NAPHTHYRIDINE STUDIES.
15.* 2-STYRYLQUINOLINE-3-CARBOXAMIDES AND THEIR CYCLIZATION TO 3-ARYL-1-OXO-1,2,3,4-TETRAHYDROBENZO[b][1,6]NAPHTHYRIDINES

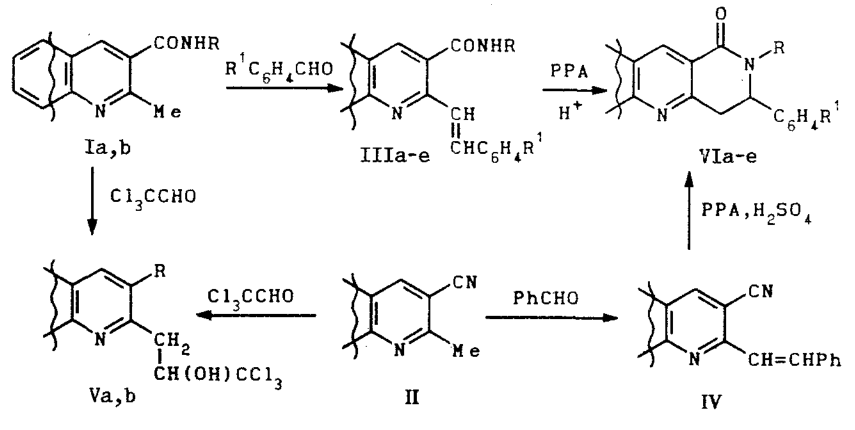
S. V. Ukhov and M. E. Konshin

Condensation of 2-methylquinoline-3-carboxamides or the acid nitrile with benzaldehydes gave 2-styrylquinoline-3-carboxamides or the nitrile. It was shown that these compounds cyclize to the 2-substituted 3-aryl-1-oxo-1,2,3,4-tetrahydrobenzo[b][1,6]naphthyridines using polyphosphoric acid or sulfuric acid.

It has been shown [1] that 2-styrylquinoline-3-carboxanilides cyclize to 2-aryl-1-oxo-3-phenyl-1,2,3,4-tetrahydrobenzo[b][1,6]naphthyridines when heated with polyphosphoric acid. In order to broaden the scope of this reaction we have studied the condensation of the amides Ia and Ib and the nitrile II of 2-methylquinoline-3-carboxylic acid with derivatives of benzaldehyde, furfural, and chloral.

This work has shown that Ia, b and II, when treated with substituted benzaldehydes in xylene (170°C) in the presence of pyridine, give 2-styrylquinoline-3-carboxamides (IIIa-e, Table 1) and 2-styryl-3-cyanoquinoline (IV), respectively.

Under these conditions, p-nitrobenzaldehyde, salicylaldehyde, and furfural show much tarring and the target product is not isolated. Compound Ia does not react with benzaldehyde when refluxed in acetic anhydride for 3 h. At the same time, p-nitrobenzaldehyde condenses with aniline Ia over 1 h to form anilide IIIc. This is apparently connected with the high electrophilicity of the aldehyde group in this compound when compared with the analogous benzaldehyde.



Ia R = C_6H_5, b R = $C_6H_5CH_2$; IIIa-d R = C_6H_5, a R^1 = p-CH_3O, b R^1 = m-Br, c R^1 = p-NO_2,
d R^1 = p-$(CH_3)_2N$; IIIe R = $C_6H_5CH_2$, R^1 = H; Va R = C_6H_5NHCO, b R = CN; VIA-c
R = C_6H_5, a R^1 = H, b R^1 = p-CH_3O, c R^1 = m-Br; d R = $C_6H_5CH_2$, R^1 = H; e R = H, R^1 = H

The IR spectra of amides IIIa-e show absorption bands at 1630-1640 cm^{-1} (CO) and 3280-3310 cm^{-1} (NH). The PMR spectra show a multiplet at 7.43-7.50 (benzene protons and CH=CH group), a singlet at 8.20-8.36 (4-H), and a singlet at 10.1 ppm (NH).

Heating amide Ia and nitrile II with chloral in anhydrous pyridine gave the amides of 2-(2-hydroxy-3,3,3-trichloroprop-1-yl)quinoline-3-carboxylic acid (Va) and 2-(2-hydroxy-3,3,3-trichloroprop-1-yl)-3-cyanoquinoline (Vb). The structures of Va, b are confirmed by their IR and PMR spectral data (see Experimental).

It was found that amides IIIb, e undergo intramolecular cyclization to the corresponding 2-substituted 3-aryl-1-oxo-1,2,3,4-tetrahydrobenzo[b][1, 6]naphthyridines (VIc, d) when heated in polyphosphoric acid at 135°C for 3.5 h. The anilide IIIc does not cyclize under these conditions.

---

*For Communication 14, see [1].

Perm Pharmaceutical Institute, Perm 614600. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 1, pp. 92-94, January, 1992. Original article submitted May 10, 1990; revision submitted January 12, 1991.

TABLE 1. Parameters for the Compounds Synthesized

Compound	Empirical formula	mp, °C	Yield, %*
IIIa	$C_{25}H_{20}N_2O_2$	222...22'	76
IIIb	$C_{24}H_{17}BrN_2O$	240...241	74
IIIc	$C_{24}H_{17}N_3O_3$	239...241	65
IIId	$C_{26}H_{23}N_3O$	222...224	40
IIIe	$C_{25}H_{20}N_2O_2$	192...194	80
IV	$C_{18}H_{12}N_2$	149...151	31
Va	$C_{19}H_{15}Cl_3N_2O_2$	172...174	50
Vb	$C_{13}H_9Cl_3N_2O$	127...128	53
VIa	$C_{24}H_{18}N_2O$	228...230**	(77)
VIb	$C_{25}H_{20}N_2O_2$	281...283	(50)
VIc	$C_{24}H_{17}BrN_2O$	172...174	60
VId	$C_{25}H_{20}N_2O$	227...229	90
VIe	$C_{18}H_{13}N_3O$	226...228	86 (65)

---

*For VIa-e the quoted yields are those obtained with polyphosphoric acid (for H_2SO_4 in brackets).

**Literature data, see [1].

In order to explore the potential cyclization of 2-styryl-3-cyanoquinoline to benzo[b][1,6]naphthyridines, compound IV was heated in polyphosphoric acid. 1-Oxo-3-phenyl-1,2,3,4-tetrahydrobenzo[b][1,6]naphthyridine (VIe) was obtained in good yield.

It was also of interest to study the possible cyclization of amides III and nitrile IV using concentrated H_2SO_4. In fact, prolonged heating at 45°C of solutions of the anilide of 2-styrylquinoline-3-carboxylic acid, amide IIIa, and nitrile IV in concentrated H_2SO_4 give the naphthyridines (VIa, b, e).

Evidently the cyclization proceeds via formation of a carbenium ion arising from the reaction of the acid with the styryl fragment of III or IV. This is confirmed by the observation that a solution of IIIa in concentrated H_2SO_4 gives a red coloration going brown upon cyclization.

The structures of VIb-e are confirmed by their spectral data. In the IR spectra there are observed bands at 1660-1670 (CO) and, for VIe at 3180 cm^{-1} (NH). In contrast to the spectra of nitrile II or amides IIIa-e, VIe shows the absence of absorptions for the CN or amide NH groups, respectively. The PMR spectra of VIb-e show proton signals at 3.40-3.78 (4-CH_2), 5.10-5.69 (3-H), 8.8-8.9 (10-H), and 7.67-7.81 ppm (benzene ring). For naphthyridine VIe a singlet for NH at 9.1 ppm is also observed.

EXPERIMENTAL

IR spectra were recorded on a UR-20 instrument in Vaseline mull or in CCl_4 for Va, b. PMR spectra were recorded on an RYa-2310 (60 MHz) instrument for 5% solutions in DMSO-d_6 and with HMDS internal standard.

Elemental analysis for C, H, Cl, and N agreed with that calculated.

Syntheses of Ia, b and 2-methyl-3-cyanoquinoline have been reported in [1-3], respectively.

2-Styrylquinoline-3-carboxamides (IIIa-e). A mixture of amide Ia, b (3 mmoles), the corresponding aldehyde (5 mmoles), piperidine (3-4 drops), and p-xylene (2 ml) was heated at 170-175°C for 5 h. After cooling, the precipitated amide III was filtered off and crystallized from ethanol—dioxane (1:1).

Anilide IIIc was also prepared by refluxing a solution of anilide Ia (0.87 g, 3 mmoles), p-nitrobenzaldehyde (0.75 g, 5 mmoles) and acetic anhydride (5 ml) for 1 h. After cooling, the precipitate was separated and crystallized from ethanol.

2-Styryl-3-cyanoquinoline (IV) was prepared similarly to amides IIIa-e from 2-methyl-3-cyanoquinoline (1.5 g, 9 mmoles) and benzaldehyde (1.4 g, 13 mmoles). The solvent and part of the unreacted nitrile II were steam distilled and the residue dissolved in benzene, filtered through an Al_2O_3 column, and the product IV crystallized from benzene.

2-(2-Hydroxy-3,3,3-trichloroprop-1-yl)quinoline-3-carboxanilide (Va). A mixture of anilide Ia (1.1 g, 4 mmoles) and chloral (0.61 g, 4 mmoles) in absolute pyridine (5 ml) was heated on a steam bath for 2 h. The cooled mixture was poured into water and the precipitated anilide Va filtered and crystallized from benzene. IR spectrum: 1660 (CO), 2930 (CH_2), 3350

(NH), 3580 cm^{-1} (OH). PMR spectrum: 3.68 (2H, s, CH_2), 4.94 (1H, s, CH), 7.81 (m, H_{arom} and OH), 10.85 ppm (1H, s, NH).

2-(2-Hydroxy-3,3,3-trichloroprop-1-yl)-3-cyanoquinoline (Vb). A mixture of nitrile II (2 g, 12 mmoles), chloral (1.76 g, 12 mmoles), and absolute pyridine (5 ml) was heated on a steam bath for 4 h. The cooled product was poured into water and the precipitate filtered and dried. A solution of the dry product in benzene was passed through an Al_2O_3 column and Vb was crystallized from benzene—hexane (1:1). IR spectrum: 2240 (CN), 2930 (CH_2), 3590 cm^{-1} (OH). PMR spectrum: 3.85 (2H, s, CH_2), 4.91 (1H, s, CH), 7.95 (5H, m, H_{arom} and OH), 8.66 ppm (1H, s, 4-H).

3-Aryl-1-oxo-1,2,3,4-tetrahydrobenzo[b][1, 6]naphthyridines (VIa-e). A. Amide IIIb, e or nitrile IV (3 mmoles) in polyphosphoric acid (40 g) was held at 135°C for 3.5 h. The cooled product was poured into water, neutralized with sodium carbonate solution, and the precipitate filtered and crystallized from ethanol.

B. 2-Styrylquinoline-3-carboxaniline [1], amide IIIa, or nitrile IV (1 mmole) in concentrated H_2SO_4 (3 ml) was held at 45°C for 20 h. The cooled product was poured into water, neutralized with sodium carbonate solution, and the precipitate filtered and crystallized from ethanol—dioxane (1:1).

LITERATURE CITED

1. S. V. Ukhov and M. E. Konshin, *Khim. Geterotsikl. Soedin.*, No. 2, 238 (1989).
2. S. V. Ukhov and M. E. Konshin, Paper No. 120-B-90, Perm Pharmaceutical Institute, Moscow (1990); VINITI January 8, 1990.
3. *Beilsteins Handbuch der Organischen Chemie*, Vol. 22, Springer Verlag, Berlin (1935), p. 83.