by vacuum distillation, and the residue was washed with 1% HCl. The yield was 0.3 g. IR spectrum: 1170, 1360 (SO_2); 3342 cm^{-1} (NH).

LITERATURE CITED

1. I. Collins and H. Suschitzky, J. Chem. Soc., C, 1523 (1970).
2. D. J. Berry, B. J. Wakefield, and J. D. Cook, J. Chem. Soc., C, 1227 (1971).
3. H. Pfanz and H. Dorn, Arch. Pharm., 289, 651 (1956).
4. S. D. Moshchitskii, A. A. Zeikan', A. A. Kisilenko, and V. P. Kukhar', Khim. Geterotsikl. Soedin., No. 1, 70 (1978).
5. E. Spinner, J. Chem. Soc., 1237 (1960).
6. V. A. Ignatov, N. V. Zhorkin, P. A. Pirogov, L. M. Litvinenko, and R. S. Burmistrova, in: Synthesis and Study of Effective Chemicals for Polymeric Materials [in Russian], No. 3, Tambov (1969), p. 285.
7. L. S. Sologub, S. D. Moshchitskii, L. N. Markovskii, and Ya. N. Ivashchenko, Khim. Geterotsikl. Soedin., No. 9, 1232 (1970).
8. D. Kh. Yarmukhametova, and I. V. Geplanova, Izv. Akad. Nauk SSSR, Ser. Khim., No. 3, 489 (1966).
9. H. Kwart and R. W. Body, J. Org. Chem., 30, 1188 (1965).
10. E. Ager, B. Iddon, and H. Suschitzky, J. Chem. Soc., 1530 (1970).

SUBSTITUTION REACTIONS INVOLVING THE 2,6-METHYL GROUPS OF 1,4-DIHYDROPYRIDINES

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4,4-Disubstituted 1,4-dihydropyridines (I) are brominated with bromine in chloroform to give 2,6-bis(bromomethyl)-4,4-disubstituted 1,4-dihydropyridines (II), whereas 2,6-bis(dibromomethyl)-4,4-disubstituted 1,4-dihydropyridines (III) are obtained in the case of bromination of I in acetic acid. The bromine atoms in II and III are labile and readily undergo nucleophilic substitution.

Prior to our previous studies [1-3] substitution reactions involving the 2,6-methyl groups of 1,4-dihydropyridines were unknown. A communication regarding the possibility of nitration of the 2,6-methyl groups in polysubstituted 1,4-dihydropyridines was published recently [4].

We have investigated the bromination of 4,4-dialkyl-1,4-dihydropyridines. It is known [7] that 1,4-dihydropyridines undergo oxidation when they are treated with bromine. The bromination of 1,4-dihydropyridinecarboxylic acid esters leads to the formation of tetrabromo derivatives, the structures of which have not been proved [5, 6].

The 4-C—C=O bond undergoes cleavage to give 8-[10',12'-dioxodiindeno[1,2-b:2',1'-e)-11'-pyridyl]-1-naphthoic acid in the reaction of dioxane dibromide with spiro[2-oxoacenaphthene-1,11'-10',12'-dioxo-5',11'-dihydrodiindeno(1,2-b:2',1'-e)pyridine] [8].

We have shown that the 2,6-methyl groups to give dibromo derivatives Ia-d are brominated selectively in the bromination of 2,6-dimethyl-3,5-dicyano-4,4-dialkyl-1,4-dihydropyridines with bromine in chloroform [1, 3] or with dioxane dibromide in dioxane. (See scheme at top of next page).

Tetrabromo derivatives IIa-c were obtained by the action of excess bromine or 1,4-dihydropyridines in glacial acetic acid; we were able to obtain tetrabromo derivatives in chloroform only for 1,4-dihydropyridines with spiro rings in the 4 position. In all of these

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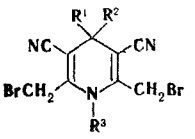

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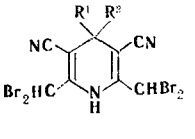


II

a $R^1=R^2=CH_3$; $R^3=H$; b $R^1=CH_3$; $R^2=C_3H_7$; $R^3=H$; c $R^1=R^2=C_2H_5$; $R^3=H$; d $R^1+R^2=(CH_2)_5$; $R^3=H$; II a $R^1=R^2=CH_3$; b $R^1+R^2=(CH_2)_5$; c $R^1+R^2=(CH_2)_4$

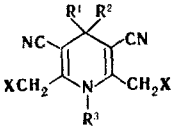
cases bromine attacks only the 2,6-methyl groups without affecting the alkyl groups in the 4 position.

In all liklihood the bromination of 1,4-dihydropyridines does not proceed via a radical mechanism. Evidence for this is provided by the PMR data (chemical polarization of the nuclei was not observed) and from the fact that the addition of radical initiators (benzoyl peroxide) and illumination have no effect on the reaction. We were unable to obtain bromo derivatives Ia-d by bromination with N-bromosuccinimide.

The structures of I and II can be proved unambiguously by means of the PMR spectra. Signals of 2,6-methylene groups at 4.10-4.80 ppm (Ia-e) and signals of 2,6-methylidyne groups at 6.60-7.30 ppm (IIa-c) appear in place of the signals of 2,6-methyl groups at 2.0-2.1 ppm in the PMR spectra of bromo compounds Ia-d and IIa-c.

A new band at 245-270 nm appears in the UV spectra of Ia-d and IIa-c, and the long-wave band is shifted bathochromically as compared with the band of the starting dihydropyridines (from 338-345 to 350-370 nm). The structures of Ia-e and IIa-c are also confirmed by the IR spectra.

In order to verify the lability of the halogen in derivatives I and II we carried out nucleophilic substitution reactions with secondary amines, sodium amide, sodium thiocyanate, potassium iodide, sodium methoxide, and the sodium salt of 2-phenylindane-1,3-dione. The halogen-exchange reactions were carried out under mild conditions, and substitution products III were formed in good yields.

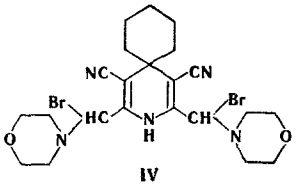


III a-k

IIIa-h $R^1=R^2=CH_3$ $R^3=H$; a $X=N_3$; b $X=SCN$; c $X=OCH_3$; d $X=I$; e X = phenylindanedionyl; f X = morpholino; g X = piperidino; h $X=N(C_2H_5)_2$; i $R^1=R^2=C_2H_5$, $R^3=H$, X = morpholino; j $R^1=R^2=R^3=CH_3$, X = morpholino

Compounds III are stable crystalline products, except for IIIa, b which slowly undergo decomposition in light. Their structures were cofirmed completely by their IR, UV, and PMR spectra (Table 2). C-Substitution to give IIIe occurs in the reaction with the sodium salt of 2-phenylindane-1,3-dione; this is proved by the presence of a characteristic pair of carbonyl absorption bands at 1705 and 1740 cm^{-1}. The long-wave maximum in the UV spectra of III is shifted bathochromically as compared with the maximum of 2,6-dimethyl-1,4-dihydropyridines (from 338-345 to 350-370 nm). This shift follows the trend of the change in the σ^* constants for substituents in the 2,6-methyl groups.

In the case of tetrabromo derivative IIb only two bromine atoms are exchanged to give IV even under severe conditions.



IV

Some of the compounds obtained lower the arterial pressure 60-80% in doses of 0.5 mg/kg.

Thus reactions involving substitution in the 2,6-methyl groups of 1,4-dihydropyridine open up possibilities for the synthesis of biologically active compounds in the 1,4-dihydropyridine series.

TABLE 1. Brominated 1,4-Dihydropyridines (I-II)

Compound	mp, °C	Empirical formula	Found/Calc. %				IR spectrum, cm^{-1}	UV spectrum, λ_{max}, nm (log ε)	PMR spectra, δ, ppm	Yield, %
			C	H	Br	N				
Ia	147—149	$C_{11}H_{11}Br_2N_3$	38,2 / 38,3	3,1 / 3,2	47,0 / 46,4	12,1 / 12,0	1661, 2207, 3225, 3260, 3280	208, 245, 369 (4,61; 4,65; 4,30)	1,51 (6H, 4,4-CH_3), 4,25 (4H, 2,6-CH_2)	80
Ib	157—159	$C_{13}H_{15}Br_2N_3$	41,7 / 41,8	3,9 / 4,0	41,8 / 42,9	11,0 / 11,2	1661, 2205, 3225, 3260, 3281	210, 251, 350 (4,55; 4,53; 4,21)	1,50 (3H, 4-CH_3), 1,62 (3H, Pr—CH_3), 2,02 (4H, Pr—CH_2), 4,11 (4H, 2,6-CH_2), 9,65 (1H, NH)	35
Ic	160—162	$C_{13}H_{15}Br_2N_3$	41,9 / 41,8	3,8 / 4,0	43,6 / 42,9	11,0 / 11,2	1660, 2205, 3225, 3260, 3278	210, 250, 370 (4,67; 4,54; 4,02)	1,1 (6H, Et—CH_3), 1,6 (4H, Et—CH_2), 4,21 (4H, 2,6-CH_2), 10,35 (1H, NH)	58
Id	140—141	$C_{14}H_{15}Br_2N_3$	43,6 / 43,6	3,9 / 3,8	42,2 / 41,5	11,0 / 10,9	1661, 2207, 3220, 3260, 3279	208, 247, 370 (4,53; 4,45; 4,01)	1,65 (10H, ring CH_2), 4,40 (4H, 2,6-CH_2), 11,02 (1H, NH)	62
IIa	167—168	$C_{11}H_9Br_4N_3$	26,4 / 26,2	1,9 / 1,7	—	8,4 / 8,3	1568, 2203, 3260	208, 267, 361 (4,10; 3,91; 3,51)	1,35 (6H, 4,4-CH_3), 6,85 (2H, 2,6-CH)	70
IIb	221—222	$C_{14}H_{13}Br_4N_3$	30,8 / 30,9	2,3 / 2,4	59,6 / 58,9	7,3 / 7,3	1661, 2207, 3220, 3260, 3280	208, 270, 360 (4,33; 4,94; 4,11)	1,65 (10H, ring-CH_2), 7,3 (2H, 2,6-CH), 9,82 (1H, NH)	60
IIc	188—189	$C_{13}H_{11}Br_4N_3$	29,8 / 29,5	2,4 / 2,1	—	8,2 / 7,9	1572, 2200, 3260	208, 250, 371 (4,42; 4,32; 4,05)	1,97 (8H, ring-CH_2), 6,65 (2H, 2,6-CH), 9,65 (1H, NH)	85

TABLE 2. 2,6-Disubstituted 1,4-Dihydropyridines III

Compound	mp, °C	Empirical formula	Found/Calc. %			Reaction conditions (solvent, reaction time, and temp.)	IR spectra, cm^{-1}	UV spectra, λ_{max}, nm (log ε)	PMR spectra, ppm	Yield, %
			C	H	N					
IIIa	98—99 (dec., ethanol—water 1 : 1)	$C_{11}H_{11}N_9$	49,3 / 49,1	4,3 / 4,1	46,3 / 46,8	Dioxane 1 h, 100°	1623, 1662, 2110, 2200, 3248—3300 (broad band)	218 (4,81), 272 (4,80), 349 (4,35)		42
IIIb	187—188 (ethanol—water 1 : 2)	$C_{13}H_{11}N_5S_2$	51,0 / 51,8	3,9 / 3,6	23,1 / 23,2	Dioxane 30 min, 100°	1629, 1670, 2159, 2202, 3235, 3276, 3294	222 (4,79), 270 (4,63), 356 (4,32)	1,55 (6H, 4,4-CH_3), 4,12 (4H, 2,6-CH_2), 7,68 (1H, NH)	34
IIIc	98—100 (benzene—hexane 1 : 2)	$C_{13}H_{17}N_3O_2$	62.9 / 63,1	6,8 / 6,8	17,8 / 17,0	Acetone, 2 h, 100°	1110, 1630, 1668, 2200, 3295, 3250	218 (4,91), 277 (4,50), 350 (4,43)	1,52 (6H, 4,4-CH_3), 3,51 (6H, OCH_3), 4,46 (4H, 2,6-CH_2), 8,18 (1H, NH)	70
IIId	163—164 (ethanol—water 1 : 2)	$C_{11}H_{11}I_2N_3$	30,6 / 30,0	2,6 / 2,5	9,3 / 9,5	Acetone, 30 min, 100°	1618, 1650, 2203, 3115, 3223, 3281	210 (4,77), 250 (4,62), 370 (4,25)	—	67
IIIe	225—227	$C_{41}H_{29}N_3O_4$	78,2 / 78,4	4,5 / 4,6	6,8 / 6,7	Dioxane 30 min, 100°	1670, 1705, 1740, 2203, 3275, 3250	208 (4,01), 230 (4,87), 257 (3,67), 370 (3,09)	0,88 (6H, 4,4-CH_3), 3,37 (4H, 2,6-CH_2), 7,36 (9H, arom. CH), 8,08 (1H, NH)	64
IIIf	163—164 (ethanol—water 1 : 1)	$C_{19}H_{27}N_5O_2$	64,0 / 63,8	7,9 / 7,5	19,5 / 19,6	Benzene, 24 h, 25°	1626, 1660, 2201, 3119, 3296	205 (4,88), 217 (4,74), 270 (4,75), 350 (4,22)	1,43 (6H, 4,4-CH_3), 2,52 (8H, $O(CH_2)_2$), 3,41 (4H, 2,6-CH_2), 3,76 (8H, $N(CH_2)_2$)	43
IIIg	160—162	$C_{21}H_{31}N_5$	71,5 / 71,4	9,0 / 8,7	19,6 / 19,8	The same	1606, 1660, 2195, 3270	218 (4,60), 221 (4,51), 227 (4,11), 345 (4,02)	1,41 (6H, 4,4-CH_3), 1,52 (12H, ring-CH_2), 2,41 (8H, $N(CH_2)_2$), 3,27 (4H, 2,6-CH_2)	52
IIIh	90—92	$C_{19}H_{31}N_5$	69,8 / 69,3	9,3 / 9,4	21,4 / 21,2	Benzene, 2 h, 25°C	1606, 1660, 2199, 3306	205 (4,92), 218 (4,73), 271 (4,02), 350 (4,11)	1,11 (12H, Et—CH_3), 1,43 (6H, 4,4-CH_3), 2,57 (8H, NCH_2), 3,48 (4H, 2,6-CH_2)	40
IIIi	130—132	$C_{21}H_{31}N_5O_2$	65,2 / 65,4	8,0 / 8,0	17,7 / 18,2	The same		205 (4,72), 218 (4,83), 260 (4,55), 340 (4,21)	0,94 (6H, Et—CH_3), 1,53 (4H, Et—CH_2), 2,49 (8H, $O(CH_2)_2$), 3,41 (4H, 2,6-CH_2), 3,75 (8H, $N(CH_2)_2$)	41
IIIj	134—135	$C_{20}H_{27}N_5O_2$	60,1 / 59,9	6,6 / 6,3	16,3 / 16,3	„ „		207 (4,55), 221 (4,40), 278 (4,30), 347 (4,02)	1,38 (6H, 4,4-CH_3), 2,52 (8H, $O(CH_2)_2$), 3,41 (4H, 2,6-CH_2), 3,48 (8H, $N(CH_2)_2$), 3,81 (3H, N—CH_3)	38
IV	162—164	$C_{22}H_{28}Br_2N_5O_2$	47,3 / 47,6	5,01 / 5,06	12,3 / 12,6	„ „		205 (4,72), 219 (4,73), 280 (4,51), 350 (4,07)	1,79 (6H, 4,4-CH_3), 2,52 (8H, $O(CH_2)_2$), 3,76 (8H, $N(CH_2)_2$), 6,68 (2H, 2,6-CH)	51

EXPERIMENTAL

The IR spectra of suspensions of the compounds in Nujol and hexachlorobutadiene were recorded with a UR-20 spectrometer. The UV spectra of solutions of the compounds in ethanol were recorded with a Specord UV-vis spectrophotometer. The PMR spectra were recorded with a Perkin–Elmer spectrometer with tetramethylsilane as the standard.

2,6-Bis(bromomethyl)-3,5-dicyano-4,4-dimethyl-1,4-dihydropyridine (Ia). A) A 0.3-ml (5.8 mmole) sample of bromine was added to a solution of 0.5 g (2.7 mmole) of 2,4,4,6-tetramethyl-3,5-dicyano-1,4-dihydropyridine in chloroform, and the mixture was maintained at 30°C for 10 min. The solvent was then removed by vacuum distillation, and the residue was crystallized from ethanol–water (1:1) to give yellow crystals of Ia. Compounds Ib-d were similarly obtained (see Table 1).

B) A 1.2-g (5 mmole) sample of freshly prepared dioxane dibromide was added to a solution of 2,4,4,6-tetramethyl-3,5-dicyano-1,4-dihydropyridine in dioxane, and the mixture was heated at 50°C for 30 min. The solvent was removed by vacuum distillation, and the residue was crystallized from ethanol–water (1:1).

2,6-Bis(dibromomethyl)-3,5-dicyano-4,4-dimethyl-1,4-dihydropyridine (IIa). A 0.6-ml (0.01 mole) sample of bromine was added to a solution of 0.5 g (2.7 mmole) of 2,4,4,6-tetramethyl-3,5-dicyano-1,4-dihydropyridine in glacial acetic acid, and the mixture was refluxed for 2 h. The precipitated IIa was crystallized from ethanol–water (1:2) (see Table 1).

Spiro[cyclohexane-1,4'-2',6'-bis(bromomethyl)-3',5'-dicyano-1',4'-dihydropyridine] (IIb). A 0.6-ml (0.01 mole) sample of bromine was added dropwise to a solution of 0.5 g (2.2 mmole) of spiro(cyclohexane-1,4'-2',6'-dimethyl-3',5'-dicyano-1',4'-dihydropyridine) in chloroform, and the mixture was stirred at room temperature for 10 min. The solvent was then removed by vacuum distillation, and the residue was crystallized from ethanol–water (1:1) to give the product in the form of yellow crystals (see Table 1).

2,6-Bis(azidomethyl)-4,4-dimethyl-3,5-dicyano-1,4-dihydropyridine (IIIa). A solution of 0.83 g (0.015 mole) of sodium azide in water was added to a solution of 2.1 g (6 mmole) of Ia in dioxane, and the mixture was heated on a water bath for 1 h. It was then poured over ice, and the resulting precipitate was crystallized from ethanol–water (1:2). Compounds IIIb-e were similarly obtained (see Table 2).

2,6-Bis(morpholinomethyl)-4,4-dimethyl-3,5-dicyano-1,4-dihydropyridine (IIIf). A 1.9-ml (0.024 mole) sample of morpholine was added to a solution of 2.1 g (6 mmole) of Ia in dry benzene, and the mixture was allowed to stand at room temperature for 24 h. The precipitated morpholine hydrobromide was separated, and the filtrate was vacuum evaporated. The residue was crystallized from ethanol–water (1:2). Compounds IIIg-j and IV were similarly obtained (see Table 2).

LITERATURE CITED

1. A. M. Kats, V. V. Solov'eva, and G. Ya. Dubur, USSR Inventor's Certificate No. 545639 (1975); Byull. Izobr., No. 5, 90 (1977).
2. V. V. Kastron, A. M. Kats, G. Ya. Dubur, and G. O. Silenietse, USSR Inventor's Certificate No. 568641 (1976); Byull. Izobr., No. 30, 55 (1977).
3. A. M. Kats, V. V. Kastron, and G. Ya. Dubur, Khim. Geterotsikl. Soedin., No. 4, 555 (1977).
4. J. Kuthan and A. Kurfürst, Tetrahedron Lett., 2073 (1976).
5. A. Hantzsch, Ann., 215, 1 (1882).
6. B. Benary, Ber., 51, 567 (1918).
7. O. Mumm and J. Diederichsen, Ann., 538, 195 (1939).
8. G. Ya. Dubur, Master's Dissertation, Institute of Organic Synthesis of the Academy of Sciences of the Latvian SSR, Riga (1962).