1,3-DIPOLAR CYCLOADDITIONS OF HETEROCYCLIC NITRILE OXIDES TO SUBSTITUTED N-PHENYLMALEINIMIDES*

Eva JEDLOVSKÁ[a], Ľubor FIŠERA[a], Igor GOLJER[b], Mária KONOPÍKOVÁ[a] and Leonid I. BELENKII[c]

[a] *Department of Organic Chemistry and*
[b] *Central Laboratory of NMR Spectroscopy,*
Faculty of Chemical Technology, Slovak Technical University, 812 37 Bratislava, Czechoslovakia
[c] *Institute of Organic Chemistry, Academy of Sciences U.S.S.R., 117913 Moscow, U.S.S.R*

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Cycloadditions of 2-furannitrile oxide (*Ia*), 5-nitro-2-furannitrile oxide (*Ib*), 5-(3-nitrophenyl)-2--furannitrile oxide (*Ic*), 5-(4-nitrophenyl)-2-furannitrile oxide (*Id*), and 2,5-dimethyl-3-furanitrile oxide (*Ie*) with 4- or 2,6-disubstituted N-phenylmaleinimide are described. Investigated were also cycloadditions of 2,5-dimethyl-3-thiophenenitrile oxide (*IVa*), 2,4,5-trimethyl-3-thiophenenitrile oxide (*IVb*), 2,3-dimethyl-4-ethyl-3-thiophenenitrile oxide (*IVc*), 2,5-dimethyl-4--(1-methylethyl)-3-thiophenenitrile oxide (*IVd*), and 3,5-di(1,1-dimethylethyl)-2-thiophenenitrile oxide (*V*) with N-(2,6-dimethylphenyl)maleinimide. The steric course of these reactions is discussed.

The outstanding properties of commercial fungicides Dimetachlon containing a pyrrolidine-2,3-dione ring and Hymexazole (3-hydroxy-5-methylisoxazole)[1] prompted us to synthesize compounds characteristic of a fused N-phenylsubstituted pyrrolidine and isoxazoline rings in connection with our previous interest in heterocyclic substances with pesticide activity.

The above mentioned compounds were obtained by a 1,3-dipolar cycloaddition of 2-furannitrile oxide (*Ia*), 5-nitro-2-furannitrile oxide (*Ib*), 5-(3-nitrophenyl)-2--furanitrile oxide (*Ic*), 5-(4-nitrophenyl)-2-furannitrile oxide (*Id*), 2,5-dimethyl-3--furannitrile oxide (*Ie*), 2,5-dimethyl-3-thiophenenitrile oxide (*IVa*), 2,4,5-trimethyl--3-thiophenenitrile oxide (*IVb*), 2,5-dimethyl-4-ethyl-3-thiophenenitrile oxide (*IVc*), 2,5-dimethyl-4-(1-methylethyl)-3-thiophenenitrile oxide (*IVd*), and 3,5-di(1,1-dimethylethyl)-2-thiophenenitrile oxide (*V*) to N-(4-X-phenyl)maleinimide (X = H, Cl) or N-(2,6-Y,Z-phenyl)maleinimide (Y, Z = CH_3, C_2H_5). Nitrile oxides *Ia*, *Id* were generated in situ from the corresponding hydroximic chlorides[2,3], *Ie*, *IVa*–*IVd* and *V* from the appropriate oxime[4–6] and sodium hypochlorite in the presence of the dipolarophile under catalysis of triethylamine. Cycloadditions run smoothly and

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in good to very good yields (48–92%) affording 3,5-disubstituted 4,6-dioxo-3a,4,6,6a-tetrahydropyrrolo[3,4-*d*]ixosazoles *II*, *III*, *VI*, and *VII*. Their structure was corroborated by a synthetic approach and spectral (UV, IR, ^{1}H and ^{13}C NMR) evidence (Tables I–VIII).

TABLE I

Characteristic data of isoxazolines *II* and *III*

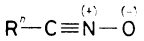
Compound	Formula (M.w.)	Calculated/Found			M.p., °C Yield, %	ν(C=O)	λ_{max} (log ε)
		% C	% H	% N			
IIa	$C_{15}H_{10}N_2O_4$ (282·2)	63·82 63·86	3·57 3·65	9·92 10·11	208–210 82	1 725	276 (3·20)
IIb	$C_{15}H_9N_3O_6$ (327·2)	55·05 54·57	2·77 2·97	12·51 12·56	238–240 67	1 732	240 (3·21) 333 (3·11)
IIc	$C_{21}H_{13}N_3O_6$ (403·3)	62·53 62·34	3·24 3·34	10·42 10·59	263–265 63	1 728	238 (3·27) 361 (3·37)
IId	$C_{17}H_{14}N_2O_4$ (313·3)	65·16 64·99	4·50 4·71	8·94 8·91	130–131 92	1 724	238 (3·04)
IIe	$C_{15}H_9ClN_2O_4$ (316·7)	56·86 56·58	2·86 2·81	8·84 8·72	215–217 53	1 728	248 (3·19) 281 (3·21)
IIf	$C_{21}H_{12}ClN_3O_6$ (437·8)	57·61 57·68	2·76 2·77	9·59 9·45	263–264 75	1 726	248 (3·31) 318 (3·37)
IIg	$C_{17}H_{13}ClN_2O_4$ (344·7)	59·23 58·80	3·80 3·42	8·12 7·96	140–141 65	1 738	250 (3·30)
IIh	$C_{15}H_8FN_3O_6$ (345·2)	52·18 52·41	2·33 2·53	12·22 12·38	260–262 65	1 725	237 (3·21) 335 (3·12)
IIi	$C_{21}H_{12}FN_3O_6$ (421·3)	59·86 59·60	2·86 3·01	9·77 9·85	272–274 69	1 725	240 (31·3) 318 (3·26)
IIj	$C_{17}H_{13}FN_2O_4$ (328·3)	62·29 61·98	3·98 4·12	8·53 8·50	146–147 71	1 728	200 (3·44)
IIIa	$C_{17}H_{14}N_2O_4$ (310·3)	65·80 65·99	4·54 4·76	9·02 9·12	165–167 48	1 720	279 (3·02)
IIIb	$C_{17}H_{13}N_3O_6$ (355·3)	57·46 57·70	3·97 3·91	11·82 11·52	233–235 56	1 730	262 (2·79) 333 (3·08)
IIIc	$C_{23}H_{17}N_3O_6$ (431·4)	64·03 64·12	3·97 4·18	9·74 9·60	266–268 63	1 725	360 (3·30)
IIId	$C_{19}H_{18}N_2O_4$ (338·3)	67·44 67·29	5·36 5·26	8·27 8·21	192–193 74	1 730	272 (2·73)

TABLE I
(*Continued*)

Compound	Formula (M.w.)	Calculated/Found % C	% H	% N	M.p., °C Yield, %	ν(C=O)	λ_{max} (log ε)
IIIe	$C_{19}H_{18}N_2O_4$ (338·3)	67·44	5·36	8·27	192—194	1 724	276
		67·73	5·24	8·19	48		(3·18)
IIIf	$C_{25}H_{21}N_3O_6$ (459·4)	65·35	4·60	9·14	268—271	1 728	359
		65·32	4·68	9·11	69		(3·22)
IIIg	$C_{21}H_{22}N_2O_4$ (366·4)	68·83	6·05	7·64	163—165	1 742	272
		68·53	6·20	7·41	82		(2·69)
IIIh	$C_{18}H_{16}N_2O_4$ (324·3)	66·65	4·97	8·63	188—190	1 726	281
		66·93	4·91	8·99	76		(3·06)
IIIi	$C_{18}H_{15}N_3O_6$ (369·3)	58·53	4·09	11·37	199—201	1 730	334
		58·43	4·08	11·26	53		(3·11)
IIIj	$C_{24}H_{19}N_3O_6$ (445·4)	64·71	4·29	9·43	252—254	1 722	359
		64·51	4·33	9·48	75		(3·19)
IIIk	$C_{20}H_{20}N_2O_4$ (352·4)	68·16	5·72	7·94	179—180*A*	1 725	272
		68·13	5·62	7·93	150—151*B*		(2·68)
					76		

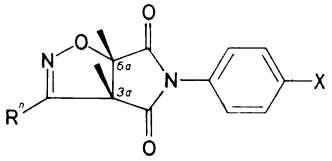
TABLE II
Characteristic data of isoxazolines *VI* and *VII*

Compound	Formula (M.w.)	Calculated/Found % C	% H	% N	M.p., °C Yield, %	ν(C=O)	λ_{max} (log ε)
VIa	$C_{19}H_{18}N_2O_3S$ (354·4)	64·38	5·11	7·90	153—154	1 725	266
		64·49	5·28	8·11	87		(2·92)
VIb	$C_{20}H_{20}N_2O_3S$ (368·4)	65·19	5·37	7·60	229—230	1 730	260
		65·23	5·54	7·78	62		(2·91)
VIc	$C_{21}H_{22}N_2O_3S$ (382·4)	65·94	5·79	7·32	179—181	1 725	261
		66·15	5·87	7·60	71		(2·90)
VId	$C_{22}H_{24}N_2O_3S$ (396·5)	66·64	6·10	7·06	230—231	1 725	247
		66·90	6·05	7·20	90		(2·88)
VII	$C_{25}H_{30}N_2O_3S$ (408·3)	73·53	7·40	6·86	188—190	1 730	292
		73·05	7·36	7·01	68		(2·84)



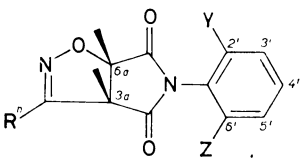
I

Compound	R^n	
I a	R^1	R^1= 2-furyl
I b	R^2	R^2= 5-nitro-2-furyl
I c	R^3	R^3= 5-(3-nitrophenyl)-2-furyl
I d	R^4	R^4= 5-(4-nitrophenyl)-2-furyl
I e	R^5	R^5= 2,5-dimethyl-3-furyl



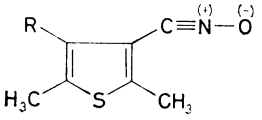
II

Compound	R^n	X
II a	R^1	H
II b	R^2	H
II c	R^4	H
II d	R^5	H
II e	R^1	Cl
II f	R^3	Cl
II g	R^5	Cl
II h	R^2	F
II i	R^3	F
II j	R^5	F

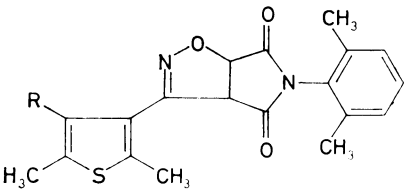


III

Compound	R^n	Y	Z
III a	R^1	CH_3	CH_3
III b	R^2	CH_3	CH_3
III c	R^4	CH_3	CH_3
III d	R^5	CH_3	CH_3
III e	R^1	C_2H_5	C_2H_5
III f	R^4	C_2H_5	C_2H_5
III g	R^5	C_2H_5	C_2H_5
III h	R^1	CH_3	C_2H_5
III i	R^2	CH_3	C_2H_5
III j	R^4	CH_3	C_2H_5
III k	R^5	CH_3	C_2H_5



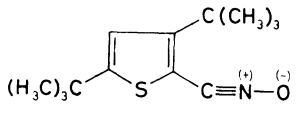
IV



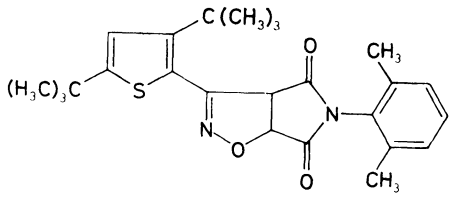
VI

Compound	R
IV a, *VI a*	H
IV b, *VI b*	CH_3
IV c, *VI c*	C_2H_5
IV d, *VI d*	$(CH_3)_2CH$

Diastereomers *A* and *B*, differing in the arrangement (*syn* and *anti* forms) of their methyl and ethyl groups at the phenyl ring and the bridgehead protons H-3a and



V



VII

H-6a of the fused isoxazoline were obtained from furannitrile oxides and N-(2-ethyl--6-methylphenyl)maleinimide. Analysis of ^{1}H NMR spectra of the crude reaction mixtures revealed the mutual ration of both isomers to be 1 : 1. Formation of atropoisomers could be explained by two various diastereomeric transition states resulting

TABLE III

^{1}H NMR chemical shifts (δ, ppm) and coupling constants (J, Hz) of compounds *IId*, *IIg*, *IIj*, *IIId*, *IIIg*, *IIIk*

Compound	H-3a	H-6a	CH_3 CH_3	H-4′	H (arom.)
IId	5·39	5·87 (9·7)	2·50 2·73	6·71	7·48—7·81 (m, 5 H)
IIg	4·80	5·39 (9·6)	2·14 2·34	6·16	7·74 (d, 2 H); 7·26 (d, 2 H)
IIj	5·03	5·52 (9·6)	2·15 2·40	6·35	7·20 (d, 2 H); 7·24 (d, 2 H)
IIId[a]	5·12	5·68 (9·5)	2·16 2·41	6·38	7·04—7·20 (m, 3 H)
IIIg[b]	5·24	5·80 (9·3)	2·26 2·53	6·47	7·19—7·41 (m, 3 H)
IIIk[c] *A*	5·12	5·68 (9·2)	2·15 2·41	6·37	7·07 (d, 1 H); 7·16 (d, 1 H) 7·21 (dd, 1 H)
IIIk[d] *B*	5·27	5·80 (9·3)	2·23 2·46	6·42	7·16 (d, 1 H); 7·21 (d, 1 H) 7·31 (dd, 1 H)

[a] 1·82 (s, 3 H, CH_3); 2·07 (s, 3 H, CH_3); [b] 0·95 (t, 3 H, CH_3); 1·12 (t, 3 H, CH_3); 2·19 (dd, 2 H, CH_2); 2·48 (dd, 2 H, CH_2); [c] 1·02 (t, 3 H, CH_3); 1·80 (s, 3 H, CH_3); 2·28 (dd, 2 H, CH_2); [d] 0·82 (t, 3 H, CH_3); 2·11 (s, 3 H, CH_3); 2·28 (dd, 2 H, CH_2).

from the rotation hindrance of the benzene ring in the arylmaleinimide groupig during the 1,3-dipolar cycloaddition. The nitrile oxide attacked, then, the double bond from the methyl or ethyl side of the asymmetrically substituted maleinimide.

Only diastereomers *A* and *B* of 3-(2,5-dimethyl-3-furyl)-5-(2-ethyl-6-methylphenyl)-2,4-dioxo-3a,4,6,6a-tetrahydropyrrolo[3,4-*d*]isoxazole (*IIIk*) could be separated on a silica gel-packed column (eluent hexane–ethyl acetate 5 : 1); with other derivatives the separation led to mixtures enriched by one isomer (c. 70%). Diastereomers *IIIk* markedly differ in some physicochemical constants (m.p., NMR chemical shift values). Their structure was ascertained from ^{1}H and ^{13}C NMR spectral data of pure diastereomers of *IIIk* and the model compound *IIIa* (3-(2-furyl)-5-(2,6-dimethylphenyl)-4,6-dioxo-3a,4,6,6a-tetrahydropyrrolo[3,4-*d*]isoxazole). The sterochemical arrangement was proved by the nuclear Overhauser effect between the bridgehead protons H-3a, H-6a and the methyl group, employing the NOE DIFFERENCE modification[7]. The minimum energy conformation was calculated by

TABLE IV

^{13}C NMR chemical shifts (δ, ppm) of compounds *IId*, *IIg*, *IIj*, *IIId*, *IIIg*, *IIIk*

Compound	C-3	C-3a	C-6a	C-4	C-6
IId[a]	148·4	56·6	80·0	170·9	172·2
IIg[b]	150·5	58·56	82·9	168·1	169·2
IIj[c]	148·1	56·5	79·9	170·7	171·9
IIId[d]	149·2	57·6	80·9	171·0	172·0
IIIg[e]	149·5	57·9	81·1	172·0	173·3
IIIk[f] *A*	149·2	57·5	80·8	171·4	172·6
IIIk[g] *B*	148·7	56·45	80·1	171·0	172·3

[a] C(furan): 106·6, 109·2, 150·0, 151·3; 12·82 (CH_3), 13·81 (CH_3); C(arom.): 126·8, 128·8, 129·5, 131·5; [b] C(furan): 106·6, 110·45, 151·17, 151·9; 13·7 (CH_3), 12·8 (CH_3); C(arom.): 122·1, 129·15, 137·5; [c] C(furan): 106·5, 108·1, 149·9, 151·2; 12·7 (CH_3), 13·6 (CH_3); C(arom.); 115·7, 129·0, 159·9, 163·2; [d] C(furan): 107·0, 109·9, 151·0, 152·3; 12·8 (CH_3), 13·8 (CH_3); C(arom.): 128·8, 128·9, 130·7, 136·2; 16·8 (CH_3), 17·2 (CH_3); [e] C(furan): 107·3, 110·2, 151·3, 152·5; 13·1 (CH_3), 14·1 (CH_3); C(arom.): 127·6, 127·7, 130·7, 142·3, 143·2; 14·8 (CH_3), 15·1 (CH_3), 24·6, 24·9 (CH_2); [f] C(furan): 107·0, 109·1, 151·0, 152·2; 12·8 (CH_3), 13·8 (CH_3); C(arom.): 127·4, 128·8, 130·2, 136·1, 142·9; 14·9 (CH_3), 16·8 (CH_3), 24·3 (CH_2); [g] C(furan): 106·5, 108·96, 150·3, 151·3; 12·91 (CH_3), 13·7 (CH_3); C(arom).: 126·97, 128·5, 128·9, 129·7, 136·5, 141·06; 14·4 (CH_3), 17·34 (CH_3), 23·9 (CH_2).

TABLE V

^{1}H NMR chemical shifts (δ, ppm) and coupling constants (J, Hz) of compounds *II* and *III*

Compound	H-3a	H-6a	H-3′	H-4′	H(arom.)
IIa[a]	5·17	5·79 (9·6)	6·68 (3·6)	7·25	7·37—7·52 (m, 5 H)
IIb	5·31	5·9 (9·0)	7·43 (3·5)	7·84	7·31—7·56 (m, 5 H)
IIc[b]	5·25	5·80 (9·0)			7·30—7·54 (m, 7 H) 8·03 (d, 2 H); 8·32 (d, 2 H)
IIe[c]	5·08	5·72 (9·0)	6·51 (3·5)	7·15	7·32—7·50 (m, 5 H)
IIf	5·26	5·79 (9·0)	7·32 (3·5)	7·48	7·35 (d, 2 H); 7·58 (d, 2 H) 7·75 (dd, 1 H); 8·19 (d, 2 H) 8·52 (d, 1 H)
IIh	5·35	5·95 (9·1)	7·50 (3·9)	7·07	7·27—7·48 (m, 4 H)
IIi	5·24	5·77 (9·9)	7·31 (3·5)	7·48	7·33—7·38 (m, 4 H); 7·76 (dd, 1 H) 8·2 (d, 2 H); 8·51 (d, 1 H)
IIIa[d]	5·3	5·89 (9·2)	6·71 (3·5)	7·19	7·14 (d, 2 H); 7·26 (d, 1 H)
IIIb[e]	5·45	6·04 (9·2)	7·41 (3·5)	7·5	7·12—7·32 (m, 3 H)
IIIc[f]	5·39	5·98 (9·0)	7·37 (3·5)	7·51	8·03 (d, 2 H); 8·32 (d, 2 H) 7·13—7·39 (m, 3 H)
IIIf[g]	5·31	5·90 (9·0)	7·30 (3·5)	7·44	7·05—7·32 (m, 3 H); 7·96 (d, 2 H) 8·23 (d, 2 H)
IIIh[h]	4·64	5·54 (9·0)	6·28 (3·5)	7·23	7·04—7·22 (m, 3 H)
IIIi[i] *A*	5·35	5·95 (7·8)	7·37 (3·5)	7·7	7·07—7·23 (m, 3 H)
IIIi[j] *B*	5·35	5·96 (9·3)	7·39 (3·6)	7·70	7·05—7·24 (m, 3 H)
IIIj[k]	5·4	5·90 (9·0)	7·37 (3·5)	7·52	7·13—7·36 (m, 3 H); 8·05 (d, 2 H); 8·31 (d, 2 H)

[a] 7·80 (d, 1 H, H-5′, J = 1·2 Hz); [b] the H-3′ and H-4′ signals are overlapped by H(arom.); [c] the H-5′ signal is overlapped by H(arom.); [d] 7·94 (d, 1 H, H-5′, J = 1·8 Hz); [e] 1·8 (s, 3 H, CH_3); 2·17 (s, 3 H, CH_3); [f] 1·78 (s, 3 H, CH_3); 2·16 (s, 3 H, CH_3); [g] 0·70 (t, 3 H, CH_3); 1·0 (t, 3 H, CH_3); 2·40 (m, 4 H, CH_2); [h] 7·55 (d, 1 H, H-5′); [i] 0·74 (t, 3 H, CH_3); 0·99 (t, 3 H, CH_3); 1·69 (s, 3 H, CH_3); 2·06 (s, 3 H, CH_3); 2·19 (q, 2 H, CH_2); [j] 0·76 (t, 3 H, CH_3); 1·01 (t, 3 H, CH_3); 1·70 (s, 3 H, CH_3); 2·07 (s, 3 H, CH_3); 2·01 (q, 2 H, CH_2); 2·41 (q, 2 H, CH_2); [k] 0·80 (t, 3 H, CH_3); 1·1 (t, 3 H, CH_3); 1·78 (s, 3 H, CH_3); 2·17 (s, 3 H, CH_3); 2·09 (q, 2 H, CH_2).

means of the MM2 programme[9,10] (Fig. 1). The 2D APT technique and 2D hetero-correlated ^1H ^{13}C NMR were used to ascribe the correct chemical shift data in the ^{13}C spectra; modification enabling to gain one-bond ^1H–^{13}C correlations and the HETCOR long-range technique[8] were applied. The COSY technique[8] was helpful with some more complicated molecules offering more information on the ^1H NMR interaction.

TABLE VI
^{13}C NMR chemical shifts (δ, ppm) of compounds *II* and *III*

Compound	C-3	C-3a	C-6a	C-4	C-6
IIa[a]	145·75	56·5	81·9	171·2	172·45
IIb[b]	144·7	54·72	82·0	170·0	171·3
IIc[c]	144·8	55·3	81·2	170·4	171·7
IIe[d]	141·8	55·8	81·8	171·0	172·3
IIf[e]	144·7	55·75	81·4	170·2	171·6
IIh[f]	145·3	55·7	83·0	170·8	171·9
IIi[g]	144·8	55·4	81·13	170·5	171·9
IIIa[h]	145·2	55·85	80·9	170·3	171·5
IIIb[i]	143·5	55·15	82·2	169·9	170·8
IIIc[j]	145·06	55·7	81·3	170·5	171·8
IIIf[k]	145·3	56·14	81·6	171·13	172·4
IIIh	145·1	55·2	81·4	170·2	172·1
IIIi[l]	144·7	55·5	82·55	170·1	171·1
IIIj[m]	145·0	55·8	81·3	170·4	171·6

[a] C(furan): 112·75, 116·9, 143·9, 146·6; C(arom.): 127·7, 129·6, 129·8, 133·0; [b] C(furan): 113·7, 118·1, 144·1, 152·25; C(arom).: 126·9, 128·9, 131·5; [c] C(furan): 111·9, 118·38, 143·5, 146·6; C(arom.), 124·46, 124·8, 126·9, 128·8, 128·96, 131·6, 134·7, 153·2; [d] C(furan): 109·6, 118·7, 142·3, 145·2; C(arom.): 129·0, 129·6; [e] C(furan): 110·30, 118·5, 142·7, 148·4; C(arom.): 123·1, 129·0, 129·3, 130·3, 130·7, 131·0, 133·6, 153·0; [f] C(furan): 113·5, 116·5, 145·4; C(arom.): 116·8, 118·4, 129·9, 129·8, 161·5, 164··8; [g] C(furan): 110·43, 116·2, 142·8, 148·5; C(arom).: 123·0, 127·85, 127·89 129·4, 130·18, 130·6, 130·9, 153·1, 160·17, 163·4; [h] 16·4 (CH_3), 17·3 (CH_3); C(furan): 112·2, 116·6, 141·8, 146·5; C(arom.): 128·2, 128·55, 129·4, 129·5, 135·1, 136·4; [i] 16·5 (CH_3), 17·2 (CH_3); C(furan): 113·6, 118·4, 144·9, 152·5; C(arom.): 128·2, 128·5, 129·2, 135·0, 136·4; [j] 16·45 (CH_3), 17·29 (CH_3); C(furan): 111·9, 118·4, 143·2, 146·7; C(arom.): 124·5, 124·9, 126·9, 128·2, 128·5, 128·8, 129·7 134·6, 134·9, 136·4, 140·9, 153·4; [k] 14·7 (CH_3), 15·3 (CH_3), 23·7 and 24·2 (CH_2); C(furan): 112·2, 118·75, 143·4, 146·9; C(arom.): 124·7, 125·2, 127·2, 128·4, 130·2, 134·9, 141·1, 142·5, 153·6; [l] 14·6 (CH_3), 15·2 (CH_3), 16·9 (CH_3), 17·7 (CH_3), 23·2 (CH_2), 23·66 (CH_2); C(furan): 113·7, 113·8, 118·47, 118·54, 143·5, 152·4; C(arom.): 127·1, 127·2, 128·45, 128·7 130·0, 134·9, 136·3, 140·9, 142·2; [m] 14·4 (CH_3), 15·0 (CH_3), 16·6 (CH_3). 17·43 (CH_3), 23·4 (CH_2) 23·9 (CH_2); C(furan): 111·9, 118·4, 118·6, 143·1, 146·6; C(arom): 124·4, 124·9, 126·8, 128·1, 128·4, 129·7, 134·5, 134·9, 136·4, 140·9, 142·2, 153·3.

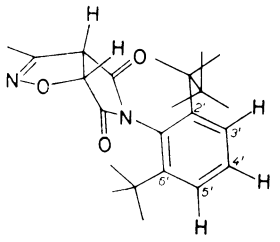
Signals of the model compound *IIIa* were ascribed according to the NOE effect as follows: the singlet at δ 2·14 to the methyl group in a *syn* arrangement toward the bridgehead protons H-3a and H-6a, the singlet at δ 1·75 to the methyl group in an *anti* arrangement. This assignment is in agreement with the shielding effect of H-3a and H-6a protons on the methyl groups. Repulsion of protons of the *syn* arranged methyl group is reflected by the increase of chemical shift values.

TABLE VII

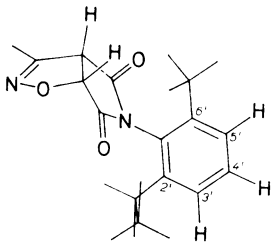
^{1}H NMR chemical shifts (δ, ppm) of compounds *VI* and *VII*

Compound	H-3a	H-6a	CH_3, CH_3 (phenyl)	CH_3, CH_3 (thienyl)	H(arom.)
VIa[a]	5·2	5·71 ((9·0)	1·81 2·07	2·32 2·50	7·04—7·20 (m, 4 H)
VIb[b]	5·40	5·76 (9·0)	1·88 2·02	2·20 2·44	7·06—7·20 (m, 3 H)
VIc[c]	5·35	5·7 (9·1)	1·88 2·02	2·22 2·43	7·05—7·20 (m, 3 H)
VId[d]	5·21	5·77 (9·0)	1·98 2·02	2·32 2·34	7·1—7·22 (m, 3 H)
VII[e]	5·14	5·77 (9·1)	1·97 2·06	—	7·18—7·22 (m, 3 H)

[a] The H-4′ signal overlapped by H(arom.); [b] 2·12 (s, 3 H, CH_3); [c] 1·02 (t, 3 H, CH_3); 2·60 (q, 2 H, CH_2); [d] 1·16 (d, 3 H, CH_3, J = 6 Hz); 1·23 (d, 3 H, CH_3); 2·95—3·05 (m, 1 H, CH); [e] 1·31 (s, 9 H, t-butyl); 1·35 (s, 9 H, t-butyl); 6·97 (s, 1 H, H-4′).



A



B

FIG. 1

Minimal energy conformations calculated employing the MM2 programme

Irradiation of the methyl group in the diastereomer *B* of *IIIk* at δ 2·11 in the NOE experiment resulted in an intensity change of protons H-3a and H-6a; this is an evidence for their *syn* arrangement in respect to the methyl group. This effect could not be encountered with the reverse arrangement. Analogously, singlet of the methyl group at δ 2·49, due to the observed NOE effect at H-3a proton, could be ascribed to the methyl group at C-2 of the furan ring. It could further be deduced that the furan and isoxazoline rings are in an *s-trans* conformation, because only this plane arrangement would allow this effect. The H-3a signal of diastereomer *A* of compound *IIIk* appears only when the methyl group in position C-2 of the furan ring was irradiated at δ 2·41. The methyl group signal from the benzene ring of isomer *B* was observed at higher δ values when compared with signal of the *A* isomer (δ 2·11 and 1·80, respectively). The same phenomenon emerged also with triplets of methyl protons (the *A* and *B* isomers δ 1·02 and 0·82, respectively). Further minimal differences in the ^{1}H and ^{13}C NMR spectra of isomers *A* and *B* were found in the remaining regions of the spectra. Only signals of H-3a and H-6a protons of isomer *A* resonated at lower δ values in comparison with those of the *B* isomer (δ 0·35).

TABLE VIII

^{13}C NMR chemical shifts (δ, ppm) of compounds *VI* and *VII*

Compound	C-3a	C-6a	C-3	C-4 C-6	CH_3(thienyl)	CH_3(phenyl)
VIa[a]	57·88	80·89	150·80	171·05 172·10	14·60 15·66	16·88 17·47
VIb[b]	57·52	80·83	151·02	170·4 172·5	13·66 14·72	17·16 17·39
VIc[c]	57·67	80·91	151·02	170·47 172·2	14·69 14·80	17·28 17·44
VId[d]	58·82	81·10	151·39	170·34 171·20	14·15 14·15	17·28 17·46
VII[e]	59·89	81·53	150·59	170·26 171·56	— —	17·44 17·54

[a] C(arom.) and C(thiophene): 124·28, 127·50, 128·87, 129·02, 130·04, 130·64, 136·19, 136·29, 137·05, 140·53; [b] 12·55 (CH_3), 124·8, 128·79, 129·0, 129·99, 130·08, 131·5, 136·12, 137·05, 138·0; [c] 12·36 (CH_3), 21·18 (CH_2), 124·5, 128·83, 129·02, 130·01, 130·56, 130·59, 136·16, 136·88, 137·94, 139·61; [d] 21·66, 28·69 (isopropyl) 125·2, 128·85, 129·02, 130·01, 130·68, 136·24, 136·67, 136·85, 142·57; [e] 30·98, 32·20, 35·03, 35·26 (t-butyl), 119·34, 124·71, 128·90, 129·04, 130·08, 130·60, 136·36, 136·96, 153·54 158·80.

The H-3a and H-6a protons in compounds *II* and *III* containing a 2,5-dimethyl-3--furyl residue appeared at δ 4·80–5·39 (H-3a) and δ 5·39–5·87 (H-6a), J = 9·2 to 9·6 Hz (Table III). Compounds containing a substituted 2-furyl residue had higher chemical shift values (δ 5·08–5·45 for H-3a and 5·72–6·04 for H-6a, Table V); this is in accordance with the shielding effects of substituents. Similarly, the chemical shift values of compounds *VI* and *VII*, embodying a 2- or 3-thienyl residue are in line with the shielding effects of substituents. Signals for H-3a and H-6a appeared at δ 5·14–5·40 and 5·71–5·77 (J 9·0–9·1 Hz), respectively (Table VII).

The chemical shift values of carbons associated with methyl groups attached to the furan or benzene rings were estimated from the heterocorrelated ^{1}H and ^{13}C NMR spectra. The respective quartets at δ 12·91 and 13·7 of isomer *B* were assigned to methyl groups at C-5 and C-2 of the furan ring; the methyl group bound to the benzene ring was downfield shifted (δ 17·34 for *B* and 16·8 for the *A* isomer).

A considerable antifugal in vivo effect displayed only derivatives *IIg* and *IIId*, not exceeding, however, that of preparations commonly used.

EXPERIMENTAL

The melting points are uncorrected, the ^{1}H and ^{13}C NMR spectra of deuteroacetone or deuterodimethyl sulfoxide solutions containing tetramethylsilane were recorded with a Varian VXR 300 apparatus and are given in ppm on the δ scale. The IR spectra ($\tilde{\nu}$, cm^{-1}) of KBr pellets and the UV spectra of methanolic solutions (λ, nm; ε, m^2 mol^{-1}) were measured with a Specord 71 R (Zeiss, Jena) and M-40 spectrophotometers, respectively; the UV spectra were taken in temperated cells. The reaction course was monitored by thin-layer chromatography on Silufol sheets chloroform being the eluent; detection by UV_{254} light. The products were chromatographically purified on a silica gel-packed column with chloroform or hexane–ethyl acetate (5 : 1) as eluents.

3-(2,5-Dimethyl-3-furyl)-5-(X,Y,Z-phenyl)-4,6-dioxo-3a,4,6,6a-tetrahydropyrrolo[3,4-*d*] isoxazoles *II* and *III*

A solution of 2,5-dimethyl-3-furancarbaldoxime[5] (10 mmol) in dichloromethane (25 ml) was during 1 h added to a stirred mixture consisting of N-arylmaleinimide (10 mmol) in dichloromethane (c. 25 ml), sodium hypochlorite (15 ml, 12%) and triethylamine (0·2 ml) at 0°C. The mixture was stirred at room temperature overnight, the organic layer was separated and the aqueous one was repeatedly extracted with dichloromethane. The combined extracts were dried with sodium sulfate, the solvent was evaporated under reduced pressure and the product was chromatographically purified and crystallized from ethanol.

Applying this procedure also 3-(2,5-dimethyl-4-R-3-thienyl)-5-(2,6-dimethylphenyl)-4,6-dioxo--3a,4,6,6a-tetrahydropyrrolo[3,4-*d*]isoxazoles *VI* and 3-(3,5-di-t-butyl-2-thienyl)-5-(2,6-dimethylphenyl)-4,6-dioxo-3a,4,6,6a-tetrahydropyrrolo[3,4-*d*]isoxazoles *VII* were obtained.

3-(5-X-2-Furyl)-5-(X,Y,Z-phenyl)-4,6-dioxo-3a,4,6,6a--tetrahydropyrrolo[3,4-*d*]isoxazoles *II* and *III*

Triethylamine (2 ml) in ether (30 ml) was dropped into a stirred solution of the appropriate furancarbohydroximoyl chloride[2,3] (10 mmol) and N-arylmaleinimide (10 mmol) dissolved in

ether at −15°C. The mixture was then stirred at −10°C for 1 h, the mixture was left at room temperature overnight, the product was chromatographically purified through a silica gel column and crystallized from ethanol.

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