Anal. Calcd. for $C_{39}H_{24}N_8O_{14}\cdot{}^1/_2C_2H_5OH$: C, 56.41; H, 3.20; N, 13.16. Found: C, 56.50; H, 3.11; N, 12.71.

4,4′-Bis(1-methylene-2-oximidomethylpyridinium Picrate)-bibenzyl (XV).—The quaternization of picolinic aldoxime with 4,4′-bis(bromomethyl)bibenzyl[16] was carried out in N-methylpyrrolidone in the usual way. A portion of the crude product was converted to the picrate which formed a bright yellow powder from ethanol, m.p. 130–131°.

(16) J. L. R. Williams and K. R. Dunham, U. S. Patent 2,843,567; *cf.*, *Chem. Abstr.*, **52**, 16798h (1958).

Anal. Calcd. for $C_{40}H_{28}N_{10}O_{16}\cdot C_2H_5OH$: C, 53.05; H, 3.60; N, 14.73. Found: C, 52.75; H, 3.50; N, 14.41.

9,9′-Ethylenebis(acridizinium Bromide) (XVII).—The cyclization of 2.5 g. of the crude bromide (XV) was carried out as in the case of the homolog (XIV). The product consisted of 1.1 g. (40%) of small bright orange needles from ethanol–water, m.p. above 390°, λ_{max} (log ϵ), 245 (4.79), 252 (4.80), 362 (4.52), 376 (4.20), 393 (4.26), and 395* (4.12); λ_{min}, 249 (4.78), 314 (3.34), 368 (4.17), and 388 (4.03).

Anal. Calcd. for $C_{28}H_{22}Br_2N_2$: C, 61.56; H, 4.06; N, 5.13. Found: C, 61.37; H, 4.11; N, 5.41.

Aromatic Cyclodehydration. LI.[1] Phenanthridizinium Derivatives Bearing a Carboxyethyl Group

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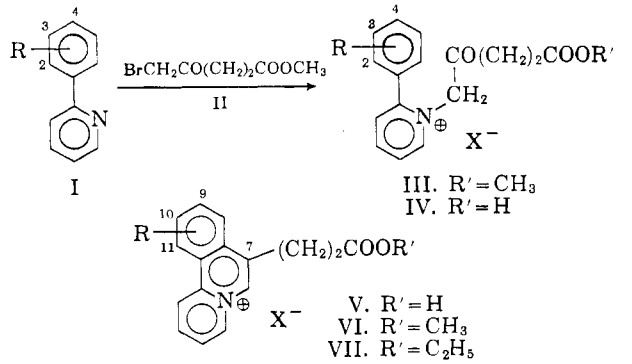
The quaternary salt formed by the reaction of methyl δ-bromolevulinate with 2-phenylpyridine may be cyclized to afford the 7-(β-carboxyethyl)benzo[*a*]quinolizinium ion. The synthesis was extended to two of the 2-tolylpyridines.

Analogy suggests that any extensive application of phenanthridizinium[3] salts in medicinal chemistry will require that there be one or more functional groups in addition to the quaternary nitrogen. To date, fully aromatic phenanthridizinium salts bearing a methoxyl[4] or hydroxyl[3] group have been prepared, but with the exception of the 1,2,3,4-tetracarbomethoxyphenanthridizinium ion reported by Diels and co-workers[5,6] it appears that no derivatives having functional groups have been synthesized. The present communication describes some experiments directed toward the introduction of the carboxyl or a carboxylalkyl group into the 7-position of the phenanthridizinium nucleus.



It seemed probable that the carboxyl function could be introduced into the phenanthridizinium nucleus by quaternization of a 2-phenylpyridine with a suitable ω-bromoketo ester, $BrCH_2CO(CH_2)_nCOOR$ followed by cyclization. Preliminary attempts at quaternization using ethyl bromopyruvate[7] (n = 0) were unsuccessful, the major product being the hydrobromide of the base I. The next higher homolog, γ-bromoacetoacetic ester (n = 1) was not studied since it seemed obvious that in boiling mineral acid, rapid hydrolysis and decarboxylation of the quaternary salt would occur. The next higher homolog, methyl δ-bromolevulinate (II. n = 2) is easily obtained[8] and quaternizes readily with 2-phenyl- and 2-tolylpyridines (I) to afford ether-insoluble liquid salts (III). The crude salts were not purified, but used directly in the cyclization reaction. Cyclization in boiling hydrobromic acid proved slower (6–16 days) than was the case with the simple 1-acetonyl-2-arylpyridinium salts (2–3 days) studied earlier.[9] In nearly all cyclization attempts, uncyclized keto acid (IV) was recovered along with the product (V). Where the methyl group was in the *ortho* position of the phenyl ring (I. R = 2-CH_3), no cyclization product was detected, even after a reflux period of fifteen days, 39% of starting material being recovered as uncyclized keto acid (IV. R = 2-CH_3). This was not too surprising since the methyl at the 2-position impedes the achievement of the coplanarity essential for cyclization. The related 1-acetonyl-2-(*o*-tolyl)pyridinium salt cyclized in only 9% yield under the conditions which produced a 71% yield from the *p*-tolyl analog.[9]

The 7-(β-carboxyethyl)phenanthridizinium (V) perchlorates melted above 200° and showed the characteristic instability toward alkali. Efforts to prepare the zwitterion either by addition of potassium hydroxide to an alcoholic solution of the perchlorate or by action of silver oxide on the bromide yielded unstable products which showed the characteristic carboxylate anion absorption at 1575 cm.$^{-1}$, but were not analytically pure. Esterification of the new acids (V) in absolute methanol (hydrogen chloride catalyst) occurred in good yield. In one case (V. R = 9-CH_3) esterification was likewise brought about *via* the acid chloride, which was formed as a milky suspension by stirring a suspension of the acid in carbon tetrachloride with oxalyl chloride at room temperature. If the resulting milky suspension

(1) For the preceding communication of this series see C. K. Bradsher and N. L. Yarrington, *J. Org. Chem.*, **28**, 78 (1963).

(2) Taken from part of a dissertation submitted by N. L. Y. in partial fulfillment of the requirements for the Ph.D. degree, Duke University. This investigation was supported by a research grant (H-2170) from the National Heart Institute of the National Institutes of Health.

(3) The name phenanthridizinium has been proposed [C. K. Bradsher and K. B. Moser, *J. Am. Chem. Soc.*, **81**, 1941 (1959)] as a simpler alternative to the *Chem. Abstr.* designation, benzo[*a*]quinolizinium.

(4) L. E. Beavers, Ph.D. dissertation, Duke University, 1955.

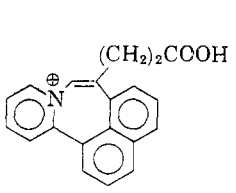
(5) O. Diels and J. Harms, *Ann.*, **525**, 73 (1936).

(6) O. Diels and K. Alder, *ibid.*, **498**, 16 (1932).

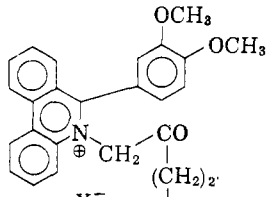
(7) C. F. Ward, *J. Chem. Soc.*, **123**, 2207 (1923).

(8) H. Dannenberg and S. Läufer, *Ber.*, **89**, 2242 (1956).

(9) C. K. Bradsher and K. B. Moser, *J. Am. Chem. Soc.*, **81**, 1941 (1959).



VIII



IX

was stirred with methanol or ethanol, the expected ester was formed.

When 2-(1-naphthyl)pyridine[10] was quaternized with methyl δ-bromolevulinate, and the crude salt cyclized, it afforded a yellow powder in 24% yield. The ultraviolet absorption spectrum of this new substance suggests that, as in the case of simpler analogs,[11] cyclization has occurred into the alpha position of the naphthalene ring to form a new seven-membered ring (VIII) rather than into the beta position to form a six-membered ring.

The quaternization product (IX), obtained by the reaction of 6 - (3,4 - dimethoxyphenyl)phenanthridine with methyl α-bromolevulinate, when heated with hydrochloric acid underwent cleavage rather than cyclization.

Experimental

All analyses were carried out by Dr. Ing. A. Schoeller, Mikroanalytisches Laboratorium, Kronach, Germany. The melting points were determined with the Mel-Temp apparatus and are uncorrected. The ultraviolet absorption spectra were determined in 95% ethanol using 1-cm. silica cells in the Cary Model 11 recording spectrophotometer.

7-(β-Carboxyethyl)phenanthridizinium (V. R = H) Perchlorate.—An intimate mixture of 2.95 g. (0.019 mole) of 2-phenylpyridine[12] with 4.09 g. (0.019 mole) of methyl δ-bromolevulinate[8] (II) in a 50-ml. glass-stoppered round-bottomed flask was gently heated on the steam bath until the mixture formed a golden brown resin on cooling. The resin was washed thoroughly with ether and then dissolved in 30 ml. of 48% hydrobromic acid. The solution was heated without a condenser until the temperature reached 125° and then refluxed for 16 days. The dark-colored solution was filtered to remove some of the decomposition products and the filtrate evaporated *in vacuo*. The residue was dissolved in 75 ml. of water, the solution treated with Norit, filtered, and again evaporated *in vacuo*. The residue was dissolved in 20 ml. of water, the solution filtered and treated with 9 ml. of 23% perchloric acid. On cooling, 4.84 g. of a tan product precipitated and was collected. Recrystallization of the crude material from hot water yielded 2.3 g. (34.5%) of small light tan needles, m.p. 239–240°, λ_{max} (log ε), 225 (4.32), 238 (4.40), 269 (4.30), 282 (4.34), 326 (3.67), 340 (3.94), and 355 mμ (4.06).

Anal. Calcd. for $C_{16}H_{14}ClNO_6$: C, 54.64; H, 4.01; N, 3.98. Found: C, 54.65; H, 4.03; N, 4.10.

A second fraction which separated from the solution on standing proved to be **1-(2-keto-4-carboxybutyl)-2-phenylpyridinium (IV. R = H) perchlorate.** It was recrystallized from water as elongated rectangles m.p. 202–204°.

Anal. Calcd. for $C_{16}H_{16}ClNO_7$: C, 51.98; H, 4.34; N, 3.79. Found: C, 52.00; H, 4.43; N, 3.95.

7-(β-Carbomethoxyethyl)phenanthridizinium (VI. R = H) perchlorate was prepared in 96% yield by refluxing the free acid (V) overnight with methanol saturated with hydrogen chloride, m.p. 188–190°. The analytical sample was recrystallized from methanol as aggregates of flat needles, m.p. 189.5–190.5°.

Anal. Calcd. for $C_{17}H_{16}ClNO_6$: C, 55.82; H, 4.41; N, 3.83. Found: C, 55.97; H, 4.24; N, 4.10.

7-(β-Carboxyethyl)-9-methylphenanthridizinium (V. R = 9-CH₃) Perchlorate.—Starting with 4.06 g. of 2-(*p*-tolyl)pyridine[13] and following the procedure for (V. R = H), except that refluxing in acid was stopped after 6 days, a 54% yield of nearly colorless, long, well formed prisms was obtained by crystallization from hot water, m.p. 233–234°, λ_{max} (log ε), 228 (4.42), 242 (4.44), 274 (4.48), 325 (3.84), 340 (4.07), and 355 mμ (4.20); λ_{min} 232 (4.36), 256 (4.33), 318 (3.76), 330 (3.77), and 347 (3.83).

Anal. Calcd. for $C_{17}H_{16}ClNO_6$: C, 55.82; H, 4.42; N, 3.83. Found: C, 55.88; H, 4.69; N, 3.92.

From the mother liquor 1.23 g. of **1-(2-keto-4-carboxybutyl)-2-(*p*-tolyl)pyridinium (IV. R = 4-CH₃) perchlorate** was obtained as colorless microcrystalline aggregates, m.p. 163–165°.

Anal. Calcd. for $C_{17}H_{18}ClNO_7$: C, 53.20; H, 4.73; N, 3.65. Found: C, 53.12; H, 4.67; N, 3.55.

7-(β-Carbomethoxyethyl)-9-methylphenanthridizinium (VI. R = 9-CH₃) Perchlorate. (a) **By Fischer Esterification.**—Esterification of V (R = 9-CH₃) in the usual way afforded 77% yield of product, m.p. 175–178°. The analytical sample crystallized from methanol as colorless hexagonal platelets, m.p. 173–175°.

(b) *Via* **the Acid Chloride.**—To a suspension of 200 mg. of the free acid (V. R = 9-CH₃) in 20 ml. of dry carbon tetrachloride 0.3 ml. of oxalyl chloride was added and the mixture stirred overnight. To the resulting milky suspension 25 ml. of anhydrous methanol was added and stirring continued for 5 hr. The solvents were vacuum-evaporated and the residue washed with ether. Once recrystallized from methanol it afforded colorless platelets, m.p. 174–175°. The melting point was not depressed when the substance was mixed with the product from procedure a.

Anal. Calcd. for $C_{18}H_{18}ClNO_6$: C, 56.92; H, 4.78; N, 3.69. Found (procedure a): C, 56.97; H, 4.91; N, 3.84.

7-(β-Carboethoxyethyl)-9-methylphenanthridizinium (VII. R = 9-CH₃) perchlorate was prepared *via* the acid chloride essentially as described for the lower homolog (VI. R = 9-CH₃) except that the crude acid chloride was stirred with absolute ethanol for 24 hr., yield 88%, m.p. 157–161°. The analytical sample was crystallized from ethanol as colorless needle clusters, m.p. 165–167°.

Anal. Calcd. for $C_{19}H_{20}ClNO_6$: C, 57.95; H, 5.12; N, 3.56. Found: C, 57.71; H, 5.01; N, 3.71.

7-(β-Carboxyethyl)-10-methylphenanthridizinium (V. R = 10-CH₃) Salts.—Starting with 4.06 g. of 2-(*m*-tolyl)pyridine[13] (I. R = 3-CH₃), and following the 6-day cyclization procedure, it was found that before perchloric acid could be added, the bromide crystallized from 20 ml. of water affording 3.75 g. (45%) of felted needles, m.p. 244–248°. The analytical sample crystallized from water as nearly colorless needles, m.p. 250–251°.

Anal. Calcd. for $C_{17}H_{16}BrNO_2$: C, 58.97; H, 4.66; N, 4.06. Found: C, 58.74; H, 4.56; N, 4.08.

The mother liquor was treated with dilute perchloric acid and the resulting brown precipitate crystallized from ethanol–water (Norit), affording 1.16 g. of the perchlorate, m.p. 202–205°. The analytical sample formed slender colorless needles from ethanol–water, m.p. 219–221°, λ_{max} (log ε), 228 (4.38), 243 (4.54), 263 (4.35), 285 (4.39), 332*[14] (3.56), 347 (3.97), and 362 mμ (4.11); λ_{min} 229 (4.36), 256 (4.33), 271 (4.32), 322 (3.54), and 353 (3.87).

Anal. Calcd. for $C_{17}H_{16}ClNO_6$: C, 55.81; H, 4.41; N, 3.83. Found: C, 55.83; H, 4.38; N, 4.01.

The methyl ester (VI. R = 10-CH₃) of the perchlorate, prepared by direct esterification afforded colorless crystals, m.p. 196–198°, in 77% yield. The analytical sample crystallized from methanol as colorless well formed needles, m.p. 197–199°.

Anal. Calcd. for $C_{18}H_{18}NClO_6$: C, 56.92; H, 4.78; N, 3.69. Found: C, 56.64; H, 4.59; N, 3.82.

1-(2-Keto-4-carboxybutyl)-2-(*o*-tolyl)pyridinium (IV. R = 2-CH₃) Perchlorate.—Starting with 4.06 g. of 2-(*o*-tolyl)pyridine[9] (I. R = 2-CH₃) and carrying out the usual quaternization procedure followed by 15 days refluxing in hydrobromic acid 3.6 g. of tan-colored crystals was precipitated as the perchlorate, m.p. 159–168°. Recrystallized from water it formed colorless rectangular platelets, m.p. 170–171°.

Anal. Calcd. for $C_{17}H_{18}ClNO_7$: C, 53.20; H, 4.72; N, 3.65. Found: C, 53.52; H, 4.57; N, 3.70.

(10) C. K. Bradsher and L. E. Beavers, *J. Am. Chem. Soc.*, **78**, 2459 (1956).

(11) C. K. Bradsher and J. W. McDonald, *J. Org. Chem.*, **27**, 4482 (1962).

(12) 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.

(13) J. S. Meek, R. T. Merrow, and S. J. Cristol, *J. Am. Chem. Soc.*, **74**, 2667 (1952).

(14) The asterisk (*) is used to denote a shoulder.

7-Methylbenzo[1,m]morphanthridizinium[15] (VIII) Perchlorate.—The quaternization of 2.05 g. of 2-(1-naphthyl)pyridine[10] was carried out as usual, and the crude salt cyclized by refluxing it for 100 hr. with hydrobromic acid. The product was isolated as the perchlorate and crystallized from ethanol as a bright yellow powder, m.p. 205–210°, yield 1.01 g. (24%). The analytical sample was crystallized from ethanol–water as a yellow microcrystalline powder, m.p. 214°, λ_{max} (log ϵ), 242 (4.69), 291 (4.30), and 380 mμ (3.88); λ_{min} 265 (4.05) and 344 (3.51).

Anal. Calcd. for $C_{20}H_{16}ClNO_6$: C, 59.78; H, 4.01; N, 3.49. Found: C, 60.13; H, 4.36; N, 3.54.

5-(2-Keto-4-carbomethoxybutyl)-6-(3,4-dimethoxyphenyl)-phenanthridinium (IX) Perchlorate.—The quaternization of 1.57 g. of 6-(3,4-dimethoxyphenyl)phenanthridine[16] with 1.05 g. of methyl α-bromolevulinate (II) was carried out in 5 ml. of N-methylpyrrolidone by heating on the steam bath for about 3 hr. The solution was cooled and ether added until the solution was turbid. In the refrigerator, 1.4 g. (51%) of yellow crystals was deposited from the solution, m.p. 146–160°. Recrystallization from ethanol gave bright yellow crystals, m.p. 170–171°. A sample, converted to the perchlorate for analysis, formed a yellow microcrystalline powder, m.p. 193–195°.

Anal. Calcd. for $C_{27}H_{26}NClO_9$: C, 59.62; H, 4.82; N, 2.58. Found: C, 59.52; H, 4.66; N, 2.97.

The bromide IX was dissolved in 25 ml. of concentrated hydrochloric acid, 5 ml. of ethanol added, and the mixture refluxed for 4.5 hr. On cooling, a yellow microcrystalline powder precipitated, and was recrystallized from ethanol–ether, m.p. 123°. This substance showed no significant absorption in the carbonyl region of the infrared spectrum, and analysis indicated that the product was 6-(3,4-dimethoxyphenyl)phenanthridine hydrochloride.

Anal. Calcd. for $C_{21}H_{18}ClNO_2$: C, 71.69; H, 5.15; N, 3.98. Found: C, 72.01; H, 5.03; N, 4.05.

(15) The name morphanthridizinium has been proposed [K. B. Moser and C. K. Bradsher, *J. Am. Chem. Soc.*, **81**, 2547 (1959)] for the pyro[1,2-*a*]-benzo[*d*]-3*H*-azepinium system.

(16) P. Mamalis and V. Petrow, *J. Chem. Soc.*, 703 (1950).

Aromatic Cyclodehydration. LII.[1] Carbonyl Derivatives as Intermediates in the Acridizinium Synthesis

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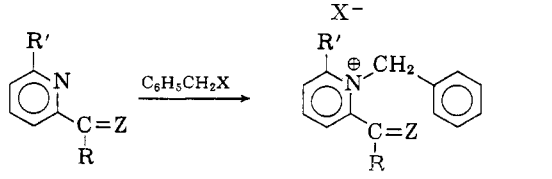
Received August 17, 1962

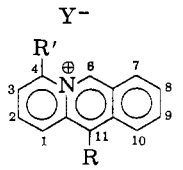
A search has been made for a picolinaldehyde derivative which might offer more advantage in the synthesis of acridizinium salts than does picolinaldoxime. The new 2-(1,3-dioxolan-2-yl)pyridine is superior to any known picolinaldehyde derivative in both the yield and quality of the acridizinium salt produced. Similarly, the dioxolan from 6-methyl-2-picolinaldehyde afforded the 4-methylacridizinium ion while that prepared from 2-acetylpyridine gave improved yields of 11-methylacridizinium salts.

The first synthesis of the acridizinium ion VII[3] involved the quaternization of 2-picolinaldehyde (I. Z = O) with benzyl bromide, followed by the acid-catalyzed cyclization of the crude salt (IV. Z = O). More recently,[4] it was shown that the unstable aldehyde (I. Z = O) could be replaced by the oxime (I. Z = NOH), with beneficial results.



I. R = R′ = H
II. R = CH_3, R′ = H
III. R = H, R′ = CH_3

IV. R = R′ = H
V. R = CH_3, R′ = H
VI. R = H, R′ = CH_3



VII. R = R′ = H
VIII. R = CH_3, R′ = H
IX. R = H, R′ = CH_3

Although the new procedure proved extremely useful,[5] there remained unsolved problems. One problem involved the rather low yield usually obtained in the cyclization of ketoximes (II. Z = NOH), and another, the complete failure of 6-methyl-2-aldoximinopyridine (III. Z = NOH) in the synthesis. A third, but minor problem, was the difficulty in the separation of the acridizinium ion from the hydroxylamine salt released in the cyclization reaction.

It seemed probable that a study of carbonyl derivatives other than the oxime might provide an intermediate which would be superior to the oxime in at least some respects. A number of derivatives related to the oxime (I. Z = NOH) were examined. The most successful of these was the semicarbazone (I. R = $NNHCONH_2$), which could be quaternized with benzyl bromide to afford a salt (IV. Z = $NNHCONH_2$) (68% yield), which when cyclized in hydrobromic acid, and then converted to the perchlorate, afforded a 47% yield of the acridizinium ion (VII). The yields, although fairly good, are inferior to those obtained with the oxime, in both the quaternization and cyclization steps, and separation of the acridizinium ion from the semicarbazide salts is tedious and accompanied by losses. The semicarbazone (III. Z = $NNHCONH_2$) of 6-methylpicolinaldehyde failed completely in the quaternization reaction with benzyl bromide. When the thiosemicarbazone (I. Z = $NNHCSNH_2$) was used, quaternization of the pyridine nitrogen[6] evidently did not occur, for the crude reaction product with benzyl bromide yielded no acridizinium ion on heating with

(1) For the preceding communication of this series see C. K. Bradsher and N. L. Yarrington, *J. Org. Chem.*, **28**, 81 (1963).

(2) This research was supported by a research grant (CY-5509) of the National Cancer Institute of the National Institutes of Health.

(3) C. K. Bradsher and L. E. Beavers, *J. Am. Chem. Soc.*, **77**, 4812 (1955).

(4) C. K. Bradsher, T. W. G. Solomons, and F. R. Vaughan, *J. Org. Chem.*, **25**, 757 (1960).

(5) *E.g.*, C. K. Bradsher and N. L. Dutta, *J. Am. Chem. Soc.*, **82**, 1145 (1960); C. K. Bradsher and T. W. G. Solomons, *ibid.*, **82**, 1808 (1960); C. K. Bradsher and N. L. Dutta, *J. Org. Chem.*, **26**, 2231 (1961).

(6) It has been observed that reaction of thiosemicarbazones with α-chloro ketones occurs readily at the sulfur atom, J. McLean and F. J. Wilson, *J. Chem. Soc.*, 556 (1937).