PREPARATION AND REACTIONS OF 2-AMINO-3-CYANO-4,5-BIS(3,4-METHYLENEDIOXYBENZYL)FURAN

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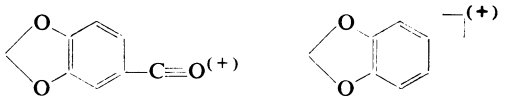
Treatment of 2-hydroxy-1,4-bis(3,4-methylenedioxyphenyl)-3-butenone with propanedinitrile (*I*) catalyzed by diethylamine afforded 2-amino-3-cyano-4,5-bis(methylenedioxybenzyl)furan (*II*). The latter reacted with formamide to 4-amino-5,6-bis-(3,4-methylenedioxybenzyl)furo[2,3-*b*]-pyrimidine (*III*), and with aldehydes to the corresponding azomethines *IVa*—*IVe*. The structure of products was adduced from spectral (IR, UV, ^{1}H NMR, and mass) data. The inhibition of incorporation of [U^{14}C]-adenine and [U^{14}C]-L-valine for DNK synthesis and proteosynthesis of leukemia P-388 cells was tested with derivatives *II* and *III*.

The *o*-amino-cyano derivatives are usualy starting compounds for various syntheses[1,2], although also their biological activity has been reported[3-5]. One of the synthetic routes leading to those products employs the reaction of acyloins with propanedinitrile to furnish directly 2-amino-3-cyano-4,5-disubstituted furan derivatives[6,7]. We used this method for preparation of aminofuran derivatives[7-9]; another paper[10] concerns the mechanism of their formation.

This paper was aimed to synthesize 2-amino-3-cyano-4,5-bis(3,4-methylenedioxybenzyl)furan (*II*) needed for preparation of 4-amino-5,6-bis(3,4-methylenedioxybenzyl)furo[2,3-*b*]pyrimidine (*III*) or the corresponding azomethines *IVa*—*IVe*. As known, *e.g.*[3,11], analogous derivatives are biologically active. Therefore, derivatives *II* and *III* were tested on leukemia cells P-388 to ascertain their inhibition effect on DNK synthesis and proteosynthesis.

Aminofuran *II* was prepared as an analogue of our, already reported[7-10] 2-amino-3-cyano-4,5-disubstituted furan. The IR spectrum of *II* revealed typical bands of a NH_2 group (ν_{max} 3 420, 3 324, 3 258, 3 208, 1 660 cm^{-1}) and of a CN group (ν_{max} 2 220 cm^{-1}), this being in line with the IR values of analogous derivatives[7]. The UV spectrum showed four absorption bands of which the λ_{max} value of the last one at 333 nm (log ε = 4·23) is indicative of a conjugation of NH_2 and CN groups through the furan ring. This is in agreement with the hypothesis[12] rationalizing the stability of these derivatives considering this conjugation effect. This conjugation was also seen on the magnitude of the amino group chemical shift in the ^{1}H NMR spectrum. The value $\delta(NH_2)$ = 7·49 ppm indicated, when compared with analogous

aminofurans[13,14], a delocalization of *p* electrons of the amino group. The mass spectrum of *II* displayed the peak of molecular radical ion (100%), and other peaks at *m/z* 149 (*a*) and 121 (*b*). The fragmentation pattern followed that of 2-amino--3-cyano-4,5-diphenylfuran[7].



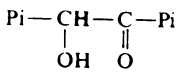
a *b*

Aminofuran *II* reacted with formamide to form 4-amino-5,6-bis(3,4-methylene dioxybenzyl)furo[2,3-*b*]pyrimidine (*III*) in a 87% yield (Scheme 1). Preparation of these substances is described in the literature first of all from the biological activity standpoint[3,15–19]. The IR spectrum of *III* revealed, in addition to other bands, absorption diagnostic of NH_2 group (ν_{max} 3 461, 3 380, 3 288, 1 650 cm^{-1}). The UV spectrum contained five absorption bands at λ_{max} 207, 261, 298, 328, 340 nm. The ^1H NMR spectrum had characteristic chemical shifts $\delta(CH_2)$ = 5·97 ppm (s), $\delta(CH_2)$ = 6·07 ppm (s) and $\delta(H_{pyrimidine})$ = 8·16 ppm (s). The chemical shift value of the pyrimidine proton is in good accordance with the data reported[7,20]. The most intense peak (100%) in the mass spectrum of *III* belonged to the molecular ion radical. In contrast to mass spectrum of *II*, that of *III* did not contain the typical *m/z* 149 fragment; peak at *m/z* 121 (10%) characterizes the presence of piperonyle substituent.

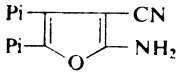
Inhibition effect of compounds *II* and *III* upon leukemia P-388 cells[21] was found to be for [U ^{14}C]-L-valine and [U ^{14}C]-adenine 90·0% and 62·1%, respectively, for compound *II*, and 32·3% and 5·5% for compound *III*. The inhibition of incorporation value of [U ^{14}C]-valine for derivative *II* is relatively high and well comparable with that of 2-amino-3-cyano-4,5-diphenylfuran (94·2%, ref.[22]).

Azomethines *IVa–IVe* were obtained by reacting *II* with aldehydes in 48–83% yield (Table I). Azomethines often serve as starting substances for synthetic purposes[13,23–26]; their ^1H and ^{13}C NMR data were reported[27,28]. The IR spectral data of *IVa–IVe* are listed in Table II; the ν_{max} value for azomethine grouping is in a good agreement with that already published[29,30]. The UV spectra of *IVa–IVe* (Table II) were measured in methanol or chloroform solutions, spectrum of 4-nitrophenyl derivative *IVb* was alternatively recorded in dioxane. The λ_{max} values of the longest wave-band are influenced *inter alia* by the solvent, *e.g.* azomethine *IVd* had λ_{max} = 450 nm in methanol and 500 nm in chloroform. Similarly, a long-lasting heating of this compound resulted in a wavelength shift from λ_{max} = 450 nm to λ_{max} = 475 nm. This shift is likely associated with the transition from the *s-cis* to *s-trans* configuration. Substituent effect in position 4 and 5 upon the value of the longest-wave-band for chromonyl derivative *IVe* and its analogues *V–VII* (ref.[7])

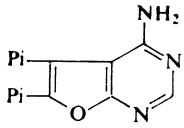
was studied (Table III). As it follows from the λ_{max} data, the greatest increment to conjugation of the whole molecule imposes the 3,4-methylenedioxybenzyl substituent and makes *e.g.* 63 nm when compared with the phenyl derivative. The UV spectra of azomethines are analyzed in detail in[31].



I

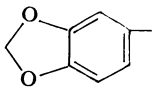


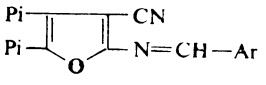
II



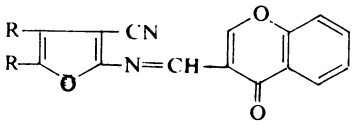
III

where Pi =





IVa, R = C_6H_5—CH=CH—
IVb, R = 4-$NO_2C_6H_4$—
IVc, R = 2-furyl
IVd, R = 5-nitro-2-furyl
IVe, R = 3-chromonyl



V, R = C_6H_5
VI, R = 2-furyl
VII, R = 2-thienyl

TABLE I
Azomethines *IV*

Azomethine Ar	Formula (M_r)	M.p., °C (yield, %)	Calculated/Found		
			% C	% H	% N
IVa	$C_{28}H_{18}N_2O_5$	218	72·36	3·97	6·14
Phenylvinyl-	(456·4)	(73)	72·21	3·93	6·20
IVb	$C_{26}H_{15}N_3O_7$	245—248	64·86	3·24	8·73
4-Nitrophenyl-	(481·4)	(65)	64·65	3·10	8·68
IVc	$C_{24}H_{14}N_2O_6$	174—180	67·60	3·31	6·57
2-Furyl-	(426·4)	(48)	67·58	3·30	6·55
IVd	$C_{24}H_{13}N_3O_8$	125	61·15	2·78	8·91
5-Nitro-2-furyl-	(471·4)	(67)	61·20	2·79	8·88
IVe	$C_{29}H_{16}N_2O_7$	290	69·04	3·19	5·55
3-Chromonyl-	(504·4)	(83)	69·12	3·21	5·60

TABLE II

IR and UV spectral data of azomethines *IV*

Azomethine	IR spectrum[a], ν_{max}, cm^{-1}	UV spectrum, λ_{max}, nm, (log ε)	
		methanol	chloroform
IVa	2 891, 2 232, 1 668, 1 620, 1 543, 1 501, 1 475, 1 448, 1 235, 1 163, 1 038, 982, 820	212 (4·60) 247 (4·28) 300 (4·46) 323 (4·49) 435 (4·39)	306 (4·43) 327 (4·47) 444 (4·37)
IVb	3 187, 2 860, 2 220, 1 703, 1 602, 1 501, 1 477, 1 448, 1 387, 1 339, 1 242, 1 194, 1 101, 1 038, 1 005, 979, 940, 852, 821	213 222 265 269 333 322 455[b] 462[c]	267 (4·52) 305 (4·26) 365 (4·06)
IVc	3 113, 2 995, 2 232, 1 610, 1 585, 1 559, 1 508, 1 483, 1 450, 1 242, 1 105, 1 043, 940, 818	212 (4·56) 236 (4·30) 294 (4·31) 318 (4·38) 420 (4·28)	302 (4·28) 324 (4·35) 432 (4·25)
IVd	3 128, 2 908, 2 237, 1 696, 1 540, 1 510, 1 473, 1 350, 1 330, 1 245, 1 168, 1 101, 1 045, 1 028, 973, 265, 935, 820	212 (4·59) 249 (4·20) 311 (4·45) 450 (4·14)[d]	307 (4·48) 357 (4·21) 500 (4·28)
IVe	2 972, 2 905, 2 848, 2 232, 1 658, 1 620, 1 548, 1 506, 1 480, 1 462, 1 332, 1 310, 1 240, 1 105, 1 046, 936, 872, 818	215 (4·69) 257 (4·32) 324 (4·36) 474 (4·49)	303 (4·43) 320 (4·42) 433 (4·26)

[a] In KBr; [b] saturated solution; [c] saturated dioxane solution; [d] λ_{max} shifted to 475 nm after a longer heating.

TABLE III

Difference between the long-wave λ_{max} bands of azomethine *IVe* and azomethine derivatives

Compound	λ_{max}, nm, methanol (log ε)	$\Delta\lambda_{max}$, nm
IVe	474 (4·49)	0
V	411 (4·34)	63
VI	420 (4·10)	54
VII	418 (4·07)	56

EXPERIMENTAL

Melting points were measured on a Kofler hot-stage, the ^{1}H NMR spectra of hexadeuteriodimethyl sulfoxide solution were taken with a Tesla BS 487 B apparatus operating at 80 MHz; internal reference hexamethyldisiloxane, 25°C. The IR and UV spectra were recorded with UR-20 and Specord UV-VIS (Zeiss, Jena) apparatuses, respectively, and the mass spectra with AEI MS 902 S instrument. 2-Hydroxy-1,4-bis(3,4-methylenedioxybenzyl)-3-butanone (*I*) was prepared *via* benzoin condensation of 3,4-methylenedioxybenzaldehyde analogously as benzoin[32]. Compound *II* and *III* (concentration 100 μg/ml in dimethyl sulfoxide) were biologically tested according to[21].

2-Amino-3-cyano-4,5-bis(3,4-methylenedioxybenzyl)furan (*II*)

Diethylamine (2·2 ml) was added to a stirred solution of *I* (12 g, 40 mmol) and propanedinitrile (4·1 g, 62 mmol) in dimethylformamide at 25°C. The solution was poured after 24 h onto crushed ice, the precipitate was filtered off and crystallized from ethanol. Yield 8·1 g (58%), m.p. 240°C. For $C_{19}H_{12}N_2O_5$ (348·3) calculated: 65·61% C, 3·47% H, 8·04% N; found: 65·29% C, 3·41% H, 8·12% N. IR spectrum (KBr), ν_{max}, cm^{-1}: 3 420, 3 324, 3 258, 3 208, 1 660 (NH_2), 2 220 (CN), 1 048 (C—O—C), 1 591, 1 505, 1 243. UV spectrum (methanol), λ_{max}, nm (log ε): 207 (4·69), 256 (4·21), 293 (4·17), 333 (4·23). ^{1}H NMR spectrum (hexadeuteriodimethyl sulfoxide), δ, ppm: 5·92 (2 H, s, CH_2), 6·02 (2 H, s, CH_2), 6·65—6·89 (6 H, m, H_{arom}), 7·49 (2 H, s, NH_2). Mass spectrum, *m/z* (rel. intensity, %): 349 (25), 348 (100) $M^{+\cdot}$, 304 (27), 263 (9), 188 (12), 150 (10), 149 (73), 135 (8), 123 (8), 122 (10), 121 (11), 109 (10), 105 (10), 97 (13), 95 (15), 94 (10), 93 (9), 91 (9), 85 (11), 83 (16), 81 (17), 77 (11), 73 (11), 71 (18), 70 (11), 69 (23), 67 (14), 65 (10), 60 (11), 58 (8), 57 (41), 56 (21), 55 (33), 45 (9), 44 (43), 43 (42), 42 (14), 41 (43), 39 (21).

4-Amino-5,6-bis(3,4-methylenedioxybenzyl)furo[2,3-*b*]pyrimidine (*III*) (ref.[33])

Solution of *II* (0·8 g, 2·3 mmol) in formamide (15 ml) was refluxed for 30 min cooled and poured into water. The precipitate was filtered off and crystallized from ethanol. Yield 0·75 g (87%), m.p. 272°C. For $C_{20}H_{13}N_3O_5$ (375·3) calculated: 64·00% C, 3·49% H, 11·19% N; found: 64·21% C, 3·51% H, 11·10% N. IR spectrum (KBr), ν_{max}, cm^{-1}: 3 461, 3·380, 3 288, 1 650 (NH_2), 1 040 (C—O—C), 2 900, 1 592, 1 503, 1 480, 1 448, 1 240, 1 230, 987, 933. UV spectrum (methanol) λ_{max}, nm (log ε): 207 (4·79), 261 (4·04), 298 (4·36), 328 (4·54), 340 (4·41). ^{1}H NMR spectrum (hexadeuteriodimethyl sulfoxide), δ, ppm: 5·97 (2 H, s, CH_2), 6·07 (2 H, s, CH_2), 6·79—6·99 (6 H, m, H_{arom}), 8·16 (1 H, s, H-flyrimidine), NH_2 overlapped by phenyl protons. Mass spectrum, *m/z* (rel. intensity, %): 377 (5), 376 (38), 375 (100) $M^{+\cdot}$, 374 (47), 344 (10), 316 (9), 314 (6), 304 (6), 289 (5), 191 (6), 190 (5), 177 (7), 176 (5), 167 (6), 165 (6), 163 (6), 151 (8), 150 (12), 148 (6), 135 (6), 128 (30), 127 (15), 123 (9), 122 (9), 121 (10), 119 (6), 115 (6), 111 (8), 110 (6), 109 (10), 105 (11), 104 (6), 97 (12), 96 (8), 95 (13), 94 (8), 93 (9), 91 (9), 88 (8), 87 (9), 85 (12), 84 (7), 83 (15), 82 (8), 81 (15), 79 (6), 78 (11), 76 (8), 75 (7), 74 (7), 73 (15), 71 (25), 70 (12), 69 (25), 68 (6), 67 (13), 65 (11), 63 (9), 60 (15), 58 (7), 57 (41), 56 (19), 55 (36), 53 (8), 51 (8), 50 (8), 45 (38), 44 (47), 43 (44), 42 (12), 41 (44), 39 (19).

Azomethines *IVa—IVe*

Solution of *II* (0·348 g 1 mmol) and of an appropriate aldehyde (1 mmol) in ethanol (30 ml) was refluxed for 2—4 h, the solvent was removed and the residue was separated on an alumina (Brockmann II) column with benzene–acetone (1 : 1) as eluent. The orange coloured fractions worked up in a usual way afforded azomethines *IVa—IVe* in 48—83% yields (Table I).

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