SYNTHESIS AND REACTIONS OF NOVEL 1,3-DIPYRIDINYL-1,3--PROPANEDIONES*

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Claisen condensation leading to new 1,3-dipyridinyl-1,3-propanediones *Id*—*If* is described. The series of 3,5-dipyridinylpyrazoles *IIa*—*IIf* was completed and N-phenyl derivatives *IIg*—*IIi*, as well as isoxazoles *IIIa* and *IIIb*, were prepared.

Many β-diketones represent valuable intermediates for the synthesis of heterocyclic compounds. This also applies to 1,3-dipyridinyl-1,3-propanediones of which only the "symmetric" compounds *Ia*—*Ic* are known so far[1-3].

In the present communication we describe the preparation and reactions of "unsymmetric" 1,3-dipyridinyl-1,3-propanediones, i.e. 1-(2-pyridinyl)-3-(3-pyridinyl)--1,3-propanedione (*Id*), 1-(2-pyridinyl)-3-(4-pyridinyl)-1,3-propanedione (*Ie*) and 1-(3-pyridinyl)-3-(4-pyridinyl)-1,3-propanedione (*If*). We obtained these β-diketones by Claisen condensation of acetylpyridines with ethyl pyridinecarboxylates in the presence of potassium tert-butoxide. In this manner we prepared the diketone *Id* from ethyl 2-pyridinecarboxylate and 3-acetylpyridine or from ethyl 3-pyridinecarboxylate and 2-acetylpyridine, the diketone *Ie* from ethyl 2-pyridinecarboxylate and 4-acetylpyridine and the diketone *If* from 3-acetylpyridine and ethyl 4-pyridinecarboxylate.

The prepared β-diketones are stable crystalline compounds which, according to ^{1}H NMR spectra, are fully enolized.

We tried to prepare 3,5-dipyridinylpyrazoles and their 1-phenyl derivatives by condensation of β-diketones *Id*—*If* with hydrazine or phenylhydrazine. Pyrazoles *IIb* (ref.[4]), *IIIc* (ref.[3]) and their 1-phenyl derivatives[4] are already known. Also described is pyrazole *IIe*, obtained by reaction of hydrazine with 1-(2-pyridinyl)-3-(4--pyridinyl)-2-propen-1-one[5]. With the exception of unsuccessful condensation of phenylhydrazine with the diketone *If*, we obtained pyrazole derivatives *IIa*, *IId*, *IIe*, *IIg*—*IIi*. The structure of the derivatives *IIh* and *IIi* was determined on the basis

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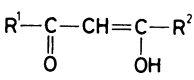
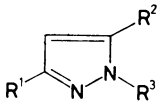
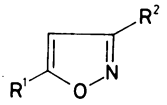
of 2D homocorrelated ^{1}H NMR spectra (COSY); the reaction gives that isomer in which the carbon atom bearing the 2-pyridinyl moiety is more distant from the phenyl-substituted pyrazole nitrogen. It seems that repulsion between the lone electron pair on the 2-pyridyl nitrogen atom and the π-electrons of the benzene ring is decisive.



I



II



III a, $R^1 = R^2 =$ 2-Py
III b, $R^1 = R^2 =$ 3-Py
III c, $R^1 =$ 2-Py ; $R^2 =$ 4-Py
III d, $R^1 =$ 4-Py ; $R^2 =$ 2-Py

In formulae *I* and *II*:
a, $R^1 = R^2 =$ 2-Py ; $R^3 =$ H
b, $R^1 = R^2 =$ 3-Py ; $R^3 =$ H
c, $R^1 = R^2 =$ 4-Py ; $R^3 =$ H
d, $R^1 =$ 2-Py ; $R^2 =$ 3-Py ; $R^3 =$ H
e, $R^1 =$ 2-Py ; $R^2 =$ 4-Py ; $R^3 =$ H
f, $R^1 =$ 3-Py ; $R^2 =$ 4-Py ; $R^3 =$ H
g, $R^1 = R^2 =$ 2-Py ; $R^3 =$ Ph
h, $R^1 =$ 2-Py ; $R^2 =$ 3-Py ; $R^3 =$ Ph
i, $R^1 =$ 2-Py ; $R^2 =$ 4-Py ; $R^3 =$ Ph

Py = pyridinyl ; Ph = phenyl

Finally, we tried to synthesize the hitherto undescribed 3,5-dipyridinylisoxazoles by condensation of diketones *Ia–If* with hydroxylamine. We obtained only isoxazoles *IIIa* and *IIIb*; the diketone *Ie* afforded a product which according to ^{1}H NMR spectrum was a mixture of isomeric isoxazoles *IIIc* and *IIId* and resisted to separation attempts. Reaction of diketones *Ia–Ic* with hydroxylamine in boiling pyridine is reported[6] to give the corresponding dioximes. As shown by TLC of the reaction mixtures, the dioximes were formed also in our experiments but we were able to isolate the isoxazoles *IIIa* and *IIIb* by repeated crystallization.

EXPERIMENTAL

Proton NMR spectra were measured on a Bruker AM 400 instrument (400·13 MHz) in deuteriochloroform with tetramethylsilane as internal standard. Chemical shifts are given in ppm (δ-scale), coupling constants J in Hz. Thin-layer chromatography was performed on Silufol UV 254 sheets (Kavalier, Czechoslovakia) in chloroform–methanol (5 : 1). Spots were detected with a Universal UV Lampe Camag (Mutenz, Switzerland) at 254 nm and 366 nm or with iodine vapours.

1-(2-Pyridinyl)-3-(3-pyridinyl)-1,3-propanedione (*Id*)

Potassium tert-butoxide (1·1 g, 10 mmol) was added to a stirred mixture of ethyl 2-pyridinecarboxylate[7] (1·5 g, 10 mmol) and 3-acetylpyridine[8] (1·3 g, 10 mmol). An exothermic reaction

commenced immediately. After cooling, the solid enolate was dissolved in water (20 ml) and the solution was decomposed with acetic acid (2 ml). The precipitated product (2·1 g, 93%) melted at 111—112 °C (water). Similarly was performed the condensation of 2-acetylpyridine[9] with ethyl 3-pyridinecarboxylate which gave the same product in 26% yield. ^{1}H NMR spectrum ($CDCl_3$): 7·38—7·45 m, 2 H (H-5, H-5′); 7·58 s, 1 H (CH); 7·85 dt, 1 H (H-4, ^3J(4, 5 and 3) = 7·7, ^4J(4, 6) = = 1·5); 8·15 d, 1 H (H-3, ^3J(3, 4) = 7·9); 8·29 dd, 1 H (H-4′, ^3J(4′, 5′) = 7·9; ^4J(4′, 2′ and 6′) = = 1·7); 8·70—8·76 m, 2 H (H-6, H-6′); 9·26 d, 1 H (H-2′, ^4J(2′, 4′ and 6′) = 1·9); 9·45 s, 1 H (OH, temperature dependent shift). For analysis see Table I.

Diketone Ie was prepared by condensation of ethyl 2-pyridinecarboxylate with 4-acetylpyridine[10]. ^{1}H NMR spectrum ($CDCl_3$): 7·44—7·47 m, 1 H (H-5); 7·61 s, 1 H (CH); 7·81—7·88 m, 3 H (H-4, H-3′, H-5′); 8·17 d, 1 H (H-3, ^3J(3, 4) = 7·9); 8·71 d, 1 H (H-6, ^3J(6, 5) = 4·8); 8·78 d, 2 H (H-6′, H-2′, ^3J(6′, 5′) = 5·9); 9·60 s, 1 H (OH).

Diketone If was obtained from ethyl 4-pyridinecarboxylate[11] and 3-acetylpyridine. For yields' melting points and analyses see Table I. ^{1}H NMR spectrum ($CDCl_3$): 7·42—7·46 m, 1 H (H-5); 6·88 s, 1 H (CH); 7·76 d, 2 H (H-3′, H-5′, ^3J = 6·1); 8·26 td, 1 H (H-4, ^3J(4, 5) = 8, ^4J(4, 2 and 6) = 1·9); 8·78—8·81 m, 3 H (H-2′, H-6′, H-6); 9·20 d, 1 H (H-2, ^4J = 2·2).

3-(2-Pyridinyl)-5-(4-pyridinyl)pyrazole (*IIe*)

To a hot solution of *Ie* (1·12 g, 5 mmol) in methanol (80 ml) was added 30% hydrazine (1·5 ml, 14 mmol) and the mixture was refluxed for 8 min. After concentration in vacuo, the separated product was crystallized from aqueous ethanol (1 : 1), yield 0·8 g (72%), m.p. 217—219°C (reported[5] m.p. 223—224°C). For analysis see Table I, for ^{1}H NMR spectrum Table II.

Physical data and analyses of pyrazoles *IIa—IId*, *IIf* and their ^{1}H NMR spectra are given in Tables I and II.

1-Phenyl-3-(2-pyridinyl)-5-(4-pyridinyl)pyrazole (*IIi*)

Freshly distilled phenylhydrazine (0·55 g, 5 mmol) and a drop of acetic acid were added to a hot solution of *Ie* (0·55 g, 2·5 mmol) in ethanol (20 ml). The reaction mixture was refluxed for 27 h, the solvent evaporated and the oily product chromatographed on a column of silica gel in chloroform; yield 0·13 g (17%) of product, m.p. 117°C (cyclohexane). For analysis see Table I, for ^{1}H NMR spectrum Table II. Physical properties, analyses and ^{1}H NMR spectra of compounds *IIg* and *IIh* are given in Tables I and II.

3,5-Di-(2-pyridinyl)isoxazole (*IIIa*)

A solution of hydroxylamine hydrochloride (1 g, 14·4 mmol) and anhydrous potassium carbonate (1 g) in water (10 ml) was boiled to remove the dissolved carbon dioxide and then added to a solution of compound *Ia* (1 g, 4·4 mmol) in methanol (80 ml). The reaction mixture was heated to 40°C for 3 h, concentrated and the obtained mixture of the product and potassium chloride extracted with diethyl ether. The extract was dried over magnesium sulfate and the solvent evaporated to give an oily residue which crystallized, m.p. 173—174°C (water); yield 280 mg (28%). The product was homogeneous according to HPLC. For analysis see Table I. ^{1}H NMR spectrum ($CDCl_3$): 7·31—7·37 m, 2 H (H-5, H-5′); 7·56 s, 1 H (CH isoxazole); 7·78—7·85 m, 2 H (H-4, H-4′); 7·94 td, 1 H (H-3′, ^3J = 7·9, ^4J = 1·1); 8·11 td, 1 H (H-3, ^3J = 7·9, ^4J = 1·1); 8·71—8·74 m, 2 H (H-6, H-6′).

TABLE I

Physical and analytical data of compounds *I*—*III*

Compound Yield, %	M.p., °C (solvent)	Formula (M.w.)	Calculated/Found		
			% C	% H	% N
Id	111—112	$C_{13}H_{10}N_2O_2$	69·02	4·46	12·38
93	(water)	(226·2)	68·79	4·58	12·16
Ie	132—134	$C_{13}H_{10}N_2O_2$	69·02	4·46	12·38
59	(water–ethanol)	(226·2)	68·83	4·57	12·27
If	188—189	$C_{13}H_{10}N_2O_2$	69·02	4·46	12·38
84	(water)	(226·2)	69·26	4·55	12·33
IIa	190·5—191	$C_{13}H_{10}N_4$	70·26	4·54	25·21
81	(water–ethanol)	(222·3)	69·98	4·74	25·21
IIb	231—232[a]	$C_{13}H_{10}N_4$	70·26	4·54	25·21
81	(2-propanol)	(222·3)	70·32	4·73	25·25
IIc	257[b]	$C_{13}H_{10}N_4$	70·26	4·54	25·21
90	(water–ethanol)	(222·3)	69·97	4·75	25·00
IId	173—174	$C_{13}H_{10}N_4$	70·26	4·54	25·21
63	(water–ethanol)	(222·3)	70·11	4·74	25·22
IIe	217—219[c]	$C_{13}H_{10}N_4$	70·26	4·54	25·21
72	(water–ethanol)	(222·3)	69·98	4·72	25·17
IIf	198[d]	$C_{13}H_{10}N_4$	70·26	4·54	25·21
81	(water–ethanol)	(222·3)	70·32	4·70	25·28
IIg	119	$C_{19}H_{14}N_4$	76·49	4·73	18·78
40	(sublimed)	(298·4)	76·66	4·92	19·05
IIh	131—132	$C_{19}H_{14}N_4$	76·49	4·73	18·78
24	[e]	(298·4)	76·77	5·01	18·83
IIi	117	$C_{19}H_{14}N_4$	76·49	4·73	18·78
17	(cyclohexane)	(298·4)	76·66	5·01	19·06
IIIa	173—174	$C_{13}H_9N_3O$	69·95	4·06	18·82
28	(water)	(223·2)	69·99	4·27	18·66
IIIb	198	$C_{13}H_9N_3O$	69·95	4·06	18·82
41	(water)	(223·2)	69·66	4·31	18·63

[a] Ref.[4] gives m.p. 230·5—232°C; [b] ref.[3] gives m.p. 247—250°C; [c] ref.[5] gives m.p. 223—224°C; [d] no m.p. in ref.[12]; [e] column chromatography.

TABLE II

^{1}H NMR spectra of pyrazoles *IIa*—*IIi*

Proton coupling	Compound								
	IIa	*IIb*	*IIc*	*IId*[a]	*IIe*[a]	*IIf*[a]	*IIg*[a]	*IIh*[a]	*IIi*[a]
H-2 $^3J(^4J)$		9·02 s	8·72 dd 4·5 (1·6)			9·03 d (2·3)			
H-2′ $^3J(^4J)$				9·11 d (1·5)	8·65—8·70	8·70 dd 4·5 (1·6)		8·62 d (2·1)	8·57 dd 4·5 (1·5)
H-3 $^3J(^4J)$	7·92 s		7·44 dd 4·5 (1·6)	7·71 d 7·9	7·90 d 7·6		8·11 d 8	8·11 d 8	8 7·9
H-3′ $^3J(^4J)$					7·70—7·81	7·66 dd 4·5 (1·6)	7·35—7·43		7·18 dd 4·5 (1·6)
H-4 $^3J(^4J)$	7·78 dt 7·9 (1·8)	8·03—8·05		7·79 dt 7·8 (1·7)	7·70—7·81	8·04 td 8 (1·9)	7·76 dt 8 (1·6)	7·75 dt 8 (1·4)	7·77 dt 8 (1·6)
H-4′ $^3J(^4J)$				8·21 td 7·9 (1·8)			7·66 dt 8 (1·7)	7·53 td 8 (1·8)	
H-5 $^3J(^4J)$	7·26 dt 4·9 (1·2)	7·39—7·42	7·64 dd 4·5 (1·6)	7·28 t 5·8	7·24—7·28	7·39—7·42	7·21—7·28	7·22—7·28	7·28 dt 6·7 (1·0)
H-5′ $^3J(^4J)$				7·35—7·39	7·70—7·81	7·66 dd 4·5 (1·6)	7·21—7·28	7·22—7·28	7·18 dd 4·5 (1·6)
H-6 $^3J(^4J)$	8·67 td 4·9 (1·3)	8·63 dd 4·8 (1·7)	8·72 dd 4·5 (1·6)	8·66 s	8·65—8·70	8·64 dd 4·8 (1·6)	8·69 d 4·2	8·67 d 4·5	8·69 d 4·2
H-6′ $^3J(^4J)$				8·59 dd 4·8 (1·6)	8·65—8·70	8·70 dd 4·5 (1·6)	8·57 d 4·1	8·56 dd 4·8 (1·3)	8·57 dd 4·5 (1·5)
Other signals	7·42 s (CH); 11·08 s (NH)	6·95 s (CH)	7·10 s (CH)	7·08 s (CH); 11·85 s (NH)	7·12 s (CH); 11·50 s (NH)	7·03 s (CH)	7·35—7·43 (CH, C_6H_5)	7·27 s (CH); 7·34—7·37 (C_6H_5)	7·34 s (CH); 7·38—7·46 (C_6H_5)

[a] In pyrazoles *IId*—*IIi* the protons 2′,3′,4′,5′ and 6′ belong to the pyridine nucleus of higher locant number.

3,5-Di-(3-pyridinyl)isoxazole (*IIIb*)

The title compound was prepared from compound *Ib* analogously as described for *Ia*; m.p. 198°C, for analysis see Table I. ^{1}H NMR spectrum ($CDCl_3$): 6·98 s, 1 H (CH isoxazole); 7·41 to 7·47 m, 2 H (H-5, H-5′); 8·15 d, 1 H (H-4′, ^3J = 8, ^4J = 1·9); 8·21 td, 1 H (H-4, ^3J = 8, ^4J = 1·9); 8·71–8·74 m, 2 H (H-6, H-6′); 9·09–9·11 m, 2 H (H-2, H-2′).

The elemental analyses (Dr L. Helešic, Head) and the NMR *spectra (Dr P. Trška, Head) were obtained in the Laboratories of this Institute.*

REFERENCES

1. Laffert J. J., Case F. H.: J. Org. Chem. *32*, 1591 (1967).
2. Kuick L. F., Adkins H.: J. Am. Chem. Soc. *57*, 143 (1935).
3. Fabbrini L.: Il Farmaco, Ed. Sci. *9*, 603 (1954).
4. Ferles M., Kafka S., Šilhánková A., Šputová M.: Collect. Czech. Chem. Commun. *46*, 1167 (1981).
5. Samula K.: Rocz. Chem. *47*, 1543 (1973).
6. Babska A., Bielski L., Kuczynski L., Respond S., Witek H.: Pol. J. Pharmacol. Pharm. *25*, 175 (1973).
7. Fürst H., Jeresaroff I.: Arch. Pharm. *283*, 238 (1950).
8. Strong F. M., McElvain S. M.: J. Am. Chem. Soc. *55*, 816 (1933).
9. Bruice T. C.: J. Am. Chem. Soc. *79*, 702 (1957).
10. Burrus H. O., Powell G.: J. Am. Chem. Soc. *67*, 1468 (1945).
11. Camps R.: Arch. Pharm. *240*, 345 (1902).
12. Kanth F. W., Neher R.: Experientia *27*, 959 (1971).

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