The buff needles were recrystallized from benzene–hexane to give material of m.p. 129.5–130.5° dec. with softening at 125–128°. The substance gave a green color with phenol and concentrated sulfuric acid.[19] With sodium pentacyanoammine ferroate, it gave a green color which gradually changed to violet.[20]

Anal. Calcd. for $C_{17}H_{16}O_3N_2$: C, 68.90; H, 5.44; N, 9.46. Found: C, 69.10; H, 5.57; N, 9.68.

Oxidation of IIIa to IV.—To a solution of 0.10 g. of IIIa in 10 cc. of 10% sulfuric acid was added dropwise 6 cc. of a solution of 1 g. of potassium dichromate in 10 cc. of 10% sulfuric acid. The resulting mixture was stirred at room temperature for 4 hours, treated with solid sodium carbonate until basic and extracted with benzene. The benzene solution was dried over magnesium sulfate and evaporated *in vacuo*. The residue was taken up in ethanol, the solution brought to a faint turbidity by the addition of water and then slowly evaporated at room temperature *in vacuo* until the onset of crystallization. The product, 0.05 g. of clustered, colorless needles, melted at 139–141°. The m.p. was not depressed on admixture with an authentic sample of IV.[4a]

Kinetics of the Decomposition of Ib.—The light source was a General Electric Type AH-4 mercury lamp, which operates at 8 atmospheres working pressure. The quantum output of this lamp was essentially constant over periods of several hours. This was demonstrated as follows. The light from the arc was collimated by two slits, 2 × 20 mm., placed 5 and 17 cm. from the lamp. The beam was intermittently interrupted by a rotating sector at a frequency of 1080 cps. A No. 929 blue-sensitive phototube and a Wratten No. 50 filter were used to isolate the 435.7 mμ line. The phototube was operated at 20 volts and the resulting alternating signal amplified in a high gain, highly degenerated, narrow band amplifier. The output was rectified and observed on a 1 milliampere meter. In two separate determinations the initial readings (milliamp.) were 0.82 and 0.83 and the readings after 2 and 3 hours, respectively, were 0.82 and 0.81.

The rate runs of Fig. 2 were followed spectrophotometrically at the absorption maximum of Ib (359 mμ). Since the effective wave length appears to be limited to the 366 mμ line, the beam was not filtered. The optical path was set up vertically, the beam passing through the bottom of the reaction vessel, a Pyrex beaker. The reaction solutions were stirred to eliminate concentration gradients and the solutions were of sufficient depth to provide "infinite" optical thickness (at least 99% absorption of incident radiation) even after 90% reaction and after removal of the necessary aliquots. The aliquots were diluted when necessary to a convenient concentration for spectrophotometry, these operations being carried out rapidly and with minimum exposure to light.

Acknowledgment.—The authors are indebted to Mr. Gerald B. Porter for determining the constancy of the light source.

LOS ANGELES 7, CALIFORNIA

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[19] C. Liebermann, *Ber.*, **7**, 247 (1874), *et seq.*

[20] (a) O. Baudisch, *ibid.*, **54**, 413 (1921); (b) F. Feigl, "Qualitative Analysis by Spot Tests," Elsevier Publ. Co., Inc., New York, N. Y., 1946, p. 321.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF SOUTHERN CALIFORNIA]

Studies on Dihydropyridines. III. An Absolute Asymmetric Synthesis and an Attempted Conversion of Carbon Atom Asymmetry to Biphenyl Asymmetry[1]

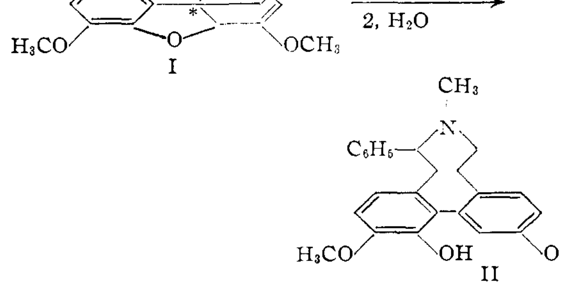
BY JEROME A. BERSON AND EARLENE BROWN

RECEIVED AUGUST 2, 1954

A novel type of asymmetric induction reaction is proposed, *i.e.*, one in which a center of carbon atom asymmetry is destroyed concomitant with the generation of a new center of biphenyl asymmetry. An absolute asymmetric decomposition of a 4-(2′-nitrophenyl)-1,4-dihydropyridine with circularly polarized light is described.

Asymmetric induction is possible whenever products arise *via* diastereomeric transition states. In detail, most asymmetric inductions have involved creation or destruction of a new carbon atom asymmetric center in the presence of a previously existing one in the same molecule[2] or in a molecule of a catalyst[2a,b] or reagent.[2a,b,3] An example which involves creation of a center of molecular (allene) asymmetry is the *d*-camphor-10-sulfonic acid-catalyzed dehydration of 1,3-diphenyl-1,3-di-(1-naphthyl)-propene-2-ol-1.[4]

The present report initiates a study of a little-known type of asymmetric induction, *i.e.*, one in which a center of biphenyl-type asymmetry is created at the expense of destruction of a center of carbon atom asymmetry. As far as we are aware, only two examples of this type of asymmetric "transfer" are known. The conversion of thebaine (I) to phenyldihydrothebaine (II)[5] involves[6] loss



I

II

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[1] This work was supported in part by a Frederick Gardner Cottrell Grant from Research Corporation.

[2] *Cf. inter alia* (a) F. Ebel in "Stereochemie," edited by K. Freudenberg, Vol. II, Franz Deuticke, Leipzig and Vienna, 1932, pp. 580–584; (b) R. L. Shriner, R. Adams and C. S. Marvel in "Organic Chemistry," second edition, edited by H. Gilman, Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1943, pp. 308–312. For later literature, see (c) D. J. Cram and F. A. Abd Elhafez, THIS JOURNAL, **74**, 5828 (1952); (d) V. Prelog, *Helv. Chim. Acta*, **36**, 308 (1953); (e) E. E. Turner and M. M. Harris, *Quart. Rev.*, **1**, 299 (1947); (f) P. I. Pollak and D. Y. Curtin, THIS JOURNAL, **72**, 961 (1950).

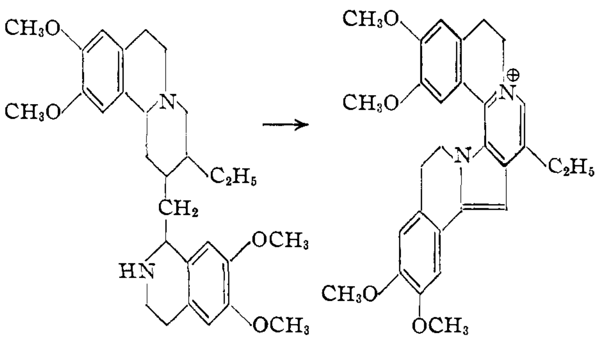
[3] (a) G. Vavon and B. Angelo, *Compt. rend.*, **224**, 1435 (1947); (b) G. Vavon, C. Riviere and B. Angelo, *ibid.*, **222**, 959 (1946); (c) H. S. Mosher and E. La Combe, THIS JOURNAL, **72**, 3994 (1950); (d) A. Streitwieser, *ibid.*, **75**, 5014 (1953); (e) W. von E. Doering and T. Aschner, *ibid.*, **71**, 838 (1949); (f) W. von E. Doering and R. W. Young, *ibid.*, **72**, 631 (1950); (g) A. Bothner-By, *ibid.*, **73**, 846 (1951).

[4] P. Maitland and W. H. Mills, *Nature*, **135**, 994 (1935).

[5] (a) M. Freund, *Ber.*, **38**, 3234 (1905); (b) L. Small, L. J. Sargent and J. A. Bralley, *J. Org. Chem.*, **12**, 1839 (1947).

[6] R. Robinson, *Nature*, **160**, 815 (1947).

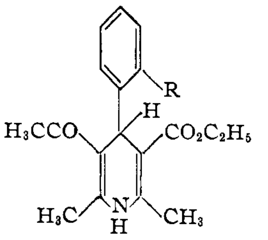
of asymmetry at C* and establishment of an asymmetric biphenyl system. II is obtained as a mixture of unequal quantities of two diastereomers. A case more closely related to our projected studies, in that the product embodies *only* biphenyl asymmetry, is the conversion of emetine (III) to optically active rubremetinium salts (IV).[7]



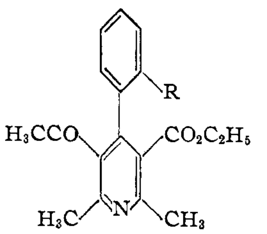
III IV

In order to simplify the problem and allow an assessment of the efficiency of asymmetric transfer, several criteria must be met: (i) the starting material must be resolvable; (ii) it should embody only one center of carbon atom asymmetry; (iii) it should be readily convertible to a product containing only biphenyl asymmetry; (iv) the product should have complete optical stability under the conditions of the conversion, or at least the optical half-life should be conveniently measurable; (v) it is desirable that both starting material and product be available in optically pure form.

An attractive approach to the satisfaction of these requirements involves the resolution of a 4-aryl-1,4-dihydropyridine (V) and its dehydrogenation to the corresponding 4-arylpyridine (VI).

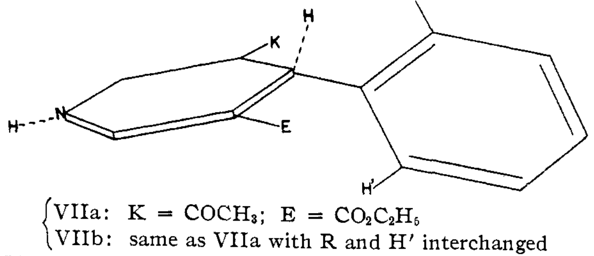


V



VI

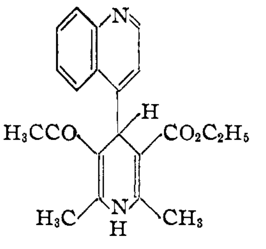
If the transition state for the dehydrogenation of V involves an arrangement in which the C_4–H bond is not completely broken and the heterocyclic ring begins to approach aromaticity, a given enantiomer of V will give rise to two diastereomeric transition states (VIIa and VIIb).



VIIa: K = $COCH_3$; E = $CO_2C_2H_5$
VIIb: same as VIIa with R and H' interchanged

An inspection of Fisher–Hirschfelder models shows that, in the resting molecule (V), there is no interference between R and the C_3 and C_5 substituents, because of the tetrahedral nature of C_4. As reaction proceeds, however, C_4 assumes more and more sp^2 character, and the two rings approach coaxiality. There will therefore be some stage (VIIa-b) at which steric interference between R and the C_3 and C_5 substituents will become sufficiently important to impart an energetic preference for one rotational configuration of the phenyl ring over the other. Completion of the reaction will lead to a predominance of one enantiomer of VI. The efficiency of asymmetric transfer will then depend upon the relative stabilities of the diastereomeric transition states, and this should be a function of the bulk of R and the C_3 and C_5 substituents.

In practice, dihydropyridines of the type V are synthetically accessible.[8] It is, however, necessary to incorporate an acidic or basic "handle" into the group R or elsewhere in the molecule, because the heterocyclic nitrogen of the dihydropyridines is non-basic. Our attempts to prepare V (R = CO_2H), V (R = OCH_2COOH) and V (R = $CH_2N(CH_2)_5$) by the standard method[8] have so far been unsuccessful. We have succeeded in preparing VIII, but this substance has so far resisted attempts to prepare crystalline salts with α-bromo-*d*-camphor-π-sulfonic acid and with Reychler's acid. (The weakly basic quinoline nitrogen effectively limits the range of resolving agents to sulfonic acids.) Attempts were also made to exchange the iodine of the methiodide of VIII for an optically active anion by treatment with silver α-bromo-*d*-camphor-π-sulfonate. These failed to yield a crystalline salt. Resolution by exchange of the methosulfate with barium α-bromo-*d*-camphor-π-sulfonate also failed.



VIII

Absolute Asymmetric Decomposition of a 4-(2'-Nitrophenyl)-1,4-dihydropyridine.—Our failure to achieve resolution of a dihydropyridine of the type V by classical means has led us to consider the possibility of effecting at least a partial resolution of such a substance by absolute asymmetric decomposition. We have shown that 4-(2'-nitrophenyl)-1,4-dihydropyridines are smoothly converted to the corresponding 4-(2'-nitrosophenyl)pyridines by ultraviolet light.[9] The possibility exists, therefore, that irradiation of V (R = NO_2) with *circularly polarized* ultraviolet light would cause one enantiomer to decompose more rapidly than the other, and, if the reaction is interrupted before it is complete, should lead to partially resolved V (R = NO_2).[10]

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[7] R. B. Woodward as quoted by R. F. Tietz and W. E. McEwen, THIS JOURNAL, **75**, 4945 (1953).

[8] J. A. Berson and E. Brown, *ibid.*, **77**, 444 (1955).

[9] J. A. Berson and E. Brown, *ibid.*, **77**, 447 (1955).

[10] For a discussion of absolute asymmetric synthesis, see W. Kuhn in "Stereochemie," edited by K. Freudenberg, Vol. I, Franz Deuticke, Leipzig and Vienna, 1933, pp. 321–323, p. 382 ff.

Theoretical considerations indicate that the observed rotation of V ($R = NO_2$) in such an experiment should be small. Thus, the asymmetric efficiency of any photochemical decomposition depending on the Cotton effect[11] is a function of g, the anisotropy factor[10] (defined as $g = (\epsilon^+ - \epsilon^-)/\epsilon$, where ϵ^+ and ϵ^- are the extinction coefficients of the *d*- and *l*-isomers, respectively, for light circularly polarized in a given sense, and ϵ is the extinction coefficient of the racemic compound. The anisotropy factor is in turn inversely proportional to f, the oscillator strength of the photochemically active absorption band,[12] a quantity which is a constant times the integrated intensity of the band.[13] While optically pure enantiomers of V ($R = NO_2$) are not now available, and consequently g is experimentally inaccessible, it would be expected to be very small. Thus for V ($R = NO_2$), f is roughly 10^3 times that for the photochemically active band of α-azidopropionic acid dimethylamide, a compound successfully submitted to absolute asymmetric synthesis in the elegant experiment of Kuhn and Knopf.[14]

Nevertheless, partial conversion of V ($R = NO_2$) to VI ($R = NO$) in ethanol with circularly polarized ultraviolet light (366 mμ) resulted in asymmetric decomposition. Two separate experiments were allowed to proceed to 37 and 39.5% completion, respectively. Solutions of the residues showed observed rotations (sodium D line) of $-0.022 \pm 0.006°$ and $-0.022 \pm 0.004°$. After 100% reaction, the observed rotation was $+0.002 \pm 0.003°$.[15]

A requirement for observable absolute asymmetric synthesis which is superimposed upon that of the anisotropy factor is that *products must arise directly or very nearly directly from the primary photochemical process*, since the probability of asymmetry persisting through a chain reaction of any appreciable length must be vanishingly small.[20] Since the change V ($R = NO_2$) → VI ($R = NO$) is very probably intramolecular,[9] this mechanistic requirement is satisfied. It is presumably for this reason that observable rotations were obtained in our experiments, despite the unfavorable value of f.

Attempted Asymmetric Transfer.—Oxidation with dichromate at 10–15° of optically active V ($R = NO_2$), obtained from the irradiation experiments, gave VI ($R = NO_2$) which was not observably active, even in solutions several times more concentrated than those in which activity of V ($R = NO_2$) was observed. This is presumably not attributable to thermal racemization of the pyridine (VI, $R = NO_2$), since interference calculations on the basis of group radii indicate that VI ($R = NO_2$) should be only difficultly racemized. However, since the rotation of the starting material was very low, an especially efficient asymmetric transfer and/or an especially high specific rotation for optically pure VI ($R = NO_2$) would be required for observable activity in the product.

Attempts are being continued to prepare an appropriately substituted 1,4-dihydropyridine in optically pure form by chemical resolution.

Experimental

Optical System for Producing Circularly Polarized Light.—The optical system was set up on a Hilger optical bench in a light-tight dark room. The only illumination was the exciting source itself, the General Electric Type AH-4 mercury arc lamp. All wall and bench surfaces were painted dull black to minimize stray reflections. The source was mounted in a black asbestos housing fitted with the Corning No. 5874 filter to isolate the 366 mμ line. A 6.25 inch collimating lens was placed in front of the source at the focal length (4 inches). The collimated, essentially monochromatic beam was polarized by reflection from a 5.5 × 8 inch plate of black Carrara glass.[21] The plate was mounted in an adjustable clamp and rotated carefully until the reflected beam was plane polarized. Plane polarization was tested by passing the beam through a Nicol prism onto a fluorescence screen (glass coated with "Lubriseal" stopcock grease) and was evidenced by total extinction of the image on the screen when the Nicol prism was rotated to the "crossed" position. The plane polarized beam was passed through a mica quarter-wave plate[22] of the proper thickness to achieve circular polarization. The emergent beam was tested for circular polarization with a companion quarter-wave plate, a Nicol prism and a fluorescent screen.

Irradiation of V ($R = NO_2$) with Circularly Polarized Light.—A solution of 0.6239 g. of V ($R = NO_2$)[8] in 1700 cc. of 95% ethanol was irradiated in ten equal successive portions in a flat-sided vessel exposed to the circularly polarized beam. Each portion was irradiated for 24–36 hours. The solutions were combined and the extent of reaction determined spectrophotometrically (37% reaction). The solvent was removed *in vacuo* and the residue taken up in 15 cc. of glacial acetic acid. This solution ($l = 1$ dcm.) was too opaque for polarimetry, due to the end absorption of V ($R = NO_2$) in the visible. It was diluted tenfold with acetic acid. The rotation was measured (D line) with a Rudolf polarimeter, reading directly to 0.001°. It showed a small but definite levorotation. The average of fifteen readings was $-0.022 \pm 0.006°$ ($l = 1$ dcm., c 0.416).

In a second experiment run to 39.5% reaction, irradiation of a solution of 0.0818 g. of V ($R = NO_2$) in 100 cc. of 95% ethanol gave a product, which after being worked up as above, showed α_D $-0.022 \pm 0.004°$ ($l = 1$ dcm, c 0.395). This value is an average of twenty-two readings constituting independent checks by the two authors. The values found independently were $-0.022 \pm 0.004°$ and $-0.022 \pm 0.003°$.

As further checks on the reality of the rotations, solutions of racemic V ($R = NO_2$) and of total irradiated product after a run allowed to proceed to 100% reaction were examined polarimetrically. For racemic V, α_D $+0.003 \pm 0.005°$ ($l = 1$ dcm., c 0.40 in acetic acid). For the "infinity" run, α_D $+0.002 \pm 0.003°$ ($l = 1$ dcm., c 0.423 in acetic acid).

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(11) A. Cotton, *Ann. chim.*, [7] **8**, 347 (1896).

(12) W. Kuhn, *Trans. Faraday Soc.*, **26**, 293 (1930).

(13) $f = mc/N\pi e^2 \int \epsilon \, d\nu$, where m = mass of the electron, c = velocity of light, N = Avogadro's number, e = charge on the electron, ϵ = molecular extinction coefficient and ν = frequency in cm.$^{-1}$.

(14) W. Kuhn and E. Knopf, *Z. physik. Chem.*, **7B**, 292 (1930).

(15) The possibility is not rigorously excluded that part of the observed rotation may be due to optically active VI ($R = NO$), arising by asymmetric transfer. Calculations assuming additivity of covalent radii[16] indicate radius sums of 3.21 Å. for NO *vs.* $CO_2C_2H_5$ and 3.47 Å. for NO *vs.* $COCH_3$. Even neglecting the buttressing effect[17,18] of the 2- and 6-methyl groups, VI ($R = NO$) might have a detectable optical half-life, since the radius sums are appreciably greater than the empirical minimum value (2.90 Å.) needed[19] for observable restricted rotation at room temperature.

(16) L. Pauling, "The Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 1939, p. 154.

(17) S. L. Chien and R. Adams, THIS JOURNAL, **56**, 1787 (1934).

(18) M. Rieger and F. H. Westheimer, *ibid.*, **72**, 19, 28 (1950).

(19) W. M. Stanley and R. Adams, *ibid.*, **52**, 1200 (1930).

(20) This has been pointed out by Kuhn and Knopf (reference 14) but often ignored in subsequent discussions of asymmetric synthesis.

(21) H. T. Dailey and H. C. Benedict, THIS JOURNAL, **51**, 809 (1929).

(22) F. A. Jenkins and H. E. White, "Fundamentals of Optics," 2nd edition, McGraw-Hill Book Co., Inc., New York, N. Y., 1950, p. 528.

Dehydrogenation of Optically Active V ($R = NO_2$).—The total residue from the first of the irradiation experiments, containing optically active V ($R = NO_2$), was taken up in 25 cc. of acetic acid, cooled to 15° and treated dropwise over a period of 20 minutes with a solution of 1.25 g. of potassium dichromate and 2 cc. of sulfuric acid in 15 cc. of water. The temperature was maintained below 15° for an additional hour and 15 minutes and then allowed to rise to room temperature. After 8 hours at room temperature, the solvents were removed by lyophilization at −80°, the residue treated with water, made basic with sodium carbonate, extracted with benzene and the extract dried over magnesium sulfate. The solvent was evaporated and the residue examined polarimetrically. No rotation was observed, α_D +0.001 ± 0.005° (l = 1 dcm., 2.65 in ethanol).

Acknowledgments.—The authors are indebted to Dr. John R. Holmes of the Department of Physics for valuable advice on the design of the optical system and to Dr. Arthur W. Adamson and Mr. Arthur Seibel for aid in its construction. The generous support of Research Corporation is gratefully acknowledged.

LOS ANGELES 7, CALIFORNIA

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

Aromatic Cyclodehydration. XXIX.[1] 7-Methyl- and 7-Phenylbenzo[a]quinolizinium Salts

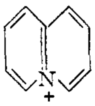
BY C. K. BRADSHER AND LEO E. BEAVERS[2]

RECEIVED JULY 19, 1954

By cyclodehydration of N-acetonyl- and N-phenacyl-α-phenylpyridinium salts the first fully aromatic benzoquinolizinium salts have been prepared. The structure of 7-methylbenzo[a]quinolizinium bromide has been demonstrated by its oxidation to phthalic acid.

Frequently overlooked in discussions of aromatic systems are what might be called the cationoid aromatics. These interesting compounds owe their aromaticity to the existence of a hetero atom in a higher valence state. Simple and familiar examples of such systems are the pyrillium (I, X = O) and thiapyrillium (I, X = S) salts in which a CH of the benzene ring is replaced by an oxonium or sulfonium linkage. The simplest aromatic system incorporating the ammonium nitrogen is the quinolizinium ion II. Despite the large amount of research done in the field of heterocyclic chemistry, compounds containing this aromatic structure have received little attention. When the present work was undertaken only a few compounds were believed or known to contain the quinolizinium nucleus.[3] The even smaller groups of wholly aromatic quinolizinium salts (all rings aromatic[3a,b,c,f]) consisted of a few complex compounds which, with the exception of the tetracarbomethoxy quinolizinium derivatives[3b] of Diels and Alder, were tetracyclic in nature.


I


II

It was felt that the much needed knowledge of the chemistry and pharmacology of the aromatic quinolizinium salts must come from a study of derivatives simpler and more readily available than those previously reported. For this reason the present synthesis of the first aromatic benzologs of the quinolizinium ion was undertaken.

When this work was substantially complete Boekelheide and Gall[4] published a new and convenient synthesis for 3,4-dihydroquinolizinium[5] iodide and showed that it could be dehydrogenated to quinolizinium iodide (II) in yields up to 15%.[6]

It was hoped that we might be able to apply the methods of aromatic cyclodehydration to the synthesis of some benzoquinolizinium salts. As has been pointed out earlier,[7] these methods obviate the necessity for dehydrogenation and are well suited for the synthesis of compounds which are not resistant to high temperatures.

The starting material for our synthesis was the easily prepared α-phenylpyridine[8] which did not quaternize satisfactorily with α-chloroacetone or α-bromoacetone, but at room temperature with freshly prepared α-iodoacetone afforded the expected salt (III, $R = CH_3$; X = I) in 85–90% yield.

It was anticipated that the cyclization of the new salt might prove much more difficult than had been observed in the case of the carbocyclic analog[9] since the positive charge on the nitrogen atom would strongly deactivate the phenyl nucleus. Actual cyclization experiments with the new iodide (III, $R = CH_3$, X = I) were very unsatisfactory, the

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[1] For the previous communication of this series see THIS JOURNAL, **76**, 4140 (1954).

[2] Public Health Service Research Fellow of the National Institutes of Health (1952–1954).

[3] (a) W. Schneider and K. Schroeter, *Ber.*, **53B**, 1459 (1920); (b) O. Diels and K. Alder, *Ann.*, **505**, 103 (1933); (c) S. Sugasawa and K. Kakemi, *Ber.*, **71B**, 1860 (1938); (d) R. B. Woodward and B. Witkop, THIS JOURNAL, **71**, 379 (1949); (e) R. B. Woodward and W. M. McLamore, *ibid.*, **71**, 379 (1949); (f) R. Schwyzer, *Helv. Chim. Acta*, **35**, 867 (1952).

[4] V. Boekelheide and W. G. Gall, THIS JOURNAL, **76**, 1832 (1954).

[5] According to the nomenclature employed by Boekelheide and Gall structure II is to be referred to as the dehydroquinolizinium ion. We feel that this usage violates established custom in the naming of aromatic nuclei, and throughout the present paper have employed the terminology of *Chemical Abstracts*, which designates II as the quinolizinium ion (*C. A.*, **46**, 13667 (1952)).

[6] The paper of Boekelheide and Gall (ref. 4) also revealed that Beaman and Woodward had prepared quinolizinium salts in very poor yield.

[7] C. K. Bradsher and A. K. Schneider, THIS JOURNAL, **60**, 2960 (1938); C. K. Bradsher, *Chem. Revs.*, **38**, 447 (1945).

[8] J. C. W. Evans and C. F. H. Allen, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 517.

[9] C. K. Bradsher and W. J. Jackson, THIS JOURNAL, **76**, 734 (1954).