ON REACTIVITY OF 2,6-DICHLORO-3,5-DIFORMYL-1,4,4-TRIMETHYL--1,4-DIHYDROPYRIDINE

Antonín KURFÜRST and Pavel ŠEBEK

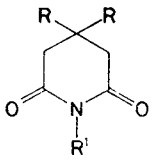
Department of Organic Chemistry,
Prague Institute of Chemical Technology, 166 28 Prague 6

Received September 9, 1988
Accepted November 3, 1988

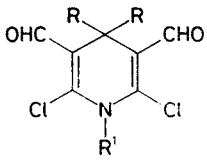
2,6-Dichloro-3,5-diformyl-4,4-dimethyl-1,4-dihydropyridines *IIb—IId* have been prepared by the Vilsmeier–Haack reaction of glutarimides *I*, and possible chemical transformations of the trimethyl derivative *IIc* have been examined. The bis-oxime *IVa* and bis-(2,4-dinitrophenylhydrazone) *Vb* are formed by the respective reactions of the formyl groups. The nucleophilic substitutions of chlorine give the corresponding derivatives *IX—XII*. The cyclocondensation reaction of compound *IIc* with the respective reagents gives the condensed heterocyclic derivatives *VI*, *XIII*, and *XIV*. The physico-chemical characteristics of the *II—XIV* compounds prepared are described.

In recent years increasing attention of synthetic chemists has been paid[1,2] to studies of chemical transformations of substituents attached at various positions of 1,4-dihydropyridine nucleus. A synthesis of new type of polysubstituted 1,4-dihydropyridines *II* (R = H, R^1 = H, aryl) has been published recently[3–5]. These compounds undergo a number of transformations[4,5] at the formyl and chloro substituents. The aim of this present work is investigation of possibilities of preparation of 1,4-dihydropyridines of the type *II* (R = CH_3, R^1 = H, alkyl, aryl), which can be expected to possess a greater stability[1,6] due to the double substitution at the 4 position, and investigation of their further transformations.

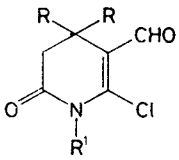
Glutarimides *I* (R = H, R^1 = H, aryl) react with dimethylformamide and phosphoryl trichloride in chloroform at 70°C to give tetrahydropyridones *III* (R = H, R^1 = H, aryl)[3], whereas the reaction performed without solvent and with excess phosphoryl trichloride at 100°C gives the dihydropyridines of the type *II* (ref.[4]). In contrast to this, glutarimide *Ic* gives dihydropyridine *IIc* under both conditions mentioned, the yield of *IIc* being only 23% in chloroform, and compound *IIIc* was not isolated from the reaction mixture. In attempts to obtain higher yields of dihydropyridine *IIc* glutarimide *Ic* was chloroformylated at 100°C (various reaction times – see Experimental). The highest yield of compound *IIc* (65%) was obtained after heating of glutarimide *Ic* with dimethylformamide and excess phosphoryl trichloride at 100°C for 4 h. Longer heating again decreases the yield of *IIc*. The chloroformylation conditions found were also applied to preparation of compounds *IIb* and *IId*.



I



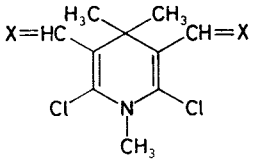
II

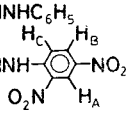


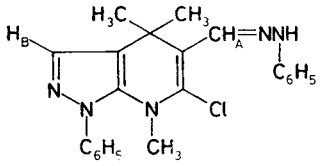
III

In formulae *I*–*III*: *a*, R = R' = H *b*, R = CH_3; R' = H *c*, R = R' = CH_3 *d*, R = CH_3; R' = C_6H_5

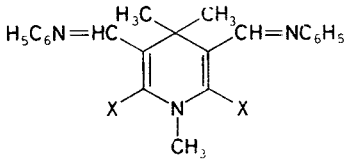
Dihydropyridine *IIc* was chosen for study of further transformations, since it is relatively stable and accessible in the highest yields. First we studied the possibility of selective transformations of 3- and 5-formyl groups by reactions typical of the aldehydic group. Reaction of dihydropyridine *IIc* with excess hydroxylamine in



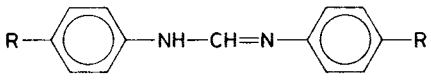
IV a, X = NOH
IV b, X = CHCOOH
V a, X = $NNHC_6H_5$
V b, X = 



VI



VII a, X = Cl
VII b, X = NHC_6H_5

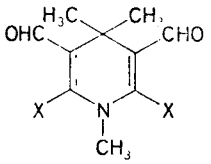


VIII a, R = H
VIII b, R = CH_3

ethanol gave the bis-oxime *IVa*. Whereas the reaction of dihydropyridine *IIc* with phenylhydrazine gives the labile product *Va* which is cyclized to pyrazolodihydropyridine *VI* during attempts at its isolation by column chromatography on silica gel, the reaction with 2,4-dinitrophenylhyrazine produces the stable bis-hydrazone *Vb*. The reaction of dihydropyridine *IIc* with excess aniline in benzene medium at room temperature or by refluxing gave none of the presumed products *VIIa,b* or *IXc*. Only formamidine hydrochloride *VIIIa* was isolated from the reaction mixture. Other products of this reaction are unstable and decompose during attempts at their isolation from the complex reaction mixture, hence the mechanism of formation of compound *VIIIa* could not be suggested. An analogous reaction of dihydropyridine *IIc* with *p*-toluidine gave the product *VIIIb*.

The attempts at oxidation of formyl groups of compound *IIc* into carboxylic groups by action of silver oxide or potassium permanganate were unsuccessful in contrast to analogous indole[7], pyrrole[8], or isoxazole[9] derivatives. In both cases only the starting substance *IIc* was isolated from the reaction mixture. Also unsuccessful was the atempt at preparation of compound *IVb* by the Perkin synthesis, i.e. heating of dihydropyridine *IIc* with acetanhydride and sodium acetate. Instead of the expected reaction of the formyl groups, the chloro substituents underwent nucleophilic substitution with sodium acetate to give the compound *X*.

The reactions of dihydropyridine *IIc* with excess sodium alkoxides in absolute dimethylformamide medium gave the respective 2,6-dialkoxy derivatives *XI*.Higher yields of compound *XIa* were obtained from the reaction with ethanol under the conditions of phase transfer catalysis. Dialkoxydihydropyridines *XIa*, *XIb* are very unstable already at room temperature, whereas the diphenoxyderivative *XIc* is stable. Alkylthio derivatives *XIIa* and *XIIb* were prepared by reaction of dihydropyridine *IIc* with bis-(S-methylisothiouronium) sulfate and with benzyl thioalcohol in the presence of triethylamine, respectively. Heating of dihydropyridine *IIc* with excess piperidine or morpholine in benzene gives the products *IXa* or *IXb*, respectively. Under the



IXa, X = —N⬡

IXb, X = —N⬡O

IXc, X = —NHC_6H_5

X, X = —$OCOCH_3$

XIa, X = —OCH_2CH_3

XIb, X = —$OCH(CH_3)_2$

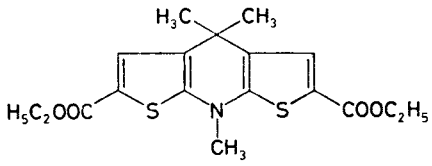
XIc, X = —OC_6H_5

XIIa, X = —SCH_3

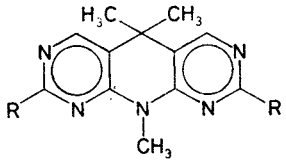
XIIb, X = —$SCH_2C_6H_5$

same conditions pyrrolidine gives a tarry polymeric product. Dialdehyde *IXa* reacts neither with phenylhydrazine nor with hydroxylamine. This fact is due obviously to the inaccessibility of the formyl groups sterically hindered by bulky substituents at 2,4,6-positions of 1,4-dihydropyridine nucleus.

As dihydropyridine *IIc* contains a 3-chloropropenoyl grouping in its molecule, possibilities were investigated of syntheses of condensed heterocycles by application of known[10-12] reactions of β-chloro-α,β-unsaturated ketones. The reaction of dihydropyridine *IIc* with ethyl thioglycolate in ethanol catalyzed with trimethylamine gives a complex mixture of products, whereas in the presence of sodium carbonate the same reaction gave 65% yield of bis-thienodihydropyridine *XIII*. The heating of dihydropyridine *IIc* with excess formamide gave pyridodipyrimidine *XIVa*. The reaction of dihydropyridine *IIc* with benzamidinium chloride gave pyridodipyrimidine *XIVb*.



XIII



XIVa, R = H
XIVb, R = C_6H_5

Structure of all the newly prepared compounds was verified by elemental analyses, ^{1}H NMR and IR spectra. The chemical shift values and integral intensities in ^{1}H NMR spectra of the compounds prepared correspond to the structures *II*, *IVa*, *Vb*, *VI*, *VII*–*XIV*. A common feature of the ^{1}H NMR spectra of compounds *IIc*, *IVa*, *Vb*, *VI*, *IX*–*XIV* is the signals of two equivalent methyl groups in the region 1·38–2·12 ppm and those of N-methyl groups in the region of 2·81–4·25 ppm. Whereas the IR spectra of compounds *II*, *IVa*, *IXa,b*, *X*, and *XII* exhibit separated bands of valence vibrations of C=O and/or C=N bonds in the region of 1 625 to 1 680 cm^{-1} and the bands[1,6] of characteristic vibrations of 1,4-dihydropyridine skeleton in the region of 1 510–1 625 cm^{-1}, the spectra of dihydropyridines *Vb*

and *XI* only exhibit the skeletal vibrations of the whole conjugated system[1] in the region of 1 565–1 660 cm^{-1}. The IR spectra of condensed heterocycles *VI*, *XIII*, and *XIV* exhibit a number of bands due to valence vibrations of the system of C=C and/or C=N bonds in the region of 1 400–1 620 cm^{-1}. Bis-oxime *IVa* is decomposed during recrystallization, hence its structure could be confirmed only by spectral methods.

The above-given results of investigation of chemical reactivity of 1,4-dihydropyridine *IIc* indicate high reactivity of chloro substituents at 2- and 6-positions to nucleophilic reagents and decreased reactivity of 3- and 5-formyl groups due to the steric hindrance caused by the 4-substituents or also 2- and 6-substituents.

EXPERIMENTAL

The temperature data were not corrected. The melting points were measured with a Boetius apparatus. The infrared spectra were measured with a Perkin–Elmer 325 apparatus. The ^1H NMR spectra were measured with a Bruker AM 400 (400·133 MHz) apparatus using tetramethylsilane as the internal standard (δ = 0 ppm). The mass spectra were measured by the field desorption method using a JEOL DX 303/DA 5000 apparatus. The purity of the compounds synthetized and the course of the reactions were followed by means of TLC on Silufol and Alufol layers (Kavalier, Votice, ČSSR).

The starting 3,3-dimethylglutaric acid was obtained by oxidative splitting[13] of dimedone or by acid hydrolysis[14] of 2,4-dicyano-3,3-dimethylglutarimide prepared by the Guareschi condensation[15] of acetone with ethyl cyanoacetate and ammonia. N-Substituted glutarimides *I* were prepared[16] by reaction of 3,3-dimethylglutaric acid with corresponding N-substituted formamides.

2,6-Dichloro-3,5-diformyl-1,4-dihydropyridine *IIa*

Phosphoryl trichloride (55 g, 360 mmol) was added drop by drop to a suspension of 2 g (18 mmol) glutarimide *Ia* in 5·2 g (72 mmol) absolute dimethylformamide with exclusion of moisture, with stirring and cooling with an ice bath. Thereafter, the mixture was stirred at room temperature 1 h and in a 100°C bath 1·5 h. After cooling the reaction mixture was decomposed by pouring it onto 100 g ice. The solution was neutralized to pH 7 by addition of 4M-NaOH solution. The yellow precipitate formed was collected by suction, washed with water, and dried in a dessiccator. Recrystallization from 2-butanone gave 2·3 g (63%) compound *IIa*, m.p. 187–189°C (ref.[4] gives m.p. 166–168°C).

Chloroformylation of Glutarimide *Ic* in Chloroform

Glutarimide *Ic* (1 g, 6·5 mmol) was dissolved in 10 ml chloroform, and 0·75 g (9·8 mmol) absolute dimethylformamide was added thereto. Phosphoryl trichloride (4 g, 26 mmol) was added drop by drop to the reaction mixture with cooling (ice bath). The reaction mixture was stirred at room temperature 1 h and heated on a 70°C bath 50 h. Chloroform was removed by vacuum distillation, and the residue was poured onto 50 g ice. The aqueous solution was neutralized to pH 7 by addition of 4M-NaOH solution. The precipitate was collected by suction, washed with water, and dried in a dessiccator. Recrystallization from a mixture of ethanol–water (1 : 1) gave 0·45 g (29%) compound *IIc*.

Chloroformylation of Glutarimides *Ib*—*Id* in Excess Phosphoryl Trichloride — General Procedure

A solution of 7·1 mmol glutarimide *I* in 28·4 mmol absolute dimethylformamide was stirred with exclusion of moisture, and 106 mmol phosphoryl trichloride was added dropwise with cooling (ice bath). The reaction mixture was stirred at room temperature 3—4 h. Then the bath temperature was increased to 100°C within 0·5 h. After a definite interval of heating (see below) the unreacted phosphoryl trichloride was distilled off in vacuum. The residue was poured onto 25 g ice, and the mixture obtained was treated in the same way as in the above procedure of chloroformylation in chloroform.

2,6-*Dichloro*-3,5-*diformyl*-4,4-*dimethyl*-1,4-*dihydropyridine* IIb. After four hours of heating the yield of compound *IIb* was 60%, m.p. 180—181°C. For $C_9H_9Cl_2NO_2$ (234·1) calculated: 46·19% C, 3·90% H, 30·30% Cl, 5·98% N; found: 46·31% C, 3·85% H, 29·83% Cl, 5·91% N. ^{1}H NMR spectrum (deuteriochloroform): 1·48 s, 6 H ($(CH_3)_2$); 3·50 s, 1 H (NH); 8·20 s, 2 H (CHO). IR spectrum ($CHCl_3$), $\tilde{\nu}_{max}$ (cm^{-1}): 3 420 m (N—H); 3 020 w, 2 940 w, 2 880 w, 2 780 w (C—H); 1 675 s (C=O); 1 625 s, 1 575 w (dihydropyridine skeleton); 1 495 w, 1 455 s, 1 380 m, 1 360 m (C–H).

2,6-*Dichloro*-3,5-*diformyl*-1,4,4-*trimethyl*-1,4-*dihydropyridine* IIc. The yields of compound *IIc* (m.p. 137·5—138·5°C) were 30%, 65%, 22%, and 5% after three, four, five, and ten hours of heating, respectively. For $C_{10}H_{11}Cl_2NO_2$ (248·1) calculated: 48·42% C, 4·47% H, 28·61% Cl, 5·65% N; found: 48·51% C, 4·60% H, 29·11% Cl, 5·82% N. ^{1}H NMR spectrum ($CDCl_3$): 1·84 s, 6 H ($(CH_3)_2$); 4·25 s, 3 H (NCH_3); 9·95 s, 2 H (CHO). IR spectrum ($CHCl_3$), $\tilde{\nu}_{max}$ (cm^{-1}): 3 020 w, 2 940 w, 2 880 w, 2 780 w (C–H); 1 670 s (C=O); 1 615 s, 1 535 w (dihydropyridine skeleton); 1 465 w, 1 440 w, 1 380 m, 1 360 m (C–H).

2,6-*Dichloro*-1-*phenyl*-3,5-*diformyl*-4,4-*dimethyl*-1,4-*dihydropyridine* IId. After four hours of heating the yield of compound *IId* was 39%, m.p. 123—125°C. For $C_{15}H_{13}Cl_2NO_2$ (310·2) calculated: 58·08% C, 4·22% H, 22·86% Cl, 4·52% N; found: 58·25% C, 4·49% H, 22·73% Cl, 4·39% N. ^{1}H NMR spectrum (deuteriochloroform): 1·78 s, 6 H ($(CH_3)_2$); 7·29—7·60 m, 5 H ($N-C_6H_5$); 9·94 s, 2 H (CHO). IR spectrum ($CHCl_3$), $\tilde{\nu}_{max}$ (cm^{-1}): 3 020 w, 2 940 w, 2880 w, 2 780 w (C—H); 1 680 s (C=O); 1 618 s, 1 545 w (dihydropyridine skeleton); 1 470 w, 1 420 w, 1 380 m, 1 360 m (C—H).

Reaction of Compound *IIc* with Hydroxylamine

Solutions of 1·2 g (18 mmol) hydroxylamine hydrochloride and 1 g (4 mmol) dihydropyridine *IIc* in the minimum amount of absolute ethanol were added to a solution of sodium ethoxide prepared from 0·42 g (18 mmol) sodium and 10 ml absolute ethanol, and the mixture was left to stand at room temperature 5 days. Then ethanol was evaporated in a vacuum evaporator without heating the bath. The crystalline residue was washed with water, collected by suction, and dried in a dessiccator. Yield 0·98 g (91%) 2,6-dichloro-3,5-bis(formhydroximoyl)-1,4,4-trimethyl-1,4-dihydropyridine *IVa*, m.p. 101°C (with decomposition). ^{1}H NMR spectrum ($DCON(CD_3)_2$): 1·65 s, 6 H ($(CH_3)_2$); 3·32 s, 3 H (NCH_3); 8·00 s, 2 H (CH=N); 11·13 s, 2 H (NOH). IR spectrum ($CHCl_3$), $\tilde{\nu}_{max}$ (cm^{-1}): 3 300 m (O—H); 3 000 w, 2 940 w (C—H); 1 625 s (C=N); 1 610 s, 1 555 s dihydropyridine skeleton); 1 380 w, 1 360 m (C—H); 1 320 s (O—H);, 960 s (N—O). Mass spectrum, *m/z* (relative intensity, %): 280 (10), 279 (8), 278 (14), 227 (10) 266 (11), 267 (7), 264 (62), 263 (12), 262 (100), 246 (8), 244 (15), 242 (16), 230 (11), 228 (23), 226 (27), 210 (13), 208 (24), 194 (10), 192 (7), 190 (27), 182 (6), 177 (10), 176 (7), 174 (7), 165 (12), 149 (40), 140 (6), 139 (21), 135 (5), 133 (8), 121 (27), 105 (13), 93 (12), 81 (27), 76 (30), 65 (21).

Reaction of Compound *IIc* with Phenylhydrazine

A solution of 1 g (4 mmol) dihydropyridine *IIc* and 0·9 g (8 mmol) phenylhydrazine in methanol was refluxed 2 h, According to TLC (Silufol, chloroform) the reaction mixture contained two substances with $R_F = 0{\cdot}7$ and $R_F = 0{\cdot}3$. After evaporation in a vacuum evaporator the raw product was washed with cyclohexane and submitted to column chromatography (silica gel, benzene–cyclohexane 1 : 1). The fractions containing the substance with $R_F = 0{\cdot}3$ were combined and evaporated (the substance with $R_F = 0{\cdot}7$ originally present was not found by TLC in the eluate). Recrystallization from cyclohexane gave 0·6 g (32%) 5-chloro-3-phenyl-6-(N--phenylformhydrazonyl)-4,7,7-trimethyl-4,7-dihydropyrazolo[3,4-*b*]pyridine (*VI*), m.p. 191 to 193°C. For $C_{22}H_{22}ClN_5$ (391·9) calculated: 67·39% C, 5·75% H, 9·15% Cl, 17·71% N; found: 67·14% C, 5·81% H, 9·47% Cl, 17·58% N. ^{1}H NMR spectrum (DCON$(CD_3)_2$): 1·85 s, 6 H ($(CH_3)_2$); 3·51 s, 3 H (NCH_3); 6·75—7·66 m, 10 H (Ar–H); 7·71 s, 1 H (H_A); 8·06 s, 1 H (H_B). IR spectrum (KBr), $\tilde{\nu}_{max}$ (cm^{-1}): 3 320 m (N—H); 3 050 w, 3 005 w, 2 995 w, 2 980 w , 2 930 w (C—H); 1 620 s, 1 605 s, 1 575 m, 1 560 s, 1 510 s, 1 490 s (C=C and C=N).

Reaction of Compound *IIc* with 2,4-Dinitrophenylhydrazine

A mixture of 0·4 g (1·6 mmol) dihydropyridine *IIc* and 1·3 g (6·4 mmol) 2,4-dinitrophenylhydrazine in 20 ml chloroform was heated on a 100°C bath 32 h. After cooling the crystalline product was collected by filtration and washed with ethanol. Recrystallization from benzene gave 0·62 g (47%) 2,6-dichloro-3,5-bis-(N-(2′,4′-dinitrophenyl)formhydrazonoyl)-1,4,4-trimethyl--1,4-dihydropyridine (*Vb*), m.p. 217—219°C. For $C_{22}H_{19}Cl_2N_9O_8$ (608·4) calculated: 43·57% C, 2·81% H, 11·69% Cl, 20·81% N; found: 43·62% C, 2·83% H, 11·26% Cl, 20·56% N. ^{1}H NMR spectrum (DCON$(CD_3)_2$): 2·12 s, 6 H ($(CH_3)_2$); 3·51 s, 3 H (NCH_3); 3·55 s, 2 H (N—H); 7·97 d, 1 H ($J = 9{\cdot}7$ Hz, H_C); 8·42 dd, 1 H ($J = 9{\cdot}7$ Hz; $J = 2{\cdot}6$ Hz, H_B); 8·78 s, 2 H (CH=N); 8·95 d, 1 H ($J = 2{\cdot}6$ Hz, H_A). IR spectrum (KBr), $\tilde{\nu}_{max}$ (cm^{-1}): 3 260 w (N—H); 3 100 w, 2 900 w (C—H); 1 620 m, 1 595 m (C=C and C=N); 1 505 s, 1 330 s (NO_2).

Reaction of Compound *IIc* with Aniline

A mixture of 0·5 g (2 mmol) dihydropyridine *IIc* and 1·1 g (12 mmol) aniline in 30 ml benzene was heated on a 110°C bath 6 h. The crystalline solid formed was collected by suction after cooling the reaction mixture, washed with tetrachloromethane, and dried. The product was added to a solution of sodium carbonate with stirring. The precipitate formed was collected by filtration and washed with water. The product was dried and recrystallized from a mixture of tetrachloromethane–cyclohexane (1 : 1) to give 0·61 g (77%) N,N′-diphenylformamidine (*VIIIa*), m.p. 140—142°C (ref.[17] gives m.p. 138—139°C).

Reaction of Compound *IIc* with *p*-Toluidine

In analogy with the previous procedure, 0·5 g (2 mmol) dihydropyridine and 1·8 g (16 mmol) *p*-toluidine gave 0·3 g (62%) N,N′-di-(*p*-tolyl)formamidine (*VIIIb*), m.p. 144·5—145·5°C (ref.[18] gives m.p. 141°C).

Attempt at Oxidation of Compound *IIc* with Potassium Permanganate

Dihydropyridine *IIc* (0·5 g, 2 mmol) was dissolved in hot 80% aqueous dioxane. Gradually, 1 g (6 mmol) $KMnO_4$ was added to the solution, and the mixture was heated on a 100°C bath 8 h. The reaction mixture was concentrated to a half volume, cooled, and poured in water. The

precipitate formed was collected by filtration. The starting dihydropyridine *IIc* was recovered in the amount of 0·32 g (64%).

Attempt at Oxidation of Compound *IIc* with Silver Oxide

Silver nitrate (2·8 g, 16 mmol) was added to a solution of 1·4 g (32 mmol) sodium hydroxide in 25 ml water. After addition of 1 g (4 mmol) dihydropyridine *IIc* the reaction mixture was stirred at room temperature 10 h. In order to increase the solubility of compound *IIc*, 30 ml dioxane was added, and the stirring at room temperature was continued 12 h. Extraction with chloroform recovered 0·86 g (86%) of the starting compound *IIc*.

Dialkoxylations of Compound *IIc*

Procedure A. Dihydropyridine *IIc* (4 mmol) was dissolved in 20 ml absolute dimethylformamide. After addition of 32 mmol sodium alkoxide the reaction mixture was stirred with exclusion of moisture at room temperature 4 h. The precipitate formed after pouring the reaction mixture in 400 ml water was collected by suction, washed with water, and dried.

2,6-*Diethoxy*-3,5-*diformyl*-1,4,4-*trimethyl*-1,4-*dihydropyridine* (XIa) was obtained by recrystallization of the above-mentioned precipitate; yield 42%, m.p. 107—109°C. For $C_{14}H_{21}NO_4$ (267·3) calculated: 62·94% C, 7·87% H, 5·24% N; found: 63·07% C, 7·97% H, 5·21% N. ^{1}H NMR spectrum (deuteriochloroform): 1·43 t, 6 H (CH_3); 1·72 s, 6 H ($(CH_3)_2$); 3·09 s, 3 H (NCH_3); 3·95 q, 4 H (OCH_2); 9·74 s, 2 H (CHO). IR spectrum ($CHCl_3$), $\tilde{\nu}_{max}$ (cm^{-1}): 3 010 w, 2 990 w, 2 940 w, 2 870 w (C—H); 1 640 s, 1 560 m (skeletal).

3,5-*Diformyl*-2,6-*diisopropoxy*-1,4,4-*trimethyl*-1,4-*dihydropyridine* (XIb) was obtained by column chromatography (silica gel, chloroform) of the above-mentioned precipitate; yield 16%, m.p. 136—139°C. For $C_{16}H_{25}NO_4$ (295·4) calculated: 65·11% C, 8·47% H, 4·74% N; found: 64·76% C, 8·46% H, 4·66% N. ^{1}H NMR spectrum (deuteriochloroform): 1·37 d, 12 H (CH_3); 1·70 s, 6 H ($(CH_3)_2$); 3·07 s, 3 H (NCH_3); 4·26 m, 2 H (OCH); 9·68 s, 2 H (CHO). IR spectrum ($CHCl_3$), $\tilde{\nu}_{max}$ (cm^{-1}): 3 010 w, 2 990 w, 2 930 w, 2 870 w (C—H); 1 640 s, 1 570 m (skeletal).

Procedure B. A solution of 1 g (4 mmol) dihydropyridine *IIc* in 20 ml benzene was treated with 0·2 g tetrabutylammonium bromide, 4 ml (80 mmol) ethanol, and 3·2 g (80 mmol) sodium hydroxide (in the form of 50% aqueous solution). The mixture was stirred at room temperature 20 min. The organic layer was separated, washed with 3 × 200 ml saturated NaCl solution, with water, and dried with $MgSO_4$. Benzene was distilled off, and the yellow crystalline residue was recrystallized from cyclohexane to give 0·55 g (50%) compound *XIa*.

Reaction of Compound *IIc* with Sodium Phenoxide

A mixture of 1 g (4 mmol) dihydropyridine *IIc* and 3·7 g (32 mmol) sodium phenoxide in 30 ml absolute dimethylformamide was stirred with exclusion of moisture on a 70°C bath 6 h. After cooling the mixture was poured in 400 ml water. The emulsion formed was extracted with 3 × × 100 ml chloroform, the extracts were combined and washed with 3 × 100 ml saturated NaCl solution and with water. After drying with $MgSO_4$ the solvent was distilled off, and the raw product obtained (0·82 g) was submitted to column chromatography (silica gel, tetrachloromethane, benzene) to give 0·61 g (42%) 2,6-diphenoxy-3,5-diformyl-1,4,4-trimethyl-1,4-dihydropyridine (*XIc*). For $C_{22}H_{21}NO_4$ (363·4) calculated: 72·74% C, 5·78% H, 3·85% N; found: 72·95% C, 5·62% H, 3·65% N. ^{1}H NMR spectrum (deuteriochloroform): 1·89 s, 6 H ($(CH_3)_2$); 2·81 s, 3 H (NCH_3); 7·10—7·40 m, 10 H (Ar—H); 9·67 s, 2 H (CHO). IR spectrum ($CHCl_3$),

$\tilde{\nu}_{max}$ (cm^{-1}): 3 020 m, 2 940 w, 2 880 w, 2 790 w (C—H); 1 650 s, 1 600 m, 1 595 m, 1 565 m (skeletal). Mass spectrum, *m/z* (relative intensity, %): 364 (42), 363 (35), 249 (40), 348 (100), 334 (5), 270 (12), 254 (5), 227 (10), 198 (5), 185 (9), 180 (5), 124 (4), 105 (13), 94 (24), 91 (11), 84 (15), 77 (35), 64 (11), 53 (11).

Reaction of Compound *IIc* with Bis(S-methylisothiouronium) Sulfate

Dihydropyridine *IIc* (0·5 g, 2 mmol) was dissolved in the minimum amount of hot ethanol. After addition of 1·1 g (8 mmol) bis-(S-methylisothiouronium) sulfate and 1·3 g (32 mmol) triethylamine the reaction mixture was heated on a 110°C bath 40 h. The product crystallized on cooling of the reaction mixture and was recrystallized from ethanol to give 0·37 g (68%) 3,5-diformyl-1,4,4-trimethyl-2,6-bis(methylthio)-1,4-dihydropyridine (*XIIa*), m.p. 177—179°C. For $C_{12}H_{17}NO_2S_2$ (271·4) calculated: 53·14% C, 6·27% H, 5·16% N, 23·62% S; found: 53·16% C, 6·25% H, 5·14% N, 23·30% S. ^{1}H NMR spectrum (deuteriochloroform): 1·50 s, 6 H ($(CH_3)_2$); 2·43 s, 6 H (SCH_3); 3·72 s, 3 H (NCH_3); 10·12 s, 2 H (CHO). IR spectrum ($CHCl_3$), $\tilde{\nu}_{max}$ (cm^{-1}): 3 010 m, 2 970 m, 2 930 m, 2 850 m, 2 750 w (C—H); 1 665 s (C=O); 1 580 m, 1 515 m dihydropyridine skeleton).

Reaction of Compound *IIc* with Benzyl Thioalcohol

A solution of 0·5 g (2 mmol) dihydropyridine *IIc* in ethanol was treated with 0·7 g (16 mmol) triethylamine and 0·9 g (8 mmol) benzyl thioalcohol. The mixture was heated on a 100°C bath 5 h. After cooling and addition of 100 ml ether, the precipitated triethylamine hydrochloride was removed by filtration. The filtrate was extracted with 4 × 30 ml 4M-NaOH solution and with 3 × 50 ml water. The organic phase was dried with anhydrous $MgSO_4$, and ether was distilled off. The honey-like residue was washed with petroleum ether to give 0·7 g (80%) yellow crystalline solid. Recrystallization from cyclohexane gave 2,6-bis(benzylthio)-3,5-diformyl-1,4,4-trimethyl-1,4-dihydropyridine (*XIIb*) with m.p. 62—64°C. For $C_{24}H_{25}NO_2S_2$ (423·6) calculated: 68·15% C, 5·90% H, 3·30% N, 15·15% S; found: 68·46% C, 6·06% H, 3·21% N, 15·16% S. ^{1}H NMR spectrum (deuteriochloroform): 1·43 s, 6 H ($(CH_3)_2$); 3·50 s, 3 H (NCH_3); 3·83 s, 4 H (SCH_2); 7·15—7·30 m, 10 H (Ar—H); 9·86 s, 2 H (CHO). IR spectrum ($CHCl_3$), $\tilde{\nu}_{max}$ (cm^{-1}): 3 005 m, 2 930 m, 2 850 m (C—H); 1 660 s (C=O); 1 580 m, 1 510 m (dihydropyridine skeleton).

Reaction of Compound *IIc* with Piperidine

A solution of 2 g (8 mmol) dihydropyridine *IIc* in the minimum amount of benzene was treated with 5·6 g (64 mmol) piperidine. The reaction mixture was heated on a 120°C bath 15 h. The crystalline solid precipitated on cooling was collected by suction, washed with benzene and (after evaporation of the benzene) with water. Yield 2·1 g (76%). Recrystallization from dioxane gave 3,5-diformyl-2,6-bis-(1-piperidyl)-1,4,4-trimethyl-1,4-dihydropyridine (*IXa*) with m.p. 289—290°C. For $C_{20}H_{31}N_3O_2$ (345·5) calculated: 69·46% C, 8·97% H, 12·15% N; found: 69·25% C, 9·06% H, 11·93% N. ^{1}H NMR spectrum (deuteriochloroform): 1·36 s, 6 H ($(CH_3)_2$); 1·68 m, 6 H ($(CH_2)_3$); 3·17 m, 4 H (CH_2—N—CH_2); 3·19 s, 3 H (NCH_3); 9·28 s, 2 H (CHO). IR spectrum ($CHCl_3$), $\tilde{\nu}_{max}$ (dm^{-1}): 3 000 m, 2 930 m, 2 860 m (C—H); 1 620 s (C=O); 1 560 s, 1 530 m (dihydropyridine skeleton).

Reaction of Compound *IIc* with Morpholine

A solution of 0·5 g (2 mmol) dihydropyridine *IIc* with the minimum amount of benzene was treated with 1·4 g (16 mmol) morpholine, and the mixture was heated on a 120°C bath 24 h.

After cooling the reaction mixture, the crystalline solid separated was collected by suction, washed with benzene and (after evaporation of the benzene) with water. Yield 0·5 g (72%). Recrystallization from dioxane gave 3,5-diformyl-1,4,4-trimethyl-2,6-bis(4-morpholinyl)-1,4-dihydropyridine (*IXb*) with m.p. 282–284·5°C. For $C_{18}H_{27}N_3O_4$ (349·4) calculated: 61·81% C, 7·73% H, 12·03% N; found: 61·72% C, 7·74% H, 11·89% N. ^{1}H NMR spectrum (deuteriochloroform): 1·38 s, 6 H ($(CH_3)_2$); 3·13–3·33 m, 7 H (NCH_3 + CH_2—N—CH_2); 3·82 t, 4 H (CH_2—O—CH_2); 9·40 s, 2 H (CHO). IR spectrum ($CHCl_3$), $\tilde{\nu}_{max}$ (cm^{-1}): 3 010 m, 2 970 m, 2 920 w, 2 900 w, 2 860 m (C—H); 1 630 s (C=O); 1 570 s, 1 535 m (dihydropyridine skeleton).

Reaction of Compound *IIc* with Pyrrolidine

A mixture of 0·5 g (2 mmol) dihydropyridine *IIc* and 1·1 g (16 mmol) pyrrolidine was heated in benzene medium on a bath with the temperature of 120°C. The reaction course was followed by means of TLC (Silufol, chloroform). When the starting compound *IIc* disappeared from the reaction mixture (4 h), the solution was evaporated until dry to give 0·72 g dark tarry product whereform no chemical individuum could be isolated.

Reaction of Compound *IXa* with Hydroxylamine

A solution of 0·35 g (9 mmol) sodium hydroxide in methanol was stirred, and 0·6 g (9 mmol) hydroxylamine hydrochloride was added thereto followed by a solution of 0·5 g (1·5 mmol) dihydropyridine *IXa* in chloroform. The mixture was heated on an 80°C bath 30 h. According to TLC (Silufol, acetone) the reaction mixture contained only the starting compound *IXq*. The solvents were evaporated, and the solid residue was washed with water to give 0·42 g (84%) dihydropyridine *IXa*.

Reaction of Compound *IXa* with Phenylhydrazine

A mixture of 0·5 g (1·5 mmol) dihydropyridine *IXa* and 0·4 g (3·6 mmol) phenylhydrazine was heated with chloroform on an 80°C bath 30 h. According to TLC (Silufol, acetone) the reaction mixture contained only the starting compound *IXa* which was recovered in the amount of 0·34 g (68%).

Reaction of Compound *IIc* with Ethyl Thioglycolate

A solution of 0·5 g (2 mmol) dihydropyridine *IIc* in the minimum amount of hot ethanol was treated with 0·75 g (6 mmol) ethyl thioglycolate and 0·64 g (6 mmol) anhydrous sodium carbonate. The reaction mixture was heated on a 100°C bath 11 h. The solution was concentrated to the half volume and left to stand for crystallization. The separated solid was collected, washed with water, and recrystallized from ethanol to give 0·45 g (61%) 4,4,8-trimethyl-4,8-dihydro-bis(2-ethoxycarbonylthieno[2,3-*b*:3′,2′-*e*])pyridine (*XIII*) with m.p. 215°C. For $C_{18}H_{21}NO_4S_2$ (379·5) calculated: 57·00% C, 5·53% H, 3·69% N, 16·90% S; found: 57·10% C, 5·59% H, 3·86% N, 16·96% S. ^{1}H NMR spectrum (deuteriochloroform): 1·54 s, 6 H ($(CH_3)_2$); 1·37 t, 6 H (CH_3); 3·39 s, 3 H (NCH_3); 4·34 q, 4 H (OCH_2); 7·61 s, 2 H (=C—H). IR spectrum ($CHCl_3$), $\tilde{\nu}_{max}$ (cm^{-1}): 3 020 w, 3 000 w, 2 970 w, 2 920 w (C—H); 1 570 w, 1 540 w, 1 420 s, 1 400 s (skeletal).

Reaction of Compound *IIc* with Formamide

A mixture of 0·5 g (2 mmol) dihydropyridine *IIc* and 20 ml (0·5 mol) formamide was heated with stirring on a 160–170°C bath 16 h. After cooling the reaction mixture was poured in 100 ml

dilute (1 : 1) hydrochloric acid and boiled with charcoal for a short time. The solution was filtered and the filtrate was alkalized with concentrated aqueous ammonia until strongly alkaline reaction. The emulsion formed was extracted with 3 × 100 ml chloroform. The organic phases were combined, washed with water, and dried with anhydrous $MgSO_4$. The solvent was distilled off to give the raw product (0·33 g) which was submitted to column chromatography (silica gel, benzene–chloroform 1 : 1). Yield 0·21 g (45%). Recrystallization from hexane gave 5,5,10-trimethyl-5,10-dihydropyrido[2,3-*d* : 6,5-*d'*]dipyrimidine (*XIVa*) with m.p. 182–185°C. For $C_{12}H_{13}N_5$ (227·3) calculated: 63·45% C, 5·72% H, 30·83% N; found: 63·52% C, 5·80% H, 30·26% N. ^{1}H NMR spectrum (deuteriochloroform): 1·67 s, 6 H ($(CH_3)_2$); 3·71 s, 3 H (NCH_3); 8·53 s, 2 H (=C—CH=N); 8·81 s, 2 H (=N—CH=N). IR spectrum ($CHCl_3$), $\tilde{\nu}_{max}$ (cm^{-1}): 3 040 w, 2 980 m, 2 850 w (C—H); 1 595 m, 1 585 ., 1 570 m (skeletal).

Reaction of Compound *IIc* with Benzamidine

Anhydrous sodium carbonate (2·5 g, 24 mmol) and 1 g (4 mmol) dihydropyridine *IIc* were added to a solution of 1·9 g (12 mmol) benzamidinium chloride in 20 ml ethanol. The mixture was heated on boiling water bath 34 h. The crystalline solid formed on cooling was collected by suction, washed with water (0·2 g), and the mother liquor was evaporated until dry. The residue was washed with water and little amount of cold ethanol (0·23 g). Both portions were combined and recrystallized from ethanol. Yield 0·3 g (20%) 2,8-diphenyl-5,5,10-trimethyl-5,10-dihydropyrido[2,3-*d* : 6,5-*d'*]dipyrimidine with m.p. 283–285°C. For $C_{24}H_{21}N_5$ (309·4) calculated: 76·00% C, 5·55% H, 18·42% N; found: 76·10% C, 5·70% H, 18·42% N. ^{1}H NMR spectrum (deuteriochloroform): 1·70 s, 6 H ($(CH_3)_2$); 3·96 s, 3 H (NCH_3); 7·50–7·55 m, 6 H (Ar—H, *meta*, *para*); 8·47–8·51 m, 4 H (Ar—H, *ortho*); 8·62 s, 2 H (CH=N). IR spectrum ($CHCl_3$), $\tilde{\nu}_{max}$ (cm^{-1}): 2 960 w, 2 920 w, 2 850 w (C—H); 1 590 w, 1 565 m, 1 460 w (skeletal).

REFERENCES

1. Kurfürst A., Kuthan J.: Ind. Eng. Chem., Prod. Res. Develop. *21*, 191 (1982).
2. Sausins A., Duburs G.: Heterocycles *27*, 291 (1988).
3. Weisenfels M., Kaubisch S.: Z. Chem. *21*, 259 (1981).
4. Weisenfels M., Kaubisch S.: Z. Chem. *22*, 23 (1982).
5. Weisenfels M., Scheumann L., Hambsch M.: *Hauptjahrestagung 1986, Halle 2.–4. 12. 1986*; p. 30.
6. Eisner U., Kuthan J.: Chem. Rev. *72*, 1 (1972).
7. Andreani A., Rambaldi M., Bonazzi D., Greci L.: Bull. Chim. Farm. *116*, 589 (1977).
8. Kvitko A., Panfilova E. A.: Khim. Geterotsikl. Soedn. *1973*, 507.
9. Anderson D. J.: J. Org. Chem. *51*, 946 (1986).
10. Hauptmann S., Trieu N. P.: Z. Chem. *13*, 57 (1973).
11. Klimko B. T., Michajlov B. A., Skolbinov A. P.: Zh. Obshch. Khim. *30*, 1352 (1960).
12. Bredereck H., Campper R., Morlock G.: Chem. Ber. *90*, 942 (1957).
13. Farmer H. H., Rabjohn N.: Org. Synth., Coll. Vol. IV, *1967*, 441.
14. Smith W. T., McLeod G. L.: Org. Synth., Coll. Vol. IV, p. 345. Wiley, New York 1967.
15. Guareschi I., Grande E.: Chem. Zentralbl. *II*, 439 (1899).
16. Abe K.: J. Pharm. Soc. Jpn. *77*, 118 (1957).
17. Claisen J.: J. Liebigs Ann. Chem. *287*, 366 (1895).
18. Walther A.: J. Prakt. Chem. *53*, 474 (1896).

Translated by J. Panchartek.