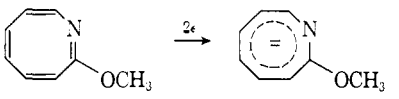
Reactions of Azocinyl Dianions with Nonenolizable Ketones and Aldehydes. Formation of 2,3-Pyridocyclobutenes[1]

Leo A. Paquette[2a] and Tsuyoshi Kakihana[2b]

Contribution from the Department of Chemistry, The Ohio State University, Columbus, Ohio 43210. *Received April 7, 1970*

Abstract: Several 2-methoxyazocinyl dianions have been treated with benzophenone and benzaldehyde to give C_6-monoalkylation products together with 2,3-pyridocyclobutene derivatives. These strained heterocyclics are formed by initial carbon–carbon bond formation at C_4, valence isomerization to a 1-methoxy-2-azabicyclo[4.2.0]-octadiene, and intramolecular 1,5-hydrogen transfer with concomitant loss of methoxide ion and aromatization. This synthetic entry to the previously unknown 2,3-pyridocyclobutene system is apparently general; for example, the action of potassium *tert*-butoxide in refluxing anhydrous tetrahydrofuran converts 3,4-dihydro-3,8-dimethyl-2-methoxyazocine in high yield to a dimethyl-2,3-pyridocyclobutene. Certain effects produced by the high degree of strain present in these fused pyridines are discussed briefly.

Earlier work has established that the species which are generated upon reaction of 2-methoxyazocines (*e.g.*, **1**) with alkali metals in liquid ammonia, tetrahydrofuran, or dimethoxyethane are the corresponding azocinyl dianions (*e.g.*, **2**).[1] Such entities are capable

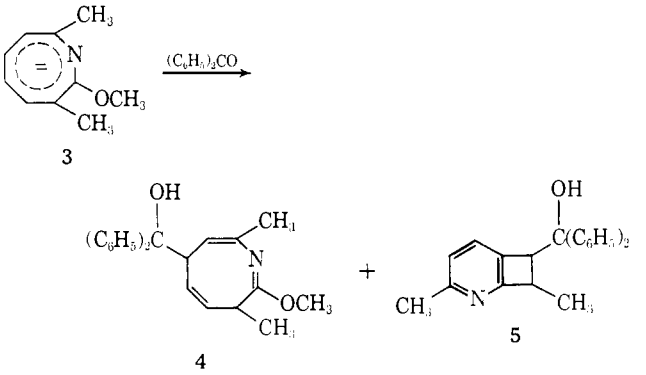


1 2

of sustaining an appreciable induced ring current (nmr studies) and are therefore decidedly aromatic. The stabilization associated with **2** has been estimated to amount to an HMO delocalization energy of approximately 90 kcal/mol relative to the classical planar azocinyl dianion.[1] Thus, when comparison is made with the cyclooctatetraenyl dianion,[3] it is seen that the introduction of a nitrogen atom into a cyclic eight-membered tetraene framework in π-equivalent fashion does not result in a disparity of π-electron conjugative properties. Although the physical properties of the two systems may be somewhat comparable, meaningful questions relating to differences in chemical behavior were still to be confronted. The striking contrasts in the electrochemical response of cyclooctatetraenyl and azocinyl radical anions have already been discussed.[4] The first information on the chemical reactivity of azocinyl dianions as derived from protonation studies was presented in the preceding paper.[1] The present investigation describes the alkylation of azocinyl dianions with benzophenone and benzaldehyde, together with the chemistry of a number of initially formed products. It was anticipated that the 3,4-, 3,6-, or 7,8-dicarbanionic nature of **2** and several of its methyl congeners would be revealed, particularly as it applies to reactions involving carbonyl groups.

Results

Upon addition of 2 molar equiv of benzophenone to an anhydrous tetrahydrofuran solution of dipotassium 3,8-dimethyl-2-methoxyazocinate (**3**) at 25°, the deep blue color characteristic of benzophenone ketyl developed immediately. This color gradually faded and gave rise during 24 hr to a dark brown reaction mixture. In a typical run, chromatography of the resulting gum on Florisil afforded in addition to recovered 3,8-dimethyl-2-methoxyazocine (7%) and benzophenone (35%) two new compounds identified as triene **4** (1.6%)



3 4 5

and 2,3-pyridocyclobutene **5** (46%). Elemental analysis showed the minor product (**4**) to have incorporated the elements of both benzophenone and hydrogen. The infrared spectrum in potassium bromide exhibits 3500 cm^{-1} hydroxyl absorption and an intense imidate peak at 1645 cm^{-1}. Its ultraviolet spectrum in ethanol is characterized by a shoulder at 243 nm (ϵ 4040) on the fringe of intense end absorption and can be considered typical of the 3,6-dihydro-2-methoxyazocinyl chromophore.[1] The nmr spectrum ($CDCl_3$) of **4** exhibits particularly significant peaks at δ 5.63 and 5.22 (d of m, J = 11.0 Hz, 1 H each, H_4 and H_5), 4.50 (d, J = 7.0 Hz, 1, H_7), 3.71–4.01 (m, 1, H_6), 3.15–3.57 (m, 1, H_3), 1.75 (s, 3, 8-CH_3), and 1.27 (d, J = 6.0 Hz, 3, 3-CH_3). Double-resonance studies confirmed that spin–spin coupling of H_3 to H_4 and H_5 was operative and ruled out any direct interaction of H_3 with H_6. From these data, **4** could be unambiguously defined as a stereoisomer of a 3,6-dihydroazocine possessing the diphenylcarbinyl alcohol function at C_6.

The major product (**5**) analyzed correctly for $C_{22}H_{21}NO$, thereby indicating loss of methanol from a structure equivalent to **4**. The infrared spectrum shows a strong hydroxyl absorption at 3330 cm^{-1}, but

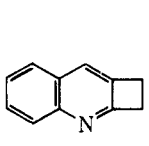
(1) Unsaturated Heterocyclic Systems. LXXVI. For the previous paper in this series, see L. A. Paquette, J. F. Hansen, and T. Kakihana, *J. Amer. Chem. Soc.*, **93**, 168 (1971).

(2) (a) To whom correspondence should be addressed; (b) Goodyear Tire and Rubber Co. Fellow, 1969–1970.

(3) T. J. Katz, *J. Amer. Chem. Soc.*, **82**, 3784, 3785 (1960).

(4) L. B. Anderson, J. F. Hansen, T. Kakihana, and L. A. Paquette, *ibid.*, **93**, 161 (1971).

lacks the band attributable to an imino ether grouping. The ultraviolet spectrum (ethanol), λ_{max} 277 (ϵ 8400), 279 sh (8250), and 287 sh nm (5550), together with intense end absorption, was reminiscent of that of pyridine derivatives,[5] although appreciably bathochromically shifted. The presence of such a newly generated heteroaromatic ring in **5** was confirmed by its nmr spectrum ($CDCl_3$) that displays, in addition to phenyl absorption (10 H) at δ 7.07–8.21, a two-proton singlet at 6.83. When account was taken of the other nmr bands, it seemed that **5** was most likely a derivative of the previously unknown 2,3-pyridocyclobutene system. In particular, the δ 3.76 absorption (d of q, J = 7.0 and 2.5 Hz, 1 H) was comparable to the chemical shift of the α-methylene protons in 1,2-dihydrocyclobuta[*b*]quinoline (**6**, δ 3.53).[6] Further structural evidence was obtained from acid-



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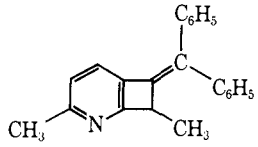

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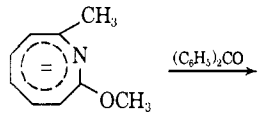
catalyzed dehydration of **5** to give **7**, $\lambda_{max}^{isooctane}$ 239 (ϵ 17,800), 276 (11,300), and 334 nm (23,600). The nmr spectrum of **7** ($CDCl_3$) shows ten benzenoid hydrogens at δ 7.15–7.64, two pyridyl ring protons at 6.97 (d, J = 7.5 Hz, 1) and 6.82 (d, J = 7.5 Hz, 1), an α-methylene proton at 4.48 (q, J = 7.0 Hz, 1), and methyl groups at 2.56 (s, 3) and 1.25 (d, J = 7.0 Hz, 3). The extension of the conjugated system incurred in passing from **5** to **7**, together with the downfield shift of the α-methylene proton, is consistent with the 2,3-pyridocyclobutene structure and inconsistent with an isomeric structure lacking either the pyridine or fused cyclobutene rings.

Dipotassium 2-methoxy-8-methylazocinate (**8**) also reacts with benzophenone, although less efficiently, to yield after hydrolysis a viscous mixture from which bis adduct **9** (6%) and pyridocyclobutene **10** (5%) could be isolated in crystalline form. From intense bands at 3450 and 1630 cm^{-1} in the infrared spectrum of **9**, the presence of hydroxyl and imidate groups could be inferred. The elemental analysis denoted that **9** embodied two diphenylcarbinyl alcohol moieties and this was confirmed by nmr analysis. Any question that the conjugation in **9** be of some type other than 3,6-dihydro was removed by comparison of the ultraviolet and nmr spectra (Experimental Section) with those of the related 3,6-dihydroazocine.[1] However, once attention is called to the presence of two protons at C_3 and the appearance of the former 8-methyl substituent as a methylene doublet (2 H, δ 2.45–2.80), it becomes structurally impossible to position the diphenylcarbinyl alcohol units other than at C_6 and the C_8 methyl group. Assignment of structure to **10** depends almost solely on rationalizing its spectra and facile dehydration to **11**. The occurrence of a gross structural change in the alkylation is attested to by the loss of the imidate functionality, by the close similarity

(5) A. I. Scott, "Interpretation of the Ultraviolet Spectra of Natural Products," Macmillan, New York, N. Y., 1964, pp 178–179.

(6) (a) M. Wilk, H. Schwab, and J. Rochlitz, *Justus Liebigs Ann. Chem.*, **698**, 149 (1966); (b) J. H. Markgraf and W. L. Scott, *Chem. Commun.*, 296 (1967); (c) J. H. Markgraf, R. J. Katt, W. L. Scott, and R. N. Shefrin, *J. Org. Chem.*, **34**, 4131 (1969).



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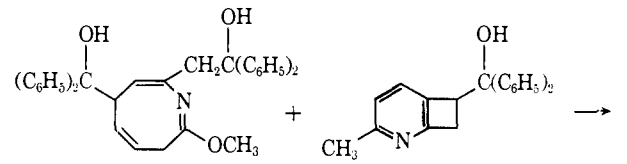
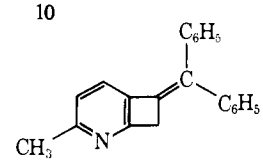


9 10



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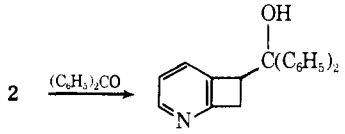
of its ultraviolet spectrum to those of **5** and other alkylated pyridines, and particularly by the relative simplicity of its nmr spectrum [$\delta_{TMS}^{CD_3COOD}$ 7.08–7.73 (m, 12, aromatic), 4.69–4.98 (m, 1, methine), 3.60–3.85 (m, 2, methylene), and 2.68 (s, 3, methyl)]. Treatment of **10** with 10% hydrochloric acid gave rise readily to **11**. Its ultraviolet spectrum reveals the introduction of added conjugation, while the nmr spectrum ($CDCl_3$) consists only of four absorptions: a ten-proton aryl peak at δ 7.24–7.51, a singlet (2 H) at 6.87 attributable to H_4 and H_5 of the pyridine ring, a singlet at 4.08 due to the α-methylene group, and a methyl singlet at 2.54.

Addition of benzophenone to dipotassium 2-methoxyazocinate (**2**) afforded **12** in 5.6% yield as the only



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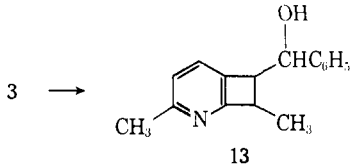
characterizable product. In contrast, attempts to condense this ketone with dipotassium 2-methoxy-3,5,6,8-tetramethylazocinate led only to reduction of the benzophenone and isolation of benzhydrol in 55% yield.

In an effort to expand somewhat on the scope of these unique transformations, **3** was treated with benzaldehyde. Addition occurred to give **13** in low

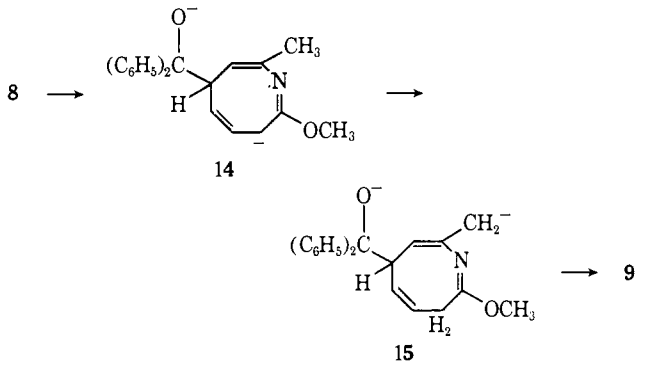


13

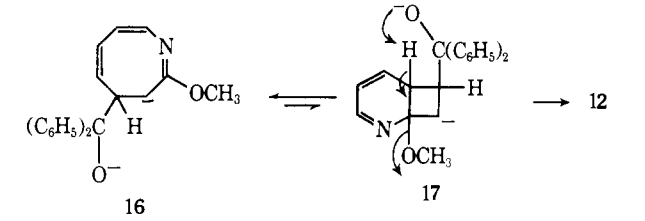
yield. The structural assignment of **13** rests on quantitative analysis, infrared absorption at 3230 cm^{-1} due to a hydroxyl group, ultraviolet maxima at 279 (ϵ 6850) and 286 sh nm (ϵ 4650) suggestive of a fused 2,3-pyridocyclobutene chromophore, and the nmr spectrum (Experimental Section).

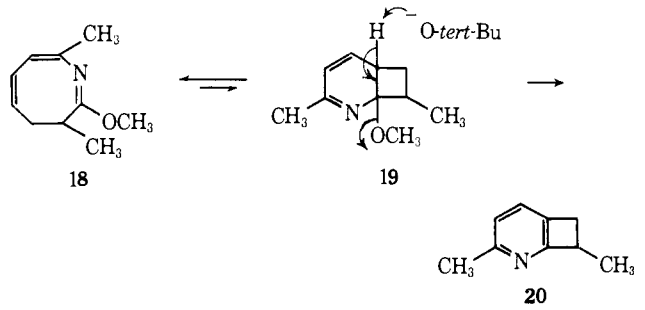
Mechanistic Considerations. With the identification of **4** and **9**, it is clear that alkylation of azocinyl dianions at C_6 is a process of some kinetic significance. Rather surprisingly, 3,6-dialkylated products analogous to

those produced from the cyclooctatetraenyl dianion[7] are not seen. In fact, **9** would appear to be the result of a proton transfer in intermediate monoanion **14** to avoid such an eventuality. Newly formed carbanion **15** then adds a second molecule of benzophenone to give **9**.



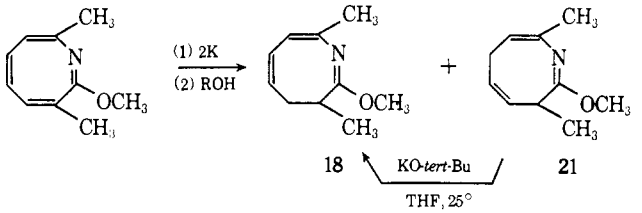
A mechanistic rationalization of the formation of 2,3-pyridocyclobutenes is based on the premise that alkylation of the azocinyl dianions at C_4 proceeds normally to afford an alkoxide (*e.g.*, **16**) which then undergoes an unusual transformation to the observed products. A reasonable pathway for the requisite loss of methanol involves valence isomerization of **16** to its bicyclic valence tautomer (**17**), followed by intramolecular 1,5-proton abstraction with concomitant ejection of methoxide ion and aromatization.[8] This proposal is consistent with the fact that 3,4-dihydro-3,8-dimethyl-2-methoxyazocine (**18**) is transformed readily in high yield to **20** when refluxed in tetrahydrofuran solution containing potassium *tert*-butoxide. Although variable-temperature nmr studies of **18** have failed to give evidence of the presence of valence tautomer **19**, it is not unreasonable that **19** is present in such small quantities that it cannot be detected spectroscopically. The passage from **19** to **20** is undoubtedly assisted by the driving force arising from the incipient aromaticity. The nmr spectrum of **20** is characterized by the presence of two pyridyl ring proton absorptions at δ 7.26 (d, J = 7.5 Hz, 1) and 6.95 (d, J = 7.5 Hz, 1), peaks for an α-methine (δ 3.77, m, 1) and two β-methylene protons (δ 3.26, d of d, J = 14.0 and 5.0 Hz, 1, 2.54, d of m, J = 14.0 Hz, 1), together with two methyl absorptions at 2.52 (s, 3) and 1.43 (d, J = 7.0 Hz, 3). The ultraviolet spectrum [$\lambda_{max}^{C_2H_5OH}$ 276 (ϵ 6760), 278 sh (ϵ 6660), and 285 sh nm (ϵ 5550)] once again testifies to the abnormal effects exerted on an electronically excited pyridine ring by fusion of a cyclobutene ring across the 2,3 positions.





The formation of 2,3-pyridocyclobutenes during the condensation of azocinyl dianions with nonenolizable ketones and aldehydes therefore appears to be an intramolecular variant of the reaction that converts **18** to **20**. The nature of the products realized in these alkylations clearly reveals that C_4 and C_6 are preferred sites of attack by the azocinyl dianions. However, because the reaction mixtures in many of the examples were dark viscous oils with the result that isolated yields of crystalline products were not high, it is conceivable that the reactivity profile remains somewhat incomplete. For this and other reasons, additional studies of the reactions of azocinyl dianions are in progress.

Additional Remarks. Attention is now turned to the facility with which 2-alkoxyazocines can be converted to the previously unknown 2,3-pyridocyclobutene system. In the particular case of 3,8-dimethyl-2-methoxyazocine, for example, reaction with 2 equiv of potassium followed by quenching of the resulting dianion with an hydroxylic proton source leads to **18** and **21**. Potassium *tert*-butoxide in tetrahydrofuran at room temperature has already been recognized to transform **21** into its more extensively conjugated counterpart (**18**).[1] At more elevated temperatures, this mixture gives **20** in high yield. It would appear from the mode of reaction of benzophenone and benzaldehyde with 2-methoxyazocinyl dianions that functionalized derivatives of the 2,3-pyridocyclobutene system are equally accessible.



Although the effects of the high degree of strain present in these fused pyridines have not been examined in detail, certain manifestations are already obvious. For example, the strain is clearly reflected in their electronic spectra in which the absorption maxima of the pyridine chromophore are shifted to higher wavelengths and are more intense than the corresponding maxima in the spectra of unstrained pyridines. An identical phenomenon is recognized in the benzocyclobutene[9] and 1,2-dihydrocyclobuta[*b*]quinoline series.[6] We have also noted that **7**, **11**, and **20** are readily extracted from 10% aqueous hydrochloric acid solutions, a fact which reveals that these substances are substantially less basic than comparable compounds lacking the fused four-membered ring. The nature

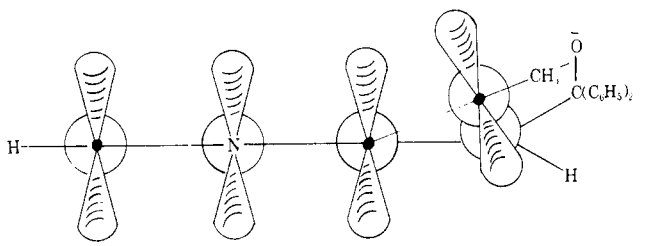
(7) T. S. Cantrell and H. Shechter, *J. Amer. Chem. Soc.*, **89**, 5877 (1967).

(8) The timing of the protonation of the carbanion in this sequence is not known. In view of the substantially diminished acidity of the α-methylene protons of **6** relative to 2-methylquinoline,[6c] however, it would appear unlikely that protonation eventuates only when water is added.

(9) M. P. Cava and D. R. Napier, *J. Amer. Chem. Soc.*, **80**, 2255 (1958); M. P. Cava, private communication.

of the abnormal hybridization changes enforced on the ring nitrogen atom because of the proximate bond angle compression becomes an attractive focus of further experimentation.

Finally, the stereochemistry of **5** and **13** is a point of some interest. The rather small coupling constant between the two cyclobutene ring protons (2.5 and 1.8 Hz, respectively) suggests that the substitution pattern is *cis*. The corresponding values for the two isomeric methylphenylbenzocyclobutenes are J_{trans} = 6.1 Hz and J_{cis} = 3.1 Hz.[10] In benzocyclobutene itself, J_{trans} = 5.0 Hz and J_{cis} = 3.5 Hz.[11] A rationalization of this stereochemical eventuality is found in the possibility that protonation of carbanion intermediates such as **22** is kinetically controlled and proceeds from the less hindered surface.



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Experimental Section[12]

Reaction of Dipotassium 3,8-Dimethyl-2-methoxyazocinate (3) with Benzophenone. To a solution of 5.0 g (30.3 mmol) of 3,8-dimethyl-2-methoxyazocine[13] in 40 ml of anhydrous liquid ammonia and 20 ml of dry tetrahydrofuran at −78° was gradually added 2.37 g (60.6 mg-atoms) of potassium metal. When the blue color persisted, the ammonia was allowed to evaporate. To the residual dark gelatinous suspension was added a solution of 11.05 g (60.6 mmol) of benzophenone and the reaction mixture immediately became deep blue. While stirring at room temperature under a dry nitrogen atmosphere for 24 hr, the mixture developed a dark brown hue. Water (100 ml) was carefully added and the organic material was extracted into three 120-ml portions of methylene chloride. The combined CH_2Cl_2 layers were dried, filtered, and evaporated to give a viscous orange oil. Chromatography of this material on Florisil (100 g) with petroleum ether (bp 30–60°) elution afforded 5.71 g of viscous yellow oil which was subjected to fractional distillation. The lower boiling fraction, bp 65° (0.15 mm), was identified as the starting azocine (0.35 g, 7% recovery); the higher boiling fraction, bp 115° (0.15 mm), gave a crystalline distillate identical with authentic benzophenone (4.50 g, 41% recovery). The distillation residue (a brown gum) was rechromatographed on Florisil (15 g). Elution with petroleum ether yielded 165 mg (1.6%) of **4** as a white solid, mp 128–129°, from hexane; ν_{max}^{KBr} 3500, 1645, 1600, 708, and 700 cm^{-1}; $\lambda_{max}^{C_2H_5OH}$ 243 sh nm (ε 4040); $\delta_{TMS}^{CDCl_3}$ 7.05–7.10 (m, 10, aryl), 5.63 (d of m, J = 11.0 Hz, 1, H_4 or H_5), 5.22 (d of m, J = 11.0 Hz, 1, H_4 or H_5), 4.50 (d, J = 7.0 Hz, 1, H_7), 3.78 (s, 3, $-OCH_3$), 3.71–4.01 (m, 1, H_6), 3.15–3.57 (m, 1, H_3), 2.52 (s, 1, –OH), 1.75 (s, 3, 8-CH_3), and 1.27 (d, J = 6.0 Hz, 3, 3-CH_3).

Anal. Calcd for $C_{25}H_{25}NO_2$: C, 79.50; H, 7.25; N, 4.03. Found: C, 79.50; H, 7.29; N, 3.94.

Continued elution of the first column with ether–petroleum ether (7:3) gave intermediate fractions containing 791 mg of a viscous gum which failed to crystallize from numerous solvents. Later fractions yielded a pale yellow resin which crystallized from ethyl acetate–hexane to deposit 4.10 g (46.2%) of **5** as colorless crystals: mp 185–186°; ν_{max}^{KBr} 3330, 1610, 1590, 705, and 690 cm^{-1}; $\lambda_{max}^{C_2H_5OH}$ 277 (ε 8400), 279 sh (8250), and 287 sh nm (5550); $\delta_{TMS}^{CDCl_3}$ 7.07–8.21 (m, 10, aryl), 6.83 (s, 2, pyridyl), 4.04 (d, J = 2.5 Hz, 1, >C*H*C(OH)<), 3.76 (d of q, J = 7.0 and 2.5 Hz, 1, α-methylene), 2.49 (s, 3, methyl), 2.31 (s, 1, –OH), and 1.23 (d, J = 7.0 Hz, 3, methyl).

Anal. Calcd for $C_{22}H_{21}NO$: C, 83.77; H, 6.71; N, 4.44. Found: C, 83.77; H, 6.76; N, 4.36.

Further elution of the column afforded only dark viscous gums.

Dehydration of 5. A mixture of 1.0 g (3.16 mmol) of **5** and 16 ml of 10% aqueous hydrochloric acid was heated at reflux for 7 hr. After cooling, the product was extracted with three 50-ml portions of methylene chloride, and the combined organic layers were washed once with water, dried, filtered, and evaporated. Recrystallization of the white crystalline residue (915 mg, 97.7%) from hexane afforded 740 mg (79%) of **7** as white prisms: mp 112–113°; ν_{max}^{KBr} 1580 and 1570 cm^{-1}; $\lambda_{max}^{isooctane}$ 239 (ε 17,800), 276 (11,300), and 334 nm (23,600); $\delta_{TMS}^{CDCl_3}$ 7.15–7.64 (two lines, 10, aryl), 6.97 (d, J = 7.5, Hz, 1, pyridyl), 6.82 (d, J = 7.5 Hz, 1, pyridyl), 4.48 (q, J = 7.0 Hz, 1, α-methylene), 2.56 (s, 3, methyl), and 1.25 (d, J = 7.0 Hz, 3, methyl).

Anal. Calcd for $C_{22}H_{19}N$: C, 88.85; H, 6.44; N, 4.71. Found: C, 88.89; H, 6.61; N, 4.66.

Reaction of Dipotassium 2-Methoxy-8-methylazocinate (8) with Benzophenone. Dianion **8** was prepared in the predescribed fashion from 1.98 g (13.3 mmol) of 2-methoxy-8-methylazocine[13] and 1.04 g (26.6 mg-atoms) of potassium. After the addition of benzophenone (4.85 g, 26.6 mmol), the mixture was stirred for 13 hr under dry nitrogen after which time water was added. Following the same work-up, the resulting mobile brown oil was chromatographed on Florisil (25 g). Elution with petroleum ether gave a viscous yellow oil which when distilled yielded 1.48 g (31% recovery) of benzophenone. Elution with ether–petroleum ether (1:2) gave in the early fractions 584 mg of a viscous semisolid, recrystallization of which from ethyl acetate and ethyl alcohol afforded 399 mg (6%) of **9** as fine white needles: mp 177–179°; ν_{max}^{KBr} 3450, 1630, and 700 cm^{-1}; $\lambda_{max}^{C_2H_5OH}$ 247 sh nm (ε 2900); $\delta_{TMS}^{CDCl_3}$ 6.75–7.47 (m, 20, aryl), 5.15–5.61 (m, 2, H_4 and H_5), 5.07 (s, 1, –OH), 4.39 (d, J = 8.0 Hz, 1, H_7), 3.63 (s, 3, $-OCH_3$), 3.31–3.69 (m, 1, H_6), 3.20 (d, J = 14 Hz, 1, H_3), 3.00 (d, J = 14 Hz, 1, H_3), 2.45–2.80 (m, 2, 8-methylene), and 2.04 (s, 1, –OH).

Anal. Calcd for $C_{34}H_{33}O_3N$: C, 81.08; H, 6.61; N, 2.78. Found: C, 81.04; H, 6.54; N, 2.75.

Continued elution with the same solvent system yielded a dark gummy semisolid, recrystallization of which from ethyl acetate gave 201 mg (5%) of **10** as a white crystalline solid: mp 219–200°; ν_{max}^{KBr} 3280, 1600, 1575, 767, 750, and 703 cm^{-1}; $\lambda_{max}^{C_2H_5OH}$ 273 (ε 8200) and 282 sh nm (5580); $\delta_{TMS}^{CD_3COOD}$ 7.08–7.73 (m, 12, aryl and pyridyl), 4.69–4.98 (m, 1, >C*H*C(OH)<), 3.60–3.85 (m, 2, α-methylene), and 2.68 (s, 3, methyl).

Anal. Calcd for $C_{21}H_{19}NO$: C, 83.69; H, 6.35; N, 4.65. Found: C, 83.45; H, 6.39; N, 4.63.

Dehydration of 10. A mixture of 377 mg (1.25 mmol) of **10** and 15 ml of 10% hydrochloric acid was heated at reflux for 7 hr. After the addition of 50 ml of water, the mixture was extracted with two 50-ml portions of methylene chloride and the combined organic layers were washed once with water, dried, filtered, and evaporated. Recrystallization of the solid residue from hexane afforded 315 mg (89%) of **11** as pale yellow plates: mp 107–108.5°; ν_{max}^{KBr} 1585, 1570, 830, 775, 750, and 700 cm^{-1}; $\lambda_{max}^{isooctane}$ 236 (ε 20,400), 244 sh (8350), 278 (15,300), and 326 nm (30,000); $\delta_{TMS}^{CDCl_3}$ 7.24–7.51 (two lines, 10, aryl), 6.87 (s, 2, pyridyl), 4.08 (s, 2, α-methylene), and 2.54 (s, 3, methyl).

Anal. Calcd for $C_{21}H_{17}N$: C, 89.01; H, 6.05. Found: C, 88.75; H, 5.91.

Reaction of Dipotassium 2-Methoxyazocinate (2) with Benzophenone. Dianion **2** was prepared in the predescribed fashion from 1.52 g (11.2 mmol) of 2-methoxyazocine[13] and 0.88 g (22.4 mg-atoms) of potassium. After the addition of 4.10 g (22.4 mmol) of benzophenone, the reaction mixture was stirred at 25° under nitrogen for 20 hr. Work-up in the usual manner afforded a somewhat mobile dark oil which was chromatographed on Florisil (30 g). Elution with petroleum ether (bp 30–60°) afforded after distillation of the combined fractions 1.47 g (36% recovery) of benzophenone. Elution with ether–petroleum ether (1:4) gave a combined yield of 1.10 g of a viscous gum which could not be crystallized; rechromatography (twice) was also unrewarding. Elution with ether–petroleum ether (1:1) gave 179 mg (5.6%) of **12** as a colorless crystalline solid, mp 162–163°, from ethyl acetate; ν_{max}^{Nujol} 3200, 1600, 770, 750, 722, and 700 cm^{-1}; $\lambda_{max}^{C_2H_5OH}$ 270 sh

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(12) All melting points were taken in open capillaries and are corrected. Infrared spectra were obtained on a Perkin-Elmer Model 137 spectrophotometer, while nmr spectra were recorded with Varian A-60, A-60A, or HA-100 spectrometers.

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(ε 6260), 274 (6350), and 280 sh nm (4660); $\delta_{TMS}^{DMSO-d_6}$ 6.53–8.32 (m, 13, aryl and pyridyl), 5.71 (s, 1, –OH), 4.44–4.77 (m, 1, >C*H*C(OH)<), and 3.22–3.58 (m, 2, α-methylene).

Anal. Calcd for $C_{20}H_{17}NO$: C, 83.59; H, 5.96; N, 4.88. Found: C, 83.40; H, 5.91; N, 4.69.

Reaction of 3 with Benzaldehyde. The dianion (**3**) was generated from 2.5 g (15.3 mmol) of 3,8-dimethyl-2-methoxyazocine and 1.2 g (30.7 mg-atoms) of potassium. To a suspension of this salt in anhydrous tetrahydrofuran (*ca.* 40 ml) was added 3.26 g (30.7 mmol) of freshly distilled benzaldehyde. A blue color did not develop in this instance. The reaction mixture was stirred at room temperature under dry nitrogen for 43 hr and evaporated to give a dark residue. Water (65 ml) was carefully added and the products were extracted with three 60-ml portions of methylene chloride. The combined organic layers were washed once with water, dried, and evaporated to afford a dark viscous oil which was chromatographed on Florisil (45 g). Elution with petroleum ether and ether–petroleum ether (1:4) yielded a viscous yellow gum (1.13 g) which resisted crystallization and further purification. Elution with ether–petroleum ether (1:1) afforded in the earlier fractions 132 mg of a colorless crystalline solid, mp 107–108° (ethyl acetate–hexane), which contained no nitrogen and was not examined further. The infrared spectrum showed peaks at 3330, 1670, 1605, and 1585 cm^{-1}. The nmr spectrum exhibited a multiplet at δ 7.26–8.29 and singlets at 4.55 and 4.45.

The later fractions contained a dark gum (705 mg). This gum and residues from the preceding recrystallization were combined and rechromatographed on Woelm neutral alumina (10 g, activity grade I). Elution with ether–benzene (7:3) gave 225 mg (6.1%) of **13**, mp 120–120.5°, from hexane; ν_{max}^{KBr} 3230, 1600, 1580, 753, and 703 cm^{-1}; $\lambda_{max}^{C_2H_5OH}$ 279 (ε 6850) and 286 sh nm (4650); $\delta_{TMS}^{CDCl_3}$ 7.64 (s, 5, aryl), 6.83 (d, J = 8.0 Hz, 1, pyridyl), 6.65 (d, J = 8.0 Hz, 1, pyridyl), 4.73 (d, J = 9.0 Hz, 1, <C*H*OH), 4.21 (s, 1, –OH), 3.63 (d of q, J = 7.0 and 1.8 Hz, 1, α-methylene), 3.18 (d of m, J = 9.0 Hz, 1, >C*H*C(OH)<), 2.41 (s, 3, methyl), and 1.45 (d, J = 7.0 Hz, 3, methyl).

Anal. Calcd for $C_{16}H_{17}NO$: C, 80.30; H, 7.16; N, 5.85: Found: C, 80.25; H, 7.12; N, 5.74.

Elution of the original column with 5% methanol in ether led to the isolation of colorless plates (210 mg), mp 124–125°, from ethyl acetate: ν_{max}^{KBr} 1690, 1630, and 1580 cm^{-1}; $\delta_{TMS}^{DMSO-d_6}$ 8.36–8.73 (series of multiplets).

Anal. Found: C, 69.30; H, 5.89.

This substance has not been identified.

Base-Induced Aromatization of 3,4-Dihydro-3,8-dimethyl-2-methoxyazocine (18). A mixture of 0.50 g (3.0 mmol) of **18**[1] and 1.12 g (19 mmol) of powdered potassium *tert*-butoxide in 10 ml of dry tetrahydrofuran was heated at reflux with stirring under anhydrous conditions for 24 hr. After cooling, water (50 ml) was added and the aqueous mixture was extracted with three 50-ml portions of ether. The combined ethereal extracts were dried, filtered, and evaporated and the residual oil was molecularly distilled. There was obtained 340 mg (85%) of **20** as a mobile colorless liquid with a penetrating odor. Vpc analysis (10% SF-96 on 60–80 mesh Chromosorb G at 145°) showed a single peak. The analytical sample was prepared by preparative scale vpc: ν_{max}^{film} 1600, 1580, and 818 cm^{-1}; $\lambda_{max}^{C_2H_5OH}$ 276 (ε 6760), 278 sh (6660), and 285 sh nm (5550); $\delta_{TMS}^{CDCl_3}$ 7.26 (d, J = 7.5 Hz, 1, pyridyl), 6.95 (d, J = 7.5 Hz, 1, pyridyl), 3.77 (m, 1, α-methine), 3.26 (d of d, J = 14.0 and 5.0 Hz, 1, β-methylene), 2.54 (d of m, J = 14 Hz, 1, β-methylene), 2.52 (s, 3, methyl), and 1.43 (d, J = 7.0 Hz, 3, methyl).

Anal. Calcd for $C_9H_{11}N$: C, 81.16; H, 8.33. Found: C, 80.80; H, 8.45.

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Reactions of Acetylimidazole and Acetylimidazolium Ion with Nucleophilic Reagents. Structure–Reactivity Relationships[1a]

David G. Oakenfull and William P. Jencks[1b]

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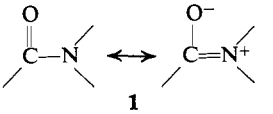
Abstract: The reactions of amines with acetylimidazolium ion exhibit a large dependence on amine basicity, $\beta = 1.0$, for amines both more and less basic than the leaving imidazole. The rapid reaction of *N*-methylimidazole with acetylimidazolium ion (and of imidazole with acetyl-*N*-methylimidazolium ion) shows that concerted proton transfer is not important in these reactions. The nucleophilic reactions with tertiary amines are inhibited by very low concentrations of added imidazole. The dependence of oxyanion reactivity upon basicity varies markedly; β values decrease with increasing basicity over the entire range from approximately 1.7 to 0. The reactions of tertiary amines with free acetylimidazole are not inhibited by imidazole and represent general base catalysis of hydrolysis; the triethylenediamine reaction exhibits a solvent deuterium isotope effect $k_{H_2O}/k_{D_2O} = 2.1$. The β values for general base catalysis of hydrolysis are 0.34 for acetylimidazolium ion and 0.55 for acetylimidazole. The β value for the nucleophilic reaction of phenolate anions with free acetylimidazole is 1.3. It is argued that the nucleophilic reactions of trifluoroethoxide ion with acetylimidazole and acetylimidazolium ion cannot proceed through a tetrahedral addition intermediate that is at equilibrium with respect to proton transfer.

In this and the following paper we describe a study of structure–reactivity relationships and mechanisms of catalysis in the reactions of a model amide, acetylimidazole, with nucleophilic reagents. Mechanistic studies on the reactions of ordinary amides are technically difficult because of the low reactivity of resonance-stabilized amides (**1**) under conditions suitable for the



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kinetic study of reactions with nucleophiles. Acetylimidazole (**2**) and its conjugate acid, acetylimidazolium ion (**3**), have a greatly enhanced reactivity because the

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