LITERATURE CITED

1. H. Meyr, F. Bossert, and H. Horstman, Ann. Chem., No. 9, 1483 (1978).
2. B. Chylinska, Pol. J. Chem., 53, 1913 (1979).
3. Z. A. Bomika, Yu. É. Pelcher, G. Ya. Duber, A. A. Krauze, and É. E. Liepin'sh, Khim. Geterotsikl. Soedin., No. 10, 1377 (1979).
4. R. Balicki and P. Nantka-Namirski, Pol. J. Chem., 53, 2121 (1979).
5. C. Seoane, J. L. Soto, and M. R. Zamorano, Heterocycles, No. 5, 639 (1981).
6. A. A. Krauze, in: Fifth Youth Conference on Synthetic and Natural, Physiologically Active Compounds Dedicated to the Sixtieth Anniversary of Soviet Armenia [in Russian], Izd. Akad. Nauk Arm. SSR, Erevan (1980), p. 23.
7. V. F. Bystrov, Usp. Khim., 41, 512 (1972).
8. A. A. Krauze, Z. A. Bomika, A. M. Shestopalov, L. A. Rodinovskaya, Yu. É. Pelcher, G. Ya. Dubur, Yu. A. Sharanin, and V. K. Promonenkov, Khim. Geterotsikl. Soedin., No. 3, 377 (1981).
9. J. Kuthan, P. Neswadba, Z. Donnerova, and P. Trska, Collect. Czech. Chem. Commun., 42, 2152 (1977).
10. F. M. Menger and J. M. Smith, J. Am. Chem. Soc., 91, 4211 (1969).
11. E. P. Kohler and B. L. Souther, J. Am. Chem. Soc., 44, 2903 (1922).

DERIVATIVES OF 4-HYDROXYQUINOLINE-3-CARBOXYLIC ACID

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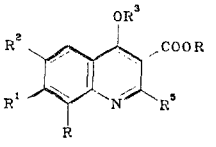
A new method for the synthesis of ethyl esters of 2-methyl-4-hydroxyquinoline-3-carboxylic acids has been proposed, and their condensation reaction with 5-nitrofurfural has been described. Data on their antiblastic activity has been presented.

Derivatives of 4-hydroxyquinoline-3-carboxylic acid have found application as coccidiostatic agents [1, 2]. Some of them have antibacterial [3, 4] and antiblastic activity [5].

For the purpose of finding new physiologically active substances in this series, we developed a method for the synthesis of ethyl 2-methyl-4-hydroxyquinoline-3-carboxylic acid and its derivatives (I-VIII) and investigated the condensation reaction of these compounds with 5-nitrofurfural (IX-XVIII).



I-XVIII

I $R=R^1=R^2=R^3=H$, $R^4=C_2H_5$, $R^5=CH_3$; II $R=R^1=R^3=H$, $R^2=R^5=CH_3$, $R^4=C_2H_5$; III $R=R^3=H$, $R^1=R^2=R^5=CH_3$, $R^4=C_2H_5$; IV $R=R^1=R^3=H$, $R^2=Br$, $R^4=C_2H_5$, $R^5=CH_3$; V $R=R^1=R^3=H$, $R^2=(CH_3)_2CH$, $R^4=C_2H_5$, $R^5=CH_3$; VI $R=R^2=R^3=H$, $R^1=Cl$, $R^4=C_2H_5$, $R^5=CH_3$; VII $R=OCH_3$, $R^1=R^2=R^3=H$, $R^4=C_2H_5$, $R^5=CH_3$; VIII $R=R^1=R^3=H$, $R^2=OCH_3$, $R^4=C_2H_5$, $R^5=CH_3$; IX $R=R^1=R^2=R^3=R^4=H$, $R^5=$ 5-nitrofurylvinyl; X $R=R^2=R^3=R^4=H$, $R^1=Cl$, $R^5=$ 5-nitrofurylvinyl; XI $R=R^1=R^3=R^4=H$, $R^2=OCH_3$, $R^5=$ 5-nitrofurylvinyl; XII $R=R^3=R^4=H$, $R^1=R^2=CH_3$, $R^5=$ 5-nitrofurylvinyl; XIII $R=R^1=R^2=H$, $R^3=COCH_3$, $R^4=C_2H_5$, $R^5=$ 5-nitrofurylvinyl; XIV $R=R^1=H$, $R^2=OCH_3$, $R^3=COCH_3$, $R^4=C_2H_5$, $R^5=$ 5-nitrofurylvinyl; XV $R=H$, $R^1=R^2=CH_3$, $R^3=COCH_3$, $R^4=C_2H_5$, $R^5=$ 5-nitrofurylvinyl; XVI $R=R^1=R^2=R^3=H$, $R^4=C_2H_5$, $R^5=$ nitrofurylvinyl; XVII $R=R^1=R^3=H$, $R^2=OCH_3$, $R^4=C_2H_5$, $R^5=$ 5-nitrofurylvinyl; XVIII $R=R^3=H$, $R^1=R^2=CH_3$, $R^4=C_2H_5$, $R^5=$ 5-nitrofurylvinyl

The method for obtaining ethyl 2-methyl-4-hydroxyquinoline-3-carboxylate not containing substituents in the benzene part of the quinoline nucleus is based on the condensation of

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aniline with acetylmalonic ester in the presence of iodine followed by cyclization of the aniline formed in boiling diphenyl oxide [6].

The experimental data obtained with the use of this method for the synthesis of various substituted derivatives of ethyl 2-methyl-4-hydroxyquinoline-3-carboxylate provide some basis to assume that the isolation of the reaction products will present considerable difficulties and that the yields will be low.

We showed that the reaction of the original substituted aniline with acetylmalonic ester can be carried out successfully when the reaction is conducted in a medium of dry benzene at 65-70°C for 16 h with the use of catalytic amounts of concentrated hydrochloric acid to accelerate the formation of the anil and with subsequent cyclization of the anil at 195-220°C without a solvent [8].

When the reaction of ethyl 2-methyl-4-hydroxyquinoline-3-carboxylate with 5-nitrofurfural is carried out in a medium of glacial acetic acid with prolonged heating, 2-[2'-(5"-nitro-2"-furyl)vinyl]-4-hydroxyquinoline-3-carboxylic acid (IX) forms. The introduction of a chlorine atom, a methoxy group, and a methyl group into the quinoline ring does not influence the course of the reaction (X-XII). The reaction takes place similarly in the presence of catalytic amounts of anhydrous zinc chloride. In a medium of acetic anhydride the reaction proceeds with the formation of the corresponding ethyl esters of 2-[2'-(5"-nitro-2"-furyl)-vinyl]-4-hydroxyquinoline-3-carboxylic acid (XIII-XV), whose hydrolysis results in the formation of acids XVI-XVIII. When the reaction is conducted in a mixture of glacial acetic acid and acetic anhydride, a mixture of product is formed. For example, XI and XIV are obtained with 13 and 42% yields, respectively. Compounds IX-XVIII are crystalline substances with colors ranging from light yellow to orange, which are difficultly soluble in water and organic solvents and soluble in DMSO and DMFA. Some physicochemical properties and data from the elemental analysis of all the compounds synthesized are given in Table 1.

The structure was proved by back synthesis and by PMR and IR spectra. The IR spectra show a strong absorption band at 1630-1650 cm^{-1}, which is characteristic of 4-hydroxyquinoline, and a band at 1700-1720 cm^{-1}, which is characteristic of the stretching vibrations of the carbonyl group. The compounds with a nitrofurylvinyl group show an absorption band at 960-980 cm^{-1} (δCH) and two bands at 1360 and 1540 cm^{-1} (νNO_2).

Ethyl esters I-VIII have characteristic chemical shifts of protons at δ 1.31 ($C-CH_3$), 2.43 ($\rangle C-CH_3$), 4.28 ($O-CH_2-C$), 7.60-8.20 (quinoline ring), 11.9 ppm ($-O-H$).

The PMR spectra of the compounds containing a nitrofurylvinyl group in position 2 of the quinoline ring (IX-XVIII) contain signals of protons in the furan ring, viz., two doublets at 7.20 and 7.80 ppm (J = 4.9 Hz), and protons of the vinyl group, viz., two doublets at 7.58 and 8.85 ppm (J = 16.0 Hz).

The antitumor effects of compounds IX-XVIII were studied on various test systems. Lymphoma L 5178 was found to be most sensitive to compound IX (the prolongation of the life of mice was 40%). Lymphoma L 1210, Lewis lung carcinoma, and Ehrlich ascites tumor are insensitive. When a methoxy or methyl group was introduced into the quinoline ring (XI and XII), low sensitivity of Ehrlich ascites tumor was noted (the prolongation of the life of mice was 40-48%). A similar effect was noted for compounds XIV and XV. Derivatives XVI-XVIII have a higher activity with respect to Ehrlich ascites tumor (the prolongation of the life of mice was 45-48%). Lymphatic leukemias L 5178 and L5178 V are insensitive to them.

EXPERIMENTAL

The IR spectra were recorded on a IKS-14 spectrophotometer (in liquid petrolatum and hexachlorobutadiene). The PMR spectra were obtained on a Bruker WH-90 instrument in 10% DMSO-d_6 solutions, and the chemical shifts were measured relative to the internal reference HMDS with an accuracy of 0.5% of the scan width. The pharmacological experimental part was carried out according to the method which we described previously in [9].

Ethyl 2-Methyl-4-hydroxy-6-methoxyquinoline-3-carboxylate (VIII). One or two drops of concentrated hydrochloric acid are added to a mixture of 15.2 g (0.1 mole) of p-anisidine, 20 g (0.1 mole) of acetylmalonic ester, and 50 ml of absolute benzene. The reaction mixture is heated at 65-70°C for 16 h. The water evolved is distilled off, and the residue is heated to 195-200°C and held for 5-15 min. After the mixture is cooled, 50 ml of ethanol are added, everything is thoroughly stirred, and the precipitate is filtered out. The latter is recrystallized from ethanol.

TABLE 1. Derivatives of 2-Methyl-4-hydroxyquinoline-3-carboxylic Acid

Compound	mp, deg C	Found, %			Empirical formula	Calculated, %			Yield, %
		C	H	N		C	H	N	
I	231—232	67,3	5,9	6,1	$C_{13}H_{13}NO_3$	67,5	5,7	6,1	62
II	252—253	67,7	6,2	5,6	$C_{14}H_{15}NO_3$	68,5	6,2	5,7	61
III	225—227	69,2	6,5	5,3	$C_{15}H_{17}NO_3$	69,5	6,6	5,4	40
IV	271—272	49,9	3,7	4,1	$C_{13}H_{12}BrNO_3$	50,3	3,9	4,5	36
V	193—194	70,2	6,7	5,5	$C_{16}H_{19}NO_3$	70,3	7,0	5,1	52
VI	286—287	59,0	4,6	5,5	$C_{13}H_{12}ClNO_3$	58,8	4,5	5,3	69
VII	215—216	64,6	5,9	5,5	$C_{14}H_{15}NO_4$	64,3	5,8	5,3	54
VIII	263—265	64,6	5,3	5,3	$C_{14}H_{15}NO_4$	64,3	5,8	5,3	81
IX	276—277	58,7	2,9	8,2	$C_{16}H_{10}N_2O_6$	58,9	3,1	8,6	47
X	>300	52,9	2,9	7,3	$C_{16}H_9ClN_2O_2$	53,3	2,5	7,8	52
XI	278—279	57,4	3,6	7,5	$C_{17}H_{12}N_2O_7$	57,3	3,4	7,8	57
XII	>300	60,9	3,9	8,1	$C_{18}H_{14}N_2O_6$	61,0	3,9	7,9	51
XIII	222—224	60,8	4,3	7,4	$C_{20}H_{16}N_2O_7$	60,6	4,1	7,1	78
XIV	189—191	58,9	4,4	6,9	$C_{21}H_{18}N_2O_8$	59,1	4,2	6,6	81
XV	188—190	61,9	4,6	6,7	$C_{22}H_{20}N_2O_7$	62,3	4,7	6,6	79
XVI	241—242	59,8	4,1	7,5	$C_{18}H_{14}N_2O_6$	61,0	3,9	7,9	89
XVII	240—243	59,6	4,1	7,3	$C_{19}H_{16}N_2O_7$	59,4	4,2	7,3	92
XVIII	238—240	62,2	4,5	7,6	$C_{20}H_{18}N_2O_6$	62,8	4,7	7,3	92

Compounds I-VII are obtained in a similar manner.

2-[2'-(5"-Nitro-2"-furyl)vinyl]-4-hydroxy-6-methoxyquinoline-3-carboxylic Acid (XI). A. A mixture of 2.61 g (0.01 mole) of quinoline VIII, 1.41 g (0.01 mole) of 5-nitrofurfural, and 25 ml of glacial acetic acid is heated at 135°C for 1 h. After the reaction mixture has cooled, the precipitate is filtered out, dried, and recrystallized from dimethylformamide. Compounds IX, X, and XII were obtained by this method.

B. The procedure for carrying out the condensation reaction with the use of anhydrous zinc chloride as a catalyst is similar to that previously described by us in [7]. The yields are, respectively, 47.2 (IX), 54.6 (X), 57.9 (XI), and 49.3% (XII).

Ethyl 2-[2'-(5"-nitro-2"-furyl)vinyl]-4-acetoxy-6-methoxyquinoline-3-carboxylate (XIV). A mixture of 2.61 g (0.01 mole) of compound VIII, 1.41 g (0.01 mole) of 5-nitrofurfural, and 30 ml of acetic anhydride is heated at the boiling point of the mixture for 30 min. After the reaction mixture has cooled (if a precipitate does not form), it is poured into ice water, and the precipitate is filtered out, dried, and recrystallized from dimethylformamide. Derivatives XII and XV are obtained in a similar manner.

Ethyl 2-[2'-(5"-nitro-2"-furyl)vinyl]-4-hydroxy-6-methoxyquinoline-3-carboxylate (XVII). A mixture of 4.26 g (0.01 mole) of compound XIV and 20 ml of concentrated hydrochloric acid is heated at the boiling point of the mixture for 30-40 min. After the mixture has cooled, the precipitate is filtered out, washed with water to a neutral reaction, dried, and recrystallized from dimethylformamide. This yields 3.52 g of derivative XVII (91.8%). Compounds XVI (89.2%) and XVIII (92.1%) are obtained by a similar method.

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LITERATURE CITED

1. C. F. Spencer, A. Engle, Yu. Chia-Nien, R. C. Fich, E. J. Watson, F. F. Ebeting, and C. A. Johnson, J. Med. Chem., 9, 934 (1966).
2. R. H. Mizzoni, F. Goble, J. Szanto, D. C. Maplesden, J. E. Brown, J. Boxer, and G. De Stevens, Experienta, 24, 1188 (1968).
3. G. Harkees, L. S. Schwab, and A. Vegotsky, J. Med. Chem., 17, No. 1, 137 (1974).
4. T. Irikura, H. Koga, and S. Murayama, French Patent No. 2,463,711; Chem. Abstr., 96, 6607 (1982).
5. E. A. Coats, K. J. Shuh, S. R. Milstein, C. S. Genther, D. M. Nene, J. Roesches, J. Schmidt, M. Pleiss, E. Wagner, and J. K. Baker, J. Med. Chem., 25, No. 1, 57 (1982).
6. J. D. London and J. Wellings, J. Chem. Soc., 3470 (1960).
7. S. A. Giller, M. Yu. Lidak, N. M. Sukhova, and K. K. Venter, Khim. Geterotsikl. Soedin., No. 2, 253 (1976).
8. M. Yu. Lidak, N. M. Sukhova, and T. V. Kapina, USSR Patent No. 567-287; published in Byull. Izobr., No. 33, 312 (1981).

9. É. Lukevits, T. V. Lapina, N. M. Sukhova, A. A. Zidermane, A. Zh. Dauvarte, and V. A. Voronova, Khim.-farm. Zh., No. 11, 53 (1981).

AMINE—AMMONIUM SALT SYSTEMS IN THE INTERPRETATION OF PMR SPECTRA

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The stepwise protonation of amines can be utilized for the interpretation of the PMR spectra of conjugated pairs consisting of an amine and its salt. A linear dependence of the proton chemical shifts on the composition of the amine—salt system has been demonstrated in the example of 2a-methyl-4-keto-trans-decahydroquinoline, making it possible to determine the proton chemical shifts, which are hidden in one of the partners by other signals, by means of extrapolation. The chemical shifts of the protons nearest the nitrogen atom vary in the following order upon protonation: $\alpha\text{-}H_a^{tert} > \alpha\text{-}He^{tert}_e \approx \beta\text{-}H_a^{tert} > \beta\text{-}H_a^{sec} \approx \beta\text{-}H_e^{sec} \approx \beta\text{-}H^{pr}$.

In the interpretation of the PMR spectra of cyclic amines, especially in the presence of other functional groups and a large number of C—H protons, it is frequently difficult to identify not only the β (δ 1.2-1.7 ppm), but also the α protons (δ 2.4-2.8 ppm). In this case, the protonated bases, i.e., the ammonium salts (generally trideutero- or trifluoroacetates or hydrochlorides), provide significant support in this case. Owing to the significantly larger chemical shift of the protons adjacent to the ammonium group (3.1-4.0 ppm for α-H, 1.7-2.4 ppm for β-H) it is possible to identify the α-protons and sometimes the β-protons. Shift reagents can also be used for the interpretation of bases; however, when other acceptor centers, such as hydroxy or keto groups, are present in the molecule, the picture may become more complicated, rather than simplified, due to the simultaneous complexation at two centers.

In this communication we shall demonstrate the possibility of the use of ammonium salts for the interpretation of the PMR spectra of amines.

The exchange rate of the protons on the nitrogen atom in protic solvents such as water and ethanol is known to be very high on the NMR time scale [1]. Therefore, mixtures of amines and their corresponding salts produce an averaged spectrum with a linear dependence of the shift on the composition of the mixture. A monoacidic base and its salt should thus act toward each other as an ideal shift reagent, which acts only at the amino group. The stepwise protonation of an amine and the construction of shift—composition diagrams may thus make it possible to reliably follow the changes in the chemical shifts of the individual protons and to determine the chemical shifts of the protons which were not identified in the base or, respectively, in the salt.

In this report we shall demonstrate the application of the method of stepwise protonation in the example of 2a-methyl-4-keto-transdecahydroquinoline (α isomer, mp 63°C), whose structure was previously proved by chemical methods [2] (the trans configuration of the methyl group relative to C_8 was confirmed by x-ray diffraction analysis [3]).

The signals of the following protons were identified in the spectrum of a solution of the base 2a-methyl-4-keto-trans-decahydroquinoline in D_2O according to the nature of the splitting of the signals, as well as with the aid of double resonance. A doublet of the 2-CH_3 group with δ 1.34 ($^3J_{2\text{-}CH_3,2\text{-}He}$ = 7.0 Hz) is easily determined in the high-field part of the spectrum. The most low-field signal with δ 3.99, which is a quintet of doublets with spin—spin coupling constants equal to 7.0 and 2.0 Hz, is assigned to the 2-H_e proton. The doublets of doublets with δ 3.10 and 2.44, which are superimposed on the absorption of other protons, can be assigned to the 3-H_a and 3-H_e protons, since they have the same spin—spin coupling constant (13.0 Hz) and, as the double resonance shows, interact with one another and

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