SYNTHESIS OF QUINOLINE-4-CARBOXYLIC ACID AND ITS DERIVATIVES

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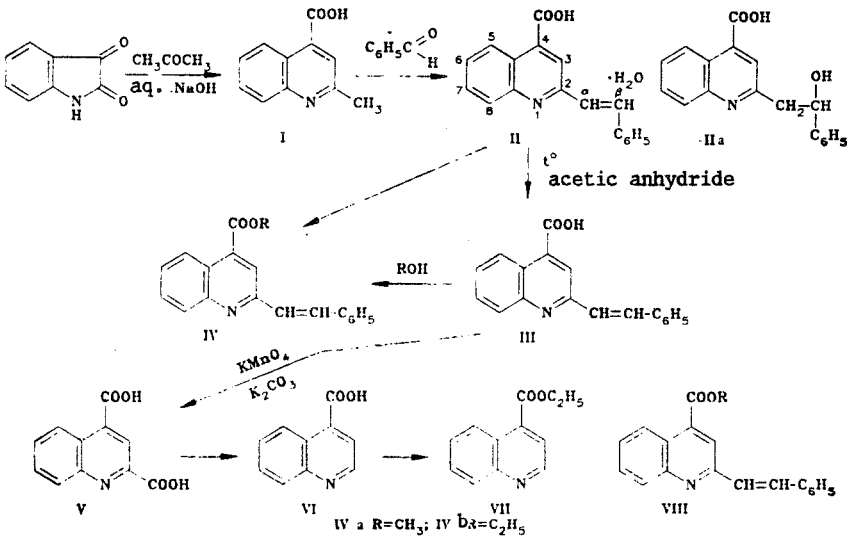
2-Methylquinoline-4-carboxylic acid was obtained by the reaction of isatin with acetone in the presence of an alkali. This acid was converted through a step involving (E)-2-styrylquinoline-4-carboxylic acid to quinoline-2,4-dicarboxylic acid, from which quinoline-4-carboxylic acid was obtained by refluxing in nitrobenzene. The structures of the synthesized compounds were confirmed by ^{1}H NMR spectroscopy using two-dimensional (2DJ) spectra.

Quinoline-2,4-dicarboxylic acid and quinoline-4-carboxylic acid are widely used to obtain biologically active substances based on them [1]. Methods for the synthesis of the former using pyruvic acid [2] and for the synthesis of the latter from lepidine [3] are known. In the present research we have developed a method for obtaining them from the accessible isatin.

Isatin is readily converted to 2-methylquinoline-4-carboxylic acid (I) when it is heated with acetone in the presence of aqueous alkali [1]. We have observed that 2-styrylquinoline-4-carboxylic acid monohydrate (II) rather than a secondary alcohol, as described in [7], is obtained in the reaction of acid I with excess benzaldehyde at 110-120°C. 2-Styrylquinoline-4-carboxylic acid (III) was obtained by the action of acetic anhydride on II at 140°C. Esterification of monohydrate II with ethanol in the presence of concentrated H_2SO_4 is accompanied by dehydration of II to ethyl 2-styrylquinoline-4-carboxylate (IVb). The structure of ester IVb was confirmed by comparison of its analytical and spectral characteristics with those for a sample obtained by esterification of acid III with ethanol in the presence of concentrated H_2SO_4 by the method in [4]. Methyl ester IVa was similarly synthesized.



Treatment of acid III with potassium permanganate in the presence of potassium carbonate at 4-6°C for 5-8 h leads to quinoline-2,4-dicarboxylic acid (V) [3]. Quinoline-4-carboxylic acid (VI) was obtained as a result of decarboxylation when it was refluxed in nitrobenzene. The structure of VI was confirmed by its esterification to ester VII and by the coincidence

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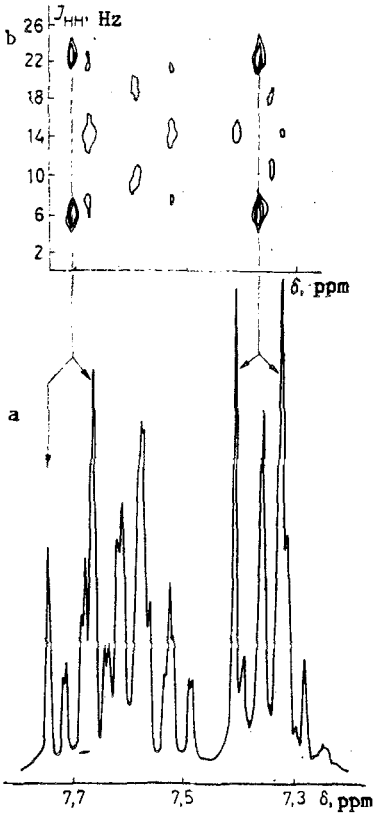

Fig. 1. Spectra of IVa at 7.2-7.8 ppm (the δ scales in Figs. 1a and 1b are identical): a) fragment of the ^{1}H NMR spectrum (in $CDCl_3$ + C_6D_6); b) 2DJ spectrum (45° projection, cross section parallel to the Jδ plane, signals of the α-H and β-H protons indicated by arrows).

of the analytical characteristics of VII with the characteristics for the ester obtained by the method in [5].

The structures of II-IVa, b were confirmed by IR spectroscopic data. It should be noted that, in addition to the presence in the spectra of carbonyl absorption bands of these compounds, one observes a band at 965-970 cm^{-1}, which can be ascribed to stretching vibrations of a CH=CH-trans fragment [6]. A similar band at 960 cm^{-1} is present in the spectrum of VIII obtained by the method in [7].

The ^{1}H NMR spectra of II-IV, in which, in addition to signals of an ethoxycarbonyl substituent (in IVa, b), one observes only signals at weak field (7.2-8.5 ppm) with an intensity of 12H, which correspond to 10 aromatic and 2 olefinic protons, are in agreement with the proposed structures of II-IV. The absence in the spectrum of II of signals of a CH_2—CH(OH) grouping makes it possible to exclude possible alternative structure IIa [7].*

In the spectra of all of the investigated compounds signals of 3-H, 5-H, and 8-H protons can be identified among the signals at 7.2-8.5 ppm; however, the assignment of the remaining signals is hindered by their marked overlapping.

In the case of IVa we were able to overcome this difficulty by means of the two-dimensional 2DJ spectrum (Fig. 1), in which two doublets at 7.38 and 7.71 ppm with spin-spin coupling constant (SSCC) $^3J \approx 16$ Hz were identified. The SSCC makes it possible to unambiguously assign these doublets to protons attached to a double bond trans-oriented relative to one another; this corresponds to an E configuration of IVa. Since II, III, and IVb are related to IVa by a method of synthesis that excludes the possibility of E,Z isomerization, it should be concluded that they are all E isomers. Compound VIII, in the spectrum of which [$CDCl_3$—C_6D_6 (6:1)] one can isolate a doublet (δ 7.89 ppm) with SSCC $^3J_{\alpha-H,\beta-H} = 16.3$ Hz, which corresponds to one of the olefin protons, corresponds to the same configuration.

*The mass spectrum of II (M^+ 275) corresponds to the proposed structure.

EXPERIMENTAL

The IR spectra of suspensions of the compounds in mineral oil were recorded with a Perkin-Elmer 457 spectrometer. The ^1H NMR spectra were obtained with XL-100A and XL-200 spectrometers. Column chromatography was carried out on activity II aluminum oxide and L 100/250 μm silica gel.

Compounds V-VII were obtained by the method in [3], while VIII was obtained by the method in [7].

2-Methylquinoline-4-carboxylic Acid (I). A mixture of 29.4 g (200 mmole) of isatin, 200 ml of acetone, and 170 ml of 20% NaOH solution was heated for 8 h. Workup gave 20 g (53%) of a product with mp 243-244°C (from water) (mp 243-245°C [1]).

2-Styrylquinoline-4-carboxylic Acid Monohydrate (II). A mixture of 3.75 g (20 mmole) of acid I and 12.5 g (120 mmole) of benzaldehyde was heated at 120°C for 3 h, after which it was cooled, and the precipitate was removed by filtration and washed with ethanol to give 4.05 g (69%) of a product with mp 294-295°C (from alcohol). IR spectrum: 3345 (OH), 965 cm^{-1} (CH=CH-trans). PMR spectrum (d_6-DMSO): 8.08 (d, 8-H, $^3J_{8-H,7-H}$ = 8.5 Hz), 8.23 (s, 3-H), 8.62 ppm (d, 5-H, $^3J_{5-H,6-H}$ = 8.3 Hz); the remaining aromatic and olefinic protons form a multiplet at 7.2-8.5 ppm. Found: C 73.9; H 5.0; N 4.8; H_2O 7.0%. $C_{18}H_{13}NO_2 \cdot H_2O$. Calculated: C 73.7; H 5.1; N 4.8; H_2O 6.1%.

2-Styrylquinoline-4-carboxylic Acid (III). A mixture of 0.59 g (2 mmole) of monohydrate II and 10 ml of acetic anhydride was heated at 140°C for 2 h, after which the acetic anhydride was partially removed by distillation to give 0.52 g (95.3%) of a product with mp 295-296°C (from DMSO) (mp 294-295°C [4]). IR spectrum: 2480 (OH), 965 cm^{-1} (CH=CH-trans). Found: C 78.4; H 4.7; N 4.7%. $C_{18}H_{13}NO_2$. Calculated: C 78.5; H 4.8; N 5.1%.

Methyl 2-Styrylquinoline-4-carboxylate (IVa). A mixture of 0.87 g (3 mmole) of II, 10 ml of methanol, and 2 ml of concentrated H_2SO_4 was refluxed for 2 h, after which it was cooled, and the solvent was removed by distillation to give 0.93 g of the reaction product, which was purified by chromatography with a column packed with aluminum oxide (elution with chloroform) to give 0.69 g (80%) of a product with mp 100-102°C. IR spectrum: 1725 (C=O), 975 cm^{-1} (CH=CH-trans). Mass spectrum: M^+ 289. PMR spectrum ($CDCl_3$): 4.03 (s, OCH_3), 8.14 (s, 3-H), 8.11 (d, 8-H, $^3J_{8-H,7-H}$ = 8.6 Hz), 8.69 ppm (d, 5-H, $^3J_{5-H,6-H}$ = 8.3 Hz); the remaining aromatic and olefinic protons form a multiplet at 7.3-7.8 ppm (9H). Found: C 78.8; H 5.0; N 4.7%. $C_{19}H_{15}NO_2$. Calculated: C 78.9; H 5.2; N 4.8%.

Ethyl 2-Styrylquinoline-4-carboxylate (IVb). A) The reaction of 0.87 g (3 mmole) of II, 10 ml of anhydrous ethanol, and 2 ml of concentrated H_2SO_4 under the conditions of the preceding experiment gave 0.65 g (72%) of IVb with mp 76-77°C (mp 76°C [4]). IR spectrum: 1730 (C=O), 970 cm^{-1} (CH=CH-trans). PMR spectrum ($CDCl_3$): 1.50 (t, $OCH_2\mathbf{CH_3}$), 4.58 (q, $O\mathbf{CH_2}$-CH_3), 8.15 (d, 8-H, $^3J_{8-H,7-H}$ = 8.6 Hz), 8.17 (s, 3-H), 8.72 ppm (d, 5-H, $^3J_{5-H,6-H}$ = 8.6 Hz) the remaining aromatic and olefinic protons form a multiplet at 7.3-7.8 ppm (9H).

B) The reaction of 0.27 g (1 mmole) of III, 5 ml of anhydrous ethanol, and 0.65 ml of concentrated H_2SO_4 under the conditions of the preceding experiment gave 0.18 g of IVb (mp 72°C), which was purified by chromatography with a column packed with silica gel (elution with chloroform) to give colorless crystals with mp 76-77°C (from petroleum ether). No melting-point depression was observed for a mixture of a sample of this product with a sample of the ester obtained from II.

2-Styrylquinoline (VIII). This compound was obtained by the method in [7]. IR spectrum: 960 (CH=CH-trans). PMR spectrum ($CDCl_3$): 8.06, 8.08 ppm (d, 5-H and 8-H, $J_{8-H,5-H} \approx J_{5-H,6-H} \approx 8.5$ Hz); the remaining aromatic and olefinic protons form a multiplet at 7.3-7.8 ppm (11H).

LITERATURE CITED

1. T. Ujiie, Chem. Pharm. Bull., 14, 461 (1966).
2. I. Houben, Methods of Organic Chemistry [Russian translation], Vol. 4, Book 2, Goskhimizdat, Moscow (1949), p. 906.
3. V. Brasyunas, Materials from the 26th Inter-VUZ Scientific Conference at Kaunas Medical Institute [in Russian], Vilnius (1978), p. 33.
4. H. John, J. Prakt. Chem., 117, 214 (1927).
5. A. D. Ainley and H. King, Proc. R. Soc., Ser. B, Biol. Sci., 125, 60 (1938).

6. L. Bellamy, Infrared Spectra of Complex Molecules, Methuen, London (1954).
7. A. Benreth, J. Parkt. Chem., 73, 383 (1906).

NEW CHIRAL ACYCLIC ANALOGS OF 2'-DEOXYNUCLEOSIDES

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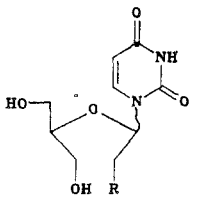
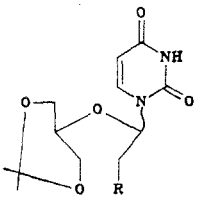
Convenient methods for the synthesis of chiral 2',3'-seco-2'-deoxynucleosides were developed. An isopropylidene protective group was used to block the 3',5'-hydroxy groups in 2',3'-seco-uridine. Conversion of the hydroxymethyl group to a methyl group was accomplished by chlorination with a mixture of CCl_4 and Ph_3P with subsequent reduction with n-Bu_3SnH. 2',3'-seco-2'-Deoxyuridine was obtained after deacetonation. The (S) enantiomer was similarly synthesized starting from 1-(α-D-arabinofuranosyl)uracil. 3'-O-tert-Butyldimethylsilyl-5'-O-(p-monomethoxytrityl)-2',3'-seco-2'-deoxyuridine, which has optically active centers at $C_{(1')}$ and $C_{(4')}$, was also synthesized.

This paper is a continuation of research devoted to obtaining chiral acyclic 2',3'-seconucleosides [1, 2] and is devoted to the development of methods for the synthesis of 5-hydroxy-4-hydroxymethyl-3-oxa-2(R and S)-pentyl derivatives of nucleic bases (2',3'-seco-2'-deoxynucleosides) in the case of uridine derivatives.

The conversion of uridine to redox derivative Ia was previously accomplished in low yields (see the literature cited in [1]). The use of chromatography on silica gel to isolate the product made it possible to increase the yield of analog Ia to 89%. Enantiomer Ib was similarly obtained in high yield starting from 1-(α-D-arabinofuranosyl)uracil [3]. It should be noted that the periodate oxidation of the trans-diol group takes place substantially slower [3] than that of the cis-diol group and is complete after 4 h at 20°C.



Ia,b; VIa,b



IIa,b-Va,b

I-VI a R-isomer; b S-isomer; I, II a,b R=OH; III a,b R=OBz; IV a, b R=Cl; V, VI a, bR=H

For the simultaneous blocking of the 3',5'-hydroxy groups* we used an isopropylidene protective group, the best method for the introduction of which was the reaction of triols Ia,b with acetone dimethylacetal in DMF in the presence of p-TsOH [4], which leads to acetonides IIa, b in 86-89% yields. The acetonation of analog Ia in the presence of 60% $HClO_4$ in acetone was described in [5]; the yield of product IIa was 45%.

The structures of the synthesized 2',3'-seco-nucleosides were confirmed by data from the PMR spectra (see Table 1), the complex character of which is explained by the presence of three $HOCH_2$ groups with diastereotopic protons. The spectra of analogs Ia, b and IIa, b correspond to the data in [1, 5]. For the subsequent proof of the structures of acetonides IIa, b we carried out benzoylation with benzoyl cyanide in dioxane in the presence of triethylamine [6]; derivatives IIIa, b were obtained in high yields. The benzoyl group shifts the signals of

*In the case of analogs I-XII for convenience we used the numbering of the atoms adopted for nucleosides.

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