,2-*a*]pyridines.—It is of interest to study the basicities of the imidazo[1,2-*a*]-pyridines and to compare these with the basicities of the corresponding 2-aminopyridines. If a linear free-energy relationship exists between these two types of compounds, one can strongly suggest that the imidazo-[1,2-*a*]pyridines are planar or nearly so.[9] It would be quite a coincidence if the free-energy changes involved in the protonation of the two systems were the same, without involving similar structural changes of the compounds. The linearity of this relationship is clearly shown by inspection of Figure 1 and of Table II. If the imidazo[1,2-*a*]pyridines are indeed either planar, or nearly so, one would expect a substantial ring current in this molecule, thus causing deshielding of the protons

TABLE II

BASICITIES OF VARIOUS IMIDAZO[1,2-*a*]PYRIDINES AND 2-AMINOPYRIDINES

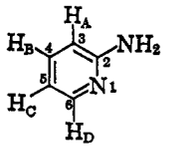
Compd	pK_a[a]	Compd no.[b]
Imidazo[1,2-*a*]pyridine	5.06	1
5-Methylimidazo[1,2-*a*]pyridine	5.55	2
6-Methylimidazo[1,2-*a*]pyridine	5.33	3
7-Methylimidazo[1,2-*a*]pyridine	5.59	4
8-Methylimidazo[1,2-*a*]pyridine	5.40	5
5,7-Dimethylimidazo[1,2-*a*]pyridine	5.96	6
2-Aminopyridine	6.14	1
2-Amino-6-methylpyridine	6.69	2
2-Amino-5-methylpyridine	6.50	3
2-Amino-4-methylpyridine	6.76	4
2-Amino-3-methylpyridine	6.52	5
2-Amino-4,6-dimethylpyridine	7.12	6

[a] In 90% ethanol–10% water, obtained by extrapolating several determinations at different concentrations, to zero concentration. [b] Compound numbers refer to those used in Figure 1.

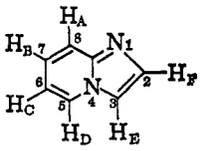
(9) Paolini and Robbins[6] have suggested that this ring system is planar, largely based on the chemical shifts of the various ring protons.

TABLE III

NMR SPECTRA OF SOME 2-AMINOPYRIDINES AND RELATED IMIDAZO[1,2-*a*]PYRIDINES



I



II

Compd		Chemical shift, τ						
No.	Substituent	H_A	H_B	H_C	H_D	H_E	H_F	Substituent
I[a]	None	2.72	3.48	3.62	1.96	...	...	...
II[a]	None	2.44	2.79	3.20	1.80	...	...	...
I[b]	5-Methyl	2.63	3.49	...	1.99	...	...	7.81
II[b]	6-Methyl	2.40	3.01	...	2.10	2.48	2.35	7.78
I[a]	4,6-Dimethyl	3.65	...	3.65	...	...	...	7.68
								7.87
I[b]	4,6-Dimethyl	3.58	...	3.76	...			7.63 (6-CH_3)
								7.81 (4-CH_3)
IIb[b]	5,7-Dimethyl	2.59	...	3.50	...	2.55	2.31	7.51 (5-CH_3)
								7.68 (7-CH_3)
I[b]	3-Methyl	...	2.67	3.35	1.97	...	...	7.88
II[b]	8-Methyl	...	3.02	3.32	1.96	2.40	2.32	7.41
I[b]	4-Methyl	3.60	...	3.50	2.04	...	...	7.76
I[a]	4-Methyl	3.52	...	3.48	2.20	...	...	7.82
II[a]	7-Methyl	2.85	...	3.54	2.08	2.48	2.43	7.80
II[b]	7-Methyl	2.64	...	3.45	2.04	2.52	2.48	7.65

[a] 1.0 *M* solution in D_2O. [b] 1.0 *M* solution in $CDCl_3$.

and of any methyl substituents on the ring. A comparison of the chemical shifts of the various protons and of the methyl groups in some imidazo[1,2-*a*]-pyridines with the "equivalent" substituents in the corresponding 2-aminopyridines (Table III) shows that almost all of the protons in the various imidazo-[1,2-*a*]pyridines are at least as deshielded as those in the corresponding 2-aminopyridines.

A comparison of the spectrum of 7-methylimidazo-[1,2-*a*]pyridine with that of the corresponding 2,3-dihydro compound (Table IV) clearly shows the contribution of the five-membered ring to the chemical shifts of H-5, H-6, H-8, and of the 7-methyl group which occurs upon introduction of the double bond into the five-membered ring. This large contribution must be partly due to the ring-current contribution of the five-membered ring. We feel that these data strongly suggest that the imidazo[1,2-*a*]pyridines are at least nearly, if not completely, planar.

A comparison of the nmr spectra of the hydrochloride salts of the 7-methyl- and 2,3-dihydro-7-methyl-imidazo[1,2-*a*]pyridines and of 2-amino-4-methylpyridine hydrochloride demonstrates the considerably enhanced aromatic character of the six-membered ring protons and of the 7-methyl group in the imidazo-[1,2-*a*]pyridine salts. Consequently, as expected, the salts of imidazo[1,2-*a*]pyridines are also at least nearly planar.

A study is currently underway which will permit some more quantitative estimates to be made regarding ring-current effects in these ten π electron nitrogen heterocyclic compounds.

Experimental Section[10]

Preparation of the Various Hydrochloride Salts.—The hydrochlorides of both the imidazo[1,2-*a*]pyridines and the substituted 2-aminopyridines were prepared by dissolving a small (weighed) amount of the free base in a slight molar excess of 0.10 *N* HCl. The resulting solutions were then freeze dried to yield fluffy white solids. The following are the melting points of the various imidazo[1,2-*a*]pyridine hydrochlorides: 6-methyl-, 145.2–149° (hygroscopic); 7-methyl-, 179–181.5°; 8-methyl-, 242–244.6°; and 5,7-dimethyl-, 284–286°.

Anal. Calcd for $C_8H_9ClN_2$: C, 56.98; H, 5.38; N, 16.62. Found for 6-methyl·HCl: C, 56.78; H, 5.60; N, 16.42. Found for 7-methyl·HCl: C, 56.69; H, 5.46; N, 16.59. Found for 8-methyl·HCl: C, 56.99; H, 5.28; N, 16.69.

Anal. Calcd for $C_9H_{11}ClN_2$: C, 59.18; H, 6.07; N, 15.34. Found for 5,7-dimethyl·HCl: C, 59.30; H, 6.17; N, 15.68.

Preparation of the Various Methiodides.—The methiodides of the imidazo[1,2-*a*]pyridines were prepared by dissolving a small weighed amount of the free base in a solution of absolute ethanol and a twofold molar excess of methyl iodide. The solution was stirred overnight and the methiodides were isolated by the addition of ether, filtration of the resulting precipitate, and finally recrystallization from ethyl acetate and absolute ethanol. The following are the melting points of the different methiodides:

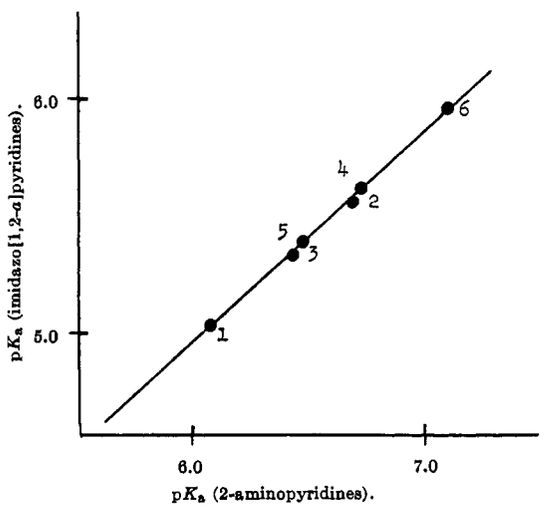
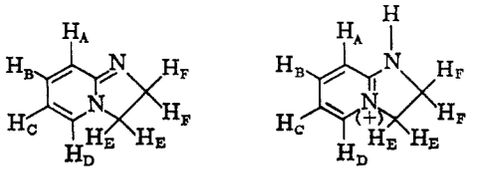


Figure 1.—Correlation of the basicities of 2-aminopyridines with the corresponding imidazo[1,2-*a*]pyridines. The numbers refer to compounds listed and numbered in Table II.

(10) Nmr spectra were obtained with a Varian A-60 spectrometer. The microanalyses were performed by Mrs. C. Warner of this department. Melting points are corrected.

TABLE IV
NMR SPECTRA OF 2,3-DIHYDROIMIDAZO[1,2-a]PYRIDINES



I II

Compd No.	Substituent	Chemical shift, τ H_A	H_B	H_C	H_D	H_E	H_F	Substituent
I[a]	7-Methyl	2.92	...	3.59	3.12	6.10[b]	6.10[b]	8.00
II[c]	7-Methyl	3.07	...	3.14	2.08	5.29	5.99	7.85

[a] $CDCl_3$ solution (1.04 *M*). [b] Broad singlet. [c] D_2O solution (1.04 *M*).

6-methyl-, 190–191.2°; 7-methyl-, 215–216°; and 8-methyl-, 288.5–289.59° dec.

Anal. Calcd for $C_9H_{11}IN_2$: C, 39.43; H, 4.04; N, 10.22. Found for 6-methyl·CH_3I: C, 39.78; H, 4.00; N, 10.41. Found for 7-methyl·CH_3I: C, 39.27; H, 3.89; N, 10.02. Found for 8-methyl·CH_3I: C, 39.40; H, 4.14; N, 10.40.

2,3-Dihydro-7-methylimidazo[1,2-a]pyridine.—A solution of 5.4 g (0.05 mole) of 2-amino-5-methylpyridine and 9.4 g (0.05 mole) of 1,2-dibromoethane in 40 ml of 95% aqueous ethanol was heated at reflux for 3 hr. To the resulting brownish red solution was then added an aqueous solution of 10.6 g (0.10 mole) of sodium carbonate in 20 ml of water and refluxing was continued for an additional 12 hr. The cooled reaction mixture was filtered and the filtrate was evaporated to about 20 ml. This solution was then extracted with three 100-ml portions of $CHCl_3$. The combined dried (anhydrous Na_2CO_3) $CHCl_3$ extracts were evaporated to dryness to leave a brown oil. Chromatography on neutral grade III alumina yields 2,3-dihydro-7-methylimidazo[1,2-a]pyridine (3.4 g) by elution with methanol–ethyl acetate (5:95). Prior to this eluent, ether eluted 0.5 g. of unreacted 2-amino-5-methylpyridine.

The material obtained from the alumina column was further purified by vacuum distillation to yield 3.2 g of the desired compound, bp 170–175° (0.5 mm).

Anal. Calcd for $C_9H_{10}N_2$: C, 71.61; H, 7.51; N, 20.88. Found: C, 71.46; H, 7.41; N, 20.59.

1,2 and 1,6 Eliminations in Substituted Xylenes

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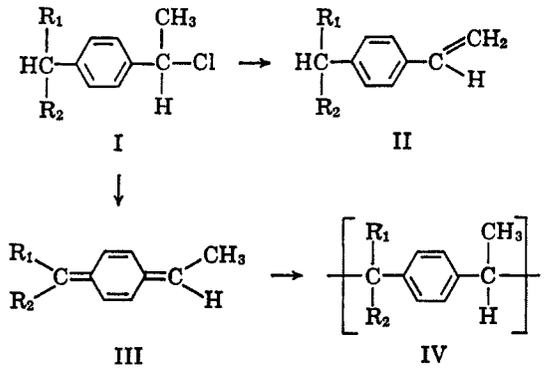
para-Substituted benzyl halides such as I are known to undergo E2 elimination[1] to produce the corresponding styrene II, but such halides can also conceivably undergo elimination by a 1,6 process to form the corresponding xylylene III. Examples of 1,6 eliminations in *p*-xylenes are known,[2-7] but in systems such as α-(*p*-tolyl)ethyl halide which can eliminate hydrogen halide by either a 1,2 or 1,6 mechanism, only the 1,2 elimination has been observed.[8] A possible synthetic modification of I which would favor 1,6 elimination



I II III IV

is the introduction of conjugated groups, R_1 and R_2, which would stabilize the xylylene III relative to the corresponding styrene II. 1,6 elimination should also be favored by factors which render the 6 proton more acidic such as adjacent cyano, carbonyl, nitro, etc., groups.

1,6 elimination at the expense of 1,2 elimination has now been observed using the systems I (R_1 = CN or COOR; R_2 = H, C_2H_5, or C_6H_5[9]) in which the protons adjacent to the group R_1 are quite acidic (pK_a of phenylacetonitrile has been reported to be 15.7 in aqueous ethylenediamine[10]). In these cases dehydrohalogenation with a base as weak as aqueous sodium hydroxide results in the formation of the intermediate xylylenes III which are isolated as high molecular weight polymers. The structures of these polymers were shown to be IV by elemental analysis, their low solubility in common solvents (unlike the corresponding polystyrenes), their high softening temperatures (again in contrast to the corresponding polystyrenes), and their infrared and nmr spectra. Although these polymers could also be formed by a stepwise substitution of the halide I by the corresponding (or polymerically equivalent) carbanion, this was shown not be of importance in the present case. Thus the reaction of I with less than stoichiometric amounts of base still

(1) H. C. Brown, I. Moritani, and Y. Okamoto, *J. Am. Chem. Soc.*, **78**, 2193 (1956).

(2) L. A. Auspos, L. A. R. Hall, J. K. Hubbard, W. Kirk, J. R. Schaefgen, and S. B. Speck, *J. Polymer Sci.*, **15**, 9 (1955).

(3) F. Johnson and W. A. Nasutavicus, *J. Org. Chem.*, **28**, 1877 (1963); A. Streitweiser and H. F. Koch, *J. Am. Chem. Soc.*, **86**, 404 (1964).

(4) H. F. Winberg, F. S. Fawcett, W. E. Mochel, and C. W. Theobald, *ibid.*, **82**, 1428 (1960).

(5) A. T. Kader and C. J. M. Stirling, *J. Chem. Soc.*, 3425 (1962).

(6) M. Szwarc, *Discussions Faraday Soc.*, **46**, (1947); M. Szwarc, *Nature*, **160**, 403 (1947); J. H. Golden, *J. Chem. Soc.*, 1604 (1961).

(7) Other literature examples such as the dehydrohalogenation of $ClCH_2C_6H_4CH_2COOCH_3$ [J. W. Baker, J. A. Brieus, and D. G. Saunders, *ibid.*, 404 (1956)] also involve the xylylene formed by 1,6 elimination (R. W. Kluiber, unpublished results).

(8) A. Klages, *Ber.*, **35**, 2245 (1902); J. Schramm, *ibid.*, **24**, 1332 (1891).

(9) R. W. Kluiber, *J. Org. Chem.*, **30**, 2037 (1965).

(10) R. Schaal, *J. Chim. Phys.*, **52**, 796 (1955).