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# Studies on Quinolizinium Salts. IX.[1] Ring-Opening Reactions of Benzo[*a*]- and Benzo[*c*]quinolizinium Bromides[2] with a Grignard Reagent and Geometrical Determinations of the Resultant Butadienes

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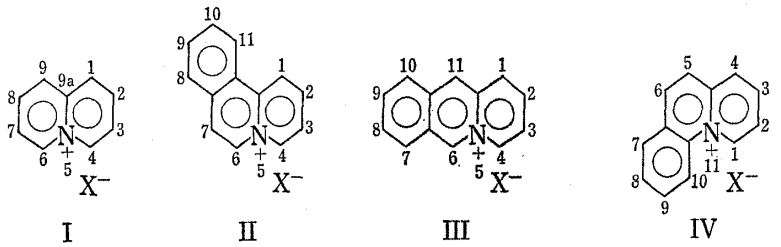
Benzo[*c*]- and benzo[*a*]quinolizinium bromides (X and XIII) were reacted with phenylmagnesium bromide in order to examine their chemical reactivities. Ring opening reactions occurred with preferential attack of the nucleophile at C-1 for X and C-4 for XIII to give phenylbutadienylquinoline (XII) and isoquinoline (XV), respectively. In connection with the structural determination of XII and XV, the nuclear magnetic resonance spectra of phenylbutadienylpyridine derivatives (VII and its derivatives) were compared with calculated spectra. The calculated band positions and intensities of the olefinic protons are in accord with the observed values.

**Keywords**——benzo[*a*]quinolizinium; benzo[*c*]quinolizinium; Grignard reaction; ring-opening reaction; butadienyl compound; quinoline derivative; isoquinoline derivative; calculated NMR spectra; NMR; geometrical determination

Previous papers described nucleophilic reactions of quinolizinium ion (I) involving the formations of butadienylpyridines,[4] quinolizines[5] and quinolines.[6] In an extension of our studies on the ion(I), the title compounds, benzologs of I, were studied in reactions with a nucleophile in order to examine their chemical behavior.

The two benzoquinolizinium salts (II and IV) are structurally isomeric with the benzo[*b*]quinolizinium salt (III) and the three salts have been all synthesized.[7] Although the



I II III IV

Chart 1

1) Part VIII: T. Miyadera and R. Tachikawa, *Tetrahedron*, **25**, 5189 (1969).
2) T. Miyadera and R. Tachikawa, Abstracts of papers, The 89th Annual Meeting of Pharmaceutical Society of Japan, Nagoya, April, 1969, p. 293.
3) Location: *1-2-58 Hiromachi, Shinagawa-ku, Tokyo.*
4) T. Miyadera, E. Ohki, and I. Iwai, *Chem. Pharm. Bull.* (Tokyo), **12**, 1344 (1964).
5) T. Miyadera and Y. Kishida, *Tetrahedron Lett.*, **1965**, 905; *idem*, *Tetrahedron*, **25**, 395 (1969).
6) T. Miyadera and R. Tachikawa, *Tetrahedron*, **25**, 837 (1969).
7) C.K. Bradsher and L.E. Beavers, *J. Am. Chem. Soc.*, **77**, 4812 (1955); C.K. Bradsher, T.W. Solomons, and F.R. Vaughan, *J. Org. Chem.*, **25**, 757 (1960); E.E. Glover and G. Jones, *J. Chem. Soc.*, **1958**, 3021; A. Fozard and C.K. Bradsher, *J. Org. Chem.*, **31**, 2346 (1966).

nucleophilic and electrophilic reactions of III[8] and IV[9] have been investigated in some detail, little information is available on the chemical reactions of II. Benzo[*b*]quinolizinium bromide (VIII) is known to react with a variety of nucleophiles affording 6-substituted-6H-benzo[*b*]quinolizines (*i.e.*, 6-phenyl-6H-benzo[*b*]quinolizine (IX) from VIII and phenylmagnesium bromide[10]), ring-opened products[11] and benzo[*b*]quinolizine derivatives.[1,12] The quinolizine ring of the benzo[*b*]quinolizine system is so stabilized by the fused benzene ring that the Grignard reaction product could be isolated without ring opening.[10] The parent 4H-quinolizine[5] and its 4-substituted derivatives (VI)[4] are considered to be transient intermediates in the nucleophilic reactions of I. One of our interests in this study was whether or not the quinolizine rings of the benzo[*a*]- and benzo[*c*]quinolizine systems are stabilized by the fused benzene ring to such an extent that they can be isolated. From this point of view benzo[*a*]- and benzo[*c*]quinolizinium bromides (X and XIII) were reacted with phenylmagnesium bromide and found to undergo ring-opening reactions analogous to quinolizinium bromide. In connection with geometrical determination of the resultant dienes, a nuclear magnetic resonance (NMR) study was also made on the 1,3-butadienyl compounds (VII and its derivatives) previously obtained.[4,6,13]

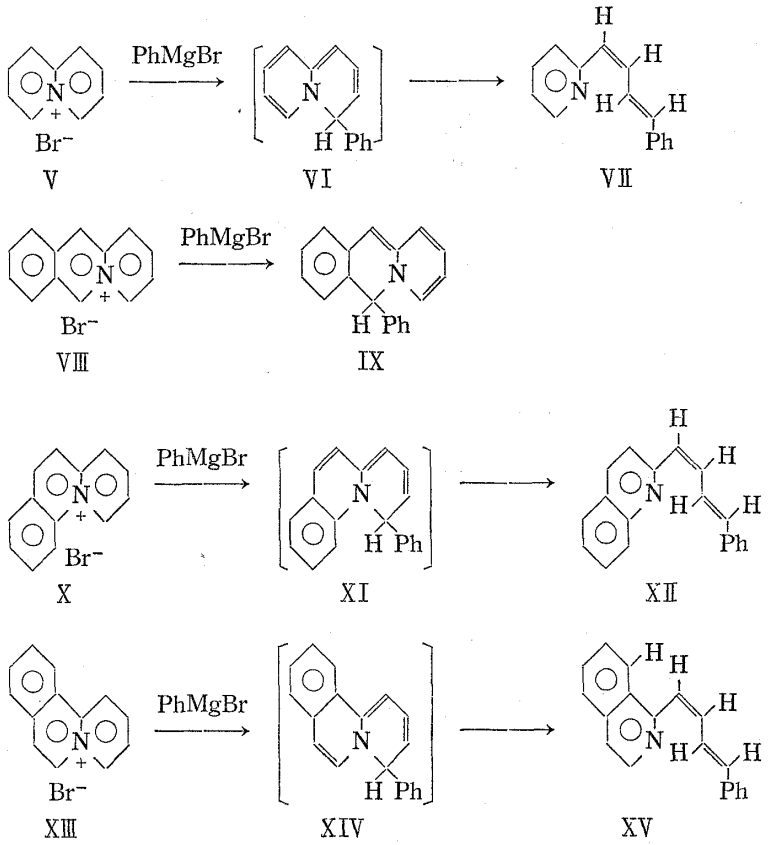



Chart 2

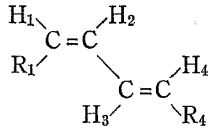
Treatment of X with excess phenylmagnesium bromide yielded XII as yellow crystals with the formula, $C_{19}H_{15}N$. On catalytic hydrogenation over palladium-charcoal the Grignard

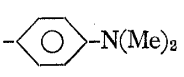
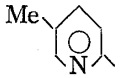
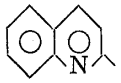
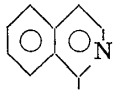
8) C.K. Bradsher, *Accounts Chem. Res.*, **2**, 181 (1969), references cited therein.
9) A. Fozard, L.S. Davies, and C.K. Bradsher, *J. Chem. Soc.*, **1971**, 3650; D. Mörler and F. Kröhke, *Ann. Chem.*, **744**, 65 (1971).
10) C.K. Bradsher and J.H. Jones, *J. Am. Chem. Soc.*, **81**, 1938 (1959).
11) C.K. Bradsher and J.P. Sherer, *J. Org. Chem.*, **32**, 733 (1967).
12) C.K. Bradsher and N.L. Yarrington, *J. Org. Chem.*, **25**, 294 (1960).
13) T. Miyadera, *Chem. Pharm. Bull.* (Tokyo), **13**, 503 (1965).

reaction product afforded 2-[1-(4-phenylbutyl)]quinoline with the consumption of two mol-equivalents of hydrogen. The structure of the hydrogenation product was determined on the basis of its NMR spectrum and analytical data. The structure of XII was conclusively determined by comparison of calculated and observed NMR spectra, although the signals of the olefinic protons could not be explained by first-order analysis.

Benzo[*a*]quinolizinium bromide (XIII) when similarly reacted with phenylmagnesium bromide gave XV as pale yellow crystals. The product was catalytically hydrogenated to 1-[1-(4-phenylbutyl)]isoquinoline with the consumption of two mol-equivalents of hydrogen. The NMR spectrum of XV reveals olefinic proton signals markedly different from those of VII and XII, some of which are overlapping with aromatic proton signals. In this diene, however, a first order analysis was possible by double resonance technique and olefinic protons were assigned as follows. If the Grignard reaction product is a 1-*cis*-3-*trans* butadiene as is the case with VII and XII, the C-3 H of the butadiene should be the most deshielded as compared with the other olefinic protons. A quartet appearing at 7.90 ppm in the decoupling experiment, overlapping with aromatic proton signals, was assigned to the C-3 H. The C-1 and C-4 protons appeared as a doublet at 7.10 ppm ($J$=11 Hz) and 6.79 ppm ($J$=15.7 Hz), respectively, and the C-2 H as a triplet at 6.77 ppm ($J$=11 Hz). It is reasonable that the C-1 H appears at a much lower field, compared with those of VII and XII, since it may be more deshielded by the benzene ring of the isoquinoline on the assumption that the proton is located as shown in the structure XV. The C-1 H should be out of the plane of the quinoline ring because of the non-bonded interaction with the C-8 H of the quinoline. The computed band positions and intensities were all in accord with the observed values (Table I).

Table I. NMR Parameters[a] of 1,4-Disubstituted-1-*cis*-3-*trans*-butadienes



| $R_1$ | $R_4$ | Solv. | $H_1$ | $H_2$ | $H_3$ | $H_4$ | $^3J_{12}$ | $^3J_{23}$ | $^3J_{34}$ | $^4J_{13}$ | $^4J_{24}$ | $^5J_{14}$ | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
|  |  | $CDCl_3$ | 6.383 | 6.512 | 8.293 | 6.726 | 11.7 | 11.2 | 15.7 | −1.0 | −0.9 | 0.6 | VII |
|  |  | $CDCl_3$ | 6.263 | 6.499 | 8.078 | 6.671 | 11.3 | 11.2 | 15.3 | −1.0 | −0.7 | 1.0 | |
|  |  | $CDCl_3$ | 6.376 | 6.479 | 8.244 | 6.710 | 11.5 | 11.1 | 15.6 | −0.9 | −0.9 | 0.8 | |
|  |  | $CDCl_3$ | 6.524 | 6.633 | 8.588 | 6.783 | 11.1 | 10.5 | 15.7 | −0.5 | −0.9 | 0.7 | XII |
|  |  | $CDCl_3$ | 7.100 | 6.765 | 7.902 | 6.788 | 11.2 | 11.7 | 15.7 | −1.0 | −0.9 | 0.6 | XV |
| COOMe | COOMe | $CDCl_3$ | 5.95 | 6.68 | 8.40 | 6.12 | 11.6 | 11.6 | 16.6 | ±0.9 | ±0.7 | ±0.7 | *b*) |

*a*) Chemical shifts and coupling constants are given in ppm and Hz.
*b*) J.A. Elvidge and P.D. Ralph, *J. Chem. Soc.* (*C*), **1966**, 387.

The Grignard reactions of X and XIII indicated that the nucleophilic attack occurred preferentially at the C-1 and C-4 position, respectively, affording XII and XV possibly through the quinolizine intermediates (XI and XIV). Both XI and XIV seem to be readily isomerized to the butadienes (XII and XV), while the tetramethoxycarbonyl derivatives derived from dimethyl acetylenedicarboxylate and quinoline or isoquinoline are known to be stable.[14]

14) R.M. Acheson, "Advances in Heterocyclic Chemistry," Vol. 1, ed. by A.R. Katritzky, Academic Press, New York and London, 1963, p. 125.

## Calculated and Observed NMR Spectra of 1,3-Butadienyl Compounds

The butadiene geometry previously assigned to VII was not entirely based on the NMR spectrum because of difficulty in explaining it by first order analysis. However, calculations involved in making geometrical assignments for the butadienes in this study provide insight into various geometrical problems. To this purpose, the chemical shifts and coupling constants of the butadienyl protons of VII and related compounds were obtained by calculation and compared with observed spectra.

Fortunately all olefinic proton signals of VII appear with complete resolution from phenyl and pyridyl proton signals, while the *trans-trans* isomer shows a spectrum much more difficult to analyze (Fig. 1b). The NMR spectrum of VII is given in Fig. 1a. A double doublet with a further small split at 8.30 ppm can be ascribed to the C-3 H of the butadiene, since it should be most deshielded under the influence of the two aromatic rings, although the molecule may not have coplanarity. Such a marked downfield shift was not observed in the NMR spectrum of the *trans-trans* isomer in which the C-3 H resonates above 7.7 ppm. The olefinic pro-

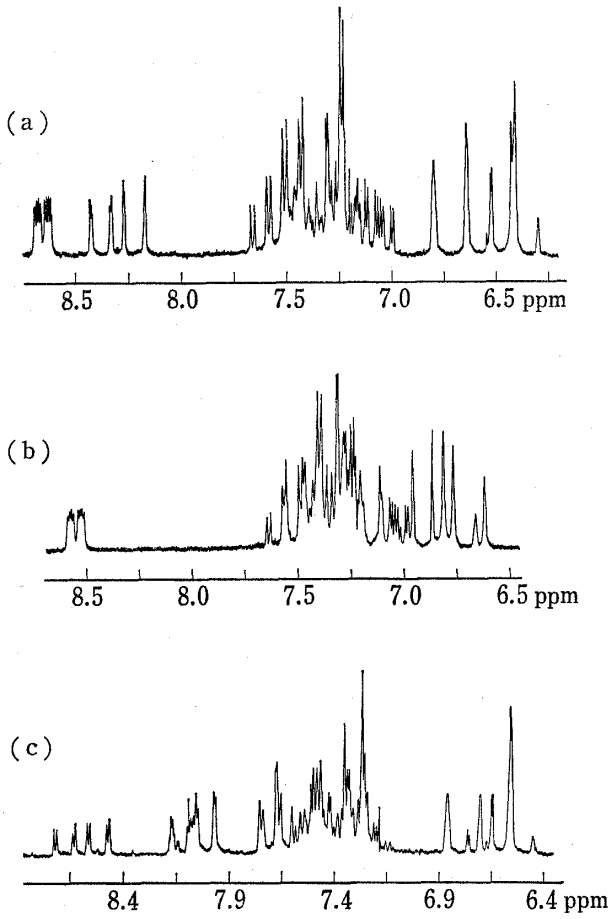



Fig. 1. NMR Spectra (100 MHz) of 1,4-Disubstituted-1,3-butadienes in $CDCl_3$ (4.1 mol %) at 32°

(a) 2-(4-phenyl-1-*cis*-3-*trans*-butadienyl)pyridine (VII);
(b) 2-(4-phenyl-1-*trans*-3-*trans*-butadienyl)pyridine;
(c) 2-(4-phenyl-1-*cis*-3-*trans*-butadienyl)quinoline (XII).

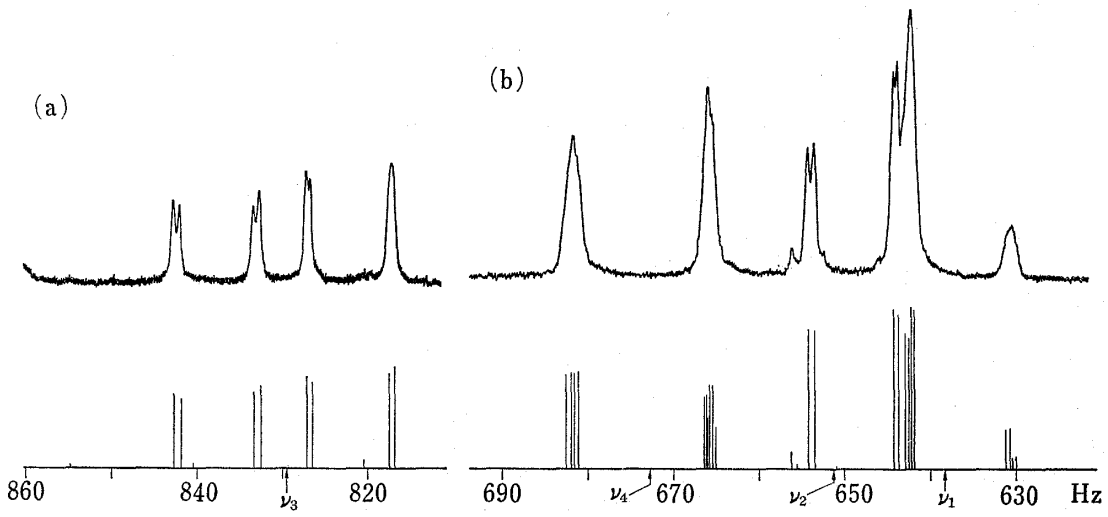



Fig. 2. Calculated and Observed Spectrum of the Olefinic Protons of VII in $CDCl_3$ (4.1 mol %) at 32°, with Lines Assigned to: (a) C-3 H; (b) C-1 H, C-2 H, C-4 H

The abscissa is in Hz at 100 MHz with respect to internal tetramethylsilane. The calculated and observed (recorded with 100 Hz/1000 sec) spectrum are not on the same intensity scale.

ton signals of VII were analyzed by calculations in accordance with the observed spectrum within experimental errors as shown in Fig. 2. The large ($J$=16.0 Hz) and moderate coupling constants ($J$=12.0 and 10.0 Hz) indicate that VII should have a *cis-trans* geometry excluding *cis-cis* and *trans-trans* structures. These coupling constants are comparable to those ($J_{\alpha\beta}$=$J_{\beta\gamma}$=11.6 Hz, $J_{\gamma\delta}$=16.6 Hz) of dimethyl *cis*($\alpha\beta$)-*trans*($\gamma\delta$)-muconate (Table I) in which $\gamma$-proton is extremely deshielded by the esters appearing at 8.40 ppm. The four olefinic protons show fine structures as the results of C-1H-C-3H and C-2H-C-4H couplings. The observed signals of the C-1 H and C-4 H are broader than those of the other two olefinic protons (Fig. 2 and Fig. 3) probably due to long range coupling with the aromatic protons. Line broaden-

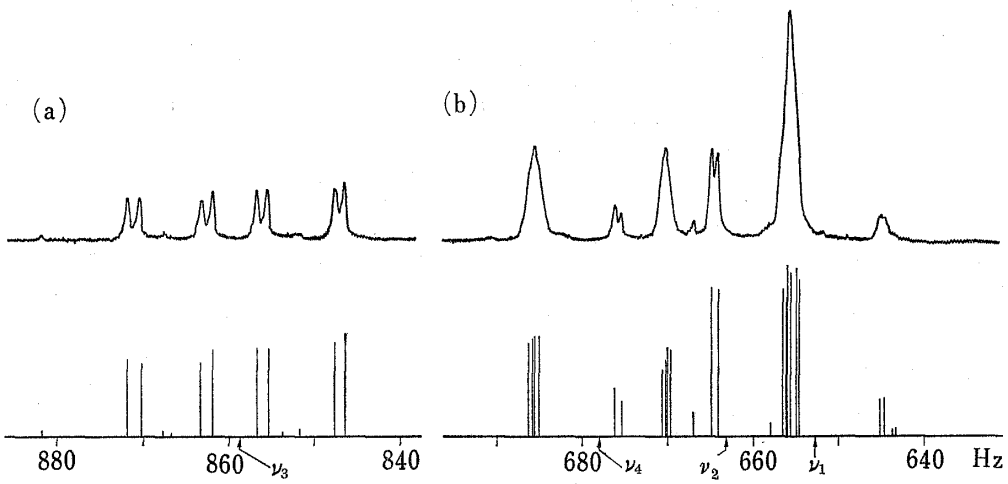



Fig. 3. Calculated and Observed Spectrum of the Butadienyl Protons of XII in $CDCl_3$ at 100 MHz, with Lines Assigned to: (a) C-3 H; (b) C-1 H, C-2 H, C-4 H

ing was an obstacle in enhancing the accuracy of the final parameters. Long range coupling between C-1 H and C-4 H is obscure, probably because of long range coupling with aromatic protons, but the half-band width of the two proton signals, 1.6—1.8 Hz, suggests the presence of a small long range coupling. The other butadienylpyridines previously obtained show some differences in spectra depending upon the chemical shifts of the olefinic protons. The introduction of a substituent on the pyridine and phenyl rings changes the spectral pattern of butadiene protons as is seen in the NMR spectra of methyl and *p*-dimethylamino derivatives. The chemical shifts and coupling constants of the olefinic protons of these derivatives are summarized in Table I. The calculated spectra are in agreement with the observed olefinic proton signals.

On the basis of the above-mentioned spectral studies the geometry of XII was similarly proved to be a 1-*cis*-3-*trans*-butadiene. The olefinic proton signals of XII are completely resolved from the aromatic proton signals as shown in Fig. 1c. The similarity of the spectral patterns of VII and XII indicates that both butadienes have the same geometry of 1-*cis*-3-*trans*. The chemical shifts and coupling constants of the butadiene protons of XII are given in Table I.

## Experimental

Melting points were uncorrected. Proton magnetic resonance spectra were recorded on a Varian A-60D and HA-100 spectrometer. Resolution for proton spectra of the HA-100 was about 0.2 Hz. The line positions were determined by a Hewlett Packard 5512A frequency counter suited for HA-100 system. Analysis was achieved with the aid of the FORTRAN programs NMRIT/NMREN[15] on an IBM 360 model 75 computer system.

15) R.C. Fergason and P.W. Marquardt, *J. Chem. Phys.*, **41**, 2087 (1964); J.A. Elvidge and P.D. Ralph, *J. Chem. Soc.*, (*C*), **1966**, 387; A.A. Bothner-By and R.H. Harris, *J. Am. Chem. Soc.*, **87**, 3445 (1965).

**Reaction of Benzo[*c*]quinolizinium Bromide (X) with Phenylmagnesium Bromide**——To a solution of phenylmagnesium bromide prepared from bromobenzene (3.14 g) and Mg (0.486 g) in tetrahydrofuran (40 ml) was added the powdered bromide (X, 1.3 g) with stirring at room temperature. After stirring for 2 hr, the mixture was cooled in ice-water and a cold aq. $NH_4Cl$ was added. The product was extracted with ether and the extract was washed and dried over anhydrous $Na_2SO_4$. The solvent was evaporated *in vacuo* and the residue was chromatographed on silica gel eluting with benzene to give 2-(4-phenyl-1,3-butadien-1-yl)-quinoline (XII, 759 mg). An analytical sample, mp 57—58°, was obtained as pale yellow needles by recrystallization from *n*-hexane. *Anal.* Calcd. for $C_{19}H_{15}N$: C, 88.68; H, 5.88; N, 5.44. Found: C, 88.46; H, 5.82; N, 5.50.

**Catalytic Hydrogenation of XII to 2-[1-(4-Phenylbutyl)]quinoline**——A solution of XII (300 mg) in EtOH (50 ml) was hydrogenated at room temperature over 5% Pd-C (50 mg). The catalyst was removed by filtration and the filtrate was evaporated *in vacuo* to leave an oily residue. The residue was distilled to give a colorless oil, bp 180—185° (bath temp.)/1 mmHg. *Anal.* Calcd. for $C_{19}H_{19}N$: C, 87.31; H, 7.33; N, 5.36. Found: C, 87.02; H, 7.54, N, 5.24. NMR (in $CDCl_3$) ppm: 1.6—2.2 (4H, m, $CH_2C\underline{H}_2C\underline{H}_2CH_2$), 2.68, 3.02 (4H, broad t, $J$=7 Hz, $C\underline{H}_2CH_2CH_2C\underline{H}_2$), 7.1—8.2 (6H, m, quinoline protons), 7.21 (5H, s, $C_6H_5$). The picrate was prepared from ether and recrystallized as yellow prisms, mp 120.5—121.5°, from ether–acetone. *Anal.* Calcd. for $C_{25}H_{22}N_4O_7$: C, 61.22; H, 4.52; N, 11.42. Found: C, 61.34; H, 4.63; N, 11.56.

**Reaction of Benzo[*a*]quinolizinium Bromide (XIII) with Phenylmagnesium Bromide**——To a solution of phenylmagnesium bromide prepared from bromobenzene (3.14 g) and Mg (0.486 g) in tetrahydrofuran (40 ml) was added the powdered bromide (XIII, 1.3 g) with stirring at room temperature. After stirring for several hr, the reaction mixture was worked up as described above. The residue obtained from the dried ether extract was chromatographed on silica gel eluting with benzene–*n*-hexane (3: 1) afforded 1-(4-phenyl-1,3-butadien-1-yl)isoquinoline (XV) (678 mg). Recrystallization from benzene gave yellow crystals, mp 122.5—123.5°. *Anal.* Calcd. for $C_{19}H_{15}N$: C, 88.63; H, 5.88; N, 5.44. Found: C, 88.66; H, 5.92; N, 5.57.

**Catalytic Hydrogenation of XV to 1-[1-(4-Phenylbutyl)]isoquinoline**——A solution of XV (300 mg) in AcOH (50 ml) was hydrogenated at room temperature over 5% Pd-C (50 mg). The catalyst was removed by filtration and the filtrate was evaporated *in vacuo* to leave an oil. Water was added to the oil and the mixture was made alkaline with $K_2CO_3$. The organic material was extracted with ether and the extract was dried over anhydrous $Na_2SO_4$. The residue obtained from the dried extract was distilled to give a colorless oil, bp 160—165° (bath temp.)/0.001 mmHg. *Anal.* Calcd. for $C_{19}H_{19}N$: C, 87.31; H, 7.33; N, 5.36. Found: C, 86.98; H, 7.58; N, 5.38. UV $\lambda_{max}^{EtOH}$ nm ($\varepsilon$): 322 (3300), 309 (2700), 283 (3500), 271 (4500), 262 (4100). NMR (in $CCl_4$) ppm: 1.5—2.2 (4H, m, $CH_2C\underline{H}_2C\underline{H}_2CH_2$), 2.64, 3.22 (4H, broad t, $J$=7 Hz, $C\underline{H}_2CH_2CH_2C\underline{H}_2$), 7.05 (5H, s, $C_6H_5$), 8.27 (1H, d, $J$=6 Hz, C-3H of the quinoline), 7.27 (1H, d, $J$=6 Hz, C-4H of the quinoline), 7.3—8.1 (4H, m, benzene ring protons of the quinoline). The picrate was prepared from ether and recrystallized from EtOH to give yellow leaflets, mp 158°. *Anal.* Calcd. for $C_{25}H_{22}N_4O_7$: C, 61.22; H, 4.52; N, 11.42. Found: C, 61.17; H, 4.65; N, 11.26.