Furan derivatives. LXXX.
Synthesis and properties of substituted furfurylidenoxindoles

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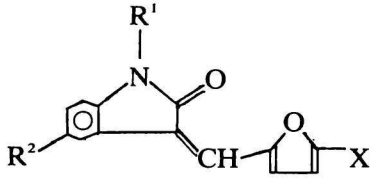
3-(5-X-2-Furfuryliden)oxindoles (X = H, NO_2, Cl, Br, I, CH_3, SCH_3, $COOCH_3$, 3-NO_2—C_6H_4, 4-NO_2—C_6H_4, $N(CH_3)_2$) as well as some of their 5-nitro and 1-acetyl derivatives were obtained by condensation of oxindole, 5-nitrooxindole, and 1-acetyloxindole, respectively, with 5-X-2-furancarbaldehydes. 1-Acetyl derivatives were prepared also by acetylation of the corresponding 3-(5-X-2-furfuryliden)oxindoles. Infrared, ultraviolet, and mass spectra of the final products were interpreted.

3-(5-X-2-фурфурилиден)-оксиндолы (X = H, NO_2, Cl, Br, I, CH_3, SCH_3, $COOCH_3$, 3-NO_2—C_6H_4, 4-NO_2—C_6H_4, $N(CH_3)_2$) как и некоторые их 5-нитро- и 1-ацетилпроизводные получились конденсацией оксиндола, или 5-нитрооксиндола и 1-ацетилоксиндола с 5-X-2-фуранкарбоальдегидами. 1-Ацетилпроизводные иригоговились тоже ацетилированием соответствующих 3-(5-X-2-фурфурилиден)-оксиндолов. У финальных соединений интерпретировались их ИК, УФ и масс-спектры.

Within the scope of the study of furan derivatives we focussed our attention on those ones which had the amide of the substituted furylacrylic acid in their molecule. Such derivatives are "isoindogenides" from which 3-(5-nitro-2-furfuryliden)oxindole has significant antibacterial properties [1, 2] and there are some indications of using it in food industry [3], cosmetics, and medicine [4, 5] as well as in textile industry [6].

For the purpose of systematic investigation of the substituted 3-(2-furfuryliden)oxindoles *I—XXVIII* (Scheme 1) a suitable method was worked out for their synthesis and the physicochemical properties of these compounds were studied. The synthesis was accomplished by condensation of 5-substituted 2-furancarbaldehydes with oxindole, 5-nitrooxindole, and 1-acetyloxindole. The substituted 1-acetylfurfurylidenoxindoles were prepared also by acetylation of the corresponding furfurylidenoxindoles



$R^1=R^2=H$; X=H, NO_2, Cl, Br, I, CH_3, SCH_3, $COOCH_3$,
I *II* *III* *IV* *V* *VI* *VII* *VIII*

3-NO_2—C_6H_4, 4-NO_2—C_6H_4, $N(CH_3)_2$
IX *X* *XI*

$R^1=H$, $R^2=NO_2$; X=H, Cl, Br, I, CH_3, SCH_3, $COOCH_3$,
XII *XIII* *XIV* *XV* *XVI* *XVII* *XVIII*

4-NO_2—C_6H_4
XIX

$R^1=COOCH_3$, $R^2=H$; X=H, NO_2 Cl, Br, I, CH_3,
XX *XXI* *XXII* *XXIII* *XXIV* *XXV*

SCH_3, $COOCH_3$, $N(CH_3)_2$
XXVI *XXVII* *XXVIII*

Scheme 1

The method worked out by Hull [1, 2] was used to prepare the corresponding 3-(5-X-2-furfuryliden)oxindoles *I*—*XI* (Table 1) by condensation of equimolar quantities of oxindole with 5-X-2-furancarbaldehydes in glacial acetic acid and anhydrous sodium acetate (method *A*). An exception was the reaction with dimethylamino-2-furancarbaldehyde where the expected condensation product *XI* was formed only by boiling for several hours in benzene under the catalytic action of piperidine. In this case the reactivity of carbonyl group of the aldehyde decreased significantly due to the +M effect of the dimethylamino group. The substituent affected also the reaction yields. It is evident from Table 1 that the yield of the reaction was higher with those aldehydes, except the compound *II*, which had an electron-withdrawing substituent at the position 5 of the furan ring. The melting points of the compounds *I* and *II*, already prepared under different conditions, were in good agreement with the data found in [1, 7].

Condensation of 5-nitrooxindole with 5-X-2-furancarbaldehydes at the same reaction conditions, *i.e.* in glacial acetic acid at the presence of anhydrous sodium acetate, resulted in the formation of 3-(5-X-2-furfuryliden)-5-nitrooxindoles *XII*—*XIX*. The substituent affected the yields of the synthesized compounds *XIII*—*XIX* (Table 1).

Similarly, the reaction of 1-acetyloxindole with 5-substituted furancarbaldehydes gave 1-acetyl-3-(5-X-2-furfuryliden)oxindoles *XX*—*XXVIII* (Table 1) in 68—90% yield.

Table 1

Substituted 3-(2-furfuryliden)oxindoles *I*—*XXVIII*

Compound	Formula	*M*	Calculated/found % C	% H	% N	Yield %	M.p., °C (Solvent)
I	$C_{13}H_9NO_2$	211.21	73.92 74.08	4.29 4.34	6.63 6.76	78.8	176—178[a] (Ethanol)
II	$C_{13}H_8N_2O_4$	256.21	60.94 61.07	3.15 3.20	10.94 11.01	59.6	268 decomp.[b] (Acetic acid)
III	$C_{13}H_8ClNO_2$	245.66	63.55 63.68	3.28 3.33	5.70[c] 5.74	80.1	255.5—257 (Ethanol)
IV	$C_{13}H_8BrNO_2$	290.11	53.82 53.92	2.78 2.83	4.83[d] 5.03	85.1	241—242 (Ethanol)
V	$C_{13}H_8INO_2$	337.11	46.31 46.43	2.39 2.47	4.15 4.22	99.0	235—237 (Ethanol)
VI	$C_{14}H_{11}NO_2$	225.24	74.65 74.80	4.92 5.02	6.22 6.31	47.3	230—232.4 (Ethanol)
VII	$C_{14}H_{11}NO_2S$	257.30	65.35 65.19	4.31 4.24	5.44[e] 5.55	68.1	184—185.5 (Ethanol)
VIII	$C_{15}H_{11}NO_4$	269.25	66.91 66.91	4.12 3.97	5.20 5.21	99.0	223—225 (Ethanol)
IX	$C_{19}H_{12}N_2O_4$	332.31	68.64 68.83	3.64 3.75	8.43 8.39	84.3	292—294.5 (Acetic acid+ +water)
X	$C_{19}H_{12}N_2O_4$	332.31	68.64 68.79	3.64 3.70	8.43 8.40	98.4	323—325 (Dimethylformamide)
XI	$C_{15}H_{14}N_2O_2$	254.28	70.85 70.82	5.55 5.46	11.02 10.94	78.7	229—231 (Ethanol)
XII	$C_{13}H_8N_2O_4$	256.21	60.94 60.70	3.15 3.27	10.94 10.92	70.3	315 decomp. (Acetic acid)
XIII	$C_{13}H_7ClN_2O_4$	290.66	53.72 53.85	2.43 2.51	9.64[f] 9.72	89.7	310 decomp. (Acetic acid)
XIV	$C_{13}H_7BrN_2O_4$	335.12	46.59 46.67	2.10 2.08	8.36[g] 8.31	86.6	310 decomp. (Acetic acid)
XV	$C_{13}H_7IN_2O_4$	382.11	40.86 40.83	1.85 1.96	7.33 7.34	82.5	305 decomp. (Acetic acid)
XVI	$C_{14}H_{10}N_2O_4$	270.24	62.22 62.23	3.73 3.51	10.37 10.32	77.7	310 decomp. (Acetic acid)
XVII	$C_{14}H_{10}N_2O_4S$	302.24	55.63 55.48	3.38 3.25	9.27[h] 9.37	78.1	288—292 (Acetic acid)
XVIII	$C_{15}H_{10}N_2O_4$	314.25	57.32 57.28	3.21 3.19	8.91 9.02	92.4	340 decomp. (Acetic acid)
XIX	$C_{19}H_{11}N_3O_6$	377.37	60.47 60.25	2.94 2.83	11.14 10.91	79.8	330 decomp. (Acetic acid)
XX	$C_{15}H_{11}NO_3$	253.25	71.14 71.30	4.38 4.30	5.53 5.52	75.4	154—155 (Ethanol)

Table 1 (Continued)

Compound	Formula	*M*	Calculated/found			Yield %	M.p., °C (Solvent)
			% C	% H	% N		
XXI	$C_{15}H_{10}N_2O_5$	298.25	60.40	3.38	9.39	90.6	233—235
			60.63	3.58	9.48		(Acetic acid)
XXII	$C_{15}H_{10}ClNO_3$	287.70	62.62	3.49	4.87[i]	80.1	146—148
			62.48	3.27	4.80		(Ethanol)
XXIII	$C_{15}H_{10}BrNO_3$	332.15	54.24	3.03	4.22[k]	90.4	167—168
			53.98	2.97	4.27		(Ethanol)
XXIV	$C_{15}H_{10}INO_3$	379.14	47.51	2.66	3.69	73.9	240—241
			47.33	2.54	3.73		(Ethanol)
XXV	$C_{16}H_{13}NO_3$	267.27	71.90	4.90	5.24	89.5	130—132
			71.82	4.93	5.25		(Ethanol)
XXVI	$C_{16}H_{13}NO_3S$	299.34	64.19	4.38	4.68[l]	86.7	153—155
			63.97	4.32	4.58		(Ethanol)
XXVII	$C_{17}H_{13}NO_5$	311.28	65.59	4.21	4.50	90.0	180—182
			65.77	4.20	4.55		(Ethanol)
XXVIII	$C_{17}H_{16}N_2O_3$	296.32	68.90	5.44	9.46	68.1	170—174
			68.78	5.42	9.32		(Benzene+cyclohexane)

a) M.p. 183°C [7]; *b*) m.p. 268°C/decomp. [1, 2]; *c*) % Cl 14.43/14.44; *d*) % Br 27.54/27.55; *e*) % S 12.46/12.44; *f*) % Cl 12.20/12.03; *g*) % Br 23.84/23.85; *h*) % S 10.59/10.48; *i*) m.p. 154°C [7]; *j*) % Cl 12.32/12.24; *k*) % Br 24.06/23.95; *l*) % S 10.71/10.56.

The second method of preparation (method *B*) of 1-acetyl-3-(5-X-2-furfuryliden)oxindoles *I* and *XXVIII* was based on acetylation of the corresponding 3-(5-X-2-furfuryliden)oxindoles with acetic anhydride at the presence of sodium acetate.

The basic spectral data of the compounds *I*—*XXVIII* are presented in Table 2. In the i.r. spectra of the synthesized compounds the absorption bands belonging to $\nu(C=O)$ were observed in the region 1765—1693 cm^{-1} With the 1-acetyl derivatives *XX*—*XXVIII*, the band at 1760—1727 cm^{-1} belonged to $\nu(C=O)_{ring}$ and the band at 1723—1702 cm^{-1} belonged to $\nu(C=O)_{COCH_3}$ [8]. In the case when the same substituent was at the position 5 of the furan ring, the increase of $\nu(C=O)_{ring}$ in the series of furfurylidene derivatives of oxindole—5-nitrooxindole—1-acetyloxindole was connected with the electron-withdrawing nature of the nitro group and mainly acetyl group which was adjacent with the carbonyl group of the ring. Greater effect of the substituent on the shift of the $\nu(C=O)_{ring}$ values was observed only with the oxindole and 5-nitrooxindole derivatives except the compounds *II* and *VII*.

The mass spectrum of 3-(5-bromo-2-furfuryliden)oxindole *IV* is shown in Fig. 1. The mass of the molecular ion $[M]^{+\bullet}$ of *m/e* 289 and of the ion of *m/e* 291 proved

Table 2

Infrared and ultraviolet spectral data of the substituted 3-(2-furfuryliden)oxindoles *I*—*XXVIII*

Compound	ν(C=O)	ν(C=C)$_{alif.}$	ν_s(C—O—C)	λ_{max} (log ε)		
I	1710	1632	1029	209 (4.54)	255 (4.11)	352 (4.53)
						364 sh (4.50)
II	1708	1635	1032	207 (4.43)	259 (4.56)	387 (4.29)
					308 (4.11)	404 sh (4.28)
III	1711	1631	1029	211 (4.62)	250 (4.26)	357 (4.94)
						368 sh (4.45)
IV	1712	1637	1022	211 (4.65)	251 (4.34)	359 (4.55)
						371 sh (4.53)
V	1711	1635	1023	209 (4.46)	254 (4.25)	366 (4.51)
VI	1700	1632	1032	210 (4.51)	247 (4.15)	359 sh (4.44)
						370 (4.45)
VII	1715	1630	1035	211 (4.61)	260 (4.44)	389 (4.51)
VIII	1713	1635	1032	208 (4.43)	227 (4.52)	358 (4.57)
						374 (4.50)
IX	1732	1640	1032	206 (4.60)	253 (4.57)	387 (4.47)
						401 (4.50)
X	1731	1621	1032	212 (4.62)	261 (4.68)	397 sh (4.49)
						412 (4.53)
XI	1693	1640	1045	217 (4.40)	245 (4.22)	483 (4.56)
						495 sh (4.51)
XII	1722	1638	1022	207 (3.94)	238 (4.31)	367 (4.51)
XIII	1726	1636	1028	207 (4.09)	241 (4.42)	343 (4.55)
XIV	1725	1638	1029	207 (4.00)	242 (4.38)	375 (4.49)
XV	1717	1637	1029	207 (4.15)	243 (4.44)	381 (4.52)
XVI	1718	1635	1030	208 (4.12)	242 (4.34)	378 (4.38)
					304 (3.92)	
XVII	1708	1630	1038	208 (4.13)	243 (4.30)	425 (4.33)
					311 (3.98)	

Table 2 (Continued)

Compound	ν(C=O)	ν(C=C)$_{alif.}$	ν(C—O—C)	λ_{max} (log ε)		
XVIII	1732	1638	1028	208 (4.10)	238 (4.36)	355 (4.15)
						373 (4.44)
XIX	1739	1639	1029	206 (4.06)	231 (4.32)	370 (4.42)
XX	1765	1635	1021	209 (4.38)	222 (4.40)	377 (3.83)
	1723					
XXI	1740	1629	1030	219 (4.47)	251 (4.24)	384 (4.13)
	1712				312 (4.06)	425 sh (4.07)
XXII	1740	1630	1033	222 (4.33)	250 (3.98)	370 (4.32)
	1710					400 sh (4.26)
XXIII	1733	1629	1032	217 (4.51)	250 (4.24)	370 (4.42)
	1709					403 sh (4.36)
XXIV	1727	1632	1022	209 (4.35)	255 (4.12)	373 (4.40)
	1709					411 sh (4.13)
XXV	1734	1629	1032	209 (4.33)	228 (4.45)	370 sh (4.43)
	1702					394 (4.49)
XXVI	1732	1618	1040	208 (4.36)	227 (4.42)	423 (4.42)
	1703					
XXVII	1750	1628	1032	217 (4.57)	250 (4.20)	358 sh (4.34)
	1710					375 (4.37)
XXVIII	1727	1627	1025	207 (4.48)	240 (4.31)	497 sh (4.69)
	1702					515 (4.62)

sh — shoulder.

the presence of one bromine atom in the molecule. The most intensive ion of the spectrum (*m/e* 210) was formed by splitting off of the bromine radical $[M\text{-}Br]^+$. The fragments of *m/e* 182 and *m/e* 154 originated from the furan and oxindole rings and could be expressed as $[M\text{-}Br—CO]^+$ and $[M\text{-}Br—CO—CO]^+$ respec-

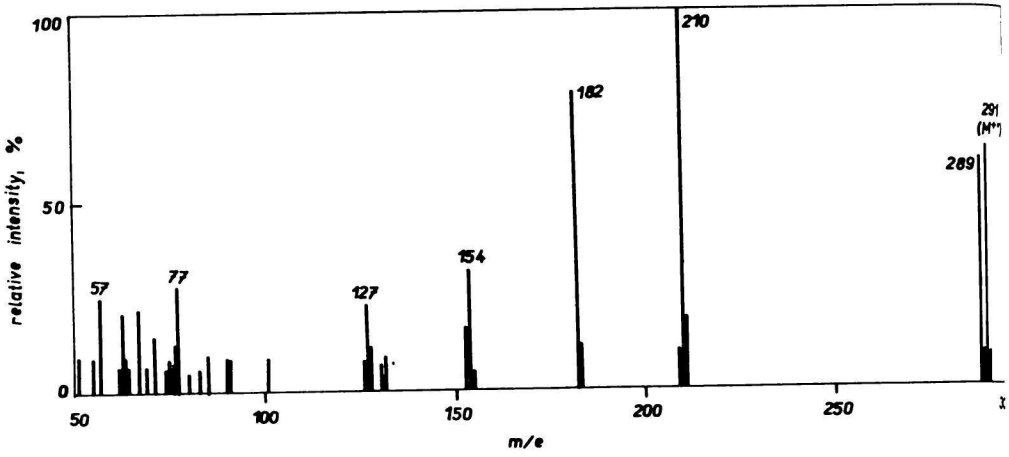


Fig. 1. Mass spectrum of 3-(5-bromo-2-furfuryliden)oxindole *IV*

tively. Like other substituted oxindoles also the ion of *m/e* 154 split off HCN [9] giving the fragment of *m/e* 127. This fragmentation was proved by the following metastable ions observable in the spectrum

$$\underset{m/e\ 289^a}{[M]^{+\bullet}} \rightarrow \underset{m/e\ 210}{[M\text{-}Br]^+};\quad m^* = 152.5,$$

$$\underset{m/e\ 210}{[M\text{-}Br]^+} \rightarrow \underset{m/e\ 182}{[M\text{-}Br—CO]^+};\quad m^* = 157.7,$$

$$\underset{m/e\ 182}{[M\text{-}Br—CO]^+} \rightarrow \underset{m/e\ 154}{[M\text{-}Br—CO—CO]^+};\quad m^* = 130.3,$$

$$[M\text{-}Br—CO—CO]^+ \rightarrow [M\text{-}Br—CO—CO—HCN]^+;\quad m^* = 104.7.$$

Lower relative intensities were characteristic of the fragments of *m/e* 144.5 and *m/e* 145.5 $[M]^{2+}$, *m/e* 79 $[^{79}Br]^+$, *m/e* 81 $[^{81}Br]^+$. The fragments of *m/e* 174 or *m/e* 172, which would represent the splitting off of the hydroxyl group from the molecular ion of the less probable enol form of this compound, were not present in the spectrum.

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a) For the isotope ^{79}Br.

The question of geometric stereoisomerism of the trisubstituted exocyclic double bond at C-3 atom of oxindole of the substituted 3-(2-furfuryliden)oxindoles will be the subject of separate work.

Experimental

5-X-2-Furancarbaldehydes (X = H, NO_2 [10], Cl [11], Br [12], I [13], CH_3 [14], SCH_3 [15], $COOCH_3$ [16], 3-NO_2—C_6H_4 [17], 4-NO_2—C_6H_4 [17], $N(CH_3)_2$ [18]) were the carbonyl component of the above-mentioned condensation reactions. Oxindole was obtained from isatin through dioxindole [19, 20]. Nitration of oxindole with the mixture of fuming nitric acid and concentrated sulfuric acid resulted in the formation of 5-nitrooxindole [21] and acetylation of the original compound with acetic anhydride gave 1-acetyloxindole [22].

The samples were dried at 90°C/2—2.66 kPa for 5 hrs before analysis. Melting points were determined on a Kofler apparatus.

The i.r. measurements were performed on a double-beam UR-20 spectrophotometer (Zeiss, Jena) in the region 700—3600 cm^{-1} With 5-nitrooxindole derivatives (due to their low solubility) KBr technique (1.5 mg/g KBr) was used.

Electronic absorption spectra in the ultraviolet and visible regions were measured by a recording UV VIS spectrophotometer (Zeiss, Jena) in 1 cm cells in ethanol of spectral purity; concentration $2.5—5.5 \times 10^{-5}$ mol l^{-1}

Mass spectra were taken by an MS 902-S instrument using the direct-insertion technique and an ionizing voltage of 70 eV; trap current 100 μA, and the temperature of the ionization chamber 100°C.

Condensation of 5-X-2-furancarbaldehydes with oxindoles (method A; I—X, XII—XXVII)

To the boiling mixture of oxindole, 5-nitrooxindole, and 1-acetyloxindole, respectively (0.01 mole), 5-X-2-furancarbaldehyde (0.01 mole), and glacial acetic acid (25 ml), anhydrous sodium acetate (0.04 mole) was added. After 45 min boiling the reaction mixture was poured into water (100 ml) and was allowed to stay overnight. The insoluble portion was sucked, washed with water and petroleum ether, and then was crystallized from a suitable solvent (Table 1).

3-(5-Dimethylamino-2-furfuryliden)oxindole (XI)

Piperidine (12 drops) was added to the boiling solution of oxindole (0.03 mole) and 5-dimethylamino-2-furancarbaldehyde (0.03 mole) in anhydrous benzene (500 ml) and the reaction mixture was heated at boiling for 9 hrs. The solvent was distilled off at reduced pressure and the crude product was crystallized from ethanol. Yield 6 g (78.8%) of dark red needles; m.p. 229—231°C.

Acetylation of 3-(2-furfuryliden)oxindoles (method B; XX, XXVIII)

The mixture of 3-(5-X-2-furfuryliden)oxindole (0.005 mole), anhydrous sodium acetate (0.04 mole), and acetic anhydride (0.03 mole) was heated at boiling for 8 hrs. The reaction mixture was

then poured into water (100 ml). The insoluble portion was sucked and washed with water and petroleum ether. The crude product was crystallized from a suitable solvent (Table 1).

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