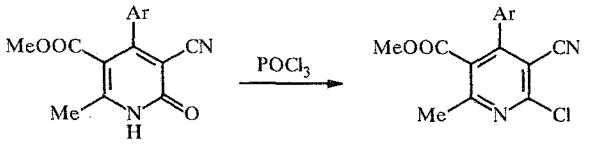
REACTIONS OF NUCLEOPHILIC SUBSTITUTION OF 4-ARYL-5-CARBOMETHOXY-6-METHYL-2-CHLORO-3-CYANOPYRIDINES

Z. A. Kalme, B. Roloff, Yu. E. Pelcher, Yu. Yu. Popelis, F. Khagen, and G. Ya. Dubur

Methods of synthesis of 5-carbomethoxy-substituted pyrazolo[3,4-b]pyridines and 3H-imidazo[4,5-b]pyridines by their reaction with hydrazine hydrate or as a result of Hofmann rearrangement of the corresponding 2-aminopyridines were developed based on 4-aryl-3-carbamoyl(or cyano)-5-carbomethoxy-6-methyl-2-chloropyridines.

In continuing the research on synthesis and investigation of potential cardiotonic agents in the series of 2-amino-3-cyanopyridine derivatives [1-3] and to obtain new N-containing heterocycles based on 3-cyanopyridines, 4-aryl-5-carbomethoxy-6-methyl-3-cyanopyridin-2(1H)-ones (Ia,b) were investigated in the present study.

In going from pyridine-2(1H)-ones Ia,b to condensed systems, the corresponding 2-chloropyridines are obtained in an intermediate stage.



Ia, b IIa, b

I, II aAr = Ph, bAr = *p*-ClC$_6$H$_4$

4-Aryl-5-carbomethoxy-6-methyl-2-chloro-3-cyanopyridines (IIa,b) were obtained in the reaction of pyridine-2(1H)-ones Ia,b with phosphorus oxychloride. The chlorine atom in 2-chloro-3-cyanopyridine II becomes mobile under the effect of the electron-acceptor nitrile group in the α-position and is comparatively easily displaced by nitrogen-containing nucleophiles – primary and secondary amines, and by hydrazine hydrate. The PMR spectra of 2-chloropyridines IIa,b only differ in the aromatic part: in the first case (IIa), the protons of the C_6H_5 group absorb as an unresolved multiplet, and a signal characteristic of a *p*-substituted phenyl ring is observed in the second (IIb).

2-Chloropyridines II form a series of new 2-aminopyridines III containing a carbomethoxy group in position 5 of the pyridine ring with different primary and secondary amines. The IR spectra of amines III exhibit absorption bands of a cyano group at 2220 cm^{-1} (20 cm^{-1} lower than for 2-chloropyridine II), which indicates a more conjugated system of 2-aminopyridines in comparison to 2-chlorpyridines (Table 1). This is reflected in the frequencies of vibrations of the ester carbonyl group, observed at 1720-1730 cm^{-1} for 2-aminopyridines III, i.e., 15-10 cm^{-1} lower than for 2-chloropyridines III (Table 2). In comparing the PMR spectra of II and III, we find that the shifts of the constants of 6-CH_3, 5-OCH_3, and Ar substituents change insignificantly in amines III. The remaining signals in the spectra of amines IIIa-h confirm the presence of the corresponding substituent in position 2. Note the shift of NCH_2 protons in the morpholine ring in IIIg by 1 ppm, indicative of their magnetic identity with OCH_2 protons. This is due to the effect of the neighboring magnetically anisotropic C≡N group.

Latvian Institute of Organic Synthesis, Riga LV-1006; Institut für Wirkstofforschung, Berlin. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 12, pp. 1646-1650, December, 1992. Original article submitted November 29, 1991.

0009-3122/92/2812-1411$12.50

TABLE 1. Properties of Synthesized Compounds II-VIII

Compound	mp, °C	IR spectrum, ν, cm^{-1}	Yield, %
IIa	117...119	1740, 2240	84
IIb	120...122	1740, 2240 _	77
IIIa	114...115	1730, 2220, 3310, 3520	70
IIIb	69...70	1720, 2220, 3100...3400	83
IIIc	130	1725, 2220	81
IIId	135	1730, 2220	68
IIIe	110...112	1725, 2220, 3300...3500	46
IIIf	56...59	1725, 2220, 3100...3400	38
IIIg	182...185	1730, 2220	41
IIIh	175...178	1730, 2220	19
IVa	273...275	1720, 3180,3290,3460	51
IVb	278...280	1720, 3180,3280,3460	48
Va	219...220	1670, 1715, 3190, 3300, 3390	74
Vb	195...196	1680, 1725, 3160, 3330	87
VIa	265...267	1650 sh 1725, 3000...3200	66
VIb	>250 decomp.	1650 sh 1725, 3000...3200	84
VIIa	109...110	1670, 1710, 3180, 3260 sh 3420	59
VIIb	130...131	1670, 1715, 3400	71
VIII	>250 decomp.	1660п, 1715, 3160	45

To synthesize pyrazolopyridines in the 5-carbomethoxy-3-cyano-2-chloropyridine series, they were reacted with hydrazine hydrate. Substitution of chlorine by a hydrazine group takes place in this case, and subsequent intramolecular condensation takes place without separation of the hydrazine derivative with formation of 3-amino-4-aryl-5-carbomethoxy-6-methyl-1H-pyrazolo[3,4-*b*]pyridines (IVa,b). Similar to derivative II, the PMR spectra of compounds IVa and IVb only differ by the character of the signal of the aromatic protons. There is no nitrile group band in the IR spectra of pyrazolopyridines IV and absorption of NH_2 and NH groups is observed in the 3180-3460 cm^{-1} region.

Hydrolysis of the nitrile group of 3-cyano-2-chlorpyridines IIa,b to an amide group (with conc. sulfuric acid) was conducted for synthesis of oxo derivatives of pyrazolo[3,4-*b*]pyridines VI.

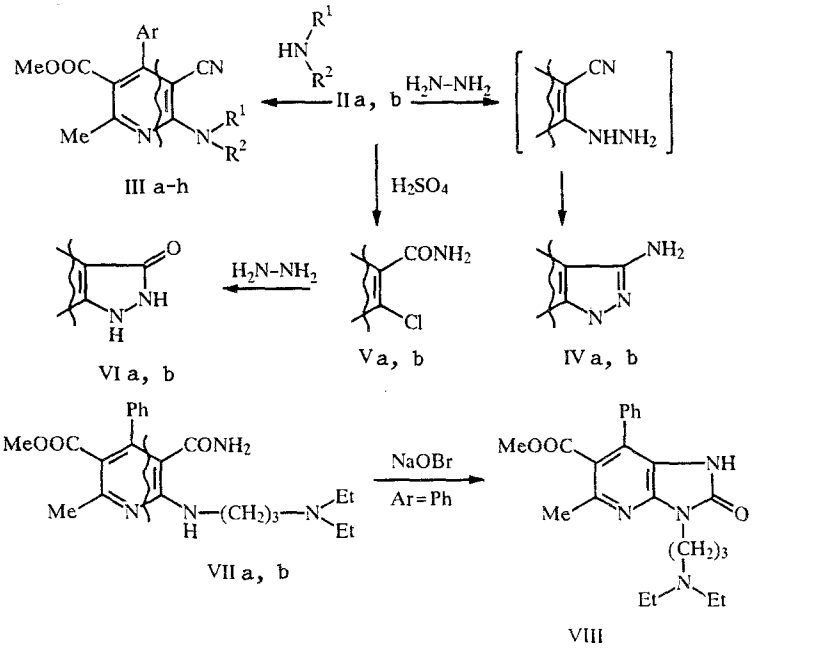
In contrast to nitriles II, the IR spectra of 4-aryl-2-carbamoyl-5-carbomethoxy-6-methyl-2-chloropyridines V exhibit a decrease in the frequency of the ester carbonyl group from 1740 to 1715-1725 cm^{-1} and the appearance of $\nu_{C=O}$ of exocyclic amide at 1670-1680 cm^{-1} (see Table 1). In going from pyridine II to V, signals characteristic of $CONH_2$ protons appear in the PMR spectra; the chemical shifts of the basic substituents (6-CH_3, OCH_3, and Ph) is even smaller than in going from 2-chloropyridines II to 2-aminopyridines III.

Substitution of the chlorine in 3-carbamoyl derivative V by a hydrazine group is accompanied by subsequent intramolecular cyclization with separation of a molecule of ammonia and the formation of 4-aryl-5-carbomethoxy-6-methyl-3-oxo-2,3-dihydro-1H-pyrazolo[3,4-*b*]pyridines (VIa,b). The structure of pyrazolo[3,4-*b*]pyridines VIa,b was confirmed by the data from the PMR spectra (see Table 2), where there is no signal from $CONH_2$ group protons and a signal of NH protons is observed in weak fields. Its width is so great that the integral intensity is difficult to determine; observation of this signal is more difficult in VIa. (See scheme on followin page.)

4-Aryl-3-carbamoyl-5-carbomethoxy-6-methyl-2-propylamino-3′-diethylaminopyridines (VIIa,b) were obtained by substitution of the chlorine in nicotinamide V by a N,N-diethylaminopropyl group. No broadened singlets (0.2-0.3 ppm distance between them) characteristic of the terminal $CONH_2$ group in compounds V are observed in the PMR spectra of amines VIIa,b. Its presence is indirectly confirmed by the change in the character and position of the NH proton of the substituent in position 2 in comparison to the position in IIIb. An intramolecular hydrogen bond is probably formed between the N—H proton and carbonyl group oxygen, which causes shielding of the proton at 1.5 ppm and a spin-spin interaction with the protons of the NCH_2 group.

The formation of imidazo[4,5-*b*]pyridines in conditions of Hofmann rearrangement of 3-carbamoyl-2-aminopyridines is interesting. The conditions of synthesis of 6-carbomethoxy-5-methyl-2-oxo-7-phenyl-3-(propylamino-3′-diethylamino)-1H-imidazo[4,5-*b*]pyridine (VIII) were found in the reaction of 3-carbamoyl-2-aminopyridine VIIa with sodium hypobromite.

Characteristic signals of all proton-containing groups are observed in the PMR spectra of VIII. The signal of the NH proton is masked by the multiplet of the phenyl substituent. Substitution of the solvent ($CDCl_3$) separates the signals.



IIIa Ar = Ph, R^1 = H, R^2 = $(CH_2)_3$-OH; b Ar = Ph, R^1 = H, R^2 = $(CH_2)_3NEt_2$; c Ar = Ph, $R^1 + R^2$ = = -$(CH_2)_2$-O-$(CH_2)_2$-; d Ar = Ph, $R^1 + R^2$ = -$(CH_2)_5$-; e Ar = Ph, $R^1 + R^2$ = -$(CH_2)_2$-NH-$(CH_2)_2$; f Ar = 4-ClC_6H_4, R^1 = H, R^2 = $(CH_2)_3$-NEt_2; g Ar = 4-ClC_6H_4, $R^1 + R^2$ = -$(CH_2)_2$-O-$(CH_2)_2$-; h Ar = =4-ClC_6H_4, $R^1 + R^2$ = -$(CH_2)_5$-; IV—VIIa Ar = Ph, b Ar = 4-ClC_6H_4

EXPERIMENTAL

The IR spectra were recorded on a Specord IR-72 (VEB Carl Zeiss Jena) and the PMR spectra were recorded in standard conditions on a Tesla BS-587 spectrometer with a working frequency of 80 MHz.

The basic properties of the synthesized substances are reported in Tables 1 and 2.

The data from elemental analyses of the compounds obtained correspond to the calculations.

5-Carbomethoxy-6-methyl-4-phenyl-2-chloro-3-cyanopyridine (IIa, $C_{15}H_{11}ClN_2O_2$). Here 0.1 ml of dry DMF was added to a suspension of 2.7 g (10 mmole) of pyridine Ia in 8 ml (200 mmole) of $POCl_3$ and the solution was boiled for 2.5 h. After cooling, the reaction mixture was poured in 30 g of ice while energetically stirring and the sediment was filtered off then recrystallized from ethanol with carbon, yielding chloropyridine IIa.

2-Chloropyridine IIb ($C_{15}H_{10}Cl_2N_2O_2$) was prepared similarly.

2-(3-Hydroxypropylamino)-5-carbomethoxy-6-methyl-4-phenyl-3-cyanopyridine (IIIa, $C_{18}H_{19}N_3O_3$). A mixture of 2.86 g (10 mmole) of chloropyridine IIa in 70 ml of isopropanol was boiled for 6 h with 1.12 g (15 mmole) of 3-aminopropanol. The reaction mixture was filtered and evaporated in a vacuum. The sediment was filtered off and recrystallized from ethanol with water. Amine IIIa crystallized after holding for 2 days at −20°C.

2-Aminopyridines IIIb, $C_{22}H_{28}N_4O_2$; IIIc, $C_{19}H_{19}N_3O_3$; IIId, $C_{20}H_{21}N_3O_2$; IIIe, $C_{19}H_{20}N_4O_2$; IIIf, $C_{22}H_{27}ClN_4O_2$; IIIg, $C_{19}H_{18}ClN_3O_3$; IIIh, $C_{20}H_{20}ClN_3O_2$, were prepared analogously. Absolute ethanol was used as the solvent for amines IIIc-h. The amine was crystallized from ethanol without additional cooling in the cases of IIIc-e, g, h.

3-Amino-5-carbomethoxy-6-methyl-4-phenyl-1H-pyrazolo[3,4-*b*]pyridine (IVa, $C_{15}H_{14}N_4O_2$). Here 7.5 ml (150 mmole) of hydrazine hydrate and 3 drops of dry DMF were added to a suspension of 2.86 g (10 mmole) of 2-chloropyridine IIa in 20 ml of absolute ethanol; the reaction mixture was boiled for 4 h. After cooling, pyrazolo[3,4-*b*]pyridine IVa was filtered off.

Pyrazolo[3,4-*b*]pyridine IVb, $C_{15}H_{13}N_4O_2Cl$, was prepared similarly. Pyrazolopyridines IVa,b were recrystallized from ethanol with addition of acetic acid.

TABLE 2. Proton Chemical Shifts of Compounds II-VIII in DMSO-D_6

Compound	δ, ppm
IIa	2,52 (3H, s, 6-CH_3); 3,50 (3H, s, O—CH_3); 7,3...7,6 (5H, m, arom)
IIb	2,57 (3H, s, 6-CH_3); 3,59 (3H, s, O—CH_3); 7,41 and 7,71 (4H, d and d, arom)
IIIa	1,68 (2H, m, C—CH_2—C); 2,34 (3H, s, 6-CH_3); 3,31 (3H, m, O—CH_3); 3,45 (2H, m, N—CH_2—C); 4,47 (2H, m, C—CH_2—O); 7,3...7,7 (6H, m, arom + NH)
IIIb*	0,99 (6H, t, N—(C—CH_3)$_2$); 1,72 (2H, m, C—CH_2—C); 2,42 (3H, s, 6-CH_3); 2,5 (6H, m, $CH_2N(CH_2C)_2$); 3,36 (3H, s, O—CH_3); 3,58 (2H, m, N—CH_2—C); 7,2...7,4 (5H, m, C_6H_5); 7,88 (1H, s, NH)
IIIc	2,39 (3H, s, 6-CH_3); 3,33 (3H, s, O—OCH_3); 3,62 (8H, s, $(CH_2)_4$); 7,2...7,5 (5H, m, arom)
IIId	1,60 (6H, s, $(CH_2)_3$); 2,36 (3H, s, 6-CH_3); 3,29 (3H, s, O—CH_3); 3,62 (4H, s, N$(CH_2)_2$); 7,2...7,5 (5H, m, arom)
IIIe	2,45 (3H, s, 6-CH_3); 2,85 (4H, m, NH$(CH_2)_2$); 3,41 (3H, s, O—CH_3); 3,67 (4H, m, N$(CH_2)_2$); 7,3...7,5 (5H, m, arom; 7,8 (1H, br. s, NH)
IIIf	0,92 (6H, t, N—(C—CH_3)$_2$); 1,68 (2H, m, C—CH_2—C); 2,36 (3H, s, 6-CH_3); 2,46 (6H, m, $CH_2N(CH_2C)_2$); 3,40 (3H, s, O—CH_3); 3,50 (2H, m, NH_2—C); 7,58 and 7,80 (4H, d and d, C_6H_5); 8,2 (1H, br.s, NH)
IIIg	2,39 (3H, s, 6-CH_3); 3,40 (3H, s, O—CH_3); 3,65 (8H, s, morpholinyl); 7,31 and 7,49 (4H, d and d, arom)
IIIh	1,57 (6H, s, C—CH_2—CH_2—CH_2—C); 2,40 (3H, s, 6-CH_3); 3,37 (3H, s, O—CH_3); 3,62 (4H, s, N$(CH_2)_2$); 7,3 and 7,5 (4H, d and d arom)
IVa	2,48 (3H, s, 6-CH_3); 3,42 (3H, s, 6-OCH_3); 4,26 (2H, s, NH_2); 7,4...7,7 (5H, m, C_6H_5); 12,33 (1H, br.s, NH)
IVb	2,48 (3H, s, 6-CH_3); 3,46 (3H, s 6-OCH_3); 4,30 (2H, s, NH_2); 7,47 and 7,83 (4H, br.s C_6H_4); 12,33 (1H, s, NH)
Va	2,43 (3H, s, 6-CH_3); 3,44 (3H, s, O—CH_3); 7,34 (5H, s, C_6H_5); 7,40 and 7,58 (2H, br.s and br.s., $CONH_2$)
Vb	2,44 (3H, s, 6-CH_3); 3,50 (3H, s, O—CH_3); 7,22 and 7,48 (4H, d and d, C_6H_5); 7,52 and 7,86 (2H, s, and br.s, $CONH_2$)
VIa	2,48 (3H, s, 6-CH_3); 3,45 (3H, s, O—CH_3); 7,37 (5H, s, C_6H_5)
VIb	2,48 (3H, s, 6-CH_3); 3,50 (3H, s, O—CH_3); 7,34 and 7,47 (4H, d and d, C_6H_4); 10...13,5 (2H, superbr. s, NH and NH)
VIIa	0,91 (6H, t, N—(C—CH_3)$_2$); 1,61 (2H, m, C—CH_2—C); 2,28 (3H, s, 6-CH_3); 2,4 (6H, m, $CH_2N(CH_2C)_2$); 3,26 (3H, s, O—CH_3); 3,30 (2H, s, NCH_2—C); 6,52 (1H, t, NH); 7,1...7,4 (5H, m, C_6H_5)
VIIb	0,89 (6H, t, N—(C—CH_3)$_2$); 1,60 (2H, m, C—CH_2—C); 2,28 (3H, s, 6-CH_3); 2,35 (6H, m, $CH_2N(CH_2C)_2$); 3,34 (3H, s, O—CH_3); 3,37 (2H, m, NCH_2—C); 6,56 (1H, t, NH); 7,15 and 7,38 (4H, d and d, C_6H_5)
VIII	0,86 (6H, t, N—(C—CH_2)$_2$); 1,74 (2H, m, C—CH_2—C); 2,3 (6H, m, $CH_2N(CH_2C)_2$); 2,39 (3H, s, 6-CH_3); 3,43 (3H, s, O—CH_3); 3,81 (2H, m, NCH_2—C); 7,2...7,5 (6H, m, C_6H_5 + NH)

*In $CDCl_3$.

4-Aryl-3-carbamoyl-5-carbomethoxy-6-methyl-2-chloropyridines (Va, $C_{15}H_{13}ClN_2O_3$; Vb, $C_{15}H_{12}Cl_2N_2O_3$). A suspension of 1 g of 2-chloropyridine IIa,b in 5 ml of conc. H_2SO_4 was held for 4-5 h at 70°C. After cooling, the reaction mixture was poured into ice water and neutralized with ammonia. The sediment was filtered off and recrystallized from ethanol.

5-Carbomethoxy-6-methyl-3-oxo-4-phenyl-2,3-dihydro-1H-pyrazolo[3,4-*b*]pyridine (VIa, $C_{15}H_{13}ClN_2O_3$). Here 3 drops of DMF was added to 1.5 g (5 mmole) of amide Va, 15 ml of absolute ethanol, and 5 ml (80 mmole) of hydrazine hydrate and boiled for 1.5 h. After cooling, the reaction mixture was poured in acidified water. The sediment formed was filtered off and recrystallized from ethanol.

Compound VIb, $C_{15}H_{12}N_3ClO_3$, was obtained similarly. The boiling time was 1 h.

3-Carbamoyl-5-carbomethoxy-6-methyl-2-(propylamino-3′-diethylamino)-4-phenylpyridine (VIIa, $C_{22}H_{30}N_4O_3$). A mixture of 3.0 g (10 mmole) of 2-chloropyridine Va and 3.25 g (25 mmole) of 3-diethylamino-1-propylamine was boiled for 30 h in 50 ml of isopropanol in the presence of 1.59 g (15 mmole) of Na_2CO_3. After the reaction ended, the solvent was evaporated and the oil formed was crystallized with ice. The sediment was filtered and recrystallized from ethanol with water.

Compound VIIb, $C_{22}H_{29}ClN_4O_3$, was prepared analogously. The reaction time was 50 h.

5-Carbomethoxy-6-methyl-2-oxo-4-phenyl-1-(3-diethylaminopropylamino)-3H-imidazo[4,5-*b*]pyridine (VIII, $C_{22}H_{28}N_4O_3$). Here 1 g (2.51 mmole) of amine VIIa was suspended in 15.7 ml of 1 N aqueous solution of NaOH cooled to 0°C and 0.15 ml of bromine was added by drops while stirring. Cooling and stirring were continued for 1 h, followed by heating in a water bath for 2 h. After cooling, the solution was filtered, and the filtrate was neutralized with hydrochloric acid. The sediment was filtered and recrystallized from ethanol.

REFERENCES

1. Z. A. Kalme, B. Roloff, Yu. Yu. Pelcher, Yu. Yu. Popelis, F. Khagen, and G. Ya. Dubur, Khim. Geterotsikl. Soedin., No. 9, 1218 (1992).
2. B. Roloff, J. S. Schafer, A. Rumler, and A. Hagen, Pharmazie, **44**, 12 (1989).
3. V. Hagen, E. Klauschen, A. Rumler, A. Hagen, S. Heer, R. Mitzner, H. Niedrich, and D. Lohmann, Pharmazie, **45**, 189 (1990).