boiled for 25 h (TLC control). The ethanol is evaporated, and the residue is chromatographed on a column (silica gel, eluent a 3:1 hexane–ether mixture). Yield 67%.

2,2-Dimethyl-3-methyl-5-ethyl-5-diethoxymethyloxazolidine (IIIi). A mixture of 0.01 mole of amino alcohol IV and 15 ml of acetone is boiled for 15 h (TLC control). Acetone is distilled off and the residue is chromatographed on a column (silica gel, eluent a 3:1 hexane–ether mixture). Yield 62%., bp 86-87°C PMR spectrum: 0.75-1.45 [overlapped t, CH_2CH_3, $CH(OCH_2CH_3)_2$, $N-CH_2CH_3$, $C(CH_3)_2$]; 1.45-1.68 (q, J = 7 Hz, CH_2CH_3); 2.2-2.53 (q, J = 7 Hz, $N-CH_2CH_3$); 2.53-2.88 (d.d, J = 8 Hz, $N-CH_3$) 3.36-3.76 (m, $2OCH_2CH_3$); 4.20 [s, $CH(OC_2H_5)_2$].

LITERATURE CITED

1. Ryohei Oda, Masaya Okano, Shokei Tokira, and Akira Miyasu, Bull. Chem. Soc. Jpn., 35, 1216 (1962).
2. P. H. Williams, G. B. Payne, W. J. Sullivan, and P. R. Van Ess, J. Am. Chem. Soc., 82, 4883 (1960).
3. I. G. Tishchenko, I. F. Revinski, and P. Nakhar, Vestn. Belorus. Univ., Ser. 2, Khim., Biol. Georgr., No. 3, 18 (1980).
4. K. A. Krasusskii, Zh. Russk. Fiz. Khim. Ova., 34, 281 (1902).
5. W. E. Hull, The Aspect 2000 Pulse Programmer. Bruker Analytische Messtechnik, Karlsruhe (1982).
6. V. V. Sokolov, K. N. Ogloblin, and A. A. Potekhin, Khim., Geterotsikl. Soedin., No. 8, 627 (1982).

SYNTHESIS OF PYRANO(THIOPYRANO)[3,4-c]PYRIDINES AND PYRANO(THIOPYRANO)[3,4-c]PYRANS

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Methods for synthesizing the condensed systems pyrano[3,4-c]pyridine, thiopyrano[3,4-c]pyridine, pyrano[3,4-c]pyran, and thiopyrano[3,4-c]pyran have been developed from the dinitriles of 2,2-dimethyltetrahydropyran(thiopyran)-ylidene malonic acids.

Plant derived pyrano[3,4-c]pyridines such as gentiamine [1], and gentianidine [2] show broad ranging pharmacological effects (hypotensive, antispasmodic, and antiinflammatory). The plant derived pyrano[3,4-c]pyran gentiopicrin is used as an anti-malarial [3].

There are few literature reports concerning synthetic methods for these heterocyclic compounds, hence we have developed syntheses for pyrano[3,4-c]pyridines, pyrano[3,4-c]pyrans, and their sulfur analogs. The dinitriles of 2,2-dimethyltetrahydropyranylidene- and 2,2-dimethyltetrahydrothiopyranylidene malonic acids (I, II) [4] have been used as starting materials. Reaction of dinitrile I with phenylsothiocyanate gave 3-amino-5,6-dihydro-6,6-dimethyl-4-cyano-2-phenyl-8H-pyrano[3,4-c]pyridin-1H-thione (IV). It is suggested that the reaction occurs via the intermediate adduct III (Scheme 1). The thio analog V was obtained similarly. The IR spectra of thiones IV and V showed bands characteristic of the nitrile group at 2220, the amino group at 3200-3500, and the thione group at 1100-1150 cm^{-1}. The UV spectra showed absorption bands in the regions 290 and 390 nm and the PMR spectra of thiones IV and V gave singlet signals at 6.8-7.0 ppm for the amino group protons (see Scheme 1 on following page).

Treatment with hydrazine led to opening of the pyridine ring in IV and V and rearrangement to the hydrazines VI and VII.

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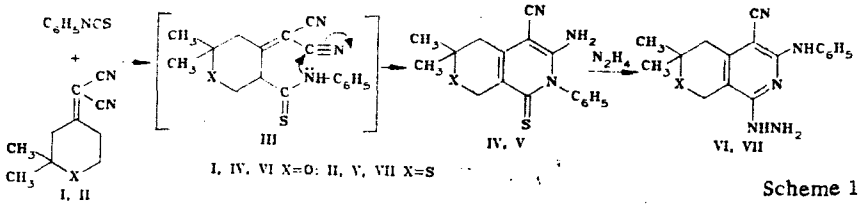
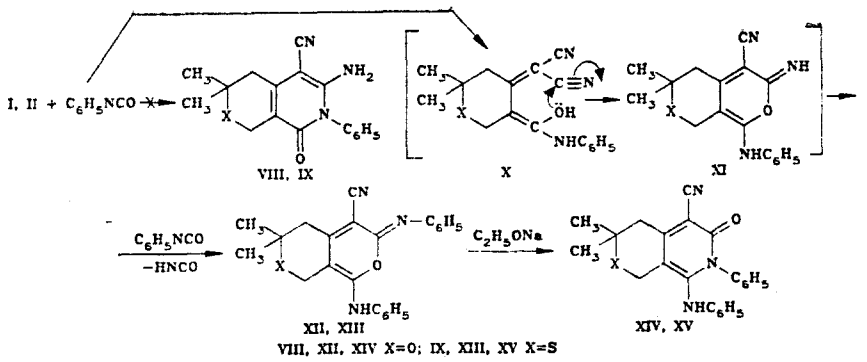


I, IV, VI X=O; II, V, VII X=S

Scheme 1

It was expected that treatment of nitriles I and II with phenylisocyanata would lead to compounds VIII and IX by analogy to IV and V. However, together with the expected products there were also observed compounds whose PMR spectra showed signals for two phenyl groups and the absence of NH_2 protons. According to mass spectrometric data the reaction can occur according to the following scheme.

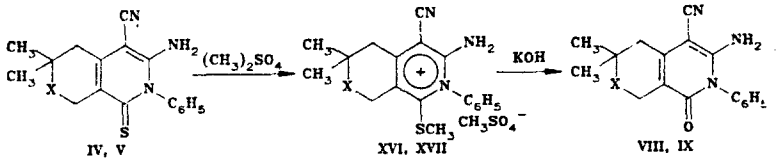


VIII, XII, XIV X=O; IX, XIII, XV X=S

The difference in reactivity of phenylisocyanate and phenylisothiocyanate with the ylidenes I and II can be explained if the reaction with phenylisocyanate takes place via intermediate X to form the imino compound XI which reacts with phenylisocyanate to give the pyrano(thiopyrano)-[3,4-c]pyrans XII and XIII. The proposed reaction of intermediate imine XI with phenylisocyanate is identical to the known reaction of phthalimide with phenylisocyanate which also occurs by the introduction of the phenyl group and separation of isocyanic acid [5].

Refluxing of XII and XIII with sodium ethylate in ethanol led to recyclization to give the more stable pyrano(thiopyrano)[3,4-c]pyridines (XIV, XV). The structural isomers XII, XIII and XIV, XV were identical by IR, PMR, and mass spectra. The UV spectra of XII and XIII showed a characteristic imino absorption at 240 nm [6]. This was absent in XIV and XV in agreement with a rearrangement to form the pyridine ring.

For preparation of VIII and IX an alternative route was chosen. Reaction of thiones IV and V with dimethylsulfate gave the corresponding pyridinium salts XVI and XVII which were hydrolyzed by base to give the desired products.



VIII, XVI X=O; IX, XVII X=S

The IR spectra of VIII and IX showed amide absorption bands at 1650-1600 cm^{-1}. When compared with thiones IV and V their UV spectra whowed a hypsochromic band shift to 275 and 330 nm in agreement with [7].

EXPERIMENTAL

IR spectra were recorded on a UR-20 instrument in paraffin mulls and UV spectra on a Specord UV-Vis in methanol. PMR Spectra were made on a Varian T-60 in DMSO-d_6 and mass spectra on an MX-1303 with ionization intensity 70 eV. TLC was carried out on Silufol UV-254 plates with iodine vapor visualization.

3-Amino-5,6-dihydro-6,6-dimethyl-2-phenyl-4-cyano-8H-pyrano[3,4-c]pyridin-1H-thione (IV). Triethylamine (0.8 ml) was added dropwise with stirring to dinitrile I (1.8 g, 0.01 mole) and phenylisothiocyanate (1.4 g, 0.01 mole) in DMF (2 ml). The mixture was heated for 1 h at 50°C, cooled, and methanol (4 ml) was added. The crystalline product was filtered off, washed with water and dried to give 2.2 g (70.7%) with mp 263-264°C (ethanol) and Rf 0.61 (pyridine–ether, 1:3). IR spectrum: 3200, 3280, 3375 (NH_2), 2220 (C≡N), 1620 (NH deformation), 1590 (C=C arom), 1110 cm^{-1} (C=S). UV spectrum, λ_{max} (log ε): 293 (3.8), 388 nm (4.3). PMR spectrum: 7.2-7.7 (5H, m C_6H_5), 6.8 (2H, s, NH_2), 4.5 (2H, t, CH_2O), 2.6 (2H, t, CH_2), 1.3 ppm (6H, s, 2-CH_3). Found: C 65.5, H 5.4, N 13.3, S 10.5%. $C_{17}H_{17}N_3OS$. Calculated: C 65.6, H 5.5, N 13.5, S 10.3%.

Thione V similarly to thione IV from dinitrile II (1.9 g, 0.01 mole), phenylisothiocyanate (1.4 g, 0.01 mole), triethylamine (0.8 ml), and DMF (2 ml) to give 2.5 g (76.4%) with mp 254-255°C (ethanol) and Rf 0.72 (pyridine–ether, 1:3). IR spectrum: 3220, 3320, 3430 (NH_2), 2220 (C≡N), 1630 (NH def.), 1605 (C=C arom), 1150 cm^{-1} (C=S). UV spectrum: 292 (3.6), 390 nm (3.9). PMR spectrum: 7.2-7.8 (5H, m, C_6H_5), 6.8 (2H, s, NH_2), 3.8 (2H, t, CH_2S), 2.9 (2H, t, CH_2), 1.4 ppm (6H, s, 2-CH_3). Found: C 62.4, H 5.1, N 12.6%. $C_{17}H_{17}N_3S_2$. Calculated: C 62.4, H 5.2, N 12.8%.

3-Anilino-1-hydrazino-5,6-dihydro-6,6-dimethyl-4-cyano-8H-pyrano[3,4-c]pyridine (VI). A mixture of thione IV (3.1 g, 0.01 mole) and hydrazine hydrate (20 ml) were refluxed for 16 h. Cooling gave a crystalline product which was washed with water and dried to give 2.6 g (84.4%) with mp 240-242°C (dioxane) and Rf 0.67 (pyridine–ethanol, 3:1). IR spectrum: 3200, 3330, 3410 (NH, NH_2), 2210 (C≡N), 1620 (NH def.), 1600 cm^{-1} (C=C arom). PMR spectrum: 8.4 (1H, s, NH), 6.8-7.8 (8H, m, C_6H_5, $NHNH_2$), 4.2 (2H, t, CH_2O), 2.4 (2H, t, CH_2), 1.1 ppm (6H, s, 2-CH_3). Mass spectrum, m/z (%): 309 (65) M^+, 294 (40), 291 (45), 277 (22), 250 (22), 233 (95), 216 (100). Found: C 65.8, H 6.1, N 22.7%. $C_{17}H_{19}N_5O$. Calculated: C 66.0, H 6.2, N 22.6%.

Compound VII was obtained similarly to VI from thione V (3.3 g, 0.01 mole) and hydrizine hydrate (20 ml) to give 2.6 g (80.0%) with mp 226-227°C (dioxane) and Rf 0.65 (pyridine–ethanol, 3:1). IR spectrum: 3220, 3345, 3415 (NH, NH_2), 2215 (C≡N), 1630 (NH def.), 1605 cm^{-1} (C=C arom). Found: C 62.8, H 5.7, N 21.4%. $C_{17}H_{19}N_5S$. Calculated: C 62.7, H 5.9, N 21.5%.

1-Anilino-5,6-dihydro-6,6-dimethyl-3-phenylimino-4-cyano-8H-pyrano[3,4-c]pyran (XII). Triethylamine (0.8 ml) was added dropwise, with stirring, at 60°C to a solution of dinitrile I (1.8 g, 0.01 mole) and phenylisocyanate (1.5 g, 0.0125 mole) in DMF (2 ml). The mixture was left for 48 h at 20°C and the crystals filtered off, washed with ethanol, and dried to give 1.3 g (35.0%) with mp 203-204°C (nitromethane) and Rf 0.66 (ether–penatne, 2:1). IR spectrum: 3230 (NH), 2200 (C≡N), 1660 (C=N), 1600 (C=C arom), 1080 cm^{-1} (C–O–C). UV spectrum: 239 (4.0), 298 (4.4), 361 nm (4.0). PMR spectrum: 9.2 (1H, s, NH), 6.7-7.3 (10H, m, 2-C_6H_5), 4.4 (2H, t, CH_2O), 2.4 (2H, t, CH_2), 1.3 ppm (6H, s, 2-CH_3). Mass spectrum: 371 (100) M^+, 356 (12), 342 (12), 328 (24), 301 (12), 295 (16), 294 (16), 279 (48), 268 (28). Found: C 73.4, H 5.8, N 11.7%. $C_{23}H_{21}N_3O_2$. Calculated: C 73.5, H 5.9, N 11.7%.

Compound XIII was obtained similarly to XII from dinitrile II (1.9 g, 0.01 mole), phenylisocyanate (1.5 g, 0.125 mole), DMF (2 ml), and triethylamine (0.8 ml) to give 1.0 g (25.8%) with mp 213-214°C (nitromethane) and Rf 0.58 (chloroform–ether, 1:3). IR spectrum: 3240 (NH), 2220 (C≡N), 1670 (C=N), 1610 cm^{-1} (C=C arom). UV spectrum: 238 (4.1), 291 (4.3), 371 nm (4.2). PMR spectrum: 9.1 (1H, s, NH), 6.8-7.2 (10H, m, 2-C_6H_5), 3.6 (2H, t, CH_2S), 2.6 (2H, t, CH_2), 1.4 ppm (6H, s, 2-CH_3). Found: C 71.4, H 5.6, N 10.8, S 8.1%. $C_{23}H_{21}N_3OS$. Calculated: C 71.3, H 5.5, N 10.8, S 8.3%.

1-Anilino-5,6-dihydro-6,6-dimethyl-3-oxo-2-phenyl-4-cyano-8H-pyrano[3,4-c]pyridine (XIV). Compound XII (0.74 g, 0.002 mole) was added to a solution of sodium ethylate in ethanol (20 ml, 3%). The mixture was refluxed for 3 h, cooled, poured into water (100 ml) and neutralized with acetic acid. The crystalline product was filtered off, washed with water, and dried to give 0.64 g (86.5%) with mp 257-258°C (nitromethane) and Rf 0.54 (ether–heptane, 2:1). IR spectrum: 3240 (NH), 2200 (C≡N), 1650 cm^{-1} (C=O). UV Spectrum: 263 (3.6), 378 nm (4.2). PMR spectrum: 6.7-7.6 (11H, m, 2-C_6H_5, NH), 4.0 (2H, t, CH_2O), 2.7 (2H, t, CH_2), 1.3 ppm (6H, s, 2-CH_3). M 371 (mass spectrometric). Found: C 73.4, H 6.1, N 11.6%. $C_{23}H_{21}N_3O_2$. Calculated: C 73.5, H 5.9, N 11.7%.

Compound XV was prepared similarly to XIV from XIII (0.78 g, 0.002 mole) and a 3% solution of sodium ethylate in ethanol (20 ml) to give 0.73 g (94.5%) with mp 208-209°C (nitro-

methane) and R_f 0.58 (acetone–ethanol, 1:8). IR spectrum: 3260 (NH), 2230 (C≡N), 1640 (C=O), 1600 cm^{-1} (C=C arom). UV spectrum: 293 (4.2), 360 nm (3.7). PMR spectrum: 7.8-8.6 (11H, m, 2-C_6H_5, NM), 3.6 (2H, t, CH_2S), 2.4 (2H, t, CH_2), 1.3 ppm (6H, s, 2-CH_3). Found: C 71.3, H 5.7, N 10.9, S 8.2%. $C_{23}H_{21}N_3OS$. Calculated: C 71.3, H 5.5, N 10.8, S 8.3%.

3-Amino-5,6-dihydro-6,6-dimethyl-1-mercaptomethyl-2-phenyl-4-cyano-8H-pyrano[3,4-c]-pyridine Methosulfate (XVI). A mixture of thione IV (3.1 g, 0.01 mole), dimethylsulfate (1.9 g, 0.015 mole) and toluene (10 ml) was refluxed for 10 min. After cooling the precipitated crystals were filtered off, washed with cold methanol and dried to give 4.3 g (98.3%) with mp 213-214°C (dioxane) and R_f 0.66 (DMF–ether, 2:3). IR spectrum: 3140, 3300 (NH_2), 2210 (C≡N), 1630 (NH def.) 1600 cm^{-1} (C=C arom). PMR spectrum: 8.4 (2H, s, NH_2), 7.4-7.9 (5H, m, C_6H_5), 4.7 (2H, t, CH_2O), 3.0 (2H, t, CH_2), 3.4 (3H, s, CH_3SO_4), 2.2 (3H, s, SCH_3), 1.3 ppm (6H, s, 2-CH_3). Found: C 52.4, H 5.4, N 9.4, S 14.7%. $C_{19}H_{23}N_3O_5S_2$. Calculated: C 52.3, H 5.3, N 9.6, S 14.7%.

Compound XVII was obtained similarly to XVI from thione V (3.3 g, 0.01 mole) dimethylsulfate (1.9 g, 0.015 mole) and toluene (10 ml) to give 4.3 g (95.6%) with mp 257-258°C (dioxane) and R_f 0.53 (chloroform–ether, 2:1). IR spectrum: 3210, 3310 (NH_2), 2220 (C≡N), 1640 (NH def.), 1590 cm^{-1} (C=C arom). PMR spectrum: 7.1-7.7 (5H, m, C_6H_5), 6.8 (2H, s, NH_2), 3.8 (2H, t, CH_2S), 3.4 (3H, s, CH_3SO_4), 2.9 (t, CH_2), 2.5 (3H, s, CH_3S), 1.4 ppm (6H, s, 2-CH_3). Found: C 50.2, H 5.0, N 9.4, S 20.9%. $C_{19}H_{23}N_3O_4S_3$. Calculated: C 50.3, H 5.1, N 9.3, S 21.2%.

3-Amino-5,6-dihydro-6,6-dimethyl-2-phenyl-4-cyano-8H-pyrano[3,4-c]pyridin-1H-one (VIII). A mixture of pyridinium salt XVI (2.2 g, 0.005 mole), aqueous potassium hydroxide (4 N, 7.5 ml) and methanol (12 ml) was refluxed for 2.5 h, left for 12 h at 20°C and diluted with water (15 ml). The crystalline products was filtered off, washed with water, and dried to give 1.3 g (87.9%) with mp 314-315°C (nitromethane) and Rf 0.73 (pyridine–ethanol, 1:2). IR spectrum: 3305, 3415 (NH_2), 2200 (C≡N), 1660 (C=O), 1640 (NH def.), 1590 cm^{-1} (C=C arom). UV Spectrum: 275 (3.3), 323 nm (3.3). PMR spectrum: 7.2-7.7 (5H, m, C_6H_5), 6.6 (2H, s, NH_2), 4.3 (2H, t, CH_2O), 2.5 (2H, t, CH_2), 1.3 ppm (6H, s, 2-CH_3). Found: C 69.2, H 5.9, N 14.1%. $C_{17}H_{17}N_3O_2$. Calculated: C 69.1, H 5.8, N 14.2%.

Compound IX was obtained similarly to VIII from the pyridinium salt XVII (2.3 g, 0.005 mole), aqueous potassium hydroxide (4 N, 7.5 ml) and methanol (12 ml) to give 1.3 g (82.2%) with mp 285-286°C (nitromethane) and R_f 0.56 (chloroform–ether, 1:1). IR spectrum: 3310, 3450 (NH_2), 2210 (C≡N), 1640 (C=O), 1630 (NH def), 1590 cm^{-1} (C=C arom). UV spectrum: 275 (4.3), 330 nm (4.2). PMR spectrum: 6.9-7.6 (5H, m, C_6H_5), 6.3 (2H, s, NH_2), 3.3 (2H, t, CH_2S), 2.5 (2H, t, CH_2), 1.2 ppm (6H, s, 2-CH_3). Found: C 65.5, H 5.4, N 13.4, S 10.4%. $C_{17}H_{17}N_3OS$. Calculated: C 65.6, H 5.5, N 13.5, S 10.3%.

LITERATURE CITED

1. F. S. Sadritdinov and N. Tuliganov, Pharmacology of the Alkaloids Gentianine and Gentinidine, Izd. Fan. Uzb. SSSR, Tashkent (1967), p. 128.
2. P. N. Natarajan, A. S. C. Wan, and V. Zaman, Plant Med., 25, 258 (1974); Chem. Abstr. 81, 58672 (1974).
3. M. Negwer, Organo-Pharmaceuticals and Their Synonyms, Vol. 1, Akad. Verlag, Verlin (1978), p. 567.
4. A. S. Noravyan, A. P. Mkrtchyan, I. A. Dzhagatspanyan, R. A. Akopyan, N. E. Akopyan, and S. A. Vartanyan, Khim.-farm. Zh., No. 9, 38 (1977).
5. P. F. Wiley, J. Am. Chem. Soc., 71, 3746 (1949).
6. Organicum [Russian translation], Vol. 1, Mir, Moscow (1979), p. 124.
7. G. F. Bol'shakov, V. S. Vatago, and F. B. Agrest, Ultraviolet Spectra of Heteroorganic Compounds, Khimiya, Leningrad (1969), pp. 16, 33.