STILBAZOLES DERIVED FROM 2,6-DIMETHYL-3,5-DICYANOPYRIDINE AND THEIR 1,4-DIHYDRO DERIVATIVES*

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Condensation of some aromatic aldehydes with 2,6-dimethyl-3,5-dicyanopyridine (*I*) afforded products of reaction with only one molecule of aldehyde. Reduction of these compounds with sodium borohydride gave the corresponding 1,4-dihydropyridines *VI—IX*. The attempted reduction of the dibromo derivative *X* afforded, instead of the brominated dihydropyridine, a product of reductive elimination of bromine molecule, in which the double bond was regenerated.

Condensation of α- or γ-methylpyridine derivatives with aromatic aldehydes affords usually stilbazoles, *i.e.* pyridine derivatives containing the styryl group in the place of the activated methyl groups[1]. This reaction is catalyzed by acid catalysts[1,2] and, in the case of quaternary salts, also by basic reagents[3]. However, no analogous pyridine derivatives, substituted in positions 3 and 5 with substituents capable of conjugation, have been hitherto known. These compounds could be interesting because they could be reduced to the corresponding dihydropyridine derivatives[4] containing an extented conjugated system in the position of the original methyl groups. In this study we have chosen 2,6-dimethyl-3,5-dicyanopyridine (*I*) as the starting pyridine derivative; in this compound the two methyl groups, capable of condensation, are equivalent and therefore there are no problems concerning the determination of the position of the condensation.

Condensation of benzaldehyde with the compound *I* in the presence of acetic anhydride, as well as piperidine, afforded 2-methyl-6-styryl-3,5-dicyanopyridine (*II*) as the only isolated product. It was not possible to obtain the product of condensation with two molecules of aldehyde even by treatment of the compound *II* with benzaldehyde or by using prolonged reaction time. Evidently, the introduction of a styryl group into the position 2 lowers remarkably the prototropic reactivity of the methyl group in the position 6. Analogous results were obtained also in the reaction with furfural, which affords compound *III*. A more complicated situation was observed in the case of vinylogs of the mentioned aldehydes. Reaction with cinnam-

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TABLE I

The IR and Electronic Spectra of Compounds *II*–*IX*

Compound	$\nu(CH_3)$	$\nu(C\equiv N)$	ν(DHP)[a]	ν(CH=CH)	γ(CH=CH)	ν(NH)	λ_{max}, nm	(ε)	λ_{max}, nm[b]
II	2 960 (m)	2 230 (s)	—	1 640 (m)	955 (m) 985 (m)	—	346	(18 900)	—
III	[c]	2 230 (m)	—	1 640 (m)	930 (m) 970 (m)	—	377	(38 200)	—
IV	[c]	2 230 (m)	—	1 630 (m)	1 000 (m)	—	378	(36 000)	—
V	2 850 (w) 2 920 (w)	2 230 (m)	—	1 615 (m)	995 (m)	—	405	(29 940)	—
VI	2 870 (w) 2 940 (w)	2 190 (s)	1 610 (w) 1 670 (m)	1 650 (m)	960 (m)	3 360 (m)	300	(30 400)	360
VII	[c]	2 200 (s)	1 610 (w) 1 670 (m)	1 645 (m)	960 (m)	3 330 (m)	330	(25 300)	385
VIII	[c]	2 220 (s)	1 665 (m)	1 630 (m)	980 (m)	3 320 (m)	336	(43 400)	388
IX	2 950 (w)	2 205 (s)	1 610 (m)	1 650 (m)	985 (m)	3 300 (m)	356	(29 160)	415

[a] Valence vibration of the dihydropyridine ring bonds. [b] Shoulder, the extinction coefficients were not calculated. [c] The band is too weak to be located.

aldehyde afforded compound *IV* as the sole product only when the condensation was acid-catalyzed. Reaction, catalyzed with piperidine lead to a complicated mixture containing only small amount of the compound *IV*. From the NMR and IR spectra of fractions from the chromatographic separation of the reaction products, we can infer that, to a certain extent, also the second methyl enters the reaction. Since in the basic medium the products are not fully dehydrated, the subsequent aldolisation reactions in the aliphatic side-chains lead to a mixture of hardly separable products. Condensation of the compound *I* with 3-(2-furyl)acrolein in an acid medium yielded also a complicated mixture, in which, however, the product *V* predominated and was isolated by chromatography.

Compounds *II*–*V* were reduced with sodium borohydride[4] to the corresponding 1,4-dihydro derivatives. This method afforded homogeneous products *VI*–*IX* which were identified spectroscopically (Table I and II). As expected, these dihydro derivatives were oxidized with nitric acid back to the starting pyridines *II*–*V*.

With the aim to introduce a triple bond into the side chain, the compound *II* was brominated to the corresponding dibromo derivative *X*. However, the attempted reduction of this derivative to the dihydro compound *XI* resulted in the debromina-

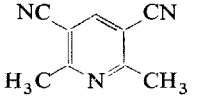
TABLE II

Chemical Shifts (p. p. m.) in the NMR Spectra of Compounds *II*—*X*

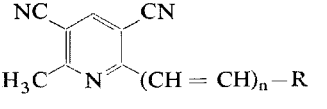
Compound	CH_3	CH[a]	CH[b]	NH	CH_2[c]	Furyl
II	2·85	7·5	8·05	—	—	—
III	2·6	7·2 7·6	7·85	—	—	6·4 6·55 7·4
IV	2·8	7·2	8·0	—	—	—
V	2·8	6·5 6·9 7·5 7·85	7·8	—	—	[d]
VI	1·9	7·15	—	5·1—5·7	3·2	—
VII	1·9	6·5	—	7·9—8·1	3·3	6·85 6·95 7·65
VIII	1·9	6·8 7·4	—	[e]	3·25	—
IX	2·2	6·4—6·8 7·5	—	5·8	3·35	[d]
X[f]	2·9	7·4	8·15	—	—	—

[a] Protons on benzene nucleus and in unsaturated chain. [b] Position 4 of the pyridine ring. [c] Position 4 of the dihydropyridine ring. [d] The signals cannot be distinguished from the signals of the unsaturated chain protons. [e] The signal was not found. [f] The shift of protons in the CHBr groups is 5·85 p.p.m.

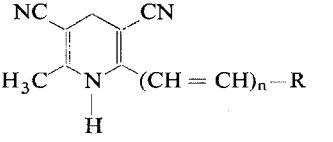
tion product *II*. This reductive elimination can probably be explained by the reductive debromination with sodium borohydride under formation of monobromo derivative from which hydrogen bromide is eliminated in the weakly alkaline medium under formation of the starting pyridine derivative *II*. The analogous reaction with 1,2-dibromo-1,2-diphenylethane and 2,6-bis(1,2-dibromo-2-phenylethyl)pyridine did not take place at all. Probably the presence of the nitrile groups in compound *X* enables reduction of the bromine on the carbon bonded to the pyridine nucleus, followed by spontaneous dehydrobromination. It was not possible to prepare the dibromo derivative *XI* derived from the dihydropyridine *VI*, even by the addition of bromine to the double bond of compound *VI*. In this reaction the dihydropyridine system was oxidized with bromine to pyridine derivative (as already observed in a series of dihydropyridine derivatives[4]), the only isolated product being compound *II*. The dehydrobromination of compound *X*, which in similar cases was carried out using ethanolic potassium hydroxide, was also unsuccessful because we were not able to prove a derivative with triple bond among the reaction products. Similarly, attempts to hydrogenate the double bond in the side chain in compounds *II* and *VI* were fruitless. The compound *II* was isolated unchanged and the dihydropyridine derivative *VI* afforded, besides the starting compound, only the product of aromatisation (*II*).



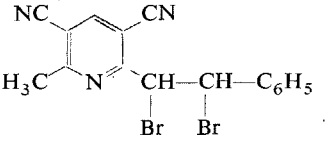
I



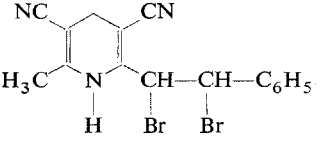
II $n = 1$, R = phenyl
III $n = 1$, R = 2-furyl
IV $n = 2$, R = phenyl
V $n = 2$, R = 2-furyl



VI $n = 1$, R = phenyl
VII $n = 1$, R = 2-furyl
VIII $n = 2$, R = phenyl
IX $n = 2$, R = 2-furyl



X



XI

Spectral data of the compounds *II*–*X* are given in Table I and II. The IR and NMR data are in accord with the anticipated structures. The configuration of the double bonds in the side chains in *II*–*IX* cannot be determined with certainty because of overlapping of the signals in the NMR spectra. Only in the case of com-

pound *III* the coupling constant was estimated to be 14 Hz, showing thus *trans*-configuration of the double bond. This conclusion is in agreement with the wave-number values of the out-of-plane deformation vibrations, γ(CH=CH) (Table I). As seen from the electronic absorption maxima, extension of the conjugated system in 2 position causes a shift of the long-wave band of about 70–130 nm in compounds *II–V* and of 10–65 nm in compounds *VI–IX* (Fig. 1). The intensive colour of the 1,4-dihydropyridine derivatives *VII* and *IX* is remarkable. When attempting to correlate the UV long-wave maxima with the excitation energy, as calculated using the simple HMO method, we have found that the correlation field is splitted into two groups of points (Fig. 2). One group is formed by the compounds *II*, *IV*, *VI* and *VIII* which contain phenyl moiety in the aldehyde part whereas the other group corresponds to compounds *III*, *V*, *VII* and *IX* with furan nucleus in the side chain. This splitting is obviously caused by an inconsistent parametrisation of benzene and furan nuclei.

The fluorescence of the dihydro derivatives *VI–IX* was also of interest. Whereas similar compounds, containing no aliphatic unsaturated group in the side chain in the 2 position, are outstanding luminophors[4], our compounds do not fluoresce. The extension of the conjugated system is expected to shift the fluorescence maximum

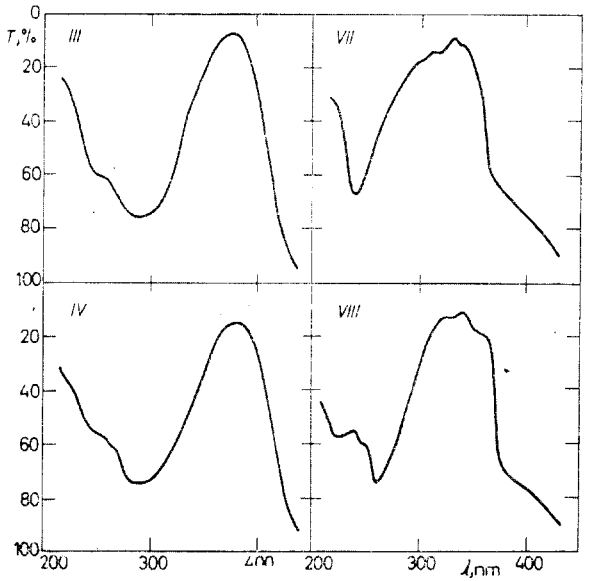


FIG. 1

Electronic Spectra of Pyridine Derivatives *III* and *IV* and Dihydropyridine Derivatives *VII* and *VIII*

to higher wavelengths. The absence of fluorescence in compounds *VI*–*IX* is apparently due to the non-planarity and flexibility of the side chain.

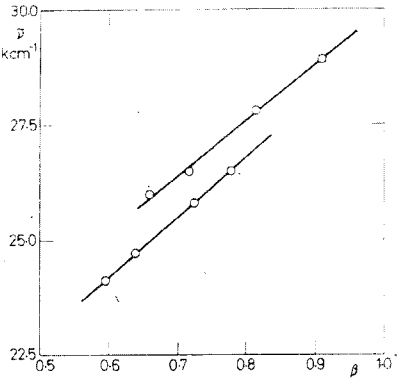


FIG. 2

Dependence of the Longest Wavelength Maximum in the Electronic Spectra of the Compounds *II*–*IX* on the HMO Excitation Energy $E(N \rightarrow V_1)$ (β)

We also attempted to describe the reactivity of some of the investigated compounds in the condensation reaction with aromatic aldehydes using the HMO method. It was not possible to use the electron densities and nucleophilic superdelocalisabilities of the methyl groups for the interpretation because they are very little sensitive to structural changes of the rest of the molecule. We used therefore the differences in energies of the methyl derivatives and the corresponding deprotonized forms.

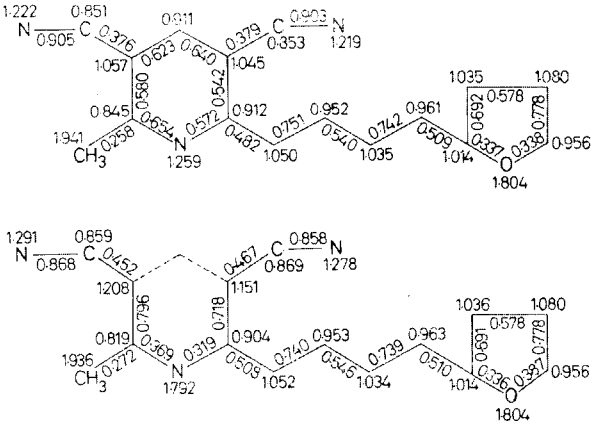


FIG. 3

Molecular Diagrams of Compounds *V* and *IX* as Calculated by HMO Method

From their values it is possible to conclude that the most facile attack of the methyl will be in compound *I* ($\Delta E = 3{\cdot}273\beta$); for compounds *II*, *IV* and *V* the indices are less favourable ($\Delta E = 3{\cdot}278$, $3{\cdot}279$ and $3{\cdot}279\beta$, respectively), and the least favourable index has the compound *III* ($\Delta E = 3{\cdot}452\beta$). The comparison of the molecular diagrams of stilbazole with the corresponding dihydro form is also interesting. It proves that the transition into the dihydro derivative enhances the conjugation with the side chains. For comparison, the molecular diagrams of the compounds *V* and *IX* are depicted in Fig. 3.

EXPERIMENTAL

Temperature data are uncorrected. Melting points were taken on a heated microscope stage (Boetius block). The IR spectra were recorded on Zeiss (Jena) UR 10 and Perkin-Elmer 325 spectrometers in chloroform solutions or by the KBr technique. The electronic spectra were measured on Optica Milano CF 4NI and Specord UV VIS spectrometers in ethanol solutions. The PMR spectra were taken on a Tesla BS 477 instrument at 60 MHz and on a Varian XL-100 spectrometer (100 MHz) in deuteriochloroform. The HMO calculations were carried out on a Tesla 200 computer by means of a standard program with the following empirical parameters: $h_N = 0{\cdot}5$, $k_{CN} = 1{\cdot}0$ for the pyridine nitrogen; $h_N = 1{\cdot}5$, $k_{CN} = 0{\cdot}8$ for the dihydropyridine nitrogen; $h_N = 0{\cdot}5$, $k_{CN} = 1{\cdot}4$ for the nitrile nitrogen; $h_{CH_3} = 2{\cdot}0$, $k_{C-CH_3} = 0{\cdot}7$; $h_O = 2{\cdot}0$, $k_{C-O} = 0{\cdot}8$. In dihydro derivatives the methylene group in the 4 position was neglected, the other parameters being: $h = 0$ for the coulombic integral and $k = 1$ for the exchange integral.

TABLE III

Condensation of 2,6-Dimethyl-3,5-dicyanopyridine (*I*) with Some Aldehydes

Product	Procedure (isolation[a])	Yield %	M.p., °C (solvent)	Formula (mol.wt.)	Calculated/Found		
					% C	% H	% N
II	*A* (1)	45	227—229 (dioxane)	$C_{16}H_{11}N_3$ (245·3)	78·34 77·90	4·52 4·65	17·13 16·91
II	*B* (1)	69					
III	*A* (1)	23	159—161 (methanol)	$C_{14}H_9N_3O$ (235·2)	71·47 71·42	3·85 4·14	17·86 18·06
III	*B* (1)	57					
IV	*A* (1)	44	230—233 (ethanol)	$C_{18}H_{13}N_3$ (271·3)	79·68 79·86	4·82 4·84	15·48 15·29
IV	*B* (2[b])	7					
V	*A* (2[c])	22	153—155 (ethanol)	$C_{16}H_{11}N_3O$ (261·3)	73·55 73·28	4·24 4·71	16·08 15·80

[a] 1 Crystallization, 2 chromatography on a silica gel column. [b] Eluant benzene–cyclohexane 1 : 2. [c] Eluant chloroform.

Condensation of 2,6-Dimethyl-3,5-dicyanopyridine (*I*) with Aldehydes

A) A mixture of compound *I* (1·57 g; 0·01 mol), aldehyde (0·23 mol) and acetic anhydride (1·4 g; 0·105 mol) was heated to 170°C for 6—8 hours. After cooling, the separated compound was purified by crystallization or chromatography.

B) A solution of compound *I* (1·57 g; 0·01 mol), aldehyde (0·023 mol) and piperidine (1 ml) in methanol (30 ml) was refluxed for 4 hours. The work-up procedure was the same as in the preceding paragraph. The synthesized compounds are listed in Table III.

Reduction of Stilbazoles *II*— *V* with Sodium Borohydride

Sodium borohydride (0·49 g; 0·013 mol) was added portionwise to a suspension of the pyridine derivative (0·005 mol) in 30 ml ethanol. The mixture was stirred for 1 hour at 40—50°C, allowed

TABLE IV

Reduction of Pyridine Derivatives *II*— *V* with Sodium Borohydride

Compound	Product (yield, %)	M.p., °C (solvent)	Formula (mol.wt.)	Calculated/Found		
				% C	% H	% N
II	*VI*	233—234	$C_{16}H_{13}N_3$	77·70	5·29	16·99
	(83)	(ethanol)	(277·3)	77·81	5·45	17·18
III	*VII*	140—141	$C_{14}H_{11}N_3O$	70·87	4·67	17·86
	(80)	(ethanol)	(237·2)	70·30	4·89	17·36
IV	*VIII*	235—238	$C_{18}H_{15}N_3$	79·09	5·53	15·38
	(51)	(dioxane)	(273·3)	78·99	5·65	15·09
V	*IX*	205—208	$C_{16}H_{13}N_3O$	72·99	4·98	15·96
	(33)	(ethanol–water)	(263·3)	72·78	5·39	16·12

TABLE V

Oxidation of Dihydropyridines *VI*—*IX*

Compound	Product	Yield, %	M.p., °C
VI	*II*	81	228—229
VII	*III*	78	158—161
VIII	*IV*	86	230—232
IX	*V*	63	151—154

to stand overnight and then diluted with water (30 ml). The separated product was filtered and crystallized. The dihydropyridine derivatives, prepared by this method, are listed in Table IV.

Oxidation of Dihydropyridines *VI—IX*

Sodium nitrite (0·42 g; 6 mmol) was added in several portions to a solution of dihydropyridine (0·6 mmol) in acetic acid (20 ml). After the evolution of nitrogen oxides had ceased, the mixture was warmed to 90°C and further sodium nitrite (0·42 g) was added. After standing overnight, the mixture was diluted with an equal volume of water and the separated product was filtered. The products were compared with authentic samples by thin layer chromatography (Silufol, detection with iodine), see Table V.

2-(1′,2′-Dibromo-2′-phenylethyl)-3,5-dicyano-6-methylpyridine (*X*)

A solution of bromine (0·8 g) in acetic acid (10 ml) was added at 60°C during 10 minutes to a solution of compound *II* (1·22 g; 5 mmol) in acetic acid (40 ml) and the mixture was heated to 60°C for 1 hour. The mixture was diluted by an equal volume of water and the separated product was filtered and crystallized from ethanol, yielding 1·4 g (70%) of the compound *X*, m.p. 167 to 168°C. For $C_{16}H_{11}Br_2N_3$ (405·1) calculated: 47·43% C, 2·73% H, 10·37% N, 39·45% Br; found: 47·07% C, 2·71% H, 9·98% N, 39·64% Br.

Attempted Reduction of Dibromo Derivative *X*

Sodium borohydride (0·24 g; 6·5 mmol) was added in several portions to a stirred solution of *X* (1 g; 2·5 mmol) in ethanol (30 ml). After standing overnight, the mixture was decomposed with water (20 ml) and the separated product was filtered. The yield of a compound, melting at 226 to 227°C, was 0·4 g (66%). The IR spectrum of this product was identical with that of the compound *II*.

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