A NEW APPROACH TO 5*H*-PYRANO[2,3-*d*]PYRIMIDINE DERIVATIVES

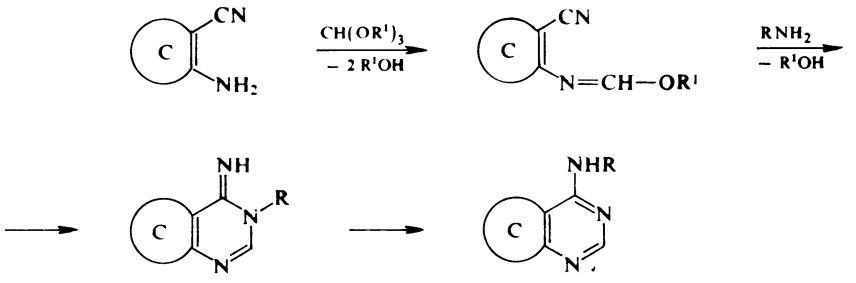
Štefan MARCHALÍN and Josef KUTHAN

Department of Organic Chemistry,
Prague Institute of Chemical Technology, 166 28 Prague 6

Received December 14th, 1983

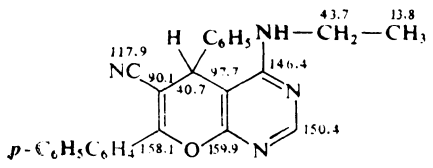
Reaction of 2-amino-3,5-dicyano-4*H*-pyran derivative *I* with triethoxymethane gives the corresponding 2-ethoxymethyleneamino derivative *II* which reacts with amines RNH_2 to give 5*H*-pyrano[2,3-*d*]pyrimidines of general formula *III*. Spectral characteristics of compounds *IIIa*–*IIIg* are discussed.

Pyrimidines with a condensed 2*H*- and 4*H*-pyran nucleus belong to little known heterocycles. So far only the derivatives with 4*H*-pyran cycle have been prepared, *viz.* from barbituric acid or its 1,3-disubstituted derivatives and tetracyanoethylene[1], from 1,3-diphenyl-2-propen-1-one[2], arylidenemalonitriles[3], from formaldehyde and 1-bromo-2-phenylacetylene[4], from aldehydes and phenylacetylene[4], and by cyclization of 5-(3-phenylpropargyl)barbituric acid[5]. These syntheses produce the 4*H*-pyran ring by condensation to the starting pyrimidine ring. There exists, however, also the opposite synthetic approach consisting in synthetic condensation of the pyrimidine ring to the starting 4*H*-pyran ring. It is known[6-8] that syntheses of this type can advantageously use homocyclic and heterocyclic *o*-enaminonitriles which give 4-aminopyrimidine derivatives according to Scheme 1. The present communication deals with the first application of this approach, where C means 4*H*-pyran nucleus, which makes use of the available[9] starting compound *I*. Condensation of this 4*H*-pyran *I* with triethoxymethane gave 6-(4-biphenylyl)-2-ethoxymethyleneamino-4-phenyl-3,5-

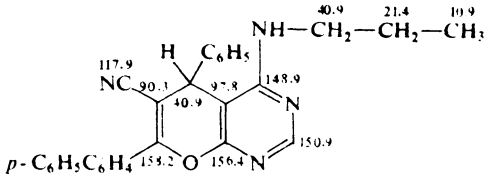


SCHEME 1

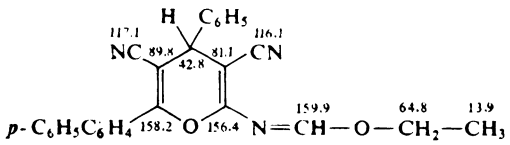
-dicyano-4*H*-pyran (*II*) which reacted with primary amines RNH_2 in ethanol or tetrahydrofurane to give 5*H*-pyrano[2,3-*d*]pyrimidines *IIIa*–*IIIf* in the yields of 39–96%. The reaction is slightly exothermic, and the less soluble products *III* are separated within few minutes. Application of hydrazine gave the compound *IIIg* which contains the hydrazine residue at 4 position. It is noteworthy that yields and melting points of the pyranopyrimidines *IIIa*–*IIIf* decrease with magnitude of the substituent R. We suppose that the mechanism of formation of the 5*H*-pyrano[2,3-*d*]pyrimidines *III* is analogous to that of pyrazole[6] and oxazole derivatives[7] (see Scheme 1), where it was possible to trap the intermediates of the type *IV*. Structure of the compounds *IIIa*–*IIIg* was verified by means of IR and NMR spectral characteristics. The ^{13}C-NMR spectra of compounds *II*, *IIIc*, and *IIId* exhibit the signals characteristic of a heterocyclic skeleton (Scheme 2) and signals of phenyl atoms in the region



IIIc



IIId

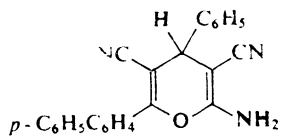


II

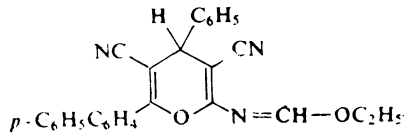
SCHEME 2

of 127·3–144·9δ which could not be resolved. The chemical shifts were assigned with the help of the published ^{13}C NMR spectra of 4*H*-pyran *I* (ref.[9]) and 2,6-diphenyl-3,5-dicyano-4-(N,N-dimethylformamidino)-4*H*-pyran[10] and by application of the APT technique. If the compounds *III* had open amidine structures, they should possess the ^{13}C NMR spectra with signals of two CN groups, as it is the case with the ethoxymethyleneamino derivative *II*, but such spectra were not observed with the compounds *IIIc* and *IIId*. The signal at 146·4δ (*IIIc*) and 148·9δ (*IIId*) corresponding to the quaternary carbon atom was assigned to the $C_{(4)}$ atom formed by the cyclization of the primary amidine. The ^1H NMR spectra of all the pyrano[2,3-*d*]pyrimidines *IIIc*–*IIIf* contain the signals of the methylene group of R substituent attached to the nitrogen atom in the form of multiplets of higher order. This fact indicates

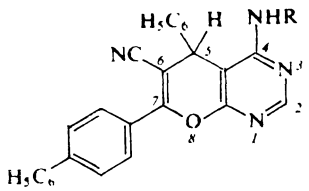
a relatively strong interaction between the protons of the methylene group with the NH proton, which would not be observable in the alternative structure *IV*, which agrees with exclusive or predominant structure of the compounds *III*. The said presumption was confirmed by measuring the ^{1}H NMR spectrum of the N-benzyl derivative *IIIf* in the presence of ^2H_2O. By elimination of the interaction of NH proton, the multiplet of methylene group of the R substituent is simplified to two doublets of the AA'XX' type located at 4·38δ and 4·66δ with the geminal coupling constant $^2J_{HH}$ = 15·0 Hz. The asymmetry of the splitting of the doublets of magnetically non-equivalent protons of the CH_2 group of benzyl group and simultaneous presence of the singlet of the H—$C_{(2)}$ proton at 8·33δ are probably due to specific non-periplanar conformation of the molecule at the N—CH_2 bond. The absorption band ν(N—H) in the IR spectra of the compounds *IIIb*–*IIIf* was also found in the region

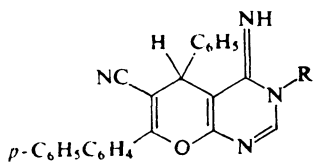


I



II





IV

IIIa, R = H
IIIb, R = CH_3
IIIc, R = C_2H_5
IIId, R = *n*-C_3H_7
IIIe, R = *n*-C_4H_9
IIIf, R = $CH_2C_6H_5$
IIIg, R = NH_2

typical for secondary amino group (Table I). Typical for the heterocyclic skeleton of the compounds *III* are the values of the proton H—$C_{(5)}$ shift at 4·46–4·75δ and the absorption band of the coupled ν(C=C) at 1 640–1 680 cm^{-1} (Table I). The 5*H*-pyrano[2,3-*d*]pyrimidine chromophore is manifested in the UV spectra of compounds *IIIb*–*IIIg* by three characteristic absorption maxima at 247 nm (log ε 4·26 –4·39), 258–271 nm (log ε 4·31–4·36), and 297–299 nm (log ε 4·33–4·37).

Unsuccessful were the experiments which applied in the said transformations the precursor type *I* with the 3-CN group replaced by 3-$COOCH_3$ group: the failure was due to inertness of this compound to triethoxymethane.

TABLE I

UV, IR, and ^{1}H NMR spectral characteristics of the 5*H*-pyrano[2,3-*d*]pyrimidines *IIIa*–*IIIg*

Compound	UV spectrum[a]		IR spectrum ($CHCl_3$)[b], cm^{-1}					^{1}H NMR spectrum (C^2HCl_3,35°C)[c]
	λ_{max}, nm	log ε	ν(N—H)	ν(=C—H)	ν(C≡N)	ν(C=C)[d] and ν(C=N)[d]		δ, ppm
IIIa	259	4·32	3 362 w	3 040 w	2 207 s	1 680 s	1 655 s	4·52 (s, 1 H, H—C(5)), 7·24–7·93 (m,
	290	4·40	3 160 w[e]			1 603 m	1 572 m	15 H, H_{arom}), 8·20 (br. s, 2 H, NH_2)
IIIb	246	4·28	3 348 w	3 010 m	2 218 w	1 658 s	1 577 m	3·37 (s, 3 H, CH_3), 4·49 (s,1 H,
	264	4·31				1 619 m		H—C(5)), 7·30–8·00 (m, 16 H,
	299	4·35						H_{arom} and NH)
IIIc	247	4·28	3 340 w	3 020 m	2 216 w	1 660 s	1 612 m	1·33 (t, 3 H, CH_3), 3·89 (m, 2 H, CH_2),
	265	4·32				1 619 m	1 577 m	4·46 (s, 1 H, H—C(5)), 7·22–8·00
	299	4·34						(m, 16 H, H_{arom} and NH)
IIId	247	4·29	3 348 w	3 018 m	2 218 m	1 660 s	1 610 m	0·94 (t, 3 H, CH_3), 1·74 (m, 2 H,
	265	4·33				1 619 m	1 575 m	CH_2), 3·78 (m, 2 H, CH_2N), 4·47
	299	4·36						(s, 1 H, H—C(5)), 7·24–8·04 (m,
								16 H, H_{arom} and NH)
IIIe	247	4·29	3 342 w	3 010 m	2 214 m	1 660 s	1 610 m	0·93 (t, 3 H, CH_3), 1·31 (m, 2 H,
	265	4·33				1 619 m	1 575 m	CH_2CH_3), 1·70 (m, 2 H, CH_2), 3·81
	298	4·35						(m, 2 H, CH_2N), 4·47 (s, 1 H,
								H—C(5)), 7·27–8·07 (m, 16 H,
								H_{arom} and NH)
IIIf	247	4·39	3 445 m	3 070 w	2 214 m	1 640 s	1 578 s	4·22–4·88 (m, 2 H, CH_2), 4·52 (s,
	258	4·36		3 014 m		1 600 i	1 506 s	1 H, H—C(5)), 6·79 (m, 2 H, H_{ortho}),
	297	4·37						7·10–8·04 (m, 18 H, H_{arom} and
								NH), 8·33 (s, 1 H, H—C(2))
IIIg	246	4·26	3 340 m	3 080 w	2 205 s	1 652 s	1 590 w	4·75 (s, 1 H, H—C(5)), 5·54 (br. s, 2 H,
	271	4·35	3 320 m	3 024 w		1 606 s	1 570 s	NH_2), 7·13–7·85 (m, 15 H, H_{arom}),
	298	4·33						8·04 (s, 1 H, NH)

[a] Ethanol, *c* 4 . 10^{-5} mol l^{-1}; [b] the compounds *IIIa* and *IIIg* were measured in KBr disc; [c] the compounds *IIIa* and *IIIg* were measured in hexadeuteriodimethyl sulphoxide; [d] the pyranopyrimidine skeleton; [e] 3 475 w (O—H), see Experimental.

EXPERIMENTAL

The temperature data are not corrected. The melting points were determined with a Boetius apparatus. The spectral characteristics were measured with a Perkin–Elmer 325 apparatus (IR), a Carl Zeiss Specord UV VIS (UV), a Varian XL-100 (^{1}H NMR), and a Tesla BS 567 (^{13}C NMR). The thermogravimetric measurements were carried with a Stanton Redcroft TG 750 apparatus. The NMR spectra were measured with tetramethylsilane as the internal standard.

6-(4-Biphenylyl)-2-ethoxymethyleneamino-4-phenyl-3,5-dicyano-5*H*-pyran (*II*)

A mixture of 4·5 g 2-amino-3,5-dicyano-4*H*-pyran[9] *I* and 10 ml triethoxymethane was boiled 5 h. The solution formed was left to stand 24 h, whereupon it separated a precipitate, which was collected by suction, washed with ethanol, and recrystallized from ethanol. Yield 4·2 g (81%), m.p. 164–166°C. For $C_{28}H_{21}N_3O_2$ (431·5) calculated: 77·93% C, 4·92% H, 9·74% N; found: 77·99% C, 5·09% H, 10·19% N. IR spectrum ($CHCl_3$), $\tilde{\nu}_{max}$ (cm^{-1}): 3 020 w (=C—H), 2 222 m (C≡N), 1 670 s, 1 622 s (the pyrane skeleton). ^{1}H NMR spectrum (C^2HCl_3), δ (ppm): 1·36 (t, 3 H, CH_3), 4·39 (q, 2 H, OCH_2), 4·42 (s, 1 H, H—$C_{(4)}$), 7·22–7·89 (m, 14 H, H_{arom}), 8·26 (s, 1 H, N=CH). UV spectrum (ethanol): λ_{max} 255 nm (log ε 4·37), 267 sh (log ε 4·38), 288 (log ε 4·44).

4-Amino-7-(4-biphenylyl)-5-phenyl-6-cyano-5*H*-pyrano[2,3-*d*]pyrimidine (*IIIa*)

A suspension of 0·6 g 2-ethoxymethyleneamino-3,5-dicyano-4*H*-pyran *II* in 10 ml ethanolic amonia (17%) was stirred at room temperature 4 h, a precipitate being formed after first 5 min already. The separated solid *IIIa* was collected by suction, washed with little water, with ethanol, and recrystallized from acetone or benzene. Yield 0·45 g (80%), m.p. 269–271°C (decomp.). For $C_{26}H_{18}N_4O.\frac{1}{2}H_2O$ (411·5) calculated: 75·88% C, 4·66% H, 13·62% N; found: 75·90% C, 4·62% H, 13·54% N. The compound *IIIa* crystallizes as semihydrate, which was confirmed by thermogravimetry. The TG curve obtained shows a mass decrease in the temperature interval of 169–271°C corresponding to splitting off of one water molecule from two molecules of *IIIa*.

7-(4-Biphenylyl)-5-phenyl-6-cyano-4-methylamino-5*H*-pyrano[2,3-*d*]pyrimidine (*IIIb*)

This compound was prepared from 4*H*-pyran *II* and aqueous solution of methylamine (35%) in similar way as *IIIa* in the yield 96%, m.p. 275–277°C (benzene–ethanol). For $C_{27}H_{20}N_4O$ (416·5) calculated: 77·85% C, 4·85% H, 13·45% N; found: 78·14% C, 4·96% H, 13·57% N.

7-(4-Biphenylyl)-4-ethylamino-5-phenyl-6-cyano-5*H*-pyrano[2,3-*d*]pyrimidine (*IIIc*)

This compound was prepared from *II* and aqueous solution of ethylamine (45%) in tetrahydrofurane in similar way as *IIIa* in the yield 93%, m.p. 256–258°C (benzene). For $C_{28}H_{22}N_4O$ (430·5) calculated: 78·11% C, 5·16% H, 13·02% N; found: 77·92% C, 5·36% H, 12·96% N.

7-(4-Biphenylyl)-5-phenyl-6-cyano-4-n-propylamino-5*H*-pyrano[2,3-*d*]pyrimidine (*IIId*)

Solution of 0·15 g n-propylamine in 1 ml tetrahydrofurane was added at once to a solution of 0·43 g 4*H*-pyran *II* in 2 ml tetrahydrofurane. The mixture was left to stand 12 h, the separated solid was collected by suction, and the filtrate was poured in 50 ml saturated solution of sodium hydrogen carbonate to give the second portion of the solid product. The combined products *IIId* were washed with little water, with ethanol, and recrystallized from a 1 : 1 acetone–ethanol mixture. Yield 0·4 g (90%), m.p. 191–193°C. For $C_{29}H_{24}N_4O$ (444·6) calculated: 78·34% C, 5·45% H, 12·61% N; found: 78·35% C, 5·74% H, 12·91% N.

7-(4-Biphenylyl)-4-n-butylamino-5-phenyl-6-cyano-4*H*-pyrano[2,3-*d*]pyrimidine (*IIIe*)

This compound was obtained from *II* and n-butylamine in similar way as *IIId* in the yield 39%, m.p. 185–187°C (ethanol). For $C_{30}H_{26}N_4O$ (458·6) calculated: 78·57% C, 5·73% H, 12·22% N; found: 78·33% C, 5·77% H, 12·43% N.

4-Benzylamino-7-(4-biphenyl)-5-phenyl-6-cyano-5*H*-pyrano[2,3-*d*]pyrimidine (*IIIf*)

A mixture of 0·43 g 4*H*-pyran *II* and 0·2 g benzylamine in 4 ml tetrahydrofurane was stirred 4 h. The solvent was distilled off at reduced pressure, and the raw oily product was dissolved in warm ethanol. The solution was cooled with solid carbon dioxide to give a yellow precipitate which was collected by suction and recrystallized from a 1 : 1 benzene–ethanol mixture. Yield 0·2 g (41%), m.p. 205–207°C. For $C_{33}H_{24}N_4O$ (492·6) calculated: 80·46% C, 4·92% H, 11·38% N; found: 80·34% C, 4·99% H, 11·40% N.

7-(4-Biphenylyl)-5-phenyl-4-hydrazino-6-cyano-5*H*-pyrano[2,3-*d*]pyrimidine (*IIIg*)

This compound was prepared from *II* and hydrazine hydrate (85%) in ethanol in similar way as *IIIa* in the yield of 81%, m.p. 204–206°C (decomp.), recrystallization from acetone. For $C_{26}H_{19}N_5O$ (417·5) calculated: 74·79% C, 4·60% H, 16·78% N; found: 74·66% C, 4·98% H, 16·70% N.

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Translated by J. Panchartek.