THE USE OF 4-R^1-BENZYLIDENE-4-PHENYLBENZOYLACETONITRILES FOR SYNTHESIS OF UNSYMMETRICALLY SUBSTITUTED 3,5-DICYANO-1,4-DIHYDROPYRIDINES AND 2-AMINO-*4H*-PYRANS*

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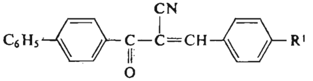
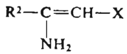
Received November 30th, 1982

3,5-Dicyano-1,4-dihydropyridine derivatives *III*—*V* have been prepared by cyclocondensation of benzylidene-4-phenylbenzoylacetonitrile (*Ia*) with the enamines *IIa*—*IIc*. 2-(4-Biphenylyl)-4-(4-R^1-phenyl)-6-methyl-3,5-dicyano-1,4-dihydropyridines *VI*—*VIII* are formed by condensation of ketonitriles *Ib*—*Id* with 3-amino-2-butenenitrile (*IIa*). Base-catalyzed reaction of compound *Ia* with enaminonitrile *IIa* gives the adduct *IX* which, on dehydration, forms 1,4-dihydropyridine *III*. 4*H*-Pyrans *X* and *XI* have been prepared by cyclocondensation of the ketonitrile *Ia* with propanedinitrile and methyl cyanoacetate, respectively.

Symmetrically substituted 1,4-dihydropyridines are prepared by the Hantzsch synthesis and cognate condensations[1]. Application of α,β-unsaturated ketones and enamines leads to unsymmetrical 1,4-dihydro derivatives[2-6]. Our previous communication[7] dealt with preparation of biphenyl analogues of α-cyanochalcones *I* and with study of spectral properties of these compounds. The aim of the present communication is to investigate reactivity of 4-R^1-benzylidene-4-phenylbenzoylacetonitriles *Ia*—*Id* with condensation reagents of the type of 3-amino-2-butanenitrile (*IIa*), ethyl 3-amino-2-butenoate (*IIb*), 3-phenyl-3-amino-2-propenenitrile (*IIc*), propanedinitrile, and methyl cyanoacetate. In the context of studies of optically interesting compounds, we were interested in applicability of the cyano derivatives



Ia, R^1 = H
Ib, R^1 = OCH$_3$
Ic, R^1 = Cl
Id, R^1 = NO$_2$



$$R^2{-}\underset{\displaystyle NH_2}{\underset{|}{C}}{=}CH{-}X$$

IIa, R^2 = CH$_3$, X = CN
IIb, R^2 = CH$_3$, X = COOC$_2$H$_5$
IIc, R^2 = C$_6$H$_5$, X = CN

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[*] Part LVI in the series On Dihydropyridines; Part LV: This Journal *48*, 3112 (1983).

Ia–*Id* to synthesis of 1,4-dihydropyridine and 4*H*-pyran heterocycles. The unsymmetrically substituted 1,4-dihydropyridine derivatives *III*–*V* were prepared by cyclocondensation of benzylidene-4-phenylbenzoylacetonitrile (*Ia*) with the enamines *IIa*–*IIc* in acetic acid. Analogous reaction of the ketonitriles *Ib*–*Id* with nitrile *IIa* gave 2-(4-biphenylyl)-4-(4-R^1-phenyl)-6-methyl-3,5-dicyano-1,4-dihydropyridines *VI*–*VIII*. Synthetically this reaction enables an unambiguous preparation of unsymmetrically substituted 1,4-dihydropyridines *III*–*VIII* in good yields (Table I).

Spectral characteristics of the synthetized 1,4-dihydro derivatives *III*–*VIII* are given in Table II. The IR spectra exhibit absorption maxima of stretching vibrations of C≡N and N—H groups, and in the case of the IR spectra of *III*, *VII*, *VIII* measured by the KBr disc technique two absorption maxima are observed which are ascribed to the C≡N groups at 3 and 5 positions of the 1,4-dihydropyridine skeleton. This fact is obviously connected with specific arrangement of the molecules *III*, *VII*, *VIII* in solid state.

The UV spectra of 1,4-dihydropyridines *III*–*VIII* contain bands of absorption maxima at 205–209 nm ($\log \varepsilon$ 4·26–4·78), 247–285 nm ($\log \varepsilon$ 4·37–4·49) and 318–360 nm ($\log \varepsilon$ 3·63–4·42). The longest-wave band corresponding to the first

TABLE I

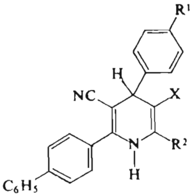
The new 1,4-dihydropyridine derivatives *III*–*VIII*

Compound Yield, %	M.p., °C (solvent)	Formula (mol. mass)	Calculated/Found % C	 % H	 % N
III 71	252–254 (C_2H_5OH—C_6H_6)	$C_{26}H_{19}N_3$ (373·5)	83·61 83·41	5·14 5·30	11·25 10·91
IV 73	181–183 (C_2H_5OH—CH_3CN)	$C_{28}H_{24}N_2O_2$ (420·5)	79·96 80·00	5·76 5·78	6·66 6·46
V 62	249–252 (C_2H_5OH—C_6H_6)	$C_{31}H_{21}N_3$ (435·6)	85·48 85·65	4·87 5·07	9·65 9·78
VI 57	177–179 (C_2H_5OH)	$C_{27}H_{21}N_3O$ (403·5)	80·36 80·36	5·26 5·28	10·42 10·52
VII 74	227–228 (C_2H_5OH)	$C_{26}H_{18}ClN_3$ (407·9)	76·55 76·60	4·46 4·51	10·30[a] 10·11[a]
VIII 85	261–263 (CH_3COCH_3—C_6H_6)	$C_{26}H_{18}N_4O_2$ (418·5)	74·62 74·71	4·34 4·38	13·39 13·49

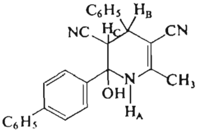
[a] Calculated: 8·67% Cl; found: 8·54% Cl.

$\pi \rightarrow \pi^*$ transition of the conjugated system is shifted hypsochromically in compound *VIII* ($R^1 = NO_2$) by 34 nm as compared with the unsubstituted compound *III*, and substitution of the 3-CN substituent in the dihydropyridine skeleton by $CO_2C_2H_5$ group (compound *IV*) causes a bathochromic shift of this band by 8 nm. A similar bathochromic shift can also be observed when comparing the UV spectra of 3,5-dimethoxycarbonyl-1,4-dihydropyridine[8] and 3,5-dicyano-1,4-dihydropyridine[9] ($\Delta\lambda_{max} = 22$ nm).

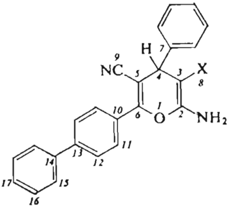
The ^1H NMR spectra confirm the structure of the synthetized 1,4-dihydropyridines *III*–*VIII*. The mixture produced by reaction of ketonitrile *Ia* with nitrile *IIa* in the presence of sodium methoxide was separated chromatographically and gave a compound with m. p. 145–147°C. IR spectrum of this compound indicates the presence of a CN group (2 192 cm^{-1}) and N—H and/or O—H bonds (3 485, 3 442 cm^{-1}). The ^1H NMR spectrum (100 MHz) shows signals of fourteen aromatic protons at 7·25–7·98δ, a singlet at 6·01δ (H_A), and two doublets with centres at 3·32 and 4·10δ ($J_{BC} = 6·5$ Hz) which we assigned to the protons



III, $R^1 = H$, $R^2 = CH_3$, $X = CN$
IV, $R^1 = H$, $R^2 = CH_3$, $X = COOC_2H_5$
V, $R^1 = H$, $R^2 = C_6H_5$, $X = CN$
VI, $R^1 = OCH_3$, $R^2 = CH_3$, $X = CN$
VII, $R^1 = Cl$, $R^2 = CH_3$, $X = CN$
VIII, $R^1 = NO_2$, $R^2 = CH_3$, $X = CN$



IX



X, $X = CN$
XI, $X = COOCH_3$

H_C – the signal at higher field – and H_B. On the basis of these data we suggest structure *IX* for this compound; this structure was confirmed further by thermogravimetry and by measurement of ^{1}H NMR spectrum after addition of trifluoroacetic acid. The resulting TG curve showed dehydratation of compound *IX* within the temperature interval 145–170°C and a mass decrease due to sublimation above 175°C. The ^{1}H NMR record of compound *IX* in $C^2H_3COC^2H_3$ with addition of trifluoroacetic acid shows characteristical signals of 1,4-dihydropyridine skeleton corresponding to the compound *III* prepared by cyclocondensation of ketonitrile *Ia* with enaminonitrile *IIa* in acetic acid (Table II). 2-(4-Biphenylyl)-2-hydroxy-4-phenyl-3,5-dicyano-1,2,3,4-tetrahydropyridine (*IX*) is formed, at the reaction conditions, by the Michael addition of nitrile *IIa* to ketonitrile *Ia*. Chatterjea[10] isolated

TABLE II

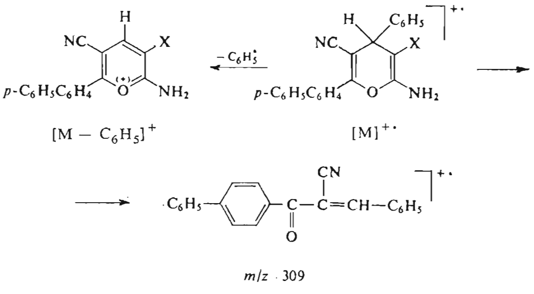
Spectral properties of 2-(4-biphenylyl)-6-methyl-1,4-dihydropyridines *III*–*VIII*

Compound	λ, nm (C_2H_5OH) λ_{max}	(log ε)	ν_{max}, cm^{-1} $\nu(N—H)^a$	$\nu(C\equiv N)^a$	δ_H, ppm ($CDCl_3$, 35°C)^b H-arom.	NH	CH	CH_3
III	209 283 352	4·38 4·37 3·65	3 285 m 3 260 m	2 206 s 2 192 s	7·21–7·87 m^c	9·69 s^c	4·50 s^c	2·07 s^c
IV	209 285 360	4·26 4·42 3·73	3 440 m 3 312 w	2 196 m	7·20–7·82 m	6·22 s	4·73 s	2·40 s^d
V	205 284 358	4·78 4·49 3·64	3 428 m	2 205 s	7·30–7·74 m	6·42 s	4·57 s	–
VI	209 282 348	4·52 4·43 3·63	3 442 m 3·300 w	2 212 s	7·16–7·66 m 6·88 d (H_{ortho})	6·62 s	4·34 s	2·05 s^e
VII	209 284 352	4·55 4·40 3·64	3 315 m 3 245 w	2 208 s 2 190 s	7·23–7·81 m	6·27 s	4·48 s	2·19s
VIII	207 247 318	4·59 4·24 4·42	3 328 m	2 200 s 2 192 s	7·27–7·98 m^c 8·28 d (H_{ortho})	9·88 s^c	4·83 s^c	2·11 s^c

[a] The compounds *III*, *VII*, *VIII* were measured by the KBr disc technique, the compounds *IV*–*VI* were measured in chloroform; [b] tetramethylsilane as reference compound; [c] measured in hexadeuteriodimethyl sulphoxide at 35°C; [d] besides that the following signals of $CO_2C_2H_5$ group were identified: 1·15 (t, 3 H, CH_3), 4·03 (q, 2 H, CH_2); [e] 3·74 (s, 3 H, OCH_3).

an adduct of similar type from reaction of ethyl 2-benzylidene-3-oxobutanoate with nitrile *IIa* in the presence of diethylamine. Similarly, dihydropyridine *VI* ($R^1 = OCH_3$) was prepared by dehydration of the reaction mixture after reaction of ketonitrile *Ib* with enaminonitrile *IIa* in the presence of piperidine. In all the cases given, obviously, we succeeded in trapping of another of not yet proven intermediates of the Hantzsch synthesis.

In analogy to ref.[11], the reaction of nitrile *Ia* with propanedinitrile and methyl cyanoacetate in ethanol in the presence of piperidine gave 2-amino-6-(4-biphenylyl)-4*H*-pyrans *X* and *XI*, respectively. The spectral characteristics of these compounds correspond to the structures *X* and *XI*. The mass spectra of compounds *X* and *XI* obtained at 70 eV contain a slightly intensive molecular ion *m/z* 375 (*X*) and *m/z* 408 (*XI*) with relative intensity below 1%. The existence of ionic species *m/z* 309, 282, 232, 181 (ionic maximum), and 153 can be explained by Scheme 1. Decomposition of the 4*H*-pyran skeleton forms the ion *m/z* 309 which represents the molecular ion of compound *Ia*. Its further fragmentation is identical with that of nitrile *Ia* studied in our previous communication[7]. The ions *m/z* 298 (*X*) and *m/z* 331 (*XI*) are formed by aromatization of the 4*H*-pyran skeleton by loss of phenyl radical from 4 position.



SCHEME 1 (X = CN, CO_2CH_3)

EXPERIMENTAL

The temperature data are not corrected. The melting temperatures were determined with a Boetius apparatus. The following apparatus was used for the spectral measurements: Perkin-Elmer 325 (IR), Carl Zeiss, Jena Specord UV VIS (UV), Varian XL-100 (^{1}H NMR), Tesla BS 567 (^{13}C NMR), LKB 9 000 and AEI MS 902 S (mass spectrum, 70 eV). The thermogravimetry of compound *IX* was carried out with a Stanton Redcroft TG-750 apparatus with Pt/Pt Rh 13 thermocouple.

Condensation of Nitriles *Ia—Id* with Enamines *IIa—IIc* in Acetic Acid

Condensation of nitrile Ia *with enamines* IIa—IIc: Mixture of 0·01 mol compound *Ia* and 0·01 mol corresponding enamine *II* in 20 ml acetic acid was boiled 8 h and left to stand overnight. The separated 1,4-dihydropyridines *III—V* were collected by suction, washed with 5 ml cold water, and recrystallized from a suitable solvent.

Condensation of nitriles Ib—Id *with nitrile* IIa: Mixture of 0·05 mol corresponding ketonitrile *I* and 0·05 mol enaminonitrile *IIa* in 15 ml acetic acid was boiled 8 h and left to stand overnight, whereupon it was decomposed by addition of 100 ml water. The separated solid was collected by suction, washed with 2% NaOH and with water until neutral. The 1,4-dihydro derivatives *VI—VIII* were recrystallized from a suitable solvent. The yields of the 1,4-dihydropyridines *III—VIII*, solvents, melting temperatures, and analytical data are given in Table I.

Reaction of Nitriles *Ia*, *Ib* with Nitrile *IIa* in Basic Medium

Reaction of compound Ia *with enamine* IIa: 0·04 g sodium was dissolved in 20 ml methanol, and 0·52 g compound *Ia* and 0·14 g nitrile *IIa* were added thereto. The mixture was boiled 5 h. The solvent was distilled off under reduced pressure, and the residue was submitted to column chromatography (500 g silica gel, 1% C_2H_5OH in $CHCl_3$). The elution gave 250 mg compound *IX* (38%) which was recrystallized from n-hexane-benzene (1 : 1), m.p. 145—147°C. UV spectrum (ethanol): λ_{max} 208 nm (log ε 4·21), 260 nm (log ε 4·49), 265 nm (log ε 4·48), inflexion at 269 nm (log ε 4·42). IR spectrum (KBr disc): 3 485 cm^{-1}, 3 442 cm^{-1} ν(O—H) and ν(N—H), 2 192 cm^{-1} ν(C≡N). ^1H NMR spectrum ($C^2H_3COC^2H_3$), δ, ppm: 2·21 (s, 3 H, CH_3), 3·32 (d, 1 H, H_C), 4·10 (d, 1 H, H_B), J_{BC} = 6·50 Hz, 6·01 (s, 1 H, H_A), 7·25—7·96 (m, 14 H, H-arom.). ^1H NMR spectrum ($C^2H_3COC^2H_3$ + CF_3CO_2H), δ, ppm: 2·28 (s, 3 H, CH_3), 4·49 (s, 1 H, CH), 7·28—7·78 (m, 14 H, H-arom.), 8·24 (s, 1 H, NH).

Reaction of compound Ib *with nitrile* IIa; 4 drops piperidine was added to suspension of 1·0 g compound *Ib* and 0·27 g enaminonitrile *IIa* in 30 ml ethanol. The mixture was boiled 5 h, the ketonitrile *Ib* being dissolved during the first 15 min to give an orange solution. The solvent was distilled off under reduced pressure, and the residue was boiled in 15 ml acetic acid 7 h. The mixture was poured in 100 ml water, and the precipitated solid was collected by suction, washed with 2% NaOH and with water until neutral. Recrystallization from ethanol gave 300 mg compound *VI* whose identity was confirmed by comparison of its spectral characteristics with those of the dihydropyridine prepared by condensation in acetic acid (Table II).

2-Amino-6-(4-biphenylyl)-4-phenyl-3,5-dicyano-4*H*-pyran (*X*)

Suspension of 0·52 g compound *Ia* in 10 ml methanol was treated with solution of 0·10 g propanedinitrile and 2 drops piperidine. The mixture was stirred at room temperature 4 h. The product precipitated on cooling was collected by suction and recrystallized from ethanol. Yield 0·55 g compound *X* (87%), m.p. 187—189°C. For $C_{25}H_{17}N_3O$ (375·5) calculated: 79·97% C, 4·57% H, 11·19% N; found: 80·03% C, 4·86% H, 11·06% N. UV spectrum (ethanol): λ_{max} 206 nm (log ε 4·52), 243 nm (log ε 4·19), 297 nm (log ε 4·32). IR spectrum (chloroform): 3 506 cm^{-1} ν_{as}(N—H), 3 415 cm^{-1} ν_s(N—H), 2 212 cm^{-1} ν(C≡N). ^1H NMR spectrum (C^2HCl_3), δ, ppm: 4·32 (s, 1 H, CH), 4·82 (s, 2 H, NH_2), 7·25—7·93 (m, 14 H, H-arom.). ^{13}C NMR spectrum (C^2HCl_3), δ, ppm, tetramethylsilane: 41·1 ($C_{(4)}$), 60·7 ($C_{(3)}$), 91·0 ($C_{(5)}$), 117·1 ($C_{(8)}$), 117·8 ($C_{(9)}$), 139·8 ($C_{(7)}$), 140·9 ($C_{(13)}$), 144·9 ($C_{(14)}$), 157·5 ($C_{(2)}$), 158·1 ($C_{(6)}$).

2-Amino-6-(4-biphenylyl)-3-methoxycarbonyl-5-cyano-4*H*-pyran (*XI*)

Suspension of 0·52 g compound *Ia* in 10 ml ethanol was treated with solution of 0·17 g methyl cyanoacetate in 10 ml ethanol and 2 drops piperidine. The mixture was boiled 10 h and left to stand overnight. The solvent was distilled off in vacuum, and the residue was recrystallized from ethanol–benzene (1 : 1) to give 0·25 g 4*H*-pyran *XI* (36%), m.p. 211–214°C. For $C_{26}H_{20}.N_2O_3$ (408·5) calculated: 76·44% C, 4·35% H, 6·86% N; found: 76·42% C, 5·34% H, 6·91% N. UV spectrum (ethanol): λ_{max} 208 nm (log ε 4·13), 265 nm (log ε 4·20), and 298 nm (log ε 4·39). IR spectrum (chloroform): 3 490 vm^{-1} ν_{as}(N—H), 3 328 cm^{-1} ν_s(N—H), and 2 208 cm^{-1} ν(C≡N). ^{1}H NMR spectrum (C^2HCl_3), δ, ppm: 3·59 (s, 3 H, OCH_3), 4·54 (s, 1 H, CH), 6·32 (s, 2 H, NH_2), 7·20–7·90 (m, 14 H, H-arom.).

Mass spectra, (ions and relative intensities, %)

V: 435 (23, $[M]^{+\cdot}$), 434 (24), 433 (76, $[M-2]^{+\cdot}$), 432 (79), 359 (29), 358 (100, $[M-C_6H_5]^+$), 356 (11), 253 (5), 216 (8), 210 (6), 181 (15), 170 (8), 153 (6), 152 (12), 150 (6), 141 (7), 125 (8), 111 (15), 109 (15), 105 (10), 97 (21), 95 (21), 92 (27), 91 (39), 86 (18), 83 (24), 81 (21).

VII: 409 (20), 408 (16), 407 (27, $[M]^{+\cdot}$), 406 (22), 372 (10), 371 (27), 296 (100, $[M-C_6H_4Cl]^+$), 295 (8), 294 (10), 279 (7), 256 (7), 202 (20), 201 (10), 200 (16), 199 (12), 167 (16), 153 (10), 152 (16), 151 (10), 149 (55), 125 (16), 123 (14), 109 (17), 101 (16), 99 (16), 97 (35), 95(27), 85 (35), 84 (18), 83 (41), 81 (28), 77 (25), 71 (59), 69 (55), 67 (25).

X: 375 (1, $[M]^{+\cdot}$), 311 (3), 310 (5), 309 (21), 308 (5), 298 (2, $[M-C_6H_5]^+$), 282 (3), 232 (2), 231 (2), 222 (3), 221 (16), 182 (15), 181 (100), 154 (39), 153 (34), 152 (46), 151 (11), 128 (5), 127 (29), 126 (5), 103 (6), 101 (4), 100 (4), 92 (6), 91 (11), 77 (12), 76 (17), 75 (7), 66 (22), 63 (8), 51 (12).

XI: 408 (1, $[M]^{+\cdot}$), 349 (2), 346 (2), 331 (3, $[M-C_6H_5]^+$), 310 (7), 309 (27), 308 (7), 282 (4), 232 (2), 231 (2), 222 (2), 221 (11), 187 (13), 186 (7), 182 (15), 181 (100), 173 (3), 156 (15), 154 (7), 153 (29), 152 (45), 151 (11), 129 (4), 128 (12), 127 (8), 102 (7), 101 (6), 91 (3), 78 (7), 77 (16), 76 (11), 75 (6), 68 (15), 59 (17), 51 (13), 50 (6).

The authors are indebted to workers of Department of Elemental Analysis (Dr L. Helešic, Head) for carrying out the elemental analyses and to workers of Central Laboratories of their Institute for measurements of the spectral characteristics and for carrying out the thermogravimetrical measurements.

REFERENCES

1. Kuthan J., Kurfürst A.: Ind. Eng. Chem., Prod. Res. Develop. *21*, 191 (1982).
2. Beyer C.: Ber. *24*, 1662 (1891).
3. Meyer H., Bossert F., Vater W., Stoepel K. (Bayer A.-G.): Ger. Offen. 2 117 571; Chem. Abstr. *78*, 16 038 (1973).
4. Meyer H., Bossert F., Vater W., Stoepel K. (Bayer A.-G.): Ger. Offen. 2 210 672; Chem. Abstr. *79*, 146 410 (1973).
5. Sato Y. (Fujisawa Pharm. Co. Ltd.): Ger. Offen. 2 629 892; Chem. Abstr. *86*, 189 726 (1977).
6. Nantka-Namirski P., Balicki R.: Acta Pol. Pharm. *31*, 279 (1974).
7. Marchalín Š., Trška P., Kuthan J.: This Journal, in press.
8. Paleček J., Ptáčková L., Kuthan J.: This Journal *34*, 427 (1969).
9. Kuthan J., Janečková E.: This Journal *29*, 1654 (1964).
10. Chatterjea J. N.: J. Indian. Chem. Soc. *29*, 323 (1952).
11. Quinteiro M., Seoane C., Soto J. L.: Ann. Quim. *74*, 678 (1978).

Translated by J. Panchartek.