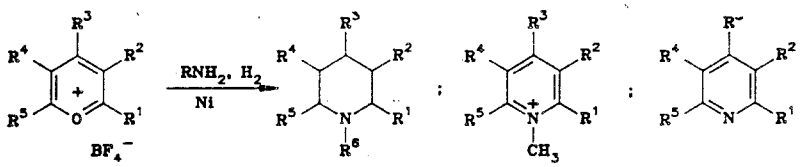
HYDROAMINATION OF PYRYLIUM SALTS

P. V. Reshetov, O. V. Fedotova, A. P. Kriven'ko, and V. G. Kharchenko

UDC 547.822.3+542.971.3+543.422.23

The catalytic reductive amination of pyrylium salts proceeded stereoselectively to give piperidine bases with a cis-structure. The reaction involved the formation of a pyridine intermediate; the course of the reaction depended on the structure of both the substrate and the aminating agent.

In earlier work we showed that pyrylium salts are converted to piperidine bases by liquid-phase catalytic reductive amination [1]. We have now studied this reaction for pyrylium tetrafluoborates with substituent groups differing in number, position, and nature (alkyl, aryl) using nucleophiles of different strengths (methylamine, ammonia, aniline).



Compound	R^1	R^3	R^5	Compound	R^1	R^3	R^5
I	C_6H_5	H	C_6H_5	XVI	C_6H_5	C_6H_5	C_6H_5
II	C_6H_5	CH_3	C_6H_5	XVII	CH_3	C_6H_5	C_6H_5
III	C_6H_5	H	C_6H_5	XVIII	C_2H_5	C_6H_5	C_6H_5
IV	C_6H_5	C_6H_5	C_6H_5	XIX	C_6H_5	H	—**
V	C_6H_5	C_6H_5	C_6H_5	XX	C_6H_5	C_6H_5	—**
VI	CH_3	C_6H_5	C_6H_5	XXI	C_6H_5	C_6H_5	—***
VII	C_2H_5	C_6H_5	C_6H_5	XXII	CH_3	CH_3	CH_3
VIII	C_6H_5	H	—**	XXIII	CH_3	CH_3	CH_3
IX	C_6H_5	C_6H_5	—**	XXIV	C_6H_5	C_6H_5	C_6H_5
X	C_6H_5	C_6H_5	—***	XXV	C_6H_5	C_6H_5	C_6H_5
XI	CH_3	CH_3	CH_3	XXVI	C_6H_5	C_6H_5	—**
XII	C_6H_5	H	C_6H_5	XXVII	C_6H_5	H	C_6H_5
XIII	C_6H_5	CH_3	C_6H_5	XXVIII	C_6H_5	C_6H_5	C_6H_5
XIV	C_6H_5	H	C_6H_5	XXIX	C_6H_5	H	—**
XV	C_6H_5	C_6H_5	C_6H_5				

*XII–XXII, R = CH_3; XXIII, R = C_6H_5; III, XIV, $R^2 = R^4 = CH_3$; V, XVI, XXV, $R^2 = CH_3$; not shown, $R^2 = R^4 = H$.

**$R^4 + R^5 = -(CH_2)_4-$.

***$R^4 + R^5$ = 2,3-(3,4-dihydronaphtho).

Hydromethylamination of 2,6-diphenylpyrylium tetrafluoborate (I) and its methyl- and dimethyl-homologs II, III, and also α-alkylpyrylium salts VIII and XI yielded the corresponding piperidines XII–XIV, XIX, and XXII in high yields (71–83%) (Table 1). The introduction of a phenyl substituent at position 4 of the pyrylium ring (compounds IV–VII and IX) results in a considerable decrease in the yield of piperidine base XV–XVIII and XX (46–57%), and to the formation of N-

N. G. Chernyshevskii Saratov State University, Saratov 410600. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, 608–611, May, 1990. Original article submitted August 18, 1989.

0009-3122/90/2605-0513$12.50

TABLE 1. Physical Data for Compounds Prepared

Compound*	Empirical formula	mp, °C**	Yield, %***	Compound*	Empirical formula	mp, °C**	Yield, %***
XII	$C_{18}H_{21}N$	108...109	71	XX	$C_{22}H_{27}N$	117...118	48 (80)
XIII	$C_{19}H_{23}N$	72...73	83				
XIV	$C_{20}H_{25}N$	85...86	75	XXI	$C_{26}H_{25}N$	108...110	75
XV	$C_{24}H_{25}N$	83...85	57 (83)	XXII	$C_9H_{20}IN$	199...201	72
				XXIII	$C_{14}H_{22}BF_4N$	111...113	54
XVI	$C_{25}H_{28}ClN$	261...263	55 (96)	XXIV	$C_{24}H_{20}BF_4N$	200...202	28
				XXV	$C_{25}H_{22}BF_4N$	278...280	25
XVII	$C_{19}H_{23}N$	79...81	51	XXVI	$C_{22}H_{22}BF_4N$	133...135	62
XVIII	$C_{20}H_{25}N$	Oil	46	XXIX	$C_{16}H_{18}BF_4N$	143...145	89
XIX	$C_{16}H_{23}N$	62...64	72 (88)				

*Compound XVI was isolated and characterized as the hydrochloride, XXII as the iodide, and XXIII as the tetrafluoborate.

**Compounds XII–XV and XIX–XXI were crystallized from EtOH, XVI from acetone, XXII, XXIII, XXV, XXVI, and XXIX from AcOEt, and XXIV from MeOH.

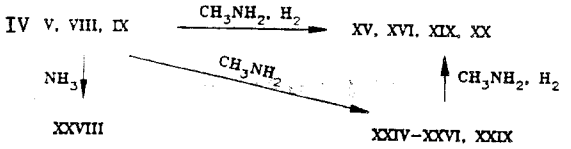
***Yields of the compounds obtained from pyridine salts are given in parentheses.

TABLE 2. ^{13}C NMR Spectra of Unsaturated Heterocyclic Compounds

Compound	Chemical shifts, ppm						
	$C_{(2)}$	$C_{(3)}$	$C_{(4)}$	$C_{(5)}$	$C_{(6)}$	N–CH_3	remaining protons
XII	70,93	36,98	25,17	36,98	70,93	42,17	21,77 (4-CH_3)
XIII	70,61	45,49	31,37	45,49	70,61	41,87	
XV	70,80	44,85	42,52	44,85	70,80	41,89	
XIX	70,58	30,76	31,16	26,60	27,30	39,89	19,97 ($C_{(7)}$); 31,14 ($C_{(8)}$); 63,38 ($C_{(9)}$); 37,68 ($C_{(10)}$)
XX	71,15	35,82	45,76	21,05	26,82	39,50	20,18 ($C_{(7)}$); 30,84 ($C_{(8)}$); 64,53 ($C_{(9)}$); 44,50 ($C_{(10)}$)
XXII	62,64	40,52	29,38	40,52	62,64	38,43	18,13 (2-CH_3, 6-CH_3); 21,04 (4-CH_3)

methylpiperidine salts XXIV–XXVI as side products. In order to avoid impurities of the latter and to increase the yield of piperidine, the reaction temperature was increased to 120°C. Under these conditions, the salt II gave 1-methyl-2,4,6-triphenylpiperidine (XV) in 83% yield. When aniline was used as aminating agent, only the trialkylsubstituted salt XI reacted to give 1-phenyl-2,4,6-trimethylpiperidine tetrafluoborate (XXIII). With substrates having an α-phenyl substituent, hydroamination was completely replaced by hydrogenation of the starting compounds yielding aliphatic-aromatic hydrocarbons [1]. With ammonia and hydrogen, the salts I and IV underwent recyclization to the pyridine bases XXVII and XXVIII.

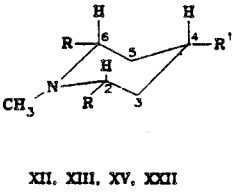
Experimental data showed that all the nucleophilic reagents used attacked regioselectively at position 2 of the pyrylium cation. Even when an unsubstituted γ-center (compounds I, III, and VIII) was present, the formation of γ-adducts was not observed. It was shown [2] that nucleophilic attack at the $C_{(4)}$ of 2,6-diphenylpyrylium tetrafluoborate is kinetically controlled, but attack at the $C_{(2)}$ position is thermodynamically controlled. Under severe conditions, hydroamination apparently gives the more thermodynamically stable product resulting from attack at the α-position. This is followed by ring-opening in the adduct, cyclization to the pyridine salt, and reduction of the pyridine, at a rate which depends on the number and position of the substituent. The possibility of the formation of piperidines from pyridine intermediates is substantiated by the ease of recyclization of the pyrylium salts to heteroaromatic systems [3]. Further experiments on the hydrogenation of the pyridine salts XXIV–XXVI and XXIX (under the conditions of hydroamination) led to the isolation of products resulting from the reduction of the heterocyclic ring, which confirmed the proposed scheme for the formation of piperidine bases, including the stage involving hydrogenation of the quaternary pyridine salts.



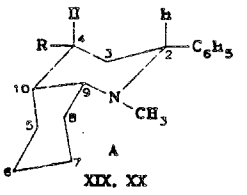
When ammonia was used as aminating agent, the pyridine quaternary salts were not obtained and the reaction stopped at the recyclization stage.

In the IR spectra of N-methylpiperidines XII–XXII, the N–CH_3 group absorbed at 2760–2820 cm^{-1}, compounds XXIV–XXIX were characterized by the pyridine ring absorption at 1550 cm^{-1}, and the spectra of tetrafluoborates XXIII–XXVI and XXIX contained absorption bands from the BF_4^- anion at 1060 cm^{-1}.

Analysis of the ^{13}C NMR spectra (Table 2) of the products of the reaction showed that the process of hydroamination is stereochemically directed with the formation of the cis-isomers.



XII, XIII, XV, XXII



XIX, XX

Quantitatively, the signals in the spectra of piperidine bases XII, XIII, XV, and XXII confirmed the symmetry of the molecule. The signals from the methyl groups of compound XXII at positions 2 and 6 (18.13 ppm) and 4 (21.04 ppm) were approximately the same as the signals from the equatorial methyl groups in 1,2,6-trimethylpiperidine hydrochloride [4] (18.30 ppm) and differed considerably from the signals from axially oriented methyl groups [5] (13.7 ppm). Signals from the methyl substituent on the nitrogen atom (38.43 ppm) indicated that it was in the equatorial position (axial methyl group appears in the strong-field region at 31.86 ppm). Moreover, the axial N–CH_3 group produced mixed signals from $C_{(3)}$ and $C_{(5)}$ in the strong-field region (24.34 ppm), which were not present in our spectra. Analogous conclusions can also be drawn from an inspection of the spectra of compounds XII, XIII, and XV, suggesting that all the substituents are in the equatorial position.

The presence in decahydroquinolines XIX and XX of a strong-field signal from $C_{(7)}$ at 19.97 and 20.18 ppm confirmed the cis-coupling of the heterocyclic rings, while the resonance signal from the $C_{(8)}$ (30.76 and 31.14 ppm) indicated that A is the preferred conformation (in conformation B this signal is at 15.65 ppm [6]).

EXPERIMENTAL

IR spectra were recorded on a UR-20 spectrometer (mineral oil), ^{13}C NMR spectra, on a Varian FT-80A ($CDCl_3$), internal standard TMS. Pyrylium salts were synthesized by the method given in [7].

Elemental analysis data for C, H, and N for all newly synthesized compounds were in agreement with calculated values.

Hydroamination of Pyrylium Salts I–XI. In an autoclave with a capacity of 150 ml were placed the pyrylium salt (10 mmoles), methanol (80 ml) containing methylamine (20 mmoles) and the catalyst – Raney nickel modified with mercury (0.5–1.0 g). The initial pressure of hydrogen was 10.1 MPa, and the reaction temperature was 100°C. After 5–7 h the catalyst was filtered off and the methanol evaporated. Bases XII–XXI were extracted with ether. Compound XVI was converted to the hydrochloride by dilute HCl. Compounds XVII and XVIII were purified by column chromatography on Al_2O_3, activity III (1 × 37). Product XXII, isolated as the tetrafluoborate, was converted to the iodide by the addition of an equimolar quantity of KI in water to a solution of XXII in acetone. Compound XXIII was freed from impurities by dissolving in water and concentrating the solution further. Pyridine salts XXIV, XXV, and XXIX remained as a crystalline residue after removal of piperidines XV, XVI, and XX with ether. Pyridine bases XXVI and XXVII crystallized after evaporation of the methanol.

Pyridine Tetrafluoborates XXIV, XXV, XXVIII, and XXIX. To the pyridine salt (25 mmoles) was added ethanol (80 ml) saturated with methylamine (50 mmoles). The mixture turned dark red as the pyrylium salt dissolved. After standing for 10–30 min, crystals of the tetrafluoborates XXIV, XXV, XXVIII, and XXIX began to separate from the solution.

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.

LITERATURE CITED

1. A. P. Kriven'ko, O. V. Fedotova, P. V. Reshetov, and V. G. Kharchenko, *Khim. Geterotsikl. Soedinen.*, No. 12, 1652 (1984).
2. G. Doddi, S. Fornarini, G. Illuminati, and F. Stegel, *J. Org. Chem.* **44**, 4496 (1969).
3. A. R. Katritsky, *Tetrahedron* **36**, 679 (1980).
4. A. J. Jones and M. M. A. Hassan, *J. Org. Chem.* **37**, 2332 (1972).
5. A. J. Jones, A. F. Casy, and K. M. McErlan, *Can. J. Chem.* **51**, 1782 (1973).
6. F. W. Vierhapper and E. L. Eliel, *J. Org. Chem.* **42**, 51 (1977).
7. J. A. VanAllan and G. A. Reynolds, *J. Org. Chem.* **33**, 1102 (1968).

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

UDC 547.747.07:543.226

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.

Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 612–616, May, 1990. Original article submitted August 10, 1988; revision submitted January 10, 1989.

0009-3122/90/2605-0516$12.50