SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF SOME PYRROLES

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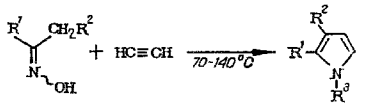
UDC 615.281:547.741

There are many examples in the literature of biologically active pyrroles which possess antiinflammatory [1], narcotic, antihistaminic, and antiadrenalin properties [2], and which reduce blood sugar levels [3]. Relatively simply-substituted pyrroles are found among these naturally-occurring antibiotics [4, 5].

We have developed a new synthesis for hitherto unknown or difficultly accessible pyrroles and their N-vinyl derivatives, possessing a variety of substituents in the 2- and 3-positions [6, 7].

The present communication describes the synthesis and testing for antimicrobial activity of a number of compounds of this type.

The syntheses of 4,5,6,7-tetrahydroindole (I) and the N-vinylpyrroles (II-VII) were accomplished by the heterocyclization of the corresponding ketoximes with acetylene [8-11]:

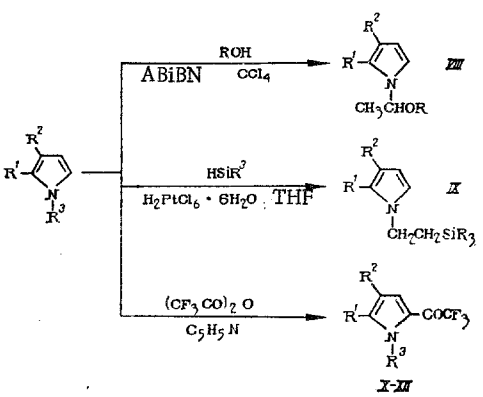


I-VII

I: $R^1=R^2=(CH_2)_4$, $R^3=H$; II: $R^1=CH_3$, $R^2=H$, $R^3=-CH=CH_2$; III: $R^1=CH_3$, $R^2=n\text{-}C_3H_7$, $R^3=-CH=CH_2$; IV: $R^1=C_6H_5$, $R^2=H$, $R^3=-CH=CH_2$; V: $R^1=C_6H_5$, $R^2=C_2H_5$, $R^3=-CH=CH_2$; VI: $R^1=C_6H_5$, $R^2=n\text{-}C_4H_9$, $R^3=-CH=CH_2$; VII: $R^1=C_6H_5$, $R^2=C_5H_{11}$, $R^3=-CH=CH_2$.

Heterocyclization proceeded smoothly at 70-140°C, usually at 90-100°C, in 3-5 h at atmospheric pressure, or under acetylene pressure in 1-2 h in the presence of the hyperbasic system strong base–dimethyl sulfoxide.

An investigation of the reactivities of these pyrroles and N-vinylpyrroles led to the synthesis of a number of new pyrroles with a variety of substituents in positions 1, 2, 3, and 5.



VIII-XII

VIII: $R^1=C_6H_5$, $R^2=H$, $R=C_2H_5$; IX: $R^1=C_6H_5$, $R^2=H$, $R=CH_3$; X: $R^1=R^2=CH_3$, $R^3=-CH=CH_2$; XI: $R^1=C_6H_5$, $R^2=H$, $R^3=-CH=CH_2$; XII: $R^1=C_6H_5$, $R^2=H$, $R^3=(CH_2)_2SC_3H_7$.

Institute for Organic Chemistry, Academy of Sciences of the USSR, Irkutsk. Kuznetsks Advanced Training Institute for Physicians. Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 15, No. 3, pp. 25-29, March, 1981. Original article submitted July 17, 1980.

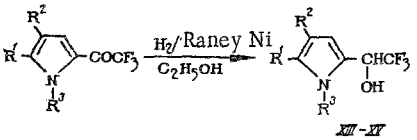
 0091-150X/81/1503-0168$07.50 © 1982 Plenum Publishing Corporation

Reaction of ethanol with N-vinyl-2-phenylpyrrole (IV) in the presence of the catalytic system azobisisobutyronitrile-carbon tetrachloride (1:4) in amounts of 10-30% of the weight of the reaction mixture gave up to 62.5% of N-(α-ethoxyethyl)-2-phenylpyrrole (VIII). The reaction was complete within 2-3 h at 75°C, and gave the Markovnikov product only.

Hydrosilylation of IV using a platinum catalyst (0.1 M $H_2PtCl_6 \cdot 6H_2O$) at 100°C for 10 h in tetrahydrofuran proceeded regioselectively to give the β-addition product, i.e., 1-(2'-triethylsilyl)-2-phenylpyrrole (IX) in yields of up to 76% [12].

Trifluoroacetylation of the N-vinylpyrroles and their derivatives in the presence of pyridine with carbon tetrachloride, methylene chloride, or benzene as solvent, which proceeded regioselectively at a single nucleophilic site, viz, the α-position of the pyrrole ring, gave the N-vinyl-2-alkyl(aryl)-3-alkyl-5-trifluoroacetylpyrroles (X-XI) and 1-(2'-propylthioethyl)-2-phenyl-5-trifluoroacetylpyrrole (XII) [13]. The reaction took place rapidly to give good yields of the desired products (up to 96%) at temperatures of −10 to +25°C.

Catalytic hydrogenation of N-vinyl-α-trifluoroacetylpyrroles at 20-60°C over Raney nickel in ethanol gave 94-97% of the 1-ethyl-2-aryl-5-(1'-hydroxy-2'2'2'-trifluoroethyl)-pyrroles (XIII-XIV):



XIII-XV

XIII: $R^1 = C_6H_5$, $R^2 = H$, $R^3 = C_2H_5$; XIV: $R^1 = CH_3OC_6H_4$, $R^2 = H$, $R^3 = C_2H_5$;
XV: $R^1 = C_6H_5$, $R^2 = H$, $R^3 = H$.

Under similar conditions, 2-phenyl-5-trifluoroacetylpyrrole was hydrogenated to the corresponding 2-phenyl-5-(1'-hydroxy-2'2'2'-trifluoroethyl)pyrrole (XV).

EXPERIMENTAL (BIOLOGICAL)

By successive serial dilution of the compounds in liquid nutrient medium, the activities of the pyrroles towards 11 strains of various species of bacteria and fungi were determined. The results are shown in Table 1.

The minimum inhibitory concentrations for the growth of microbes of the pyrroles were as follows: staphylococci 15.6-125.0 μg/ml, *E. coli* 125.0-1000.0 μg/ml, and for the causative organisms of typhoid fever and dysentery, 62.5-1000.0 μg/ml. *Pseudomonas aeruginosa* was sensitive to the compounds in doses of 250.0-1000.0 μg/ml, and *Protea* in doses of 250.0-500.0 μg/ml. Somewhat greater sensitivity towards the pyrroles was shown by the anthrax bacillus (minimum inhibitory concentration varying between 15.6 and 125.0 μg/ml), and by yeast-like fungi of the *Candida* species (fungistatic concentrations 0.25-125.0 μg/ml).

No particular sensitivity to the pyrroles was shown by the intestinal bacteria, the antibiotic resistance of which is due to chromosome (*E. coli* 355) and plasmid (*E. coli* C-600, *E. coli* W-633, *E. coli* GSH-2) determinants.

EXPERIMENTAL (CHEMICAL)

Chromatographic analyses were carried out on a Chrom-4 apparatus (Czechoslovakia) using a katharometer detector. Column length 2.5 m, liquid phase 15% silicone DS-550, thermostat temperature 170°C, carrier gas helium. Infrared spectra were recorded on a UR-20 apparatus (East Germany) as liquid films, and the PMR spectra were obtained on a Tesla-BS-487B (80 MHz) instrument (Czechoslovakia). The compounds were examined as 10% solutions, using hexamethylenedisiloxane as internal standard in carbon tetrachloride.

4,5,6,7-Tetrahydroindole (I) and the N-vinylpyrroles (II-VII) were obtained by the methods given in [8-11].

N-(α-Ethoxyethyl)-2-phenylpyrrole (VIII). A reaction mixture consisting of 3.2 g (0.02 mole) of IV, 2.8 g (0.076 mole) of ethanol, 0.76 g of carbon tetrachloride, and 0.2 g of azobisisobutyronitrile was sealed in an ampul and kept in a thermostat at 75°C for 2-3 h. The ampul was opened, 0.2 g of potassium hydroxide added, and the contents distilled *in vacuo* to give 2.6 g (62.5%) of VIII, bp 118-120°C (5 mm), d_4^{20} 1.0302, n_D^{20} 1.5490. Found, %:

TABLE 1. Antimicrobial Activity of Pyrrole Derivatives

Compound	Microorganism										
	Staph. aureus 209P	E. coli 355	E. coli C-600 PBS-52	E. coli W-633 YR-67	E. coli GSH-2	S. typhi 495	Sh. Sonnei 41	B. authracoides 297	Ps. aeruginosa 128	B. prteus vuegaris 409	C. albicans 688
	Minimum concentration which retards the growth of microbes, μg/ml										
I	62,5	250,0	500,0	500,0	250,0	250,0	250,0	62,5	500,0	—	3,9
II	62,5	250,0	250,0	1000,0	250,0	1000,0	500,0	62,5	1000,0	500,0	62,5
III	15,6	500,0	125,0	250,0	500,0	250,0	62,5	62,5	500,0	500,0	31,2
IV	31,2	125,0	250,0	62,5	250,0	125,0	62,5	31,2	250,0	500,0	0,25
V	62,5	500,0	250,0	250,0	—	62,5	—	—	—	500,0	125,0
VI	62,5	250,0	500,0	250,0	—	250,0	—	—	—	500,0	7,8
VII	125,0	500,0	500,0	250,0	250,0	250,0	500,0	62,5	500,0	250,0	125,0
VIII	125,0	250,0	1000,0	125,0	250,0	500,0	125,0	62,5	500,0	500,0	125,0
IX	125,0	250,0	1000,0	500,0	500,0	125,0	125,0	125,0	1000,0	500,0	125,0
X	125,0	500,0	500,0	250,0	250,0	250,0	62,5	250,0	250,0	500,0	125,0
XI	62,5	125,0	500,0	250,0	125,0	125,0	250,0	15,6	500,0	500,0	125,0
XII	62,5	250,0	250,0	250,0	250,0	250,0	125,0	31,2	500,0	250,0	125,0
XIII	125,0	500,0	500,0	250,0	500,0	125,0	250	62,5	1000,0	250,0	125,0
XIV	125,0	500,0	500,0	250,0	500,0	125,0	250,0	62,5	250,0	250,0	125,0
XV	125,0	250,0	125,0	250,0	500,0	250,0	250,0	62,5	500,0	500,0	62,5

C 78.54; H 7.97; N 6.83. $C_{14}H_{17}NO$. Calculated, %: C 78.11; H 7.95; N 6.52. PMR spectrum, δ, ppm: 6.85 (H^5), 6.11 (H^4), 6.00 (H^3), 5.30 (—CH—), 1.55 (CH_3 in the O—CH—CH_3 group), 2.99 and 0.95 (ethyl CH_2 and CH_3). Vinyl group absorptions in the IR spectrum of the N-vinyl-2-phenylpyrrole starting material (IV) at 1585 and 1642 cm^{-1} disappeared, and were replaced by a new band at 1117-1130 cm^{-1} typical of the ether bond C—O—C.

1-(2'-Triethylsilylethyl)-2-phenylpyrrole (IX) was obtained as described in [12].

N-Vinyl-2,3-dimethyl-5-trifluoroacetylpyrrole (X), N-vinyl-2-phenyl-5-trifluoroacetylpyrrole (XI), and 1-(2'-propylthioethyl)-2-phenyl-5-trifluoroacetylpyrrole (XII) were obtained as described in [13].

1-Ethyl-2-phenyl-5-(1'-hydroxy-2',2',2'-trifluoroethyl)pyrrole (XIII). In a rotary autoclave of 1 liter capacity was placed a solution of 4.6 g (0.017 mole) of N-vinyl-2-phenyl-5-trifluoroacetylpyrrole (XI) in 50 ml of ethanol and 1 g of Raney nickel, and hydrogen was charged to a pressure of 50 atm. The reaction mixture was kept at 20°C for 5 h. The catalyst was separated from the liquid, the solvent was removed, and the residue distilled *in vacuo* to give 4.4 g (95.7%) of XIII, mp 88-89°C (from cyclohexane). Found, %: C 62.60; H 5.08; F 21.37. $C_{14}H_{14}NOF_3$. Calculated, %: C 62.44; H 5.20; F 21.17. In the IR spectrum (ν, cm^{-1}), the shoulder at 1642 (C=C) on the very strong band at 1676 (C=O) disappeared, and bands appeared at 2940, 2985 ($H—C_{sp^3}$) and 3400 (OH).

1-Ethyl-2-(p-methoxyphenyl)-5-(1'-hydroxy-2',2',2'-trifluoroethyl)pyrrole (XIV). From 4.0 g (0.02 mole) of 1-vinyl-2-p-methoxyphenyl-5-trifluoroacetylpyrrole there was obtained, by the same method as described for XIII, 3.8 g (94.5%) of XIV, bp 162-164°C (3 mm), crystallizing in white crystals, mp 70-71°C. Found, %: C 60.64; H 5.23; F 19.42. $C_{15}H_{15}NO_2F_3$. Calculated, %: C 61.65; H 5.17; F 19.5.

2-Phenyl-5-(1'hydroxy-2',2',2'-trifluoroethyl)pyrrole (XV). Using the same method as described for the preparation of XIII, there was obtained from 5.0 g (0.021 mole) of 2-phenyl-5-trifluoroacetylpyrrole, 4.9 g (97.1%) of XV, mp 106-107°C. Found, %: C 59.82; H 4.20; F 23.42. $C_{12}H_{10}NOF_3$. Calculated, %: C 59.75; H 4.18; F 23.63.

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SYNTHESIS AND ANTIVIRAL ACTIVITY OF 2-[ARYL(HETARYL)]QUINOLINE-4-CARBOXYLIC ACIDS

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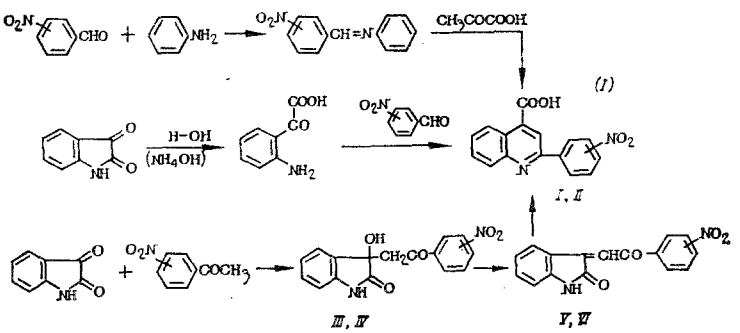
UDC 615.281.8:547.831.9

Quinoline-4-carboxylic acids and their derivatives are known to possess a variety of biological properties, and are plant growth stimulants [1-5]. We have therefore developed and studied thoroughly methods for their preparation. The classical methods for the synthesis of 2-substituted quinoline 4-carboxylic acids (Dobner and Pfitzinger cyclizations) are well known and quite general [6, 7]. However, these methods possess evident deficiencies. Thus, the yields of the acids in the Dobner cyclization are not good, due to the formation of by-products (diketopyrrolidines) [8-10]. The Pfitzinger method is not applicable for the synthesis of acids containing a nitro group, and only one instance has been described [11] of the condensation of 7-nitroisatin with acetophenone in concentrated aqueous ammonia at 130°C in an autoclave to give the amide of 2-phenyl-8-nitroquinoline-4-carboxylic acid in a yield of 8%.

In a study of the feasibility of carrying out the Pfitzinger reaction using as basic catalyst diethylamine, piperidine, ammonia, or dilute potassium hydroxide, it was found that under these conditions the condensation of isatin with acetophenone gave 3-hydroxy-3-phenacylidene-2-oxindole. This latter isomerizes in alcoholic hydrogen chloride to 2-phenylquinoline-4-carboxylic acid in a yield of 72% [12, 13].

This paper describes an investigation of the applicability of known methods for the synthesis of 2-(3-nitrophenyl)- and 2-(4-nitrophenyl)-quinoline-4-carboxylic acids (I and II).



Condensation of aniline with m- or p-nitrobenzaldehyde and pyruvic acid gave the corresponding acids containing the nitro group in the benzene moiety, in yields not exceeding 20% (method A).

Kuibishev Polytechnic Institute, Kuibishev. Belorussian Scientific-Research Institute for Epidemiology and Microbiology, Minsk. Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 15, No. 3, pp. 29-35, March, 1981. Original article submitted August 22, 1980.