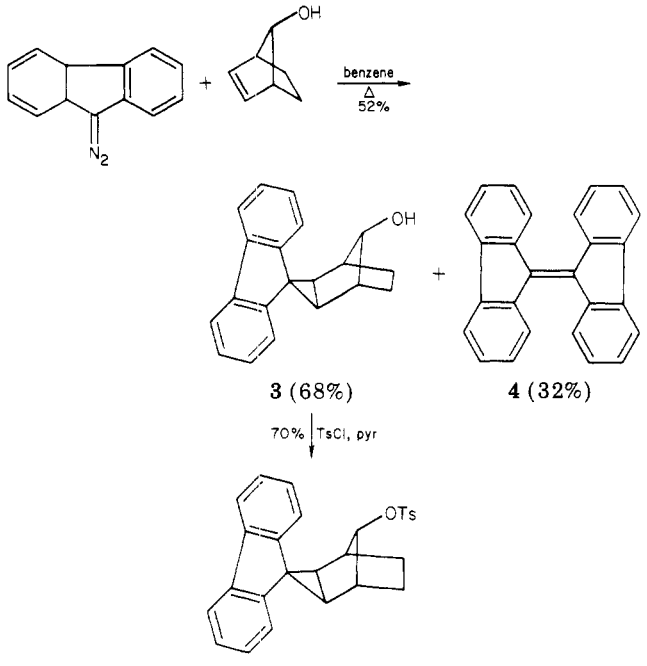
Scheme I



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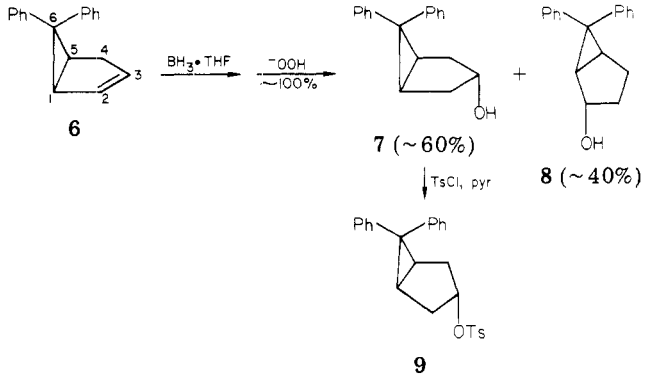
Scheme II



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Me_4Si on a Varian A-60A spectrometer. The usual splitting abbreviations are used. Sharp multiplets are given as their centers. Microanalyses were performed by Micro-Tech Laboratories.

***exo*-3,3-Fluorenylidenetricyclo[3.2.1.0^{2,4}]octan-*anti*-8-ol (3).** 9-Diazofluorene[8] (5.005 g, 24.5 mmol) was added to a solution of *anti*-7-norborneol[9] (3.371 g, 30.6 mmol) in dry benzene (30 mL). Infrared analysis of small aliquots showed little reaction at temperatures under reflux even for extended time periods (45 h). Refluxing the orange solution for 20 h did lead to reaction, however, with the IR-determined disappearance of the diazofluorene. Removal of the benzene left an orange-red solid (6.188 g). Chromatography of this dark solid on alumina (150 g) with 1:1 hexane–ether gave first an orange-red, beautifully crystalline solid identified as **bifluorenylidene** (4): 0.989 g (25%); mp 192–194 °C (from ethanol) (lit.[10] mp 194–195 °C); NMR δ 8.4 (m, H-1, -1′, -8, -8′), 7.67 (m, 4 H), 7.23 (m, 8 H). Later fractions afforded alcohol 3: 1.936 g (29%); white micrycrystalline solid; mp 189–190 °C (from benzene–petroleum ether); NMR δ 7.73, 7.27, 6.97 (3 m, ratio 3:4:1, Ar H's), 5.22 (m, H-8), 2.58 (m, H-1, -5), 1.93 (s, H-2, -4), 2.2–1.2 (br m, exo and endo H-6, -7), 1.47 (br s, OH, exchangeable); IR (KBr) ν 3600–3400, 1720, 1450, 1080 cm^{-1}. Anal. Calcd for $C_{20}H_{18}O$: C, 87.56; H, 6.61. Found: C, 87.18; H, 6.54. Tarry material remained on the column.

***exo*-3,3-Fluorenylidenetricyclo[3.2.1.0^{2,4}]oct-*anti*-8-yl Tosylate (5).** Reaction of alcohol 3 with *p*-toluenesulfonyl chloride in dry pyridine in the usual fashion[11] produced tosylate 5: 70%; white crystals; mp 182–185 °C (from benzene–hexane, 1:2); NMR δ 7.77, 7.27, 6.87 (3 m, ratio 5:6:1, Ar H's), 5.68 (sharp m, H-8), 2.67 (sharp m, H-1, 5), 2.47 (s, Ar CH_3), 1.93 (s, H-2, -4), 2.3–1.3 (br m, exo and endo H-6, -7)]. Anal. Calcd for $C_{27}H_{24}O_3S$: C, 75.67; H, 5.64. Found: C, 75.63; H, 5.62.

Solvolysis of Tosylate 5. The study was carried out on 0.0304 M tosylate 5 at 160 ± 1 °C in 80:20 (v/v) purified dioxane–water containing 2,6-lutidine as described earlier.[3] Removal of solvent from the solvolysate afforded dark, oily material with a very complex NMR spectrum. The characteristic singlet at δ 1.93 for the H-2, H-4 pair in 3 was absent, so clearly rearranged materials were formed with eventual disruption of the cyclopropyl ring. No further investigation of the products was undertaken.

6,6-Diphenylbicyclo[3.1.0]hexan-*exo*-3-ol (7). Hydroboration–oxidation of 6,6-diphenylbicyclo[3.1.0]hex-2-ene (6) was performed as reported.[6] The mixture so produced of 7 together with the isomeric *exo*-2-hydroxy alcohol 8 (ca. 3:2) was chromatographed on deactivated silica gel (60–200 mesh) as described.[6,7] Elution with ether–hexane (1:1) afforded at length a fraction rich in alcohol 7. NMR analysis using the CHOH multiplets at δ 2.87 and 4.3 for alcohols 7 and 8, respectively, indicated a ratio of 7/8 of 83.3:16.7.

6,6-Diphenylbicyclo[3.1.0]hex-*exo*-3-yl Tosylate (9). Reaction of the enriched mixture of alcohols 7 and 8 with *p*-toluenesulfonyl chloride in dry pyridine in the standard fashion[11] produced tosylate 9: 50%; white crystalline solid; mp 129.5–130 °C (upon several recrystallizations from benzene and hexane); NMR δ 7.5–7.0 (m, Ar H), 3.2 (m, H-3), 2.4 (s, Ar CH_3), 2.3–1.9 (m, H-1, -2, -4, -5)]. Anal. Calcd for $C_{25}H_{24}O_3S$: C, 74.23; H, 5.98. Found: C, 74.28; H, 5.88.

Solvolysis of Tosylate 9. Samples (0.030 M) of tosylate 9 that contained small amounts of the tosylate from alcohol 8 (~5%) were solvolyzed in dioxane–water (80:20 v/v) containing 2,6-lutidine (0.044 M) at 100, 60, and 40 °C (±0.5 °C) by using the procedure previously described.[3] The rate constants observed are given in the text. The first 5–10% of reaction was considerably faster due to the presence of the *exo*-2-tosylate. Rates for tosylate 9 were determined subsequent to the time required to consume this contaminant. The solvolysate was reduced in volume by evaporation and extracted with several portions of ether. The ether extracts were washed, dried, and stripped of solvent. Aside from minor contaminants due to the products from the *exo*-2-tosylate, the single product observed in essentially quantitative yield was olefin 6, as established by NMR comparison.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

Registry No. 3, 74808-91-6; 4, 746-47-4; 5, 74808-92-7; 6, 22524-13-6; 7, 57774-40-0; 8, 74808-93-8; 9, 74808-94-9; 9-diazofluorene, 832-80-4; *anti*-7-norbornenol, 694-70-2; *p*-toluenesulfonyl chloride, 98-59-9.

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An Unusually Selective Photochemical Reaction of a Flavin

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Photoreductive alkylation of 3-methyllumiflavin (1, 3-MLF) by β,γ-acetylenic amines has been a convenient route to model flavin compounds[1] whose structures are

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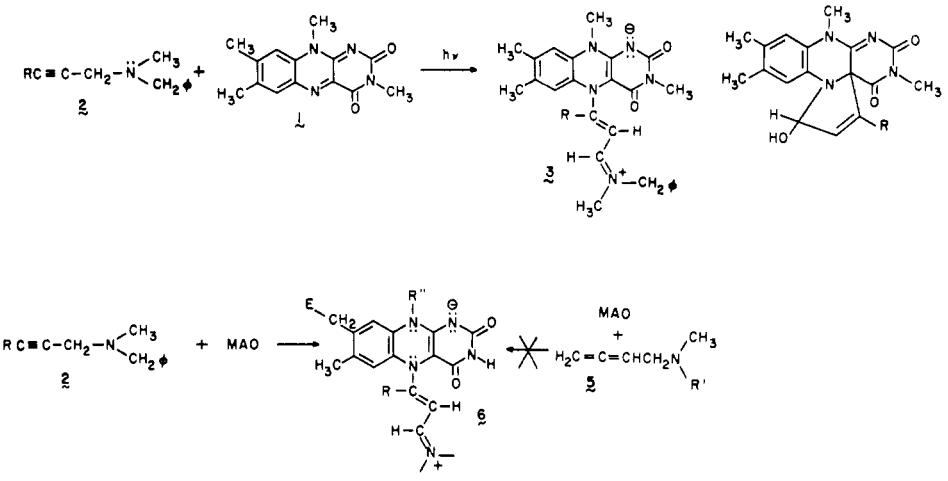
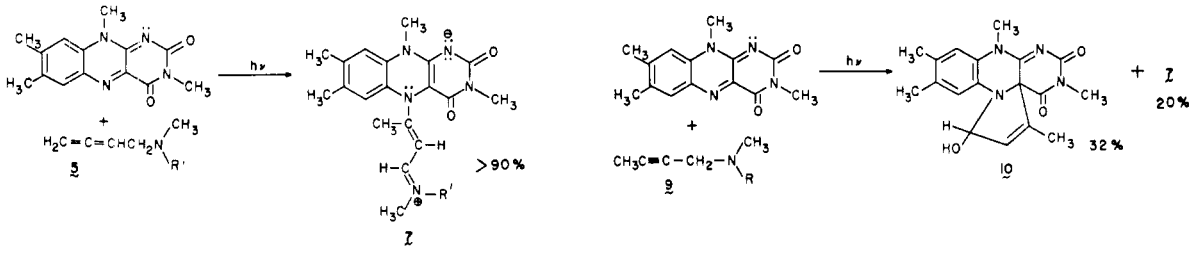
Scheme I. Similarity in Structure of Flavin Adducts 3 and 6 from Photoreaction of 3-MLF with Pargyline and Inhibition of MAO by Pargyline (2, R = H), Respectively (R'' = Ribityl-5'-phosphate-AMP residue, E = Apoprotein)



Scheme II



relevant to the products of certain flavoenzymes with acetylenic suicide inhibitors.[2-5] For example, one of the photoadducts, a flavocyanine (3, R = H) formed from 1 and the drug pargyline (2, R = H) (an antidepressant and antihypertensive agent), bears a close resemblance to the adduct between pargyline and the flavoenzyme mitochondrial monoamine oxidase (MAO, [E.C. 1.4.3.4]).[4]

Krantz[6-8] has previously reported that *N*-2,3-butadienyl-*N*-benzylmethylamine (5, R' = CH_2Ph) forms a 1:1 covalent adduct with MAO which is not a flavocyanine but has the character of a reduced (alkylated) flavin with no obvious maximal absorption above 350 nm.[9,10] In contrast, the isomeric *N*-2-butynyl-*N*-benzylmethylamine (2, R = CH_3) when treated with MAO under identical conditions forms a flavocyanine adduct 6 analogous to that observed for pargyline (see Scheme I).

In connection with the elucidation of the structure of the adduct between 5 (R' = CH_2Ph or CH_3) and MAO, we have irradiated 5 (R' = CH_2Ph or CH_3) in the presence of 3-MLF.[11] Surprisingly, the allenic amine 5 (R' = CH_3 or CH_2Ph) reacted with 3-MLF to produce flavocyanine 7 (Scheme II) in a photoreaction which was isosbestic (isosbestic points for 5, R' = CH_3, are at 411, 280, and 253 nm, Figure 1). As judged from the electronic spectra of

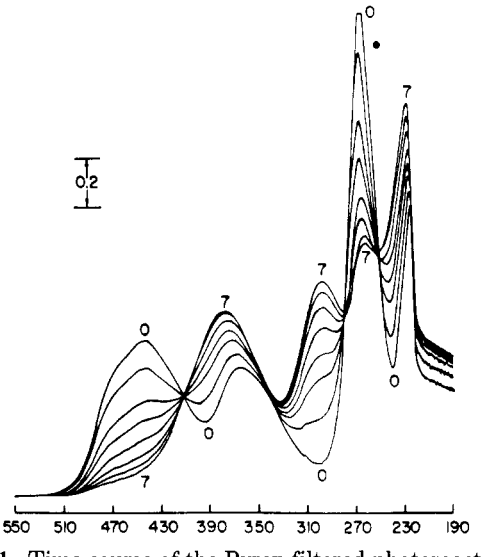


Figure 1. Time course of the Pyrex-filtered photoreaction between 3-MLF (0.5×10^{-4} M) and *N,N*-dimethyl-2,3-butadienylamine (5, R' = CH_3) hydrochloride (0.5×10^{-3} M) in 0.1 M phosphate buffer (pH 7.2) containing 20% acetonitrile. Reaction was conducted for analytic purposes in a 3-mL cuvette, irradiating through a Pyrex-filter with a 450-W mercury lamp. Spectra were recorded at 0, 0.25, 1, 2, 4, 8, 12, and 20 min of irradiation, respectively. Note isosbestic points at 412, 280, and 253 nm (*x*-axis scale is in nanometers). Similar results were obtained on a preparative scale.

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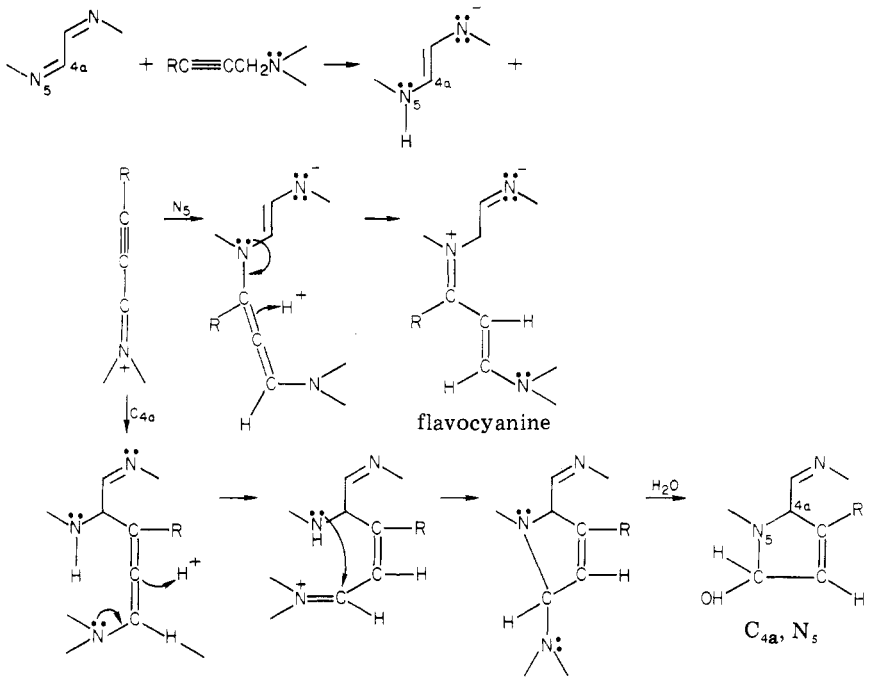
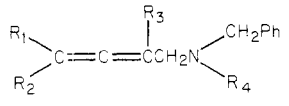
(11) The acetylenic and allenic amines 2, 5, and 9 are thermally stable in the presence of 3-MLF for days at 30 °C.

Scheme III



the products, the reaction to give flavocyanine selectively is not confined to **5** but occurs with other tertiary allenic amines (**8**, $R_1 = CH_3$, $R_2 = R_3 = H$, $R_4 = CH_2Ph$; $R_{1-3} = H$, $R_4 = CH_3CHCH_2Ph$) and with the only secondary



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amine (**8**, $R_{1-4} = H$) that was tested (but not with primary amines). With two terminal substituents on the allene (**8**, $R_1 = R_2 = CH_3$, $R_4 = CH_3$, $R_3 = H$, or **8**, $R_1 = R_2 = H$, $R_3 = R_4 = CH_3$), the product spectrum is that of a reduced flavin. Of additional interest is the observation that the photoreaction of 3-MLF with β,γ-acetylenic amine **9**, which leads to both the C_{4a}–N_5 adduct **10** and flavocyanine **7** (and minor products), gives a more complex reaction mixture than does its allenic amine isomer **5** (R′ = CH_3 or CH_2Ph).

The smooth conversion of allenic amines to a single product (>90%) with 3-MLF is unusual in the photochemistry of unsaturated amines with flavins which give mixtures resulting from attack at both the C_{4a} or N_5 positions of the isoalloxazine ring.[1] Unlike the example of β,γ-acetylenic amines, the photochemical reactions of 3-MLF with allenic amines **5** (R′ = CH_3 or CH_2Ph) give, almost exclusively, intensely absorbing flavocyanines (ca. 375 nm) and thus do not give a product that can be correlated with the allenic amine–MAO adduct (which has the spectrum of a reduced flavin).[6-8]

Although the mechanisms of both the above enzymatic and photoreactions of amines with flavins are matters of continuing research and intense controversy,[2,12] a reasonable working hypothesis can be formulated which rationalizes the formation of the known products. The primary assumption is that the enzymatic inhibition and the photoreaction resemble the turnover of substrate by enzyme in that they are all redox reactions leading to imines and reduced flavin. Hence both the C_{4a}–N_5 and flavocyanine products can be accounted for by assuming a competition

(12) Bruice, T. C. *Prog. Biorg. Chem.* **1976**, *4*, 1.

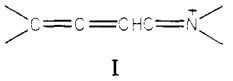
Table I. Energetics of Electron Transfer[d] from Tertiary Amines to Triplet 3-MLF (1)

$RCH_2N(R)(R_2)$	$\longrightarrow RCH_2\dot{N}^{+}(R_1)(R_2) + e$	+1.32[a]
$^3Fl\cdot$	$\longrightarrow Fl + h\nu$	−2.06[b]
$H^+ + Fl + e$	$\longrightarrow FlH\cdot$	+0.24[c]
$HFl\cdot$	$\longrightarrow \dot{F}l^{-} + H^+$	+0.44[c]
$^3Fl + RCH_2N(R_1)(R_2)$	$\longrightarrow \dot{F}l^{-} + RCH_2\dot{N}^{+}(R_1)(R_2)$	~0

[a] Guttenplan, J. B.; Cohen, S. G. *J. Am. Chem. Soc.* **1972**, *94*, 4040. [b] Sun, M.; Moore, T. A.; Song, P.-S. *Ibid.* **1972**, *94*, 1730. [c] Bruice, T. C. *Prog. Biorg. Chem.* **1976**, 1. [d] In electron volts.

between the nucleophilic C_{4a} and N_5 atoms of the reduced flavin, for the strongly electrophilic acetylenic or (allenic) immonium ion (Scheme III).

An entirely parallel path for the allenic amine involving the allenic immonium ion (I) may be written.



I

The photoredox reaction is in accord with the well-known roles of (excited) flavins[13] and amines[14-19] as one-electron acceptors and donors, respectively. The transfer

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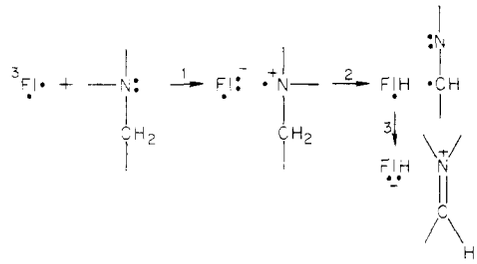
of one electron from tertiary amines to the lowest (triplet) excited state of 3-MLF is thermochemically favorable even for the formation of discrete radical cations and anions (Table I). Subsequent steps involving proton transfer within the radical pair (step 2) and electron transfer (step 3) would produce the reduced flavin–imine (redox) couple.



We speculate that the formation of distinct enzymatic and photoadducts from **5** with flavins may be traced to the forces that determine binding at the active site of the enzyme (and thus site-specific attack on the flavin prosthetic group), which are certain to be different from those forces that determine the structure of molecular complexes generated from amines and photoexcited flavins. The fact that little is known regarding the nature of such photochemical or enzymatic complexes should make this a target of future research.

Experimental Section

Melting points were determined in open glass capillaries with a Thomas-Hoover Uni-Melt apparatus and are uncorrected. IR spectra were recorded with a Perkin-Elmer Model 727 spectrophotometer. NMR spectra were recorded with Varian Associates EM-360 and HFT-80 instruments and a Bruker 360-MHz spectrometer, using tetramethylsilane as the internal standard.

Photolyses of 3-Methyllumiflavin with Amines (5, R′ = CH_3) and 9. Typically, 3-methyllumiflavin was irradiated with Pyrex-filtered light in the presence of a tenfold excess of amine (0.5×10^{-3} M) in 20% acetonitrile–80% (0.1 M) phosphate buffer, pH 7.2, under argon, and the reaction mixture was worked up according to Gärtner.[1] With *N,N*-dimethyl-2,3-butadienylamine (**5**, R′ = CH_3), we obtained >90% yields (conversions range from 80–90%) of a yellow brown powder which was characterized as 5-[3-(dimethylimino)-1-methylpropenyl]-3-methyl-1,5-dihydrolumiflavin betaine (**7**): mp 207–210 °C dec; NMR ($CDCl_3$) δ 2.22 (3 H, s) and 2.28 (3 H, s) (7,8-CH_3), 2.36 (3 H, s, 1′ CH_3), 2.94 (3 H, s, 10-NCH_3), 3.28 (3 H, s, 3-NCH_3), 3.34 (3 H, s) and 3.39 (3 H, s) ($N(CH_3)_2$), 5.27–5.42 and 5.75–5.89 (br, 2′-H, two olefinic resonances split in a ratio of 2:1), 6.82 (1 H, br s, 9-H), 6.97 (1 H, br, 6-H), 7.53 (1 H, d, $J_{2,3}$ = 12 Hz, 3′-H); UV λ_{max} (ε, mM^{-1} cm^{-1})($CHCl_3$) 413 nm (13.0), 313 (12.6); UV (CH_3OH) 387 nm (16.6), 301 (15.3); UV [pH 7.2 (phosphate buffer)] 374 nm (17.3), 299 (15.8); UV [pH 2.0 (HCl)] 368 nm (19.0), 299 (12.7); UV (CF_3CO_2H) 368 nm (19.0), 299 (12.7); IR ($CHCl_3$) ν_{max} 1640 cm^{-1} (2,4-C=O); pK_a = 4.9. The solvent dependence of the electronic spectrum of **7** is very typical of flavocyanines,[1-3] as is the value of the pK_a. Whereas **5** (R′ = CH_3) gives almost exclusively the flavocyanine **7** (80% aqueous acetonitrile, pH 7.2, 0.1 M phosphate buffer; Figure 1), the irradiation of 3-MLF with the isomeric acetylenic amine, *N,N*-dimethyl-2-butynylamine (**9**, R = CH_3) under essentially identical conditions gives two major isolable photochemical products, the flavocyanine **7** in 20% yield and, following Hemmerich,[1] 1-hydroxy-3,5,8,10,11-pentamethyl-1*H*,8*H*-benzo[*g*]pyrrolo[2,1-*e*]pteridine-4,6-dione (**10**): 32%; yellow crystals (ether); mp 194 °C; NMR ($CDCl_3$) δ 1.79 (3 H, s, 3-CH_3), 2.19 (6 H, s, 10,11-CH_3), 3.27 (3 H, s, NCH_3), 3.57 (3 H, s, NCH_3), 4.47 (1 H, disappears in D_2O, d, $J_{1,OH}$ = 11.6 Hz, 1-OH), 5.60 (1 H, d, collapses with D_2O, 1-H), 5.84 (1 H, s, 2-H), 6.72 and 6.99 (2 s, 2 H, 9,12-H); IR ν_{max} ($CHCl_3$) 1665 (6-C=O), 1705 (4-C=O), 3450 (1-OH) cm^{-1}; UV λ_{max} (ε, mM^{-1} cm^{-1}) (CH_3OH) 368 nm (4.0), 300 (sh, 5.7), 279 (13.0), 234 (17.3), 214 (20.0).

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Registry No. **1**, 18636-32-3; **5** (R′ = CH_3), 42574-40-3; **7**, 74592-22-6; **9** (R = CH_3), 14731-37-4; **10**, 74592-23-7.

A New Route to the Acridizinium Ion[1]

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Received May 29, 1980

The acridizinium (benzo[*b*]quinolizinium) ion (**4a**)[2,3] has been of interest because of its ability to react with alkenes to form cycloadducts,[4-6] some of which have proved to be of importance as synthetic intermediates.[5,7,8] With the exception of a few 6-alkyl derivatives,[9] all acridizinium salts have been prepared by the acid-catalyzed cyclization of 1-benzyl-2-formyl- (or acyl-) pyridinium salts (**3**) or a suitable carbonyl derivative[10] of these. To date the most severe limitations of this method have been those imposed by steric hindrance. For example, the reaction of benzyl bromide (**1**) for 1 month with the acetal of 6-methyl-2-formylpyridine (**2c**) followed by hydrobromic acid catalyzed cyclization of the resulting salt (**3c**) afforded only a 9% yield of the expected 4-methylacridizinium salt (**4c**).[10]

The discovery by Parham et al.[11] that *o*-bromobenzyl chloride will undergo selective bromine–lithium exchange with butyllithium at −100 °C opened the possibility for another approach to the synthesis of the acridizinium ion. If the carbinol (**6**) to be expected from the reaction of *o*-lithiobenzyl chloride (**5**) with pyridine-2-carboxaldehyde or the corresponding ketone (**2**) could be obtained, it might, on heating, afford an 11-hydroxy-6,11-dihydroacridizinium salt (**7**) (Scheme I). While no such salt had ever been isolated, it is clear from much earlier observations[12] that compounds similar to **7** must be formed in the transformation **3** → **4** and would undergo transannular dehydration in hydrobromic acid.

The major problem faced in applying the new synthesis was that the reaction of *o*-lithiobenzyl chloride with al-

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(3) Bradsher, C. K. *Acc. Chem. Res.* **1969**, *2*, 181.
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