RESEARCH IN THE FIELD OF FUROPYRIDINES.

2.† SYNTHESIS AND STERIC STRUCTURE OF 6-METHYL-1-HETARYLIDENE-3,4-DIOXO[3,4-c]PYRIDINES

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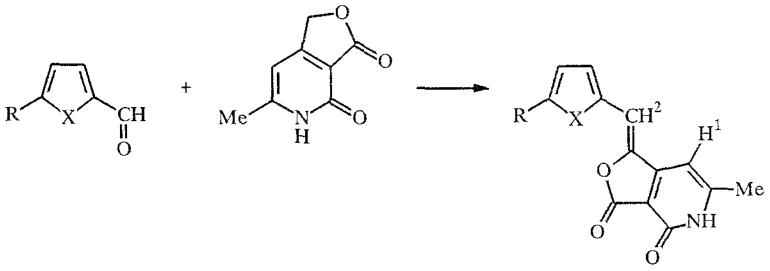
By condensation of 6-methyl-3,4-dioxo-1H-furo[3,4-c]pyridine with heteroaromatic aldehydes, furfurylidene- and thenylidenefuropyridinediones have been obtained. By means of ^{1}*H NMR spectrometry using the nuclear Overhauser effect, it has been established that these compounds have the cis-s-cis and cis-s-trans conformations, respectively.*

The reactivity of the simplest five-membered heterocycle - 2-butenolide - in reactions of condensation with aldehydes has been studied quite thoroughly [2-4]. The annelation of 2-butenolide with 2-pyridone leads to a new condensed bicyclic heterosystem that had received very little previous attention [5]. Along with this, furopyridinediones are attracting attention not only as synthetic intermediates [5], but also as convenient objects for study of the mutual influence of the simplest heterosystems. Interest has increased in dioxofuropyridines as biological agents because of the presence of the natural biological fragment butenolide in the structure [6, 7].

We have investigated the properties of 6-methyl-3,4-dioxo-1H-furo[3,4-c]pyridine in the reaction of condensation with heteroaromatic aldehydes. The reaction time was controlled by means of UV spectroscopy and thin-layer chromatography.

The condensation products I-XII were obtained from the cooled reaction medium in accordance with a method given in [8], in the form of high-melting colored crystals (Table 1), insoluble in organic solvents and in water.‡



I-XII

I—VII X = O, I R = H, II R = Me, III R = Br, IV R = I, V R = 4-ClC$_6$H$_4$, VI R = 2-NO$_2$C$_6$H$_4$, VII R = 4-NO$_2$C$_6$H$_4$, VIII—XII X = S, VIII R = H, IX R = Me, X R = Br, XI R = I, XII R = NO$_2$

The electronic spectra of the hetarylidenefuropyridinediones I-XII exhibit three or four absorption maxima (Table 1). The short-wave band corresponds to a π–π^* transition of electrons from an ethylene orbital to a carbonyl orbital of the pyridone [9]. The middle bands may pertain to a π–π^* transition in the vinylheteroaromatic fragment [2] and also to an n–π^* transition

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†For Communication 1, see [1].

‡As in Russian original; the data indicate solubility in ethanol and other solvents — Translator.

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TABLE 1. Characteristics of Compounds I-XII

Compound	Empirical formula	mp, °C (decomp.)	R_f	UV spectrum (ethanol): λ_{max}, nm (and log ε)	IR spectrum, ν, cm^{-1}				Yield, %
					C=O lact.	C=O pyrid.	C=C	C—O—C	
I	$C_{13}H_9NO_4$	300...302	0,79	210 (3,24), 248 (3,98), 385 (4,29)	1780, 1760	1675	1650, 1640, 1610, 1605	1200, 1175, 1145, 1020	85
II	$C_{14}H_{11}NO_4$	308...310	0,81	224 (4,27), 245 (4,26), 405 (4,49)	1780, 1750	1660	1640, 1605	1200, 1125, 1070, 1047, 1005	98
III	$C_{13}H_8BrNO_4$	318...320	0,84	225 (4,31), 246 (4,29), 389 (4,59)	1775, 1760	1675	1650, 1625, 1555	1175, 1135, 1125, 1100, 1055, 1035, 1015	62
IV	$C_{13}H_8INO_4$	325...327	0,80	222 (4,26), 246 (4,29), 389 (4,59)	1780, 1755	1665, 1610, 1555	1640, 1610, 1555	1200, 1190, 1175, 1130, 1050, 1035, 1005	89
V	$C_{19}H_{12}ClNO_4$	360...362	0,83	226 (4,26), 245 (4,30), 276 (4,26), 435 (4,40)	1785, 1760	1675	1645, 1620, 1560	1200, 1175, 1125, 1115, 1110, 1080, 1050, 1030	94
VI	$C_{19}H_{12}N_2O_6$	356...358	0,82	212 (4,21), 244 (4,21), 415 (4,52)	1820, 1760	1675	1645, 1620, 1570	1200, 1165, 1140, 1120, 1060, 1045, 1025	86
VII	$C_{19}H_{12}N_2O_6$	380...382	0,74	—*	1810, 1760	1675	1626, 1600, 1570	1180, 1130, 1120, 1060, 1045	84
VIII	$C_{13}H_9NO_3S$	348...350	0,70	216 (4,08), 247 (4,12), 382 (4,39)	1790, 1760	1670	1645, 1610	1200, 1150, 1130, 1045, 1020	
IX	$C_{14}H_{11}NO_3S$	316...318	0,55	212 (4,16), 235 (4,08), 250 (4,17), 402 (4,29)	1790, 1760	1670	1645, 1620	1200, 1150, 1130, 1045, 1020	66
X	$C_{13}H_8BrNO_3S$	350...352	0,63	216 (4,17), 235 (4,15), 251 (4,10), 386 (4,38)	1780, 1760	1670	1640, 1620, 1550	1200, 1155, 1130, 1040, 1020	53
XI	$C_{13}H_8INO_3S$	332...334	0,79	216 (4,17), 240 (4,09), 251 (4,07), 393 (4,31)	1775, 1750	1670	1640, 1610, 1550	1200, 1170, 1130, 1040, 1020	55
XII	$C_{13}H_8N_2O_5S$	346...348	0,71	—*	1790, 1760	1670	1645, 1620	1200, 1160, 1145, 1125, 1060, 1045, 1020	21

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*Spectrum not taken, owing to poor solubility in ethanol.

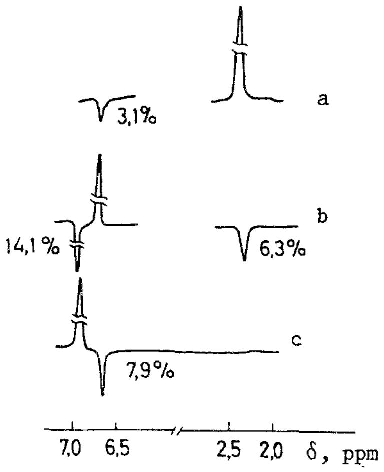

Fig. 1. NOE difference spectra. Successive irradiation of protons: a) of CH_3 group; b) 1-H; c) 2-H in compound IV.

of the carbonyl group [9]. The long-wave bands, which have a maximum in the 382-435 nm interval, pertain to a $\pi-\pi^*$ transition of the main chromophore of the molecule, as evidenced by their bathochromic shift when the polarity of the solvent is increased. The influence of the substituent R on the position of the K-band of the synthesized compounds indicates conjugation, i.e., coplanarity or a very nearly copolanar position of the heterocycles.

In the IR spectra of compounds I-XII we observe stretching vibration bands of the carbonyl group of the pyridone (1655-1675 cm^{-1}) and a doublet of the carbonyl group of the lactone (1740-1800 cm^{-1}). In all of the spectra of the ylidene derivatives I-XII, an intense band appears at 1270-1280 cm^{-1}, assigned to a stretching vibration of the unsaturated ester [10].

The TLC and PMR data (individuality of the compounds and the absence of any signal of the CH_2 group), analogous to [8], are evidence of the regiospecificity and regioselectivity of condensation through the methylene group.

Compounds I-XII may have any one of four theoretically possible stereostructures: E, Z, s-cis, and s-trans. In order to arrive at an unambiguous determination of the structure of these compounds, we used the nuclear Overhauser effect (NOE) [11] and the stereospecificity of the SSC constants ^5J and ^4J between the protons of the heteroring and H^2 of the olefinic proton [12, 13] (Table 2). In the NOE resonance spectrum, upon irradiation of the CH_3 group in compounds I-XII, the 1-H proton responds; and upon irradiation of H, both the protons of the CH group and 2-H respond, with intensities of 2-14% (Fig. 1). This is evidence that the 2-H and 1-H protons are in the cis position relative to each other; i.e., the results point to the Z-isomer of the reaction products.

The high degree of stereospecificity of the long-range interproton SSCCs ^4J and ^5J is decisive in predicting the conformation of 2-vinylheteroaromatic rings [6, 11, 12]. For the furfurylidenefuropyridinediones I-VII, we observe long-range SSC between the 2-H and 4-H protons, which is characteristic for the W-shaped position of bonds that is realized only in the s-cis-rotamer.

The absence of SSCC $^5J_{H2,H4}$ in the PMR spectra of the thenylidene derivatives VIII-X is an indication of their s-trans-conformation. This view is supported by the presence of long-range SSC between the H_5 and H_4 protons ($^5J = 0.8$ Hz) for the unsubstituted thenylidenefuropyridinedione VIII. The long-range interproton interactions in the molecules of I-X are evidence of a coplanar position of the heteroaromatic ring and the exocyclic C═C bond.

According to Dreiding molecular models, in the planar structure of the s-cis-furfurylidenefuropyridines I-VII (Fig. 2), we should observe a downfield shift of the signals of the 3-H and 2-H protons as a result of the deshielding effect of the oxygens of the lactone ring and the heteroaromatic ring in the cis-conformation [3, 4]. But on the contrary, in the PMR spectra of these compounds, we observe the usual order in the positions of the furan protons $H_5 > H_3 > H_4$ that is characteristic for a heteroring with an electron-acceptor substituent in position 2 [3, 4, 6]; not only does the olefinic proton fail to undergo a downfield shift relative to the 2-H proton of the thio analogs VIII-X that exist in the s-trans-conformation, but it actually resonates in the stronger field $\Delta\delta = 0.20$-0.44 ppm.

TABLE 2. ^{1}H Chemical Shifts δ, ppm, and SSCC J, Hz (in DMSO-d_6) of Synthesized Compounds

Compound	CH$_3$	1-H of ring	2-H of olefin	NH (broad, strong)	3-H	4-H	5-H (other protons)
I	2,38 dd, $^4J_{CH_3-H_1}$ = 0,7	6,76 q, $^4J_{H_1-CH_3}$ = 0,7	6,83 dd, $^4J_{H_2-H_3}$ = 0,6, $^5J_{H_2-H_4}$ = 0,6	12,04	7,03 ddd., $^3J_{H_3-H_4}$ = 3,5, $^4J_{H_3-H_5}$ = 0,7, $^4J_{H_3-H_2}$ = 0,6	6,68 ddd, $^3J_{H_4-H_3}$ = 3,5, $^3J_{H_4-H_5}$ = 1,8, $^5J_{H_4-H_2}$ = 0,6	7,78 dd, $^3J_{H_5-H_4}$ = 1,8, $^4J_{H_5-H_3}$ = 0,7
II	2,36 d, $^4J_{CH_3-H_1}$ = 0,7	6,68 q, $^4J_{H_1-CH_3}$ = 0,7	6,83 dd, $^4J_{H_2-H_3}$ = 0,5, $^5J_{H_2-H_4}$ = 0,9	12,00	6,93 dd., $^3J_{H_3-H_4}$ = 3,4; $^4J_{H_3-H_2}$ = 0,5	6,33 ddd, $^3J_{H_4-H_3}$ = 3,4, $^4J_{H_4-H_{CH3}}$ = 1,0, $^5J_{H_4-H_2}$ = 0,9	2,37 (3H, d, CH$_3$); $^4J_{CH_3-H_4}$ = 1,0
III	2,38 d, $^4J_{CH_3-H_1}$ = 0,7	6,68 q, $^4J_{H_1-CH_3}$ = 0,7	6,83 dd., $^4J_{H_2-H_3}$ = 0,6, $^5J_{H_2-H_4}$ = 0,6	12,18	7,01 dd, $^3J_{H_3-H_4}$ = 3,6, $^4J_{H_3-H_2}$ = 0,6	6,74 dd., $^3J_{H_4-H_3}$ = 3,6, $^5J_{H_4-H_2}$ = 0,6	—
IV	2,37 d, $^4J_{CH_3-H_1}$ = 0,8	6,68 q, $^4J_{H_1-CH_3}$ = 0,8	6,90 dd, $^4J_{H_2-H_3}$ = 0,6, $^5J_{H_2-H_4}$ = 0,6	10,70	6,91 dd., $^3J_{H_3-H_4}$ = 3,5, $^4J_{H_3-H_2}$ = 0,6	6,88 dd, $^3J_{H_4-H_3}$ = 3,5; $^5J_{H_4-H_2}$ = 0,6	—
V*	2,36d, $^4J_{CH_3-H_1}$ = 0,6	6,7 q, $^4J_{H_1-CH_3}$ = 0,6	7,00 dd, $^5J_{H_2-H_3}$ = 0,9, $^5J_{H_2-H_4}$ = 0,9	12,11	7,26 dd., $^3J_{H_3-H_4}$ = 3,8, $^4J_{H_3-H_2}$ = 0,9	7,13 dd, $^3J_{H_4-H_3}$ = 3,8, $^5J_{H_4-H_2}$ = 0,9	—
VI	2,30d, $^4J_{CH_3-H_1}$ = 0,8	6,86 q, $^4J_{H_1-CH_3}$ = 0,8	6,96 dd, $^4J_{H_2-H_3}$ = 0,8, $^5J_{H_2-H_4}$ = 0,7	11,98	7,15 dd., $^3J_{H_3-H_4}$ = 3,7, $^4J_{H_3-H_2}$ = 0,8	7,12 dd., $^3J_{H_4-H_3}$ = 3,7, $^5J_{H_4-H_2}$ = 0,7	—
VII**	2,37 d, $^4J_{CH_3-H_1}$ = 0,6	6,60 q, $^4J_{H_1-CH_3}$ = 0,6	7,10 dd, $^4J_{H_2-H_3}$ = 1,0, $^5J_{H_2-H_4}$ = 1,0	12,02	7,63 dd, $^3J_{H_3-H_4}$ = 3,6, $^4J_{H_3-H_2}$ = 1,0	7,28 dd, $^3J_{H_4-H_3}$ = 3,6, $^5J_{H_4-H_2}$ = 1,0	—
VIII	2,38 d, $^4J_{CH_3-H_1}$ = 0,7	6,67 q $^4J_{H_1-CH_3}$ = 0,7	7,24 dd, $^4J_{H_2-H_3}$ = 0,6, $^5J_{H_2-H_5}$ = 0,6	12,02	7,51 ddd, $^3J_{H_3-H_4}$ = 3,7, $^4J_{H_3-H_5}$ = 1,2, $^4J_{H_3-H_2}$ = 0,6	7,18 dd., $^3J_{H_4-H_3}$ = 3,7, $^3J_{H_4-H_5}$ = 5,1	7,79 ddd., $^3J_{H_5-H_4}$ = 5,1, $^4J_{H_5-H_3}$ = 1,2 $^5J_{H_5-H_2}$ = 0,6
IX	2,40 d, $^4J_{CH_3-H_1}$ = 0,8	6,58 q, $^4J_{H_1-CH_3}$ = 0,8	7,03 d, $^4J_{H_2-H_3}$ = 0,8	12,10	7,30 dd, $^3J_{H_4-H_3}$ = 3,6, $^4J_{H_3-H_2}$ = 0,8	6,86 dq., $^3J_{H_4-H_3}$ = 3,6, $^4J_{H_4-CH_3}$ = 0,8	2,55 d., $^4J_{CH_3-H_4}$ = 1,3
X	2,39d, $^4J_{CH_3-H_1}$ = 0,8	6,61 q, $^4J_{H_1-CH_3}$ = 0,8	7,27 d, $^4J_{H_2-H_3}$ = 0,6	12,17	7,31 dd., $^3J_{H_3-H_4}$ = 4,0, $^4J_{H_3-H_2}$ = 0,6	7,18 d., $^3J_{H_4-H_3}$ = 4,0	—

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*In chlorobenzene, 7.33 d (2-H, 8.8 Hz); 7.93 d (3-H, 8.8 Hz).

**In nitrobenzene, 8.14 d (3-H, 9.2 Hz); 8.45 d (2-H, 9.2 Hz).

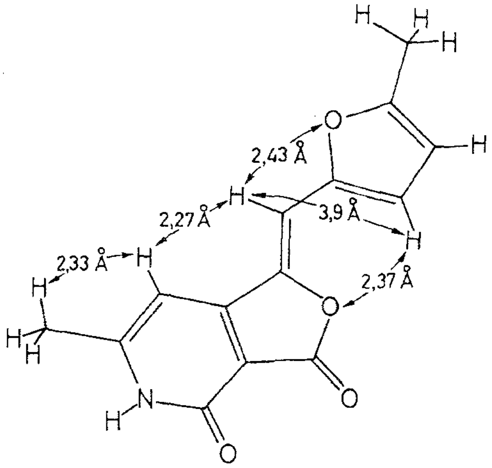

Fig. 2. Dreiding model of compound II.

On the basis of these data, together with UV spectroscopic data and the long-range SSC constants, we can assume that the plane of the furan ring deviates from the plane of the furopyridinedione; and with this deviation, the above-indicated oxygens no longer have any influence on the hydrogens as they would in the planar structure (H...O distances 2.37 and 2.43 Å, respectively), but the planarity of the heterocycles is preserved. It should be noted that the UV data and the ^{1}H NMR spectra, in accordance with the Dreiding models, correspond more closely to the E-s-cis-conformation of compounds I-VII, thus confirming the need for special studies to establish the structure of the ylidene furopyridinediones by the NOE method. An analogous deviation of the thiophene ring from the plane of the furopyridinedione is apparently observed for the thenylidene derivatives VIII-X as well; when the olefinic proton 2-H is irradiated, there is no response of 3-H in the resonance spectrum (distance 2.5 Å with complete planarity of the system).

Thus, on the basis of the ^{1}H chemical shifts and the ^{1}H–^{1}H SSCCs, with the further application of the NOE method, we have established the Z-configuration of the hetarylidenefuropyridenediones I-XII: s-cis for the furfurylidene derivaties (I-VII), cis-trans for the thenylidene derivatives (VIII-X).

EXPERIMENTAL

The electronic spectra were recorded in a Specord UV-Vis instrument. The IR spectra were taken in a UR-20 instrument. The ^{1}H NMR spectra were obtained in Bruker WM-250 and AM-300 instruments with working frequencies of 250.13 and 300.13 MHz, relative to TMS. The solvent was DMSO-d_6. The accuracy of measurement of chemical shifts was ±0.003 ppm, SSCCs ±0.05 Hz. The signals in the ^{1}H NMR spectrum were assigned by means of selective double homonuclear resonance ^{1}H–{^{1}H}. The nuclear Overhauser effect spectra were obtained by means of the Bruker NOEMULT method, preirradiation time of signal 1 sec. The spectra were taken at 50°C. The purity of the substances was monitored by UV spectroscopy or chromatography on Silufol UV-254 plates in a 20:1 ethanol–benzene system.

The elemental analyses matched the calculated compositions.

6-Methyl-3,4-dioxo-1-(2-furfurylidene)furo[3,4-c]pyridene (I). To 0.33 g (0.002 mole) of furopyridenedione in 15 ml of ethanol, heated to 60°C, 1-2 drops of piperidine, 0.29 g (0.003 mole) of furfural, and 5 ml of ethanol were added. The mixture was stirred for 5 h, while it was held at 85°C by means of a water bath. The reaction mixture was cooled, and the yellow crystals were filtered off and washed with ethanol. The filtrate was evaporated down. The residue was triturated in hot water, filtered, and washed several times with hot water. The crystals were identified as I.

Compounds II-XII were obtained analogously.

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