THE ANNELATION OF THE 2-AMINOPYRAN-4-ONE RING TO CONDENSED THIOPHENES

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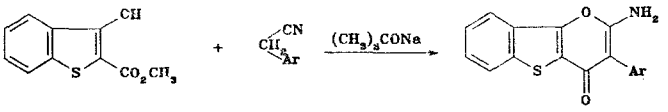
The reaction of arylacetonitriles with the methyl ester of 3-hydroxybenzo[b]thiophene-2-carboxylic acid in the presence of a basic catalyst leads to the previously unreported 2-amino-3-arylbenzo[4,5]thieno[3,2-b]pyran-4-ones. Under the same conditions, the ethyl ester of 4,6-dimethyl-3-hydroxythieno[3,2-c]pyridine-2-carboxylic acid reacts to form derivatives of a new heterocyclic system, pyrano[2',3'-4,5]-thieno[3,2-c]pyridine.

In previous work [1], we showed the possibility of annelation of the 2-aminopyran-4-one ring to the thiophene system. In the present work, we studied tricyclic compounds containing the thienopyran fragment.

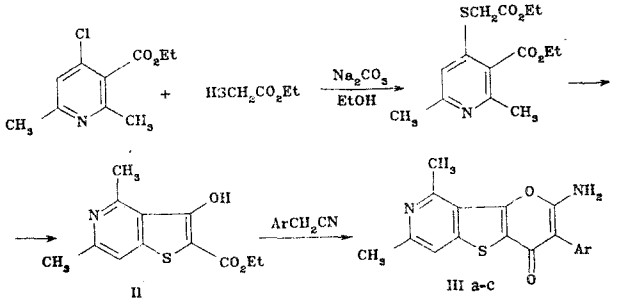
Benzo[4,5]thieno[3,2-b]pyran-4-ones have been described in only a few studies [2-4]. We have found that this heterocyclic system is formed in the reaction of arylacetonitriles with the methyl ester of 3-hydroxybenzo[b]thiophene-2-carboxylic acid under conditions described in our previous work [1]. 2-Amino-3-arylbenzo[4,5]thieno[3,2-b]pyran-4-ones (I) were thus obtained:



I a-c

Ar= a C_6H_5; b 2-ClC_6H_4; c 2,3,4-$(CH_3O)_3C_6H_2$

The PMR, IR, and UV spectra support the structures assigned to the compounds obtained and are in accord with the spectral characteristics of thieno[3,2-b]pyrans [1]. The IR spectra have two bands related to stretching vibrations of the primary amino group at 3450-3250 cm^{-1} while the band for the pyran ring carbonyl group is at 1650-1640 cm^{-1}. The UV spectra have absorption maxima λ_{max} ($\varepsilon \cdot 10^{-3}$): 205 (29), 235 (26), 255 (25), 330 nm (12).



II III a-c

Ar= a C_6H_5; b 2-ClC_6H_4; c 3,4-$(CH_3O)_2C_6H_3$

The reaction of the ethyl ester of 2,6-dimethyl-4-chloronicotinic acid with ethyl thioglycolate with subsequent intramolecular cyclization of the intermediate ester gives the ethyl ester of 4,6-dimethyl-3-hydroxythieno[3,2-c]pyridine-2-carboxylic acid (II). Hydroxyester II reacts with arylacetonitriles to form derivatives of a new three-ring heterocyclic system, pyrano[2',3'-4,5]thieno[3,2-c]pyridine (III).

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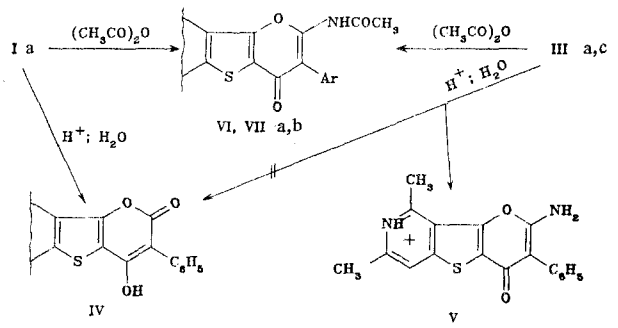
The IR spectra of products III have bands for the enaminoketone fragment at 3450-3300 and 1660-1650 cm^{-1}. The PMR spectra taken in trifluoroacetic acid have methyl group proton signals at 2.9 and 3.4 ppm. This difference in the chemcial shifts of the protons of the α-methyl and α'-methyl groups of the pyridine ring is, in all likelihood, a consequence of the effect of the close-lying oxygen atom of the pyran ring on one of these groups. The UV spectra of III and I are virtually identical, which indicates their isoelectronic structure. The following bands are characteristic, λ_{max} ($\varepsilon \cdot 10^{-3}$): 210 (19), 235 (21), 330 nm (10).

Pyranones I do not form hydrochloride salts upon treatment of their ethanolic solutions with hydrochloric acid but rather undergo hydrolysis under these conditions leading to the hydroxy derivative IV. 2-Amino-7,9-dimethyl-3-phenylpyrano[2',3'-4,5]thieno[3,2-c]pyridine-4-one is protonated under similar conditions at the pyridine ring nitrogen atom to form an insoluble salt (V). The reduction in the basicity of the amino group of the enaninoketone fragment apparently hinders the hydrolysis reaction [5]. Carboxylic acid anhydrides acylate Ia and IIIa,c to form N-acylamino derivatives VI and VIIa,b, respectively:



VI, VII a Ar=C_6H_5; VIIb Ar=3,4-$(CH_3)_2C_6H_3$

EXPERIMENTAL

The PMR spectra were taken on a ZKR-60 spectrometer with TMS as the internal standard. The IR spectra were taken on a UR-20 spectrometer in KBr pellets. The UV spectra were taken on Specord UV-VIS spectrometer in methanol.

Ethyl ester of 4,6-dimethyl-3-hydroxythieno[3,2-c]pyridine-2-carboxylic acid (II). A mixture of 55.4 ml (0.3 mole) ethyl ester of 2,6-dimethyl-4-chloronicotinic acid, 33.8 ml ethyl thioglycolate, 21.2 g (0.2 mole) anhydrous sodium carbonate, and 150 ml absolute ethanol was heated at reflux with stirring for 10 h. The precipitate was filtered off and washed with 150 ml benzene. The filtrate was evaporated in vacuum with heating on a water bath and the residue was recrystallized from ethanol to yield 55 g (73%) II with mp 131°C (from 1-propanol). Found: C, 57.2; H, 5.0; N, 5.7%. Calculated from $C_{12}H_{13}NO_3S$: C, 57.4, H, 5.2; N, 5.6%.

2-Amino-3-arylbenzo[4,5]thieno[3,2-b]pyran-4-ones (Ia-c). A mixture of 0.02 mole methyl ester of 3-hydroxybenzo[b]thiophene-2-carboxylic acid, 0.02 mole arylacetonitrile, and 0.06 mole sodium tert-butylate in 40 ml pyridine was heated at reflux for 3 h. The pyridine was evaporated in vacuum with heating on a water bath. The residue was triturated with 100 ml water and neutralized with 9 ml 50% acetic acid with stirring. The residue was filtered off and washed with water. The characteristics of Ia-c are given in Table 1.

2-Amino-3-aryl-7,9-dimethylpyrano[2',3'-4,5]thieno[3,2-c]pyridin-4-ones (IIIa-c) were obtained from the ethyl ester of 4,6-dimethyl-3-hydroxythieno[3,2-c]pyridin-2-carboxylic acid according to the method used for Ia-c (Table 1).

2-Acetylamino-3-phenylbenzo[4,5]thieno[3,2-b]pyran-4-one (VI). A mixture of 0.6 g (2 mmoles) Ia and 0.2 ml (2.1 mmoles) acetic anhydride in 5 ml pyridine was heated at reflux for 4-5 h. The pyridine was evaporated in vacuum with heating on a water bath. The precipitate was triturated in 10 ml water, filtered off, and washed consecutively with aqueous bicarbonate and water to yield 0.6 g (90%) VI with mp 199°C (from 1-propanol). Found: N, 4.3; S, 9.7%. Calculated for $C_{19}H_{13}NO_3S$: N, 4.2; S, 9.5%.

2-Acetylamino-7,9-dimethyl-3-phenylpyrano[2',3'-4,5]thieno[3,2-c]pyridin-4-one (VIIa) was obtained from IIIa by the method give for VI in 75% yield, mp 242°C (from chlorobenzene). Found: N, 7.9; S, 8.9%. Calculated for $C_{20}H_{16}H_2O_3S$: N, 7.7; S, 8.8%.

TABLE 1. Characteristics of I and III

Compound	Mp, deg C[a]	Found, %		Chemical formula	Calculated, %		Yield, %
		N	S		N	S	
Ia	285—286[b]	5,0	11,3	$C_{17}H_{11}NO_2S$	4,8	11,0	70
Ib	305—308[b]	4,3	10,0	$C_{17}H_{10}ClNO_2S$	4,3	9,8	70
Ic	297—298[b]	4,0	8,7	$C_{20}H_{17}NO_5S$	3,7	8,4	55
IIIa	279—280	8,5	10,1	$C_{18}H_{14}N_2O_2S$	8,7	10,0	90
IIIb	268		9,1	$C_{18}H_{13}ClN_2O_2S$[c]		9,0	90
IIIc	285	7,1	8,2	$C_{20}H_{18}N_2O_4S$	7,4	8,4	83

[a]Ia and Ib were crystallized from nitromethane, Ic was crystallized from DMF, IIIa was crystallized from pyridine, IIIb was crystallized from chlorobenzene, and IIIc was crystallized from 1-butanol. [b]dec. [c]Found: Cl, 9.8%. Calculated: Cl, 9.9%.

2-Acetylamino-7,9-dimethyl-3-(3,4-dimethoxyphenyl)pyrano[2',3'-4,5]thieno[3,2-c]pyridin-4-one (VIIb) was obtained by the method given for VI from IIIc in 80% yield, mp 295-297°C (dec., from chlorobenzene). Found: N, 6.4; S, 7.7%. Calculated for $C_{23}H_{20}N_2O_5S$: N, 6.4; S, 7.4%.

4-Hydroxy-3-phenylbenzo[4,5]thieno[3,2-b]pyran-2-one (IV). A mixture of 0.3 g (1 mmole) Ia in 10 ml 1-propanol was heated at reflux with 2 ml concentrated hydrochloric acid for 6 h. After removal of the alcohol in vacuum, the residue was triturated with 5 ml water, filtered, and washed with water to yield 0.25 g (70%) IV, mp above 320°C (from 1-propanol). Found: S, 10.9%. Calculated for $C_{17}H_{10}O_3S$: S, 10.9%.

Hydrochloride salt of 2-amino-7,9-dimethyl-3-phenylpyrano[2',3'-4,5]thieno[3,2-c]pyridin-4-one (V). A mixture of 0.33 g (1 mmole) IIIa in 10 ml 1-propanol was heated at reflux with 2 ml conc. HCl for 1 h. The precipitate was filtered off and washed with ethanol to yield 0.32 g (90%) V with mp 310-312° (dec., from dimethylformamide). Found: Cl, 10.2; S, 9.2%. Calculated for $C_{18}H_{15}ClN_2O_2S$: Cl, 9.9; S, 8.9%.

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