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Aromatic Cyclodehydration. LV.[1] Quaternizations with Chloroacetaldoxime

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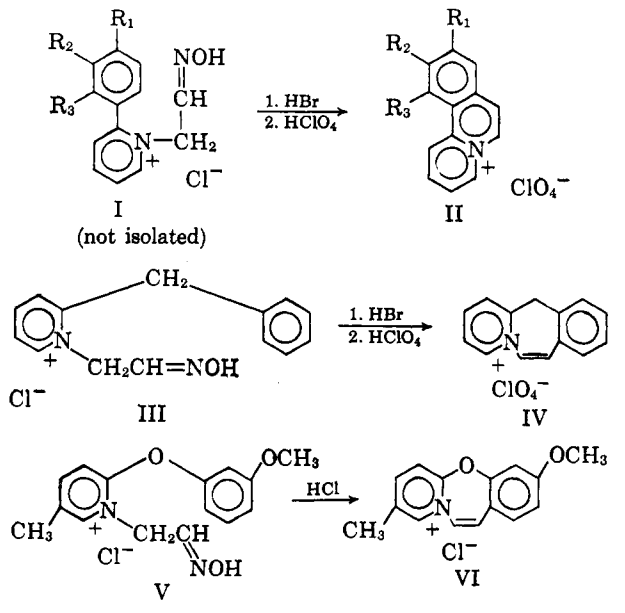
Previous attempts to obtain unsubstituted benzo[*a*]-quinolizinium salts[3] by the cyclodehydration method have been unsuccessful. It was found that chloro-, bromo-, and iodoacetals would not form quaternary salts with 2-phenylpyridine, while bromopyruvic acid afforded only the hydrobromide of the starting material.[4]

As the α-haloacetaldehydes exist predominantly as trimers or polymers, and therefore display low reactivity to quaternization, it was felt that an α-haloacetaldoxime might prove more reactive. The presence of a double bond in chloroacetaldoxime should activate the α-methylene group in the same manner as the olefin in allyl bromide or the carbonyl in bromoacetone. This activation by the carbon–nitrogen double bond in the oxime should facilitate the displacement of a halogen on the α-methylene group and permit quaternization with a tertiary amine. Our results confirm this hypothesis.

Quaternization of 2-phenylpyridine proceeded readily with chloroacetaldoxime in tetramethylene sulfone.



Cyclization with hydrobromic acid gave a mixed salt which on addition of perchloric acid was converted to benzo[*a*]quinolizinium perchlorate (II).[5] Similar procedures carried out with the three 2-tolylpyridines gave the expected methylbenzo[*a*]quinolizinium perchlorates (II, $R_1 = CH_3$; II, $R_2 = CH_3$; and II, $R_3 = CH_3$). Confirmation of cyclization in each case was given by the ultraviolet absorption spectrum of the product.

The low yield of 11-methylbenzo[*a*]quinolizinium perchlorate (12%) is apparently due to steric inhibition and is comparable to that of the 7,11-dimethyl analog (9%) reported previously.[6]

This method was successfully extended to include the preparation of the unsubstituted morphanthridizinium perchlorate[7] (IV) and a benz[*f*][1,3]oxazepinium chloride[8] (VI) having no substituent on the central nucleus.

Experimental

All analyses were carried out by Dr. Ing. A. Schoeller, Kronach, Germany. The melting points were determined in capillary tubes in a Mel Temp apparatus and are uncorrected. Ultraviolet absorption spectra were measured in 95% ethanol using 1-cm. quartz cells with a Cary Model 14 spectrophotometer. The asterisk (*) is used to denote a shoulder.

Chloroacetaldoxime.—To 40 g. of chloroacetaldehyde diethyl acetal (or the dimethyl acetal) was added a solution of 96 g. of hydroxylamine hydrochloride in 100 ml. of water and the mixture was stirred at room temperature for 72 hr. The resultant single phase solution was extracted continuously with ether in an ether extractor for 3 days. The ether extract was washed three times with water and dried over anhydrous calcium chloride. The ether was removed under vacuum (aspirator) at room temperature with slight warming to remove the final traces of solvent. The colorless oil which solidified in the refrigerator was sufficiently pure for the quaternization reactions; yield, 20 g. (85%). A sample on distillation had b.p. 64.5° (20 mm.), lit.[9] b.p. 61° (20 mm.).

Benzo[*a*]quinolizinium Perchlorate (II).—A solution containing 1 g. (0.0064 mole) of 2-phenylpyridine and 1 g. (0.011 mole) of chloroacetaldoxime in 3 ml. of dry tetramethylene sulfone was allowed to stand for 12 days in a stoppered flask at room temperature. The resultant dark viscous oil was triturated with ethyl acetate but could not be crystallized, nor could a solid perchlorate be formed by the addition of perchloric acid to a portion of it. The crude product was dissolved in 20 ml. of 48% hydrobromic acid and heated under reflux for 24 hr. The acid was removed under vacuum (aspirator) and the resultant mixed salt, isolated as a dark gum, was dissolved in 5 ml. of water. Addition of perchloric acid gave the perchlorate; yield 0.6 g. (35%), m.p. 195–196°. Crystallization from methanol (charcoal) afforded the pure product as colorless needles, m.p. 196–197° (lit.[3] m.p. 197°); λ_{max} (log ε), 217 (4.29), 222 (4.32), 237 (4.28), 256* (4.08), 269 (4.23), 278 (4.28), 323 (3.70), 337 (4.01), 354 mμ (4.14).

Anal. Calcd. for $C_{13}H_{10}ClNO_4$: C, 55.82; H, 3.79; N, 5.27. Found: C, 56.05; H, 3.72; N, 5.02.

Quaternization of 2-phenylpyridine with chloroacetaldoxime in refluxing acetone proved less satisfactory due to the greater decomposition encountered.

9-Methylbenzo[*a*]quinolizinium Perchlorate (II, $R_1 = CH_3$).—The quaternization of 2 g. of 2-(4-tolyl)pyridine by reaction with 2 g. of chloroacetaldoxime in dry tetramethylene sulfone was carried out over 6 days. Trituration with ethyl acetate, as previously described, gave a gum which was heated for 24 hr. under reflux with 20 ml. of hydrobromic acid. The perchlorate prepared as for II was crystallized (charcoal) from methanol; yield, 1.5 g. (45%); m.p. 227–229°. The analytical sample

(1) For the preceding communication of this series, see *J. Org. Chem.*, **28**, 3070 (1963).

(2) This research was supported by a research grant (CA-05509) of the National Cancer Institute of the National Institutes of Health.

(3) E. E. Glover and G. Jones [*J. Chem. Soc.*, 3021 (1958)] have reported the synthesis of benzo[*a*]quinolizinium perchlorate from 1-cyanoisoquinoline by a 4-step route. The present 2-step procedure, however, offers considerable advantage in its simplicity.

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

(5) All R groups not otherwise specified are assumed to be hydrogen.

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

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prepared by recrystallization from methanol was obtained as colorless prisms, m.p. 231–232°; λ_{max} (log ϵ), 219* (4.33), 225 (4.40), 242 (4.33), 272 (4.38), 278* (4.35), 308* (3.76), 323 (3.83), 338 (4.11), 354 mμ (4.26).

Anal. Calcd. for $C_{14}H_{12}ClNO_4$: C, 57.25; H, 4.12; N, 4.77. Found: C, 57.49; H, 4.43; N, 4.87.

The **picrate** crystallized from methanol as yellow needles, m.p. 177–178.5°.

Anal. Calcd. for $C_{20}H_{14}N_4O_7$: C, 56.87; H, 3.34; N, 13.27. Found: C, 56.60; H, 3.21; N, 13.38.

10(?)-Methylbenzo[*a*]quinolizinium Perchlorate (II, R_2 = CH_3).—This was prepared in a similar manner to its isomer (II) from 2 g. of 2-(3-tolyl)pyridine and 2 g. of chloroacetaldoxime. The perchlorate was crystallized from methanol (charcoal); yield 2 g. (61%), m.p. 221–224°. Recrystallization three times from methanol gave the analytical sample as colorless prisms, m.p. 231–232°; λ_{max} (log ϵ) 218* (4.25), 224 (4.32), 236* (4.36), 240 (4.37), 264 (4.17), 276* (4.20), 284 (4.30), 330 (3.63), 344 (3.94), 360 mμ (4.09).

Anal. Calcd. for $C_{14}H_{12}ClNO_4$: C, 57.25; H, 4.12; N, 4.77. Found: C, 56.85; H, 4.12; N, 4.76.

The **picrate** crystallized from methanol as yellow needles, m.p. 210–215°, with previous softening.

Anal. Calcd. for $C_{20}H_{14}N_4O_7$: C, 56.87; H, 3.34; N, 13.27. Found: C, 56.26; H, 3.71; N, 13.02.

11-Methylbenzo[*a*]quinolizinium Perchlorate (II, R_3 = CH_3).—Treatment of 1 g. of 2-(2-tolyl)pyridine with 1 g. of chloroacetaldoxime by the usual procedure over 12 days and heating the quaternization product under reflux for 65 hr. in 20 ml. of hydrobromic acid afforded 0.20 g. (12%) of tan colored crystals, isolated as the perchlorate. Recrystallization from methanol–ethyl acetate gave the product as light tan prisms, m.p. 209–210°; λ_{max} (log ϵ) 220 (4.62), 274 (4.69), 330 (3.77), 344 (3.97), 360 mμ (4.06).

Anal. Calcd. for $C_{14}H_{12}ClNO_4$: C, 57.25; H, 4.12; N, 4.77. Found: C, 57.61; H, 4.35; N, 4.99.

The **picrate** crystallized from methanol as yellow needles, m.p. 184–185°.

Anal. Calcd. for $C_{20}H_{14}N_4O_7$: C, 56.87; H, 3.34; N, 13.27. Found: C, 56.87; H, 3.16; N, 13.36.

1-(2-Oximidoethyl)-2-benzylpyridinium Chloride (III).—A solution containing 2 g. (0.012 mole) of 2-benzylpyridine and 1.8 g. (0.019 mole) of chloroacetaldoxime in 3 ml. of dry tetramethylene sulfone was allowed to stand in a stoppered flask at room temperature. Quaternization proceeded rapidly and after 2 days the crystalline product was collected and recrystallized from methanol–ethyl acetate; yield, 2.2 g. (71%); m.p. 204–206°. Further recrystallization from methanol–ethyl acetate gave the pure compound as colorless prisms, m.p. 205–207°; λ_{max} (log ϵ) 204 (4.17), 264* (3.73), 268 (3.75), 274* mμ (3.70).

Anal. Calcd. for $C_{14}H_{15}ClN_2O$: C, 63.99; H, 5.75; N, 10.65. Found: C, 64.18; H, 5.76; N, 10.95.

Morphanthridizinium Perchlorate (IV).—A solution of 2 g. (0.0074 mole) of the quaternary salt (III) in 20 ml. of 48% hydrobromic acid was heated under reflux for 40 hr. The acid was removed in the usual manner and the red-brown residue taken up in a small volume of water. Addition of perchloric acid gave the perchlorate which separated on cooling as a pale yellow microcrystalline material. Recrystallization from methanol–ethyl acetate afforded the pure product as colorless leaflets; yield, 1.6 g. (81%); m.p. 182–183°; λ_{max} (log ϵ), 225* (4.12), 282 (3.69), 318 mμ (3.83).

Anal. Calcd. for $C_{14}H_{12}ClNO_4$: C, 57.25; H, 4.12; N, 4.77. Found: C, 57.04; H, 4.21; N, 5.06.

5-Methyl-1-(oximidoethyl)-2-(3-methoxyphenoxy)pyridinium Chloride (V).—Quaternization of 1 g. of 5-methyl-2-(3-methoxyphenoxy)pyridine[5] with chloroacetaldoxime followed the usual procedure, and the mixture was allowed to react for 17 days. The solid obtained by trituration with ethyl acetate crystallized from methanol–ethyl acetate as colorless plates; yield, 0.77 g. (66%); m.p. 158–160°; λ_{max} (log ϵ), 222 (3.97), 253* (2.30), 275* (3.53), 281 (3.60), 303 (3.71), 315 * mμ (3.66).

Anal. Calcd. for $C_{15}H_{17}ClN_2O_3$: C, 58.34; H, 5.55; N, 9.07. Found: C, 57.84; H, 5.53; N, 9.38.

The **perchlorate** crystallized from methanol–ethyl acetate as colorless prisms, m.p. 156–157°.

Anal. Calcd. for $C_{15}H_{17}ClN_2O_7$: C, 48.33; H, 4.60; N, 7.52. Found: C, 48.62; H, 4.48; N, 7.67.

3-Methoxy-8-methylpyrido[2,1-*b*]benz[*f*][1,3]oxazepinium Chloride (VI).—The quaternary salt (V) (0.5 g.) was cyclized by heating under reflux in concentrated hydrochloric acid for 24 hr. The acid was removed as usual and the residue recrystallized with difficulty from methanol–ethyl acetate to give a tan powder; yield, 0.25 g. (61%); m.p. 265° dec.; λ_{max} (log ϵ), 289 (3.70), 314 mμ (3.71).

Anal. Calcd. for $C_{15}H_{14}ClNO_2 \cdot 0.5\ H_2O$: C, 63.26; H, 5.23; N, 4.92. Found: C, 63.17; H, 5.58; N, 5.39.

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The Hoesch Condensation of Dihydro-β-tubanol with Benzyl Cyanides

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Several dimethylpyranoisoflavones, *e.g.*, jamaicin,[1] toxicarolisoflavone,[2] osajin,[3] and pomiferin,[3] have been isolated in recent years. However, the syntheses of these compounds have not been reported. This paper presents the Hoesch condensation of dihydro-β-tubanol with benzyl cyanides and the syntheses of 2,2-dimethyl-3,4-dihydropyranoisoflavones.

The Hoesch condensation of dihydro-β-tubanol (I)[4] with benzyl cyanide (II) afforded isomeric phenylacetyldihydro-β-tubanols, having m.p. 145–147 and 81–83°, respectively. On the basis of qualitative tests and spectral data, which are summarized in Table I, the former was found to be 8-phenylacetyldihydro-β-tubanol (III) and the latter to be the 6-phenylacetyl isomer IV. 6-Phenylacetyldihydro-β-tubanol thus obtained was converted into 2,2-dimethyl-3,4-dihydropyrano[5,6–7,8]isoflavone (V), m.p. 162–164°, according to the Späth–Venkataraman method.

2,4-Dimethoxybenzyl cyanide (VI) similarly reacted with I as described, affording 8-(2,4-dimethoxyphenylacetyl)dihydro-β-tubanol (VII), m.p. 117–118°, and 6-(2,4-dimethoxyphenylacetyl)dihydro-β-tubanol (VIII), m.p. 102–104°. According to the procedure mentioned previously the deoxybenzoin VIII was transformed into 2′,4′-dimethoxy-(2,2-dimethyl-3,4-dihydropyrano)[5,6–7,8]isoflavone (IX), m.p. 191–193°.

3,4-Methylenedioxybenzyl cyanide (X) and I gave 6-(3,4-methylenedioxyphenylacetyl)dihydro-β-tubanol (XI), m.p. 95–97°, and an unidentified compound $C_{18}H_{16}O_8$, m.p. 125–127°, under the Hoesch reaction conditions.

It is of interest to note that two 8-substituted dihydro-β-tubanols III and VII are soluble in aqueous alkali, whereas 6-substituted compounds IV, VIII, and XI are insoluble, in agreement with the general property of 2-hydroxydeoxybenzoins. In contrast to the 8-substituted dihydro-β-tubanols III and VII, the 6-substituted compounds IV, VIII, and XI showed an intense color

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