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SYNTHESIS OF DERIVATIVES OF 8-CYANO-6-ETHOXYCARBONYL-3-HYDROXY-5-METHYL-IMIDAZO[1,2-*a*]PYRIDINE AND 9-ALKOXYCARBONYL-(OR 9-CARBOXY)-3-ETHOXYCARBONYL-2-METHYL-10H-BENZO[*b*]-1,8-NAPHTHYRIDINE-5-ONE FROM THE REACTION OF 2-CHLORO-5-ETHOXYCARBONYL-6-METHYLNICOTINONITRILE WITH AMINO ACIDS

A. B. Deyanov and M. E. Konshin

2-Substituted 8-cyano-6-ethoxycarbonyl-3-hydroxy-5-methylimidazo[1,2-a]pyridine was formed from the interaction of 2-chloro-5-ethoxycarbonyl-6-methylnicotinonitrile with α-amino acids in DMF. The same nitrile on boiling with anthranilic acid or its esters in butanol gave, respectively, 2-(2-carboxyanilino)- or (2-(2-alkoxycarbonylanilino)-5-ethoxycarbonyl-6-methylnicotinonitriles which cyclized on heating in PPA to give 9-alkoxycarbonyl(or 9-carboxy)-3-ethoxycarbonyl-2-methyl-10H-benzo[b]-1,8-naphthyridin-5-ones.

Keywords: 10H-benzo[*b*]-1,8-naphthyridin-5-ones, imidazo[1,2-*a*]pyridines, 2-(2carboxyanilino)-nicotinonitriles.

We have shown previously that the reaction of 2-chloro-5-ethoxycarbonyl-6-methylnicotinonitrile (**1**) with arylamines can be used to prepare biologically active derivatives of nicotinic acid [1] and also intermediates for the synthesis of pyrido[2,3-*d*]pyrimidines (Scheme 1) [2, 3].

In this work, with the objective of extending these studies and elucidating the possibility of using nitrile **1** in the synthesis of functionally substituted imidazo[1,2-*a*]pyridines, pyrido[2,1-*b*]quinazolines and benzo[*b*]-1,8-naphthyridines, we have studied the reactions of compound **1** with α-amino acids, anthranilic acid and its esters.

As a result of the investigations it was found that the reaction of nitrile **1** with α-amino acids did not result in substitution of chlorine atom by the amino acid residue, instead an intramolecular cyclization of the intermediate N-(2-pyridyl) derivative of the amino acid occurred to give 2-substituted 8-cyano-6-ethoxycarbonyl-3-hydroxy-5-methylimidazo[1,2-*a*]pyridines **2a-d** (Table 1). This was indicated by the failure of compounds **2a,b** to dissolve in aqueous sodium hydrogencarbonate, and the absence of the characteristic signals of the carboxy group protons in their ^{1}H NMR spectra (Table 2).

Perm State Pharmaceutical Academy, Perm 614990, Russia; e-mail: pfa@degacom.ru. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 4, 608-613, April, 2004. Original article submitted June 22, 2001; revision submitted March 20, 2002.

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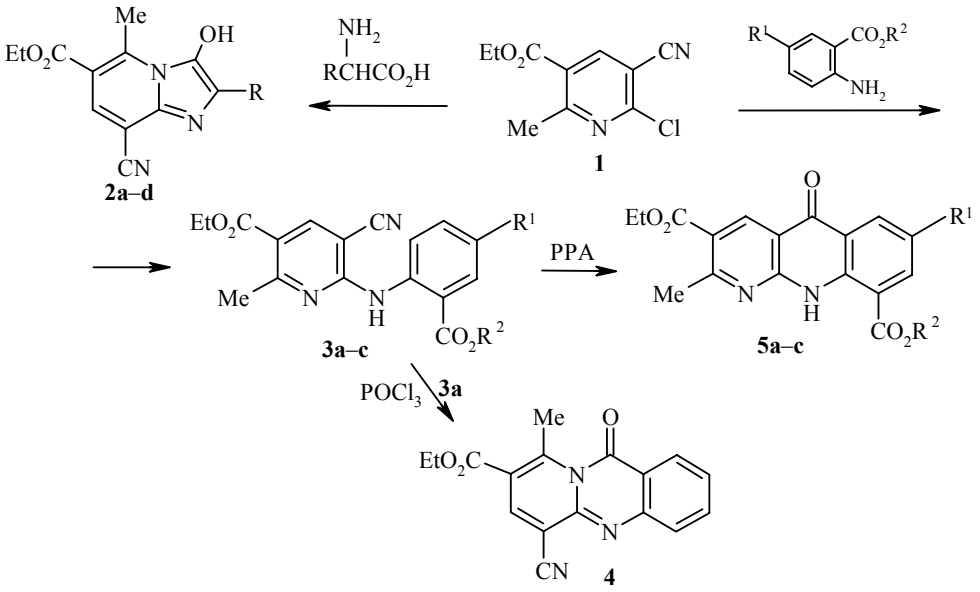
Scheme 1



2 a R = H, **b** R = CH_2OH, **c** R = CH_2CO_2H, **d** R = $CH_2CH_2CO_2H$;
3, **5 a** $R^1 = R^2 = H$, **b** $R^1 = H$, $R^2 = Et$, **c** $R^1 = R^2 = Me$

In the IR spectra of imidazopyridines **2a-d** stretching bands of the 3-OH were observed at 3510-3580 cm^{-1}, and signals of hydroxyl protons appeared at 3.67-3.82 ppm in their ^1H NMR spectra. These data, and also the absence of signals of the NH group protons permitted the conclusion that compounds **2a-d** evidently exist in the enol form, and not the carbonyl form which is in agreement with some results presented in the review [4].

TABLE 1. Characteristics of the Compounds Synthesized

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
		C	H	N		
2a	$C_{12}H_{11}N_3O_3$	58.77 / 59.02	4.52 / 4.41	17.13 / 17.38	89-92	35
2b	$C_{13}H_{13}N_3O_4$	56.72 / 56.64	4.76 / 5.03	15.27 / 15.60	100-102	46
2c	$C_{14}H_{13}N_3O_5$	55.45 / 55.70	4.32 / 4.27	13.86 / 14.06	97-99	41
2d	$C_{15}H_{15}N_3O_5$	56.78 / 57.16	4.77 / 4.75	13.24 / 13.00	93-96	42
3a	$C_{17}H_{15}N_3O_4$	62.76 / 62.98	4.65 / 4.79	12.92 / 13.09	236-237	71
3b	$C_{19}H_{19}N_3O_4$	64.58 / 64.30	5.42 / 5.58	11.89 / 12.15	208-209	74
3c	$C_{19}H_{19}N_3O_4$	64.58 / 64.74	5.42 / 5.65	11.89 / 11.92	168-169	65
4	$C_{17}H_{13}N_3O_3$	66.44 / 66.57	4.26 / 4.53	13.67 / 13.52	135-137	35
5a	$C_{17}H_{15}N_2O_5$	62.38 / 62.60	4.62 / 4.74	8.56 / 8.53	242-244	58
5b	$C_{19}H_{19}N_2O_5$	64.22 / 64.24	5.39 / 5.11	7.88 / 8.17	224-226	61
5c	$C_{19}H_{19}N_2O_5$	64.22 / 64.10	5.39 / 5.09	7.88 / 8.02	216-217	76

TABLE 2. Spectroscopic Characteristics of the Compounds Synthesized

Compound	^{1}H NMR spectrum, δ, ppm							IR spectrum, ν, cm^{-1}*			
	CH_3 (3H, s)	NH (1H, s)	H arom., m	H pyridine, s	$CH_2\underline{CH_3}$ (3H, t)	OCH_2CH_3 (3H, q)	other protons	C=O	C≡N	N–H	other
2a	2.58		—	8.25	1.30	4.22	3.28 (1H, s, 2-H), 3.67 (1H, s, 3-OH)	1720	2234	—	3580 (O–H)
2b	2.58		—	8.18	1.25	4.18	3.22 (2H, d, $C\underline{H_2}OH$), 3.71 (1H, s, 3-OH), 2.45 (1H, d, $CH_2O\underline{H}$)	1722	2230	—	3565 (O–H)
2c	2.48		—	8.12	1.28	4.18	3.28 (2H, s, $C\underline{H_2}COOH$), 3.82 (1H, s, 3-OH)	1726	2232	—	3520 (O–H)
2d	2.48		—	8.18	1.32	4.20	3.25 (4H, m, $C\underline{H_2}COOH$), 3.76 (1H, s, 3-OH)	1726	2228	—	3510 (O–H)
3a	2.68	8.68	7.02-8.15	8.28	1.25	4.32	11.65 (1H, s, $COO\underline{H}$)	1720	2230	3330	1700 (C=O), 3550 (O–H)
3b	2.81	11.68	7.42-8.26	8.42	1.38	4.35	—	1716	2228		1692 (C=O)
3c	2.70	11.43	7.23-8.18	8.39	1.35	4.21	2.26 (3H, s, R), 3.97 (3H, s, R')	1710	2230		1694 (C=O)
4	2.55	—	7.01-8.05	8.30	1.28	4.26	—	1718	2234	—	1660 (C=O)
5a	2.65	8.78	7.45-8.30	8.46	1.35	4.32	9.43 (1H, s, $COO\underline{H}$)	1718		3330	1696 (C=O), 1676 ($C_{(5)}$=O)
5b	2.62	9.18, 11.92	6.97-8.29	8.58	1.30	4.32	—	1714		3336	1700 (C=O), 1652 ($C_{(5)}$=O)
5c	2.62	11.98	7.47-8.32	8.55	1.35	4.28	3.85 (3H, s, $COO\underline{Me}$), 2.32 (3H, s, R)	1716		3412	1698 (C=O), 1652 ($C_{(5)}$=O)

* The IR spectra of compounds **3a** and **5** were obtained in CCl_4 (c = 0.05 mol/l), those of compounds **3b, 3c** – in $CHCl_3$ (c = 0.05 mol/l), the others as nujol mulls.

It might be expected that anthranilic acid and its esters would react with nitrile **1** to give substituted pyrido[2,1-*b*]quinazolin-10-one since this was observed in the case of the reaction of 2-chloronicotinamides with anthranilic acid [5]. However 2-(2-carboxyanilino)-**3a** or 2-(2-alkoxycarbonyl-4-R-anilino)-5-ethoxycarbonyl-6-methylnicotinonitriles **3b,c** were obtained as a result of this reaction.

Compound **3a** has a free carboxyl group and dissolves in aqueous sodium hydrogencarbonate solution. In the IR spectrum of compound **3a** in carbon tetrachloride solution stretching vibrations were observed at 3550 (COOH) and 3300 cm^{-1}(NH). The ^{1}H NMR spectrum of this compound has signals at 8.68 (1H, NH) and 11.65 ppm (1H, COOH) which correspond to suggested structure. This reaction stops at the acid **3a** which does not cyclize to derivative of pyrido[2,1-*b*]quinazoline, which is probably connected with steric hindrance by the methyl group at position 6. As a confirmation of this idea we carried out the reaction between 2-chloro-6-methylnicotinonitrile and anthranilic acid to give 2-(2-carboxyanilino)-6-methylnicotinonitrile.

When acid **3a** was boiled with an excess of phosphorus oxychloride for 1.5 h 4-cyanopyrido-2-ethoxycarbonyl-1-methyl[2,1-*b*]quinazolin-10-one (**4**) was obtained in 35% yield. Attempts to cyclize acid **3a** by boiling for 12 h in ethylene glycol or glacial acetic acid were unsuccessful.

Compound **4** is a crystalline substance insoluble in aqueous sodium hydrogencarbonate solution, but soluble in general organic solvents. In distinction from the spectrum of the starting acid **3a**, the IR and ^{1}H NMR spectra of compound **4** do not contain signals for the secondary amino group or OH of a carboxyl group.

The IR and ^{1}H NMR spectra of the esters **3b** and **3c** differ somewhat from the spectra of 2-arylamino-5-ethoxycarbonylnicotinonitriles [1]. For example, in the IR spectra of compounds **3b,c** in Nujol mulls or chloroform the stretching frequency due to a secondary amino group is missing and the stretching vibration band of one of the ester carbonyl groups is shifted to low frequency. In the ^{1} NMR spectra a signal for one proton is observed at 11.43 or 11.68 ppm, whereas the signal for the proton of NH group in 2-arylaminonicotinonitriles is usually observed at 9.21-9.55 ppm. The absence of stretching vibration bands in the 3100-3600 cm^{-1} region of the IR spectra and the weak field shift of the signal of the NH proton in the ^{1}H NMR spectra of esters **3b,c** indicate that they exist in the form of chelates with an intramolecular hydrogen bond between the NH groups and the neighbouring carbalkoxy group.

In the mass spectra of compounds **3b,c** the molecular ions correspond to the molecular mass. Decomposition of the molecular ions of these compounds evidently proceeds in two directions: either with elimination of alcohol and intramolecular cyclization into the ion 307 (321)* $[M - AlkOH]^+$, having the structure of pyrido[2,1-*b*]quinazolin-10-one, or by loss of alkoxycarbonyl radical with formation of the ion 280 (294) $[M - COOAlk]^+$. The preference for the second route of decomposition is indicated by the 100% intensity of the peaks of ions 280 (294), the stability of which is explained by redistribution of the positive charge onto the heterocyclic system. Fragmentation of the ions 307 (321) is related to the loss of CO molecule or the isocyanic acid radical with the formation of the ions 279 (293) and 265 (289) respectively. The ions 280 (294) lose H and are also converted into ions 279 and 293. The latter either lose the nitrile radical or are converted by *ortho*-splitting with loss of a molecule of ethanol. Further fragmentation is connected with breakdown of the heterocyclic system.

Heating of 2-arylaminonicotinonitriles in concentrated acids led to cyclization into derivatives of benzo[*b*]-1,8-naphthyridin-10-one [6]. Because under the electronic impact from the molecular ion of compounds **3b,c** ion was formed which had the structure of pyrido[2,1-*b*]quinazolin-10-one, and also that possibility of cyclization of compound **3a** was confirmed preparatively, it seemed of interest to discover which route would follow the reactions on heating these compounds in PPA.

It was established that when compounds **3a-c** were heated in PPA at 135-145°C for 2h they cyclized into 9-alkoxycarbonyl(carboxy)-3-ethoxycarbonyl-2-methyl-7H-(methyl)-10H-benzo[*b*]-1,8-naphthyridin-5-ones

* Here and below we use the value *m/z* for ion peaks.

5a-c in yields of 58-76%. Compound **5b** was also obtained by prolonged standing of compound **3b** at room temperature in concentrated sulfuric acid.

Compounds **5a-c** are yellow crystalline compounds, soluble in DMF and concentrated acetic acid. In their IR spectra, in contrast with the spectra of starting materials **3a-c** the nitrile stretching frequency has disappeared and there is one more carbonyl group band at 1652-1676 cm^{-1}. These data, and also the presence of the signal of one proton at 11.70 (11.93) ppm and a weak signal at 9.18 ppm in the ^1H NMR spectra of naphthyridones **5b,c** indicate the existence of compounds **5b,c** in both the chelate and non-chelate forms.

EXPERIMENTAL

IR spectra were recorded on UR-20 spectrometer. ^1H NMR spectra were recorded on a PC-60 (60 MHz) spectrometer for solutions of compounds **2b**, **2d**, **5a-c** in $CDCl_3$, the rest in DMSO-d_6 with HMDS as internal standard. Mass spectra were recorded on MX-1303 apparatus with direct inlet of the sample into the ion source, ionizing voltage 70 eV, standard for comparison ^{200}Hg.

2-Substituted 8-Cyano-6-ethoxycarbonyl-3-hydroxy-5-methylimidazo[1,2-*a*]pyridines (2a-d). Compound **1** (2.25 g, 0.01 mol) was dissolved in DMF (10 ml), the corresponding α-amino acid (0.015 mol) was added and the mixture was heated to complete solution of the latter and then for a further 1 h. The cooled solution was poured into water (100 ml). The precipitate was filtered off and crystallized from 2-propanol–water mixture.

2-(2-Carboxyanilino)- (3a) or 2-(2-Alkoxycarbonyl-4-R-anilino)-5-ethoxycarbonyl-6-methyl-nicotinonitriles (3b,c). Solution of compound **1** (2.25 g, 0.01mol) and anthranilic acid or its ester (0.015 mol) in butanol (25 ml) was boiled for 6 h. The precipitate formed on cooling was filtered off and crystallized (compound **3a** from a DMF water mixture, **3b,c** – from 2-propanol). Mass spectra, *m/z* (I_{rel}, %): **3b** 353 $[M]^+$ (47), 307 (15), 280 (100), 279 (60), 265 (10), 253 (25), 234 (10), 233 (12), 207 (12), 179 (9); **3c** 353 $[M]^+$ (77), 321 (23), 294 (100), 293 (87), 279 (10), 267 (24), 247 (16), 221 (10), 193 (3).

2-(2-Carboxyanilino)-6-methylnicotinonitrile (3a). Solution of nitrile **1** (1.53 g, 0.01 mol) and anthranilic acid (2.06 g, 0.015 mol) in 50% acetic acid (15 ml) was boiled for 4 h. The precipitate was filtered off, dried, and crystallized from 1:1 benzene–hexane. M.p. 140°C. Yield 1.81 g (71%). ^1H NMR spectrum, δ, ppm: 10.27 (1H, s, COOH); 8.63 (1H, s, NH); 7.25 (6H, m, arom. prot.); 2.19 (3H, s, CH_3). Found, %: C 66.6; H 4.3; N 16.4. $C_{14}H_{11}N_3O_2$. Calculated, %: C 66.4; H 4.4; N 16.6.

4-Cyanopyrido-2-ethoxycarbonyl-1-methyl[2,1-*b*]quinazolin-10-one (4). Solution of compound **3a** (3.25 g, 0.01 mol) in phosphorus oxychloride (25 ml, 0.28 mol) was boiled for 1.5 h. The mixture was cooled and poured into water (100 ml) and carefully alkalized with ammonia solution to pH 8. The precipitate was filtered off, dried, and crystallized from 85% acetic acid. M.p. 135-137°C, yield 1.07 g (35%).

9-Alkoxycarbonyl(carboxy)-3-ethoxycarbonyl-2-methyl-7H-(methyl)-10H-benzo[*b*]-1,8-naphthyridin-5-ones (5a-c). Solution of the corresponding compound **3a-c** (0.01 mol) in PPA was heated for 2 h at 135-145°C. The mixture was poured into water (100 ml), the precipitate was filtered off and crystallized from aqueous acetic acid.

3,9-Di(ethoxycarbonyl)-2-methyl-10H-benzo[*b*]-1,8-naphthyridin-5-one (5b). Compound **3b** (3.53 g, 0.01 mol) was dissolved in concentrated H_2SO_4 (25 ml) and kept at 18-22°C for 240 h. The solution was poured into water (100 ml) and carefully neutralized with ammonia solution. The precipitate was filtered off, dried and crystallized. Yield 3.02 g (89%). Melting point of mixed sample with compound **5b**, prepared in the previous experiment, gave no depression.

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