**Hydrogenation of tetrafluoborates XXIV, XXV, XXVIII, and XXIX** was carried out under the same conditions as the hydroamination of the pyrylium salts, using a pyridine:methylamine ratio of 1:1.

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# SYNTHESIS OF PYRROLE-2-CARBOXYLIC ACIDS AND THEIR N-VINYL DERIVATIVES


**L. N. Sobenina, M. P. Sergeeva, A. I. Mikhaleva, M. V. Sigalov, S. E. Korostova, N. I. Golovanova, V. N. Salaurov, E. V. Bakhareva, and N. N. Vasil'eva**



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*Haloform cleavage of 2-trifluoroacetyl- and N-vinyl-2-trifluoroacetylpyrroles gives pyrrole-2-carboxylic acids and their N-vinyl derivatives in good yields; most of these compounds do not melt between 120–190°C, but rather decompose with $CO_2$ evolution.*


The high pharmacological activity of pyrrolecarboxylic acids [1–4] is responsible for heightened interest in these compounds. N-Vinylpyrrolecarboxylic acids, however, despite their apparent potential practical value, have not been studied. The only published procedure for the synthesis of N-styrylcarboxylic acids, described in [5], gives low yields and requires special conditions and reagents.

The starting materials for the preparation of even more inaccessible mono- and disubstituted pyrrolecarboxylic acids and their N-vinyl derivatives may also be pyrroles and N-vinylpyrroles [6], however, which are readily obtained at the present time from ketoximes and acetylene via the Trofimov reaction.

In continuation of our systematic studies of pyrrole derivatives obtained using this reaction, the present paper deals with the synthesis of new representatives of 2-pyrrolecarboxylic acids and their N-vinyl derivatives, for further research into this series of biologically active compounds.

Previously unknown 2-pyrrolecarboxylic acids XVII-XXIII (Table 1) were prepared by haloform cleavage of the corresponding 2-trifluoroacetylpyrroles I–VII, according to the procedure reported in [7].

These reactions occur upon refluxing alcohol solutions of trifluoroacetylpyrroles (TFAP) in the presence of 4 N NaOH.


Irkutsk Institute of Organic Chemistry, Siberian Branch, Academy of Sciences of the USSR, Irkutsk.


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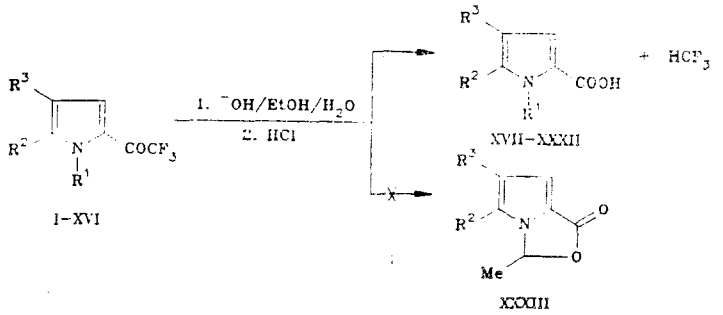



2-Trifluoroacetyl-N-vinylpyrroles VIII–XVI under these conditions (especially at the free acid isolation step) might be expected to undergo intramolecular electrophilic cyclization via the carboxyl and vinyl groups to form condensed lactones XXXIII, or intermolecular polyaddition reactions of the same type, leading to polymers. These fears proved fruitless: under the specified reaction conditions only the expected N-vinyl-2-pyrrolecarboxylic acids XXIV–XXXII were formed (Table 1).

As can be seen from the data in Table 1, the structures of substituents in the pyrrole ring have practically no effect on the acid yields, which are uniformly quite high in all cases (75–88%).

Milder conditions for the hydrolysis of trifluoroacetylated cyclic vinyl esters [8] (wet benzene, 80°C, equimolar amount of KOH) were found to be completely inadequate or unsuitable for the conversion of vinylindole XV to its corresponding acid; the former was recovered completely from the reaction mixture. When the hydrolysis reaction was carried out in wet acetonitrile (70–80°C, 5 h) in the presence of an equimolar amount of KOH 4,5,6,7-tetrahydro-2-trifluoroacetylindole (VII) was isolated in 83% yield. In this case, apparently, hydrolysis of acetonitrile to give potassium acetate proceeds more rapidly than haloformic cleavage of the trifluoroacetyl group. After neutralization of all the base the appearance of trace amounts of acid via further hydrolysis of acetonitrile acid-catalyzed hydrolysis of the N-vinyl group is observed to commence [6].

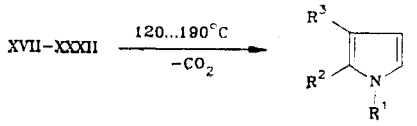

When the hydrolysis of trifluoroacetylindole XV is carried out at room temperature (10 h) while retaining the other conditions the same, N-vinyl-4,5,6,7-tetrahydro-2-indolecarboxylic acid (XXXI) is indeed formed, although in only 12% yield.

All of these newly synthesized acids XVII–XXXII are crystalline substances which are soluble in alcohol, acetonitrile, DMSO, sparingly soluble in benzene and chloroform.

Based on the results of differential thermal analysis, all of the acids obtained herein, with the exception of compounds XXII and XXX, do not melt. The observed endotherms in the temperature range 120–190°C are accompanied in all cases by weight loss, corresponding approximately to the constitution of the COOH group (Table 2). Decarboxylation of pyrrole-2-carboxylic acids occurs at this heating stage with evolution of $CO_2$; the presence of $CO_2$ in the volatile products resulting from decomposition was confirmed by GLC analysis.

TABLE 1. Characteristics of 2-Pyrrolecarboxylic Acids

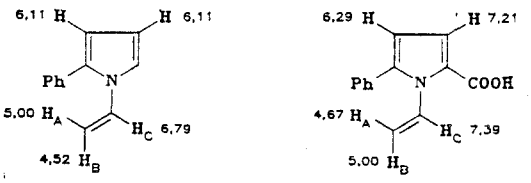
| Compound | TFAP starting material | $R^1$ | $R^2$ | $R^3$ | Molecular formula | Yield, % |
|---|---|---|---|---|---|---|
| XVII | I | H | Ph | H | $C_{11}H_9NO_2$ | 84 |
| XVIII | II | H | 4-$MeC_6H_4$ | H | $C_{12}H_{11}NO_2$ | 79 |
| XIX | III | H | 4-$EtC_6H_4$ | H | $C_{13}H_{13}NO_2$ | 81 |
| XX | IV | H | 4-$ClC_6H_4$ | H | $C_{11}H_8ClNO_2$ | 75 |
| XXI | V | H | Ph | Et | $C_{13}H_{13}NO_2$ | 83 |
| XXII | VI | H | Ph | Am | $C_{16}H_{19}NO_2$ | 87 |
| XXIII | VII | H | $(CH_2)_4$ | | $C_9H_{11}NO_2$ | 84 |
| XXIV | VIII | $CH_2$=CH | Ph | H | $C_{13}H_{11}NO_2$ | 78 |
| XXV | IX | $CH_2$=CH | 4-$MeC_6H_4$ | H | $C_{14}H_{13}NO_2$ | 82 |
| XXVI | X | $CH_2$=CH | 4-$EtC_6H_4$ | H | $C_{15}H_{15}NO_2$ | 79 |
| XXVII | XI | $CH_2$=CH | 4-$MeOC_6H_4$ | H | $C_{14}H_{13}NO_3$ | 84 |
| XXVIII | XII | $CH_2$=CH | 4-$ClC_6H_4$ | H | $C_{13}H_{10}ClNO_2$ | 78 |
| XXIX | XIII | $CH_2$=CH | Ph | Et | $C_{15}H_{15}NO_2$ | 82 |
| XXX | XIV | $CH_2$=CH | Ph | Am | $C_{18}H_{21}NO_2$ | 83 |
| XXXI | XV | $CH_2$=CH | $(CH_2)_4$ | | $C_{11}H_{13}NO_2$ | 76 |
| XXXII | XVI | $CH_2$=CH | 2-Thienyl | H | $C_{11}H_9NO_2S$ | 88 |



A greater amount of weight loss than can be accounted for by the concentration of the COOH group occurs in compounds XVII, XXI, and XXXI, and can be explained in terms of the evolution of other volatile products arising from decomposition of other groups or rings. The fact that decomposition (weight loss) is incomplete at the maximum heating temperature (300°C) indicates that partial resinification takes place during the heating process.

The IR spectra of solid-state samples of 5-substituted pyrrole-2-carboxylic acids exhibit forms characteristic of carboxylic acid dimers [9]. Broad intense bands in the region 2500–3000 $cm^{-1}$ and at 1670 $cm^{-1}$ correspond to OH and C=O stretching vibrations, respectively, and also suggest the presence of strong hydrogen bonding in these molecules. In dilute $CCl_4$ solutions, new monomer bands for the C=O and OH group stretching vibrations appear at 1720 and 3450 $cm^{-1}$, respectively, in addition to the bands for associated C=O and OH groups, which do not disappear completely even as the acid concentration in solution is decreased to $10^{-6}$ mole/liter.

The PMR spectra of 2-pyrrolecarboxylic acids were also examined (cf. Table 3). The effect of a carboxyl group on the position of the other protons in the PMR spectra of N-vinyl-2-pyrrolecarboxylic acids is illustrated by comparison of the chemical shift values in analogous spectra of corresponding pyrroles. For example:



The strong deshielding of the ring protons, as well as of the vinyl group protons ($H_B$ and $H_C$) can be attributed primarily to the electron-withdrawing effect of the COOH group. The upfield shift of the $H_A$ proton signal is due to the anisotropic influence of the carboxyl group and benzene ring.

Studies of the biological activity of these newly synthesized pyrrolecarboxylic acids revealed that compounds XXIII, XXV, XXVI, and XXVIII exhibit antispasmodic activity (based on the sensitivity threshold test to carbazole at a dose of 10 mg/kg [10]).

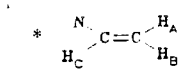
TABLE 2. Results of Thermal Analysis of 2-Pyrrolecarboxylic Acids

| Compound* | Decarboxylation | | | | | Tfin for weight loss, °C | Total weight loss, % |
|---|---|---|---|---|---|---|---|
| | $T_{in}$, °C | Tfin, °C | DTA $_{max}$, °C | weight loss, % found | weight loss, % theoret. | | |
| XVII | 152 | 185 | 160 | 30 | 23,5 | 240 | 92 |
| XVIII | 150 | 180 | 158 | 25 | 21,9 | 283 | 92 |
| XIX | 140 | 180 | 157 | 21 | 20,5 | 275 | 86 |
| XX | 150 | 185 | 163 | 22 | 19,9 | 290 | 92 |
| XXI | 142 | 190 | 148 | 25 | 20,5 | 265 | 94 |
| XXII | 127 | 185 | 156 | 20 | 17,1 | 300 | 91 |
| XXIII | 137 | 165 | 150 | 22 | 26,7 | 215 | 90 |
| XXIV | 138 | 173 | 145 | 24 | 20,7 | 237 | 96 |
| XXV | 165 | 175 | 168 | 22 | 21,9 | 270 | 99 |
| XXVI | 140 | 170 | 147 | 18 | 18,3 | 270 | 95 |
| XXVII | 120 | 150 | 137 | 21 | 18,1 | 280 | 90 |
| XXVIII | 155 | 187 | 165 | 20 | 17,8 | 275 | 92 |
| XXIX | 143 | 167 | 150 | 18 | 18,2 | 255 | 98 |
| XXX | 115 | 150 | 130 | 12 | 18,4 | 275 | 94 |
| XXXI | 138 | 157 | 147 | 32 | 22,9 | 210 | 72 |
| XXXII | 150 | 175 | 158 | 26 | 20,1 | 243 | 96 |

*Compound XXII, mp 107°C; compound XXX, mp 103°C.

TABLE 3. PMR Spectra of 2-Pyrrolecarboxylic Acids

| Compound | Chemical shifts, δ, ppm | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | $H_A$* | $H_B$* | $H_C$* | 3-H | 4-H | $R^2$ | $R^3$ | NH |
| XVII | — | — | — | 6,58 | 7,10 | 7,2...7,5 | — | 9,41 |
| XVIII | — | — | — | 6,52 | 6,97 | 7,19; 7,61; 2,34 (Me) | — | 10,46 |
| XIX | — | — | — | 6,53 | 6,83 | 7,25; 7,76; 1,25; 2,64 (Et) | — | — |
| XX | — | — | — | 6,70 | 6,84 | 7,46; 7,92 | — | 12,08 |
| XXI | — | — | — | — | 6,79 | 7,3...7,7 | 1,21; 2,61 | — |
| XXIII | — | — | — | 6,43 | — | 1,65 (5,6-$CH_2$) | 2,48 (4,47-$CH_2$) | 11,11 |
| XXIV | 4,67 | 5,00 | 7,39 | 6,29 | 7,21 | 7,36 | — | — |
| XXV | 4,68 | 5,06 | 7,43 | 6,26 | 7,20 | 2,36 (Me); 7,23; 7,39 | — | — |
| XXVI | 4,60 | 5,06 | 7,50 | 6,33 | 7,02 | 7,2; 7,4; 1,23; 2,67 (Et) | — | — |
| XXVII | 4,59 | 5,06 | 7,50 | 6,29 | 7,00 | 7,0; 7,38; 3,82 (MeO) | — | — |
| XXVIII | 4,57 | 4,99 | 7,55 | 6,30 | 7,05 | 7,4 | — | — |
| XXIX | 4,35 | 4,85 | 7,54 | — | 6,96 | 7,3...7,5 | 1,08; 2,32 | — |
| XXX | 4,43 | 4,78 | 7,41 | — | 7,10 | 7,3...7,5 | 2,3 (α); 1,21 (β, γ, δ); 0,78 (Me) | — |
| XXXI | 5,07 | 5,04 | 7,47 | — | 6,63 | 1,68 (5,6-$CH_2$); 2,64 (4,7-$CH_2$) | — | — |
| XXXII | 4,97 | 5,26 | 7,32 | 6,46 | 6,97 | 7,2; 7,7 | — | — |

*  ; $^2J_{AB}=0.9$; $^3J_{AC}=15$; $^3J_{BC}=9$ Hz.

## EXPERIMENTAL

IR spectra were recorded on a Specord IR-75 spectrophotometer using KBr pellets and solutions in $CCl_4$ (c $0.1–1\cdot10^{-6}$ mole/liter). PMR spectra were obtained on a Tesla BS-567A (100 MHz) spectrometer using solutions in DMSO-$D_6$ versus HMDS as internal standard. Thermograms were measured using a 1 MOM derivatograph (differential thermal analyzer) (Hungary); the sample was heated in an open crucible (sample weight 50 mg, maximum temperature 300°C, rate of heating 5°C/min, sensitivity of DTA and DTG: 1/10. Inert support substance, $Al_2O_3$, calcined at 1200°C).

The purities of compounds were determined by TLC analysis on Silufol UV-254 plates in an ether–hexane (1:1) eluent system.

The results of C, H, N, Cl, and S elemental analysis of the newly synthesized compounds agreed with calculations.

The 2-trifluoroacetylpyrrole starting materials were prepared according to the procedure described in [11].

**Hydrolysis of N-Vinyl-4,5,6,7-tetrahydro-2-trifluoroacetylindole (XV).** A. A solution of 1.22 g (5 mmoles) trifluoroacetylindole XV in 10 ml ethanol was refluxed for 5 h in the presence of 20 ml 4 N NaOH, diluted with 250 ml water, and acidified with hydrochloric acid to pH 6. The resulting crystals were removed by filtration and recrystallized from 50% aqueous ethanol. Yield 0.73 g (76%) N-vinyl-4,5,6,7-tetrahydro-2-indolecarboxylic acid (XXXI).

B. A solution of 1.22 g (5 mmoles) trifluoroacetylindole XV in 10 ml benzene was refluxed for 5 h in the presence of 0.28 g (5 mmoles) KOH and 2–3 drops water. After removal of the benzene 1.05 g of unreacted trifluoroacetylindole XV was recovered.

C. A solution of 1.22 g (5 mmoles) trifluoroacetylindole XV in 10 ml acetonitrile was refluxed for 5 h in the presence of 0.28 g (5 mmoles) KOH. The acetonitrile was evaporated and the remaining crystalline product was passed through a layer of $Al_2O_3$ to remove any resin. Yield 0.9 g (83%) of 4,5,6,7-tetrahydro-2-trifluoroacetylindole, identical to an authentic sample prepared according to [11].

D. A solution of 1.22 g (5 mmoles) trifluoroacetylindole XV in 10 ml acetonitrile was stirred at room temperature for 5 h in the presence of 0.28 g (5 mmoles) KOH; the resulting crystals were removed by filtration, dissolved in water, and acidified with hydrochloric acid. Yield 1.12 g (12%) of N-vinyl-4,5,6,7-tetrahydro-2-indolecarboxylic acid (XXXI). After evaporation of the acetonitrile mother liquor 0.9 g of unreacted trifluoroacetylindole XV was recovered.

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# REARRANGEMENT OF 1-ACETYLINDOXYL OXIME TO 1-ACETYL-2-CHLORO-3-IMINOINDOLINE HYDROCHLORIDE


**V. S. Velezheva and S. Yu. Ryabova**



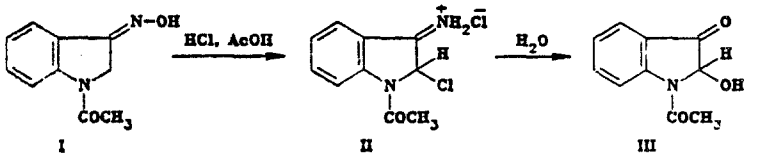
UDC 547.756:542.952



*Rearrangement of 1-acetylindoxyl oxime upon treatment with hydrogen chloride in acetic acid results in the formation of 1-acetyl-2-chloro-3-iminoindoline hydrochloride. Hydrolysis and acylation of the latter have been studied, along with reaction of 1-acetyl-2-chloro-3-(ω-chloroacetyl)aminoindole with N- and S-nucleophiles.*


We have previously demonstrated the conversion of 1-acetylindoxyl oxime (I) to 3-iminoindoline hydrogen sulfate involving simultaneous introduction of an acetoxy group in the 2-position [1].

In the present paper we propose a method for the synthesis of 2-chloro-3-iminoindoline, which is of interest for the preparation of 2-functional 3-aminoindole derivatives.




I II III

We have found that oxime I reacts with hydrogen chloride in acetic acid solution in the presence of acetic anhydride at a temperature of 13–25°C to give 1-acetyl-2-chloro-3-iminoindoline hydrochloride (II) [2]. The yield of hydrochloride II depends on the dilution factor and the amount of acetic anhydride present (Table 1).


S. Ordzhonikidze All-Union Scientific Research Chemical Pharmaceutical Institute, Moscow.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