[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

Aromatic Cyclodehydration. XLVIII.[1] The Isomorphanthridizinium System

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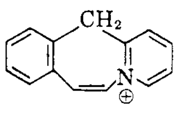
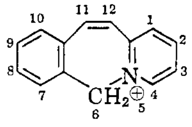
The synthesis of the new isomorphanthridizinium (pyrido[1,2-*b*][2]benz[*f*]azepinium) system has been effected. Four derivatives of the parent ring system have been prepared, and the structure of one of these demonstrated by oxidation to a phthalic acid derivative.

An earlier paper[3] described the first synthesis of the morphanthridizinium or pyrido[2,1-*b*][3]benz[*f*]azepinium system (I). A logical sequel was an attempt to prepare the hitherto unknown isomeric pyrido[1,2-*b*][2]benz[*f*]azepinium system (II). The success met with in the cyclization of 1-benzyl-2-acylpyridinium to 11-substituted acridizinium salts suggested that the new system might be made from the known 2-acetonylpyridine (III)[4] or 2-phenacylpyridine (IV)[5] by quaternization with the appropriate benzyl halide, followed by acid-catalyzed cyclodehydration.



I



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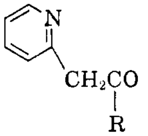
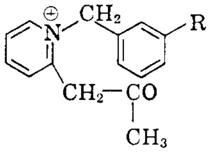
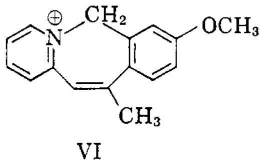


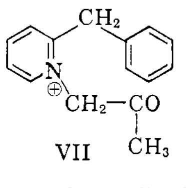
III. $R = CH_3$
IV. $R = C_6H_5$



V



VI



VII

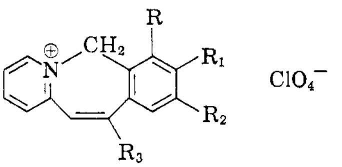
With benzyl bromide 2-acetonylpyridine afforded a crude quaternary bromide (V. R = H) which could be purified as the perchlorate. Attempted cyclization of the crude salt (V. R = H) in boiling hydrobromic acid (117 hours) was unsuccessful, the starting material being recovered (perchlorate). Cyclization attempts in liquid hydrogen fluoride or polyphosphoric acid at 100° or 140° were without success.

In order to produce a more reactive system, *m*-methoxybenzyl bromide was used as the quaternizing agent. The crude salt (V. $R = OCH_3$) was cyclized by refluxing it for twenty-five hours in concentrated hydrochloric acid, and the product, isolated as the perchlorate, had the composition expected for the desired 8-methoxy-11-methylpyrido[1,2-*b*][2]benz[*f*]azepinium (VI) perchlorate. The infrared absorption spectrum showed that there remained no significant absorption in the carbonyl region at 5.75 μ and that in the 13.3–14.3 μ region all but very weak absorption had disappeared. This evidence that cyclization had occurred was supported by oxidation (with alkaline permanganate) of the new compound to yield 4-methoxyphthalic acid.

As the systematic name for the new cation is quite complex, it is proposed that the name isomorphanthridizinium be used for the parent ion (II), showing the close structural relationship to morphanthridine and the morphanthridizinium ion (I). Table I summarizes the reaction conditions

TABLE I

ISOMORPHANTHRIDIZINIUM PERCHLORATES



	R	R1	R2	R3	Time, Hr.	Yield, %
	H	H	H	CH_3	117	0[a]
VI	H	OCH_3	H	CH_3	24	33[b]
VIII	H	O—CH_2—O		CH_3	1.5	19[c]
IX	OCH_3	OCH_3	H	CH_3	2	18[d]
X	H	OCH_3	H	C_6H_5	26	8[e]

[a] Cyclization attempted in boiling hydrobromic acid. No better results in boiling concentrated hydrochloric acid, the medium used in the cyclization of the alkoxyl analogs. [b] In 1.5 hr. the yield was 29% (based on the benzyl halide). [c] At 0.5 hr. the yield was 5%. [d] Yield based on the benzyl halide used. [e] At 1.5 hr. the yield was 4%. Quaternary salts obtained from 2-phenacylpyridine and piperonyl bromide or 2,3-dimethoxybenzyl bromide failed to cyclize.

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[1] For the preceding communication of this series, see *J. Org. Chem.*, **26**, 3273 (1961).

[2] Monsanto Chemical Co. Fellow 1959–1960. This research was supported in part by a research grant (NSF-G6215) of the National Science Foundation.

[3] K. B. Moser and C. K. Bradsher, *J. Am. Chem. Soc.*, **81**, 2547 (1959).

[4] M. G. J. Beets, *Rec. trav. chim.*, **63**, 120 (1944).

[5] M. J. Weiss and C. R. Hauser, *J. Am. Chem. Soc.*, **71**, 2023 (1949).

used and the yields of the isomorphanthridizinium perchlorates which have been synthesized. All yields (unless otherwise stated) are based on the amount of starting ketone since the intermediate quaternization product (*e.g.*, V) was not usually isolated.

In general the cyclization to form the isomorphanthridizinium system (II) appears to be more difficult than that to produce the closely related morphanthridizinium (I) system. Not only did 1-benzyl-2-acetonylpyridinium ion (V. R = H) fail to cyclize under conditions which afforded a 75% yield of cyclization product from the isomeric 1-acetonyl-2-benzylpyridinium ion (VII), but in the activated ions in which cyclization did occur, the yields of isomorphanthridizinium salts were consistently inferior to those observed in the preparation of the analogous morphanthridizinium derivatives.

No attempt was made to find the optimum conditions for the formation of isomorphanthridizinium salts, and the yields could probably be improved. In any case, the starting materials used in the synthesis are so readily available that the new heterocyclic system may be regarded as one that is easily accessible.

EXPERIMENTAL

All analyses were done by Dr. A. Schoeller, Kronach, Germany. Ultraviolet absorption spectra were taken in 95% ethanol with 1-cm. matched quartz cells using either the Warren Spectracord (W) or the Cary Spectrophotometer (C). Melting points were determined using the Mel-Temp capillary apparatus and were uncorrected.

1-Benzyl-2-acetonylpyridinium (V. R = H) perchlorate. Four grams of 2-acetonylpyridine (III)[4] and 5.3 g. of benzyl bromide were dissolved in 20 ml. of absolute ethanol and refluxed for 3 hr. The solvent was removed under vacuum and the residue washed with ether. The residual oil was dissolved in methanol and precipitated as the perchlorate by addition of perchloric acid, affording 3.1 g. (32%) m.p. 143–145°. The analytical sample was obtained from methanol as white rectangular prisms, m.p. 144.5–146°.

Anal. Calcd. for $C_{15}H_{16}ClNO_5$: C, 55.30; H, 4.84; N, 4.30. Found: C, 55.40; H, 5.07; N, 4.56.

Attempted cyclization of 1-benzyl-2-acetonylpyridinium (V. R = H) bromide. Four grams of 2-acetonylpyridine (III) was quaternized with benzyl bromide as described above, and the crude, orange, ether-insoluble bromide salt was heated for 116 hr. with 50 ml. of 48% hydrobromic acid. The crude product, isolated as the perchlorate after evaporation of the hydrobromic acid, was largely uncyclized material as judged by the strong infrared absorption peak at 5.75 μ. Negative results were also obtained when cyclization attempts were made in concentrated hydrochloric acid (120 hr.) liquid hydrogen fluoride (24 hr.) and hot (140–160°) polyphosphoric acid.

8-Methoxy-11-methylisomorphanthridizinium (VI) *perchlorate.* A mixture containing 4.8 g. of 2-acetonylpyridine (III), 8.0 g. of *m*-methoxybenzyl bromide,[6] and a few drops of dimethylformamide was allowed to stand for 75 hr. at room temperature. The resulting gum was washed with ethyl acetate and ether and then dissolved in 80 ml. of concd. hydrochloric acid. After the mixture had been refluxed for 25 hr. the acid was removed under vacuum. The fluorescent brown residue was dissolved in methanol and precipitated as an oil by addition of dilute perchloric acid. The oil was cooled and triturated with ethyl acetate yielding a solid which once recrystallized from methanol afforded 4.0 g. (33%) of a bright yellow-green solid, m.p. 228–231°. The analytical sample was prepared as irregular yellow-green prisms from methanol, m.p. 234.5–236°; (W) λ_{max} (log ε) 231(4.21), 275(4.05), 363 mμ (3.96); λ_{min} 258(3.93), 313 mμ (3.43).

Anal. Calcd. for $C_{16}H_{16}ClNO_5$: C, 56.89; H, 4.78; N, 4.15. Found: C, 56.85; H, 4.90; N, 4.44.

A similar experiment in which cyclization in hydrochloric acid was permitted to continue for only 1.5 hr. afforded a 29% yield of the desired product.

Oxidation of 8-methoxy-11-methylisomorphanthridizinium perchlorate to 4-methoxyphthalic acid. To a solution containing 1.30 g. of 8-methoxy-11-methylisomorphanthridizinium (VI) perchlorate and 0.48 g. of sodium hydroxide in 100 ml. of water, heated on a steam bath, small portions of potassium permanganate were added until the characteristic permanganate color persisted for 1 hr. The resulting solution was acidified and the manganese dioxide removed by filtration. The combined filtrate and wash solutions were saturated with sodium sulfate and extracted with ether. The ethereal solution was dried and concentrated and the residue crystallized from ethanol-benzene as colorless crystals, m.p. 160–162°. A mixed melting point with a sample of 4-methoxyphthalic acid (lit.,[7] m.p. 160°) obtained by permanganate oxidation of 2-methyl-4-methoxybenzoic acid[8] gave no depression.

8-Methoxy-11-phenylisomorphanthridizinium (X) *perchlorate.* A mixture of 4.1 g. of 2-phenacylpyridine[5] and 4.6 g. of *m*-methoxybenzyl bromide plus a few drops of dimethylformamide was warmed on the steam bath until solution occurred. The crude salt, isolated in the usual way, was cyclized in hydrochloric acid. The product (as the perchlorate) crystallized from methanol, affording 0.8 g. (8%) of product, m.p. 277–279°. An analytical sample, crystallized from methanol as tiny yellow needles, m.p. 286–286.5°, (C) λ_{max} (log ε), 244(4.07), 288 mμ(4.01); λ_{min}, 231(4.01), 266(3.87), 328 mμ (3.46).

Anal. Calcd. for $C_{21}H_{18}ClNO_5$; C, 63.08; H, 4.54; N, 3.50. Found: C, 63.00; H, 4.52; N, 3.63.

In a similar run in which refluxing in hydrochloric acid was limited to 1.5 hr. only 4% yield of cyclized product was obtained.

7,8-Dimethoxy-11-methylisomorphanthridizinium perchlorate. The crude quaternary salt obtained by reaction of 3.1 g. of 2-acetonylpyridine and 4.6 g. of 2,3-dimethoxybenzyl bromide,[9] was isolated by vacuum evaporation and cyclized in boiling hydrochloric acid. The product isolated after 2 hr. (as the perchlorate) and recrystallized from methanol gave 1.34 g. (18%) of yellow product, m.p. 204–208°. The analytical sample was obtained as yellow needle-like clusters, m.p. 224–226°, (C) λ_{max} (log ε), 249(3.96), 278(3.94), 365 mμ(3.91); λ_{min} 242(3.96), 258(3.91) and 319 mμ(3.44).

Anal. Calcd. for $C_{17}H_{18}ClNO_6$: C, 55.51; H, 4.93; N, 3.81. Found: C, 55.36; H, 5.03; N, 3.85.

8,9-Methylenedioxy-11-methylisomorphanthridizinium (VIII) *perchlorate.* Starting with piperonyl bromide and 2-acetonyl pyridine[4] and following the procedure used in the preparation of the 8-methoxy analog (VI), the crude perchlorate salt (VIII) 277–285° was prepared in 19% yield.

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(6) E. Späth, *Monatsh*, **34**, 1998 (1913).

(7) O. Jacobsen, *Ber.*, **16**, 1962 (1883).

(8) We are indebted to Dr. William Q. Beard for the sample of 2-methyl-4-methoxybenzoic acid used.

(9) R. D. Haworth and W. H. Perkin, Jr., *J. Chem. Soc.*, **105**, 1456 (1914).

The analytical sample crystallized from methanol as long yellow-green plates, m.p. 288–290°, (C) λ_{max} (log ϵ), 247-(3.93), 283 mμ(3.69); λ_{min} 233(3.74), 271(3.61), 327 mμ-(3.16).

Anal. Calcd. for $C_{16}H_{14}ClNO_6$: C, 54.63; H, 4.01; N, 3.98. Found: C, 54.67; H, 4.17; N, 3.96.

DURHAM, N. C.

[CONTRIBUTION FROM THE CHEMISTRY RESEARCH LABORATORY, AERONAUTICAL RESEARCH LABORATORIES, AIR FORCE RESEARCH DIVISION, AIR RESEARCH AND DEVELOPMENT COMMAND AND THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA AT LOS ANGELES]

The Synthesis of Spiro[cyclohexane-1,9'-fluorene] and Related Compounds[1]

SIDNEY BALDWIN

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The synthesis of the title compound (VI) is described (Chart I). A more direct route to the key intermediate spiro [cyclohexane-1,9'-fluoren]-4-one (V) is provided by the cyclization of 9,9-fluorenedipropionitrile (II) to 3-cyano-4-aminospiro-[Δ^3-cyclohexene-1,9'-fluorene] (VII) by a catalytic quantity of potassium *t*-butoxide in *t*-butyl alcohol followed by hydrolysis to the spiro ketone V in an acetic-phosphoric acid mixture. Infrared and ultraviolet spectral evidence is presented for the entirely enolic structures of 3-carbomethoxyspiro [cyclohexane-1,9'-fluoren]-4-one (IVa) and 3-carboxamidospiro-[cyclohexane-1,9'-fluoren]-4-one (VIII), respectively. The structure and spectra of the interesting diketo spirane, 11,12-dihydro-1H,10H-benzo[*h,i*]fluoranthene-3,10-(2H)-dione (XI), are also discussed.

Because spiranes are rigid molecules they may show unusual transport properties in the liquid state. It was therefore decided to investigate this class of compounds, initially restricted to five- or six-membered carbocyclic rings, as part of a general program to correlate physical properties with certain structural features.

A search of the literature at the inception of this work revealed no generally applicable method for the synthesis of spirocyclohexane compounds.[2] It occurred to us that an attractive synthetic route to these compounds is offered *via* the dicyanoethylation[3a] of the active methylene group contained in the ring of a cyclic compound, followed by cyclization of the resulting γ,γ-disubstituted dinitrile or diacid or diester derived therefrom.[4] Other workers have employed similar sequences with acyclic active methylene compounds to obtain 4-substituted cyclohexanones[5a-d] and piperidones.[5e-i] We report here the application of this method to the synthesis of spiro[cyclohexane-1,9'-fluorene] (VI) and related compounds as outlined in Chart I.[6] The dinitrile II obtained by cyanoethylation of fluorene[3b,7] was converted directly to the dimethyl ester IIIa by hydrogen chloride in methanol and

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(1) Presented before the Division of Organic Chemistry at the 137th meeting of the American Chemical Society, Cleveland, Ohio, April, 1960, Abstr. p. 29-O.

(2) Recently methods differing from those reported herein for the synthesis of spirocyclohexane-type compounds have been published. *Cf.* (a) M. Mousseron, R. Jacquier, and H. Christol, *Compt. rend.*, **239**, 1805 (1954); *Bull. soc. chim. France*, 346 (1957); M. Mousseron, H. Christol, and F. Plenat, *Compt. rend.*, **245**, 1281 (1957); (b) K. Heyns and A. Heins, *Angew. Chem.*, **68**, 414 (1956); *Ann.*, **604**, 133 (1957); (c) S. Winstein and R. Baird, *J. Am. Chem. Soc.*, **79**, 756 (1957); R. Baird and S. Winstein, *J. Am. Chem. Soc.*, **79**, 4238 (1957); (d) W. R. Hatchard, *J. Am. Chem. Soc.*, **80**, 3640 (1958).

(3) (a) H. S. Bruson, *Org. Reactions*, **V**, 79 (1949); (b) 112 (1949).

(4) When this work was started in July 1951, there were no recorded references to the use of this method for spirane synthesis. Subsequently, however, other workers have used this same approach in the synthesis of various spirocyclohexane compounds. The method of ring closure is indicated in parentheses. (a) R. Ya. Levina, N. P. Shusherina, and T. A. Kaminskaya, *Doklady Akad. Nauk, S.S.S.R.*, **86**, 79 (1952), *cf. Chem. Abstr.*, **47**, 4849 (1953) (pyrolysis of diacid with barium hydroxide). Reference to spirane synthesis appears as a footnote only in the original article without experimental details or physical constants; (b) R. P. Mariella and R. J. Clutter, Abstracts of Papers, 126th Meeting, American Chemical Society, 59-O (1954), *cf.* R. P. Mariella, R. Clutter, and H. G. Ebner, *J. Org. Chem.*, **20**, 1702 (1955) (pyrolysis of diacid with lead oxide); (c) R. H. Burnell and W. I. Taylor, *J. Chem. Soc.*, 3486 (1954) (Dieckmann condensation); (d) D. A. Stauffer and O. E. Fancher, U. S. Pat. **2,647,896** (1953), *cf. Chem. Abstr.*, **48**, 9405 (1954) and *J. Org. Chem.*, **25**, 935 (1960) (Dieckmann condensation), (sodium-potassium sand on dinitrile—*i.e.*, Thorpe reaction); (e) G. D. Johnson, W. B. Lindsey, and B. R. Jones, *J. Am. Chem. Soc.*, **78**, 461 (1956) (Dieckmann condensation); (f) K. Sheng and H. Chi-Yi, *Acta Chim. Sinica*, **22**, 138 (1956) (Dieckmann condensation). The latter journal is not abstracted by Chemical Abstracts Service. A reproduction of this article was obtained from the library of the Chemical Society, London, England; (g) F. M. Dean and K. Manunapichu, *J. Chem. Soc.*, 3112 (1957). The following cyclization attempts were unsuccessful; (lithium ethylanilide on dinitrile—*i.e.*, Ziegler-Thorpe reaction), (Dieckmann condensation on diester), (acetic anhydride on diacid); (h) P. McCloskey, *J. Chem. Soc.*, 4732 (1958) (Dieckmann condensation).

(5) (a) M. Rubin and H. Wishinsky, *J. Am. Chem. Soc.*, **68**, 838 (1946); (b) R. L. Frank and J. B. McPherson, Jr., *J. Am. Chem. Soc.*, **71**, 1387 (1949); (c) F. F. Blicke and E. Tsao, *J. Am. Chem. Soc.*, **75**, 3999 (1953); (d) E. C. Horning, M. G. Horning, N. J. Fish, and M. W. Rutenberg, *J. Am. Chem. Soc.*, **74**, 773 (1952); (e) G. B. Bachman and R. S. Barker, *J. Am. Chem. Soc.*, **69**, 1535 (1947); (f) R. C. Fuson, W. E. Parham, and L. J. Reed, *J. Am. Chem. Soc.*, **68**, 1239 (1946); (g) S. M. McElvain and G. Stork, *J. Am. Chem. Soc.*, **68**, 1049 (1946) and earlier references cited therein; (h) A. A. Cook and K. J. Reed, *J. Chem. Soc.*, 399 (1945); (i) S. M. McElvain and R. E. McMahon, *J. Am. Chem. Soc.*, **71**, 901 (1949).