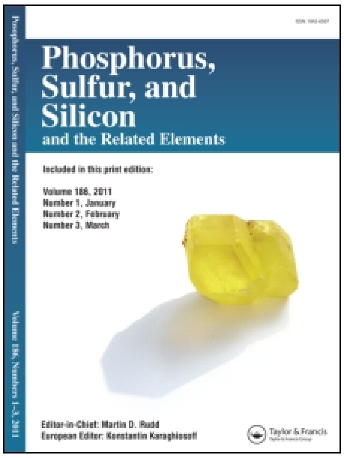

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AN UNEXPECTED CYCLIZATION DURING NUCLEOPHILIC ADDITION OF 5-MERCAPTOQUINOLINE TO PHENYLACETYLENE

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AN UNEXPECTED CYCLIZATION DURING NUCLEOPHILIC ADDITION OF 5-MERCAPTOQUINOLINE TO PHENYLACETYLENE

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Reaction of 5-mercaptoquinoline with phenylacetylene (KOH, dioxane, 160–170°C, 1 h, autoclave) gives (along with the normal adduct Z-5-styrylthioquinoline) 3-phenylthiopyrano[4,3,2-d,e]quinoline, the product of a unique intramolecular nucleophilic substitution of hydrogen by carbanion at position 4 of the quinoline ring.

Keywords: 5-Mercaptoquinoline; 3-phenylthiopyrano[4,3,2-*d*,*e*]quinoline; carbanion; nucleophilic addition; nucleophilic substitution; phenylacetylene; Z-5-styrylthioquinoline

The synthesis of novel derivatives of quinoline remains an important synthetic task as some of them are structural analogs of alkaloids,[1] enzyme inhibitors,[2] antibiotics,[3,4] as well as antitumor[5,6] and antiviral medicines.[7,8]

This article reports on the preliminary results of investigation of nucleophilic addition of 5-mercaptoquinoline **1** to phenylacetylene **2** carried out with the aim to prepare novel derivatives of quinoline, prospective synthetic intermediates, and candidates for medicines.

Phenylacetylene is known to react with thiol and thion compounds [$(NH_2)_2C{=}S$, $EtS(C{=}S)OEt$] in superbase catalytic media (KOH, DMSO, 80–140°C) to form *E*- and *Z*-isomers of distyrylsulfides.[9–13] Heterocyclic thiones (pyridine-, pyrimidine-, and quinoline-2-thiones) interact with phenylacetylene under harsh conditions (autoclave, KOH, dioxane, water, 160–200°C, 1 h) producing *Z*-isomers of the corresponding styrylsulfides only.[14–16] 5-Mercaptoquinoline **1** has not been studied as nucleophile in this reaction.

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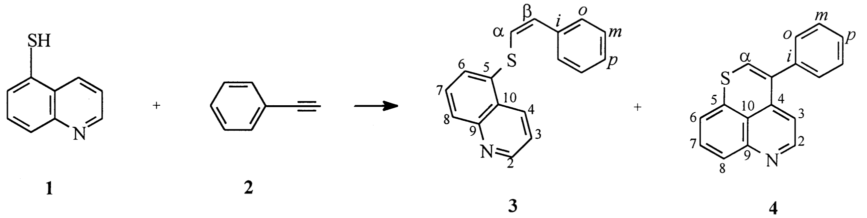
Meanwhile, as bifunctional nucleophile (pyridine moieties are also known to react with the triple bond)[17] it might react with acetylenes competitively by either its thiol or pyridine function or both, thus paving the way to a new family of the quinoline-tailored compounds.

RESULTS AND DISCUSSION

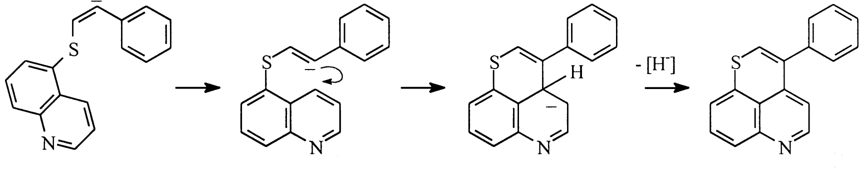
The experiments have shown that the reaction under conditions analogous to those used for the preparation of styryl derivatives of pyridine-, pyrimidine-, and quinoline-2-thiones (autoclave, KOH, dioxane, 160–170°C, 1 h),[14–16] takes an unexpected direction. Along with the anticipated *Z*-5-styrylthioquinoline **3** (30% yield), a cyclic product, 3-phenylthiopyrano[4,3,2-*d*,*e*]quinoline **4** (17% yield) has been isolated from the reaction mixture (Scheme 1).



1 **2** **3** **4**

SCHEME 1

Formation of thiopyranoquinoline **4** is likely to result from intramolecular attack of carbanion **5** at the quinoline moiety. The intermediate cyclic carbanion **6** further aromatizes by eliminating the hydride-ion (Scheme 2). Thus, the process may be considered as a unique example of nucleophilic substitution of hydrogen by the carbanion at position 4 of the quinoline moiety.



5 **6** **4**

SCHEME 2

Under milder conditions in the superbase system KOH-DMSO (95–97°C, 3 h, molar ratio **1**:**2**:KOH = 1:1:1) the reaction turns out to be chemo-, regio-, and stereospecific: Only *Z*-styrylthioquinoline **3** is formed (43% yield). Excess of KOH up to 4.5 mol per 1 mol of **1** results in a drastic (3–4 times) decrease in the yield of the adduct **3**. The same occurs when the reaction temperature is lowered to 60°C. With 0.3 mol of KOH per 1 mol of **1** (DMSO, 50–60°C, 8 h) no reaction is observed: only the mercaptoquinoline oxidation product, 5,5′-diquinolyl disulfide (14%) is isolated.

Upon heating (200–230°C), e.g., on vacuum distillation, the *Z*-isomer of **3** transforms to its *E*-isomer (20% yield). Heating the adduct *Z*-**3** in an autoclave with alkali (30% KOH, dioxane, 160–170°C, 1 h) produces both its *E*-isomer and thiopyranoquinoline **4**, the ratio *Z*-**3**:*E*-**3**:**4** being 49:35:16 respectively (^{1}H NMR). The same procedure without alkali gives the same three products in a 33:52:15 ratio.

The cyclization *Z*-**3** → **4** is another unexpected process, unknown for aryl vinyl sulfides, which is rationalized as deprotonation of isomer *E*-**3** (or *Z*-**3** with the following isomerization) to give carbanion **5** cyclizing to **4** (Scheme 2). “Non-catalytic” (“thermal”) cyclization *Z*-**3** → **4** proceed via acid-base autodissociation (under the influence of basic quinoline entity).

The isolated compounds *E*-**3**, *Z*-**3**, **4** (m.p. 88–89, 95–97, and 147–149°C respectively) are crystalline substances soluble in most organic solvents. Their structure has been proved by IR, ^{1}H, and ^{13}C NMR methods including the 2D (COSY, NOESY, HSQC, HMBC) techniques.

The ^{1}H NMR spectrum ($CDCl_3$, Bruker DPX 250 spectrometer) of thiopyranoquinoline **4** contains only one signal of olefinic proton H_α at 6.54 ppm (singlet) while the signal of H_β is absent. According to the ^{13}C NMR spectrum, this compound has a quaternary C-4 carbon atom (140.43 ppm) and this is supported by the HSQC spectrum showing no cross-peaks with the signal of this nucleus. The HMBC spectrum shows a cross-peak between the signals of H_α and C-4 through three bonds (in contrast to the analogous spectra of *E*-**3** and *Z*-**3**, where the similar correlation is not possible). All these data testify that the ring-closure to the thiopyrane cycle **4** occurs at C-4 atom of the quinoline ring.

In the ^{1}H NMR spectra of compounds **3** (*E*, *Z*) there are doublets of olefinic protons H_α and H_β (at 6.59 and 6.84 ppm, $J = 15.5$ Hz for *E*-isomer and 6.35 and 6.61 ppm, $J = 10.5$ Hz for *Z*-isomer).

To conclude, the unprecedented base-catalyzed cyclization of 5-mercaptoquinoline **1** with phenylacetylene **2** to 3-phenylthiopyrano[4,3,2-*d*,*e*]quinoline **4**, a representative of inaccessible quinoline derivatives, has been found.

Additionally, the cyclyzation of *Z*-5-styrylthioquinoline to the same quinoline derivative **4**, a process unknown in the aryl vinyl sulfide series,[13] has been fixed. The latter allows the classic adducts **3** to be transformed to the cycle **4**, thus actually increasing its yield. When optimized, these two reactions can provide straightforward route to rare arylthiopyrano[4,3,2-*d,e*]quinolines and to contribute to both the quinoline and the vinyl sulfide chemistry.

EXPERIMENTAL

IR spectra were recorded on a Specord IR-75 instrument (in KBr). ^{1}H, ^{13}C, and NMR spectra were run on a Bruker DPX-250 (250 MHz) spectrometer in $CDCI_3$, HMDS as internal standard.

3-Phenylthiopyrano[4,3,2-*d,e*]quinoline 4

A mixture of 5-mercaptoquinoline **1** (5.60 g, 35 mmol), phenylacetylene **2** (3.60 g, 35 mmol) and KOH (1.70 g, 31 mmol) in 50 mL of dioxane was heated in an autoclave at 160–170°C for 1 h and after cooling was passed through a 4 cm layer of Al_2O_3. Dioxane was removed and the residue was washed with ether to give 1.55 g (17%) of thiopyranoquinoline **4** (m.p. 147–149°C, from hexane). ^{1}H NMR (δ, ppm): 6.54 s (H_α); 7.31 d (H_o), 7.41 m (H_m, $^3J_{o\text{-}m}$ 7.5 Hz), 7.41 m (H_p) (Ph); 8.42 d (H-2), 6.52 d (H-3, $^3J_{2-3}$ 4.9 Hz), 7.14 d (H-6), 7.41 dd (H-7, $^3J_{6-7}$ 7.3 ГЦ), 7.62 d (H-8, $^3J_{7-8}$ 8.6 Hz). ^{13}C NMR (δ, ppm): 152.40 (C-2), 113.93 (C-3), 140.43 (C-4), 130.58 (C-5), 119.56 (C-6), 128.25 (C-7), 125.48 (C-8), 150.30 (C-9), 125.02 (C-10), 126.49 (C-α), 133.58 (C-β), 139.03 (C-*i*), 128.65 (C-*o*), 129.12 (C-*m*), 128.87 (C-*p*). IR (cm^{-1}): 3030, 1600, 1560, 1490, 1440, 1400, 1340, 1320, 1290, 1210, 1190, 1140, 1090, 1060, 1030, 960, 870, 860, 840, 830, 810, 770, 750, 740, 690, 630, 540, 470, 450. Anal. Calcd. for $C_{17}H_{11}NS$: C, 78.13; H, 4.24; N, 5.36; S, 12.27. Found: C, 77.94; H, 4.10; N, 5.02; S, 12.30. The solvent was removed from the ether solution and the residue was chromatographed to produce 2.72 g (30%) of *Z*-5-styrylthioquinoline **3**.

Z-5-Styrylthioquinoline 3

A mixture of 5-mercaptoquinoline **1** (5.00 g, 31 mmol), phenylacetylene **2** (3.16 g, 31 mmol), KOH (1.70 g, 31 mmol) and DMSO (50 mL) was stirred at 95–97°C for 3 h. The reaction mixture was poured into 250 mL of H_2O, extracted with ether (5 × 40 mL) and dried over K_2CO_3. Ether was evaporated in vacuum to give 3.55 g (43%), ***Z*-3** (m.p. 72–73°C, from hexane). ^{1}H NMR (δ, ppm): 6.35 d (H_α), 6.61 d (H_β, $^3J_{\alpha,\beta}$ 10.6 Hz); 7.61 d (H_o), 7.43 t (H_m, $^3J_{o\text{-}m}$ 7.4 Hz), 7.30 t (H_p,$^3J_{m\text{-}p}$ 7.4 Hz) (Ph); 8.95 d (H-2), 7.47 dd (H-3, $^3J_{2-3}$ 4.3 Hz), 8.70 d (H-4, $^3J_{3-4}$ 8.6 Hz), 7.81 d (H-6), 7.69

dd (H-7, $^3J_{6-7}$ 7.0 Hz), 8.10 d (H-8, $^3J_{7-8}$ 8.0 Hz) (quinoline skeleton). ^{13}C NMR (δ, ppm): 150.86 (C-2), 121.67 (C-3), 133.85 (C-4), 133.39 (C-5), 131.01 (C-6), 129.23 (C-7), 130.27 (C-8), 148.75 (C-9), 128.54 (C-10), 126.23 (C-α), 127.70 (C-β), 136.31 (C-i), 128.86 (C-o), 128.47 (C-m), 127.42 (C-p). IR (cm^{-1}): 3030, 3010, 1580, 1550, 1480, 1440, 1410, 1370, 1350, 1310, 1130, 1070, 1040, 970, 920, 850, 830, 790, 770, 730, 690, 630, 550, 530. Anal. Calcd. for $C_{17}H_{13}NS$: C, 77.53; H, 4.98; N, 5.32; S, 12.18. Found: C, 77.32; H, 5.00; N, 5.51; S, 12.28.

E-5-Styrylthioquinoline 3

1.00 g of *Z*-**3** was distilled in vacuum at 200-230°C (1.5 mm Hg) to give 0.20 g (20%) of *E*-**3** (m.p. 88-89°C, from hexane). ^{1}H NMR (δ, ppm): 6.59 d (H$_\alpha$), 6.84 d (H$_\beta$, $^3J_{\alpha,\beta}$ 15.5 Hz); 7.28 m (H$_o$),7.25 m (H$_m$), 7.20 m (H$_p$) (Ph); 8.95 d (H-2), 7.47 dd (H-3, $^3J_{2-3}$ 4.2 Hz), 8.67 d (H-4, $^3J_{3-4}$ 8.4 Hz), 7.75 d (H-6), 7.69 t (H-7, $^3J_{6-7}$ 7.4 Hz), 8.09 d (H-8, $^3J_{7-8}$ 7.4 Hz) (quinoline skeleton). ^{13}C NMR (δ, ppm): 150.71 (C-2), 121.45 (C-3), 133.39 (C-4), 131.86 (C-5), 130.32 (C-6), 129.16 (C-7), 129.82 (C-8), 148.60 (C-9), 128.18 (C-10), 122.98 (C-α), 131.63 (C-β), 136.15 (C-i), 125.88 (C-o), 128.60 (C-m), 127.58 (C-p). IR (cm^{-1}): 3040, 3010, 1580, 1570, 1540, 1470, 1430, 1370, 1340, 1290, 1220, 1180, 1150, 1110, 1050, 1020, 950, 940, 780, 730, 680, 640, 620, 570, 540, 530, 490, 430. Anal. Calcd. for $C_{17}H_{13}NS$: C, 77.53; H, 4.98; N, 5.32; S, 12.18. Found: C, 77.12; H, 4.74; N, 5.06; S, 12.22.

Cyclization of 3 to 4

A mixture of *Z*-**3** (0.50 g), KOH (0.15 g) and 15 mL of dioxane was heated in an autoclave at 160-170°C for 1 h and after cooling was passed through a 4 cm layer of Al_2O_3. Dioxane was removed in vacuum to give a viscous residue (according to the data of ^{1}H NMR) was composed of three products: *Z*-**3**, *E*-**3**, and **4**.

REFERENCES

[1] J. Smidrecal, *Coll. Czech. Chem. Commun.*, **53,** 3186 (1988).

[2] L. K. Wang, R. K. Johnson, and S. M. Hecht, *Chem. Res. Toxical.*, **6,** 813 (1993).

[3] W. J. Watts, C. P. Lawler, and T. Knoerzer, *Eur. J. Pharmacol.*, **239,** 271 (1993).

[4] R. Martines, R. Toscano, J. E. Lingaza, and H. Sanchez, *J. Heterocyclic Chem.*, **29,** 1385 (1992).

[5] A. K. Belousova, N. N. Blokhin, V. I. Borisov, et al., *Chemotheraphy of Malignant Tumours* (Meditsina, Moscow, 1977), p. 320.

[6] Cheur-Man Lee, *J. Med. Chem.*, **11,** 388 (1968).

[7] M. V. Rubtsov, *J. Med. Pharm. Chem.*, **2,** 113 (1960).

[8] G. Dyson and P. May, *Chemistry of Synthetic Medicines* (Mir, Moscow, 1964), pp. 1–660.

[9] B. A. Trofimov, *Heteroatomic Derivatives of Acetylene* (Nauka, Moscow, 1981), pp. 1–319.

[10] B. A. Trofimov, *Usp. Khim.*, **50,** 248 (1981).

[11] B. A. Trofimov and S. V. Amosova, *Divinyl Sulfide* (Nauka, Sibirskoe Otdelenie, Novosibirsk, 1983), pp. 1–264.

[12] B. A. Trofimov and S. V. Amosova, *Sulfur Rep.*, **3**(9), 323 (1984).

[13] B. A. Trofimov and B. A. Shainyan, *In Chemistry of Functional Groups. Suppl. S: The Chemistry of Sulfur-Containing Functional Groups*, edited by S. Patai and Z. Rappoport (Wiley, New York, 1993), ch. 14, p. 797.

[14] G. G. Skvortsova, D. G. Kim, and L. V. Andriyankova, *Khim. Geterotsikl. Soedin.*, **3,** 364 (1978).

[15] G. G. Skvortsova, Z. V. Stepanova, L. V. Andriyankova, and V. K. Voronov, *Zh. Obshch. Khim.* **52,** 1625 (1982).

[16] M. A. Andriyankov, M. V. Nikitin, and A. V. Afonin, *Izv. Akad. Nauk SSSR. Ser. Khim.*, **9,** 2098 (1989).

[17] a) L. M. Jackman, A. W. Johnson, and J. C. Tebby, *J. Chem. Soc.*, 1579 (1960); b) R. M. Acheson and A. O. Plunkett, *J. Chem. Soc.*, 2676 (1964); c) R. M. Acheson and D. A. Robinson, *J. Chem. Soc.*, 1629 (1968); d) R. M. Acheson and D. A. Robinson, *J. Chem. Soc.*, 1633 (1968); e) R. M. Acheson and R. S. Feinberg, *J. Chem. Soc. (C)*, 351 (1968); f) R. M. Acheson and M. W. Foxton, *J. Chem. Soc. (C)*, 378 (1968); g) R. M. Acheson, M. W. Foxton, and A. R. Hands, *J. Chem. Soc. (C)*, 387 (1968); h) B. A. Trofimov, L. V. Andriyankova, S. A. Zhivet'ev, A. G. Mal'kina, and V. K. Voronov, *Tetrahedron Lett.*, **43,** 1093 (2002).