ON DIHYDROPYRIDINES. XXVII.*

THE REACTION OF 3,5-DIACETYLPYRIDINE WITH COMPLEX HYDRIDES AND ORGANOMETALLIC REAGENTS

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The reduction of 3,5-diacetylpyridine (*I*) with lithium aluminium hydride or sodium borohydride yields diol *VII*, along with a small amount of isomeric 1,2- and 1,4-dihydropyridines *II* and *V*. In the reaction with methylmagnesium iodide or dimethylcadmium analogous dihydropyridines *III* and *VI* are formed in greater amounts. Also in this case the attack on functional groups under formation of hydroxy derivatives *VIII* and *IX* is prevailing. By contrast, the main product of the catalytic hydrogenation of compound *I* is 1,2-dihydropyridine *II*, compounds *V* and *VII* being formed in small amounts. The reactivity of compound *I* is interpreted with the use of simple HMO theory.

Pyridine derivatives substituted in positions 3 and 5 by cyano or ester groups exhibit enhanced reactivity of their heteroaromatic nucleus towards complex hydrides[1-5] and organometals[3,5-8] which can be utilized in the preparation of corresponding 1,2- and 1,4-dihydropyridine derivatives. In connection with that it was of interest to find whether this method can also be employed in the case of 3,5-diacetylpyridine (*I*), the 1,2-derivative of which (*II*) was reported by Eisner[9] as the product of partial catalytic hydrogenation, while analogous substances *IV*, *V* and *VI* have so far been prepared only by cyclisation reactions[10-13]. The reduction of compound *I* by complex hydrides has as yet been used only in one case. Michael and Dralle[11] have isolated only diol *VII* on using sodium borohydride. Oparina[14] reported that the product of the reaction of methyl 3,5-pyridinedicarboxylate with methylmagnesium iodide is hydroxy ketone *IX*. When repeating the described[14] procedure in our laboratory the formation of this compound has not however been proved[5].

In the present communication we wish to report the results of our study of the reaction of substance *I* with lithium aluminium hydride sodium borohydryde, methylmagnesium iodide and with dimethylcadmium. In all cases the individual components of the reaction mixture were quantitatively separated by adsorption chromatography on aluminium oxide and the formed dihydropyridines were determined also spectrophotometrically.

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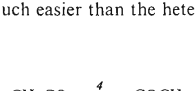
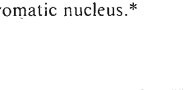
The results are summarized in Table I. It is evident that in all cases the character and amount of reaction products are influenced not only by the reactivity of substrate *I* but also by that of the reagent.

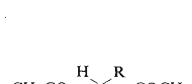
In the reaction with complex hydrides, in harmony with the work[11], only both carbonyl groups are reduced under the formation of diol *VII*, the total content of the isomeric dihydro derivatives *II* and *V* being below 2%. In accordance with analogous results obtained for 3,5-dinitriles[2,4] and 3,5-diesters[5], lithium aluminium hydride has greater tendency to form 1,2-dihydro isomer *II*. By contrast, methylmagnesium iodide and dimethylcadmium are less selective and, besides hydroxy ketone *IX* or diol *VIII*, they yield more than 10% of isomeric dihydro derivatives *III* and *VI*. It is remarkable that even little reactive dimethylcadmium attacks one keto group much easier than the heteroaromatic nucleus.*



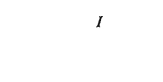
I



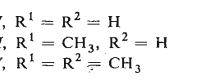
II, $R^1 = R^2 = H$
III, $R^1 = CH_3$, $R^2 = H$
IV, $R^1 = R^2 = CH_3$



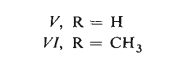
V, R = H
VI, R = CH_3



VII, $R^1 = H$, $R^2 = CH_3$
VIII, $R^1 = R^2 = CH_3$



IX



X, $R^1 = CH_3$, $R^2 = H$
XI, $R^1 = H$, $R^2 = CH_3$

Although relative amounts of 1,2- and 1,4-dihydropyridine derivatives *II* and *V* or *III* and *VI* depend on the structure of the reagent, when taking into account double statistical accessibility of positions 2 and 6 in substance *I* it can be stated that towards the nucleophilic reagents used position 4 appears to be more reactive. The chief site of the attack remains however position 3a in the side chain. This finding is in satisfactory agreement with quantum chemical prediction by means of simple HMO method on the basis of dynamic indices of chemical reactivity S_n and L_n (Table II).

* So far, only the addition of an organocadmium reagent to the heterocyclic nucleus of quarternary salts of nicotinic acid esters has been accomplished[15].

By the high reactivity of its functional groups 3,5-diketone *I* markedly differs from analogous 3,5-diesters[5] and especially from 3,5-dinitriles[2,8]. Nucleophilic reduction of compound *I* does not seem therefore the suitable method for preparing 3,5-diacetyldihydropyridines. On the other hand, in agreement with Eisner[9], we have found that in the catalytic hydrogenation of compound *I* on palladium the predominant product is 3,5-diacetyl-1,2-dihydropyridine (*II*), which is accompanied however

TABLE I

Reaction Products from 3,5-Diacetylpyridine (*I*)

Percentage is related to the unreacted starting substance.

Reagent	Recovered *I*, % (*IX*, %)	Diol (%)	Dihydropyridines (%)	Ratio 1·2-	Ratio 1·4-
$LiAlH_4$	0·9	*VII*	*II*, *V*	~50[a]	~50[a]
	(—)	(98·0)	(~2)		
$NaBH_4$	3·0	*VII*	*II*, *V*	~ 4[a]	~96[a]
		(98·0)	(~2)		
CH_3MgJ	17·6	*VIII*	*III*, *VI*	62	38
	(22·5)	(61·6)	(15·8)		
$(CH_3)_2Cd$	45·3	*VIII*	*III*, *VI*	50	50
	(88·5)	(0·9)	(10·6)		
H_2/Pd[b]	60·0	*VII*	*II*, *V*	88	12
	—	(14·3)	(71·6)	86[a]	14[a]
H_2/Pd[c]	48·7	*VII*	*II*, *V*	83	17
		(12·5)	(73·2)		

[a] Data obtained spectrophotometrically; [b] palladium on charcoal[18]; [c] palladium on ion exchanger[19,20].

TABLE II

Some HMO Chemical Reactivity Indices of Substance *I*

(h_N 0·5; h_0 1·0; h_{CH_3} 2·0; $k_{CN} = k_{CO} = 1·0$; $k_{CC(H_3)}$ 0·7)

Position	π-Electron density, q	Superdelocalizability, $S_n(\beta^{-1})$	Localization energy, $L_n(\beta)$
2	0·834	1·520	1·989
3	1·027	0·761	2·901
3a	0·631	1·924	1·854
4	0·853	1·542	1·949

with small amounts of 1,4-dihydro isomer *V* and diol *VII*. In order to obtain the pure *II* the latter compounds had to be separated chromatographically. It is of interest that the different reactivity of the heteroaromatic nucleus agrees well with the lower value of bicentric localization energy for positions 1 and 2 (L_{12} 4·69β), relative to analogous values for positions 1 and 4 (L_{14} 6·51β). The applicability of these HMO data to the interpretation of partial catalytic hydrogenation of 3,5-dicyanopyridines was demonstrated in our communication[16].

The structure of most of the reaction products was proved by comparison with authentic samples, only in the case of 2-methyl-3,5-diacetyl-1,2-dihydropyridine(*III*) and hydroxy ketone *IX* it had to be determined spectroscopically. The identification of these two compounds was made difficult by their very similar chromatographic behaviour on different adsorbents, even with different solvent systems, so that they had to be separated by repeated column chromatography, using a great excess of aluminium oxide. The PMR and IR spectra of compound *IX* comport with its structure. The physical properties of this compound (m.p. 58—60°C) are quite different, however, from those reported by Oparina[14] (m.p. 128°C). This convincingly proves our assumption[5] that the product obtained by Oparina by the Grignard reaction of methyl 3,5-pyridinedicarboxylate is in fact methyl 4-methyl-1,4-dihydropyridine-3,5-dicarboxylate (m.p. 126—127°C). The PMR spectrum of 1,2-dihydro derivative *III* agrees with its structure and its adsorption spectrum in UV region closely resembles that of the obtained 3,5-diacetyl-2,2-dimethyl-1,2-dihydropyridine (*IV*)[13] (Fig. 1). In contradistinction to compound *IV*, substance *III* is very air-sensitive, however. The latter compound was therefore further characterised after its oxidation with silver oxide to 3,5-diacetyl-2-methylpyridine (*X*), which gives different mass spectrum and melting point depression with isomeric 3,5-diacetyl-4-methylpyridine (*XI*).

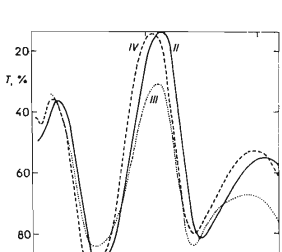


FIG. 1

Ultraviolet Spectra in Ethanol (conc. 4 . 10^{-5}M) 1-3,5-Diacetyl-1,2-dihydropyridine(*II*), 2-methyl-3,5-diacetyl-1,2-dihydropyridine(*III*); 2,2-dimethyl-3,5-diacetyl-1,2-dihydropyridine(*IV*).

EXPERIMENTAL

Temperature data are uncorrected. The IR spectra were measured on Zeiss, Model UR 10, spectrophotometer (Jena), the UV ones on Optica Milano NI 4 CF spectrophotometer. The mass spectra were recorded with LKB 9000 spectrometer at 70 eV and the PMR spectra were measured on Tesla BS 477 instrument working at 60 MHz. The chromatography was carried out on aluminium oxide of the activity III—IV (Brockmann). The presence of individual components in chromatographic fractions was checked by chromatography on thin layer of aluminium oxide (chloroform–ethanol 96 : 4). The detection was made by UV light (1,4-dihydro derivatives *V* and *VI* have the blue and 1,2-dihydro isomers *II* and *III* the yellow fluorescence) and by iodine vapours (pyridine derivatives *I*, *VII*—*XI*).

3,5-Diacetylpyridine (*I*)

To a mixture of 30 g of 3,5-diacetyl-1,4-dihydropyridine[12], 25·1 g of sodium nitrite, 930 ml of ether and 120 ml of water, 73 ml of 20% sulphuric acid were added with stirring and external cooling over the period of 100 min. After 5 h stirring at room temperature the ether layer was separated, dried by magnesium sulphate, the solvent evaporated and the residue recrystallized from light petroleum. The yield of compound *I* was 16·1 g (54·5%), m.p. 67—68°C. Lit.[11] gives m.p. 72°C.

Reaction of Compound *I* with Sodium Borohydride

To 402 mg of compound *I* dissolved in 20 ml of methanol were added in portions 92 mg of sodium borohydride with stirring and cooling (the bath temperature was —20° to —15°C) over the period of 10 min. The mixture was allowed to stir for another 30 min and then decomposed with 2% sulphuric acid, (pH 5—6). After evaporation of methanol under reduced pressure at the temperature not exceeding 35°C, the water layer was extracted with chloroform (75 ml), and after alkalinization by ammonia to pH 12—13 it was extracted by the same volume of the solvent. The combined extracts after drying with magnesium sulphate yielded 402 mg of a mixture of products. The mixture was chromatographed on aluminium oxide column (150 g, the column length 25 cm; chloroform–ethanol 98 : 2), yielding 13 mg of the starting compound *I*, 5 mg of the mixture of dihydro isomers *II* and *V* (Table I) and 382 mg of diol *VII*, b.p. 158—160°C/1 Torr. For $C_9H_{13}NO_2$ (167·2) calculated: 64·64% C, 7·84% H, 8·38% N; found 64·99% C, 7·95% H, 8·46% N. IR spectrum ($CHCl_3$): 1592 cm^{-1} (ν(C—C) and ν(C—N) of heteroaromatic ring bonds), 1096 cm^{-1} (ν(C—O) of the secondary OH group), 3150—3430 and 3600 cm^{-1} (the associated and the free O—H bond). PMR spectrum ($CDCl_3$): 1·50τ (2 H, broadened singlet of protones in positions 2 and 6); 1·93τ (1 H, broadened singlet of protons in position 4); 4·29τ (2 H, OH protons; the signal shifts to 5·33τ at 60°C); 5·00τ (2 H, quadruplet of methine protons in the side chain, J_{HH} 6·5 Hz); 8·61τ (6 H, doublet of methyl protons, J_{HH} 6·5 Hz).

Reaction of Compound *I* with Lithium Aluminium Hydride

To a suspension of 1·06 g of the reagent in 20 ml of ether, 1 g of compound *I* dissolved in 60 m of ether was added during 1 min, while stirring and cooling the mixture (—20° to —15°C). Stirring and cooling was continued for another 30 min, and then the mixture was decomposed by 2% sulphuric acid (pH 5—6). After separation of the organic layer the water phase was extracted successively with 150 ml of ether and 90 ml of chloroform. The combined extracts, after drying with magnesium sulphate, yielded 128 mg of the mixture of products which were chromatographed (70 g of aluminium oxide, the column length 25 cm, methanol–benzene 2 : 98) to afford 8 mg of the starting compound *I*, 14 mg of the mixture of dihydro isomers *II* and *V* (Table I) and 101 mg of diol *VII*. The water layer after filtration and condensation *in vacuo* was distilled, giving 791 mg of diol *VII* (Hickman flask, the bath temperature was 180—200°C).

Reaction of Compound *I* with Methylmagnesium Iodide

To 15 ml of an ethereal solution of Grignard reagent (prepared from 1 g of magnesium and 3 ml of methyl iodide), a solution of 1 g of substance *I* in 60 ml of ether was rapidly added with stirring and external cooling (the bath temperature was —20° to —15°C). Stirring was continued at the same temperature for another 30 min. Then the reaction mixture was decomposed by saturated aqueous ammonium chloride solution (12 ml), the ether layer separated and the water phase acidified by 2% sulphuric acid to pH 6—7. After extracting the water layer successively with 120 ml of ether and 90 ml of chloroform, the combined organic extracts were dried with

magnesium and the solvent evaporated *in vacuo*. The residue (810 mg) was dissolved in 1% solution of ethanol in chloroform and chromatographed on 300 g of aluminium oxide (the column length 42 cm), the 6 ml-fractions being collected. Fractions 43—60 contained a total of 125 mg of diketone *I*, while fractions 76—99 yielded 144 mg of hydroxy ketone *IX*, the analytical sample of which was obtained by distillation from Hickman flask (b.p. 155—160°C/1 Torr) and by crystallization from light petroleum (m.p. 58—60°C). For $C_{10}H_{13}NO_2$ (179·2) calculated: 67·02% C, 7·13% H, 7·82% N; found: 67·25% C, 7·40% H, 7·54% N. IR spectrum ($CHCl_3$): 1 245 cm^{-1} (ν(C—O) in tert-alcohol), 1 700 cm^{-1} (ν(C=O)), 3 250—3 400 cm^{-1} and 3 600 cm^{-1} (ν(O—H)) of the associated and the free OH group). PMR spectrum ($CDCl_3$): 1·08τ (2 H, broad singlet of α-protons); 1·66τ (1 H, triplet of the proton gamma, $J_{HH} = 2$ Hz);) 4·85τ (1 H in OH, at 60°C it shifts to 5·5τ); 7·23τ (3 H, singlet of CH_3CO protons); 8·21τ (6 H, singlet of methyl protons in $C(CH_3)_2OH$ group). Fractions 100—115 contained a mixture of hydroxy ketone *IX* and 1,2-dihydro derivative *III* (13 mg) and fractions 133—142 yielded a mixture of isomeric dihydro derivatives *III* and *VI* (9 mg). Fractions 116—132 afforded a total of 53 mg of 1,2-dihydropyridine *III*. PMR spectrum (CD_3OD): 2·07τ (1 H, doublet of olefinic proton in position 6, $J_{HH} \sim 2$ Hz); 2·27τ (1 H, multiplet of olefinic proton in position 4); 5·93τ (1 H, multiplet of methine proton in position 2); 7·70τ (3 H, singlet of protons of acetyl group in position 5); 7·80τ (3 H, singlet of protons of acetyl group in position 3); 8·85τ (3 H, doublet of methyl protons in position 2, $J_{HH} = 6$ Hz). UV spectrum (C_2H_5OH, conc. 4 . 10^{-5}M): λ_{max} 219, 312, and 393 nm (log ε 4·01, 4·11, 3·64). Fractions 143—169 (chloroform–ethanol 98 : 2) gave 31 mg of 1,4-dihydropyridine *VI* which, according to its melting point and IR spectrum, was identical with an authentic sample[13]. Fractions 206—260 (chloroform–ethanol) afforded a total of 428 mg of diol *VIII* which was identified by comparison with an authentic sample[5].

Reaction of Compound *I* with Dimethylcadmium

To 30 ml of ethereal solution of dimethylcadmium (prepared from methylmagnesium iodide and 4·5 g of cadmium(II) chloride in nitrogen atmosphere[17]) was added with stirring and external cooling (—20° up to —15°C) a solution of compound *I* in 60 ml of ether. After 30 min the reaction mixture was decomposed by 25 ml of saturated aqueous ammonium chloride solution and the product isolated in similar manner as that of the reaction with methylmagnesium iodide. The reaction yielded 244 mg of diketone *I*, 233 mg of hydroxy ketone *IX*, 19 mg of 1,2-dihydropyridine *III* and 18 mg of 1,4-dihydropyridine *VI*.

Hydrogenation of Compound *I*

A. *On palladium on charcoal*[18]: A solution of 1 g of diketone *I* in 20 ml of methanol was hydrogenated in the presence of 450 mg of 6% catalyst at 20—25°C and 745 Torr. After the consumption of hydrogen reached the value corresponding to the hydrogenation of one double bond (152 ml) the reaction was stopped, the catalyst was filtered off, washed by methanol and the filtrate was evaporated to dryness. The distillation residue (950 mg), which according to thin layer chromatography contained four compounds (R_F 0·01; 0·03; 0·39; 0·54) was chromatographed on aluminium oxide column (150 g, column lenght 24 cm, chloroform–ethanol 98 : 2), the volume of collected fractions being 35 ml. Fractions 5—8 contained a total of 604 mg of compound *I*, fractions 58—105 yielded 58 mg of diol *VII* which was converted to the hydrochloride, m.p. 111—112°C (acetone). Reported[11] m.p. 112°C. Fractions 19—51 contained a mixture of dihydropyridines *II* and *V* (Table I), 287 mg, which after repeated chromatography on aluminium oxide afforded 254 mg of 1,2-dihydro isomer *II*, m.p. 218—220°C. Lit.[9] gives m.p. 198—200°C. For $C_9H_{11}NO_2$ (165·1) calculated: 65·64% C, 6·71% H, 8·48% N; found: 65·26% C, 6·74% H, 8·23% N. UV spectrum (C_2H_5OH, conc. 4 . 10^{-5}M) λ_{max} 225, 312 and 395 nm (log ε 3·98, 4·60,

3·45). In addition to the compound *II* also 33 mg of 1,4-dihydro isomer *V* were isolated. This substance was identified by comparison with an authentic sample[13].

B. *On palladium on ion exchanger*[19,20]: A solution of 640 mg of substance *I* in 20 ml of ethanol was hydrogenated in the presence of 400 mg of 17% palladium catalyst at 22°C and the pressure 745 Torr untill 1 mol of hydrogen was consumed. In similar manner as in the previous case 312 mg of the starting compound *I*, 201 mg of 1,2-dihydro derivative *II*, 42 mg of 1,4-dihydro derivative *V* and 42 mg of diol *VII* were obtained.

3,5-Diacetyl-2-methylpyridine (*X*)

To 10 mg of 1,2-dihydro derivative *III* dissolved in 3 ml of ethanol was added freshly prepared silver oxide (from 70 mg of silver nitrate) and the mixture was allowed to stand at room temperature for 2 h with intermittent stirring. After addition of activated carbon the oxide was filtered off and the filtrate was evaporated to dryness. The residue (8 mg) was recrystallized from light petroleum and resumblimed at 90—100°C/15 Torr, m.p. 66—67°C, mixed m.p. with 3,5-acetyl-4-methylpyridine (*XI*)[13] shows depression. For $C_{10}H_{11}NO_2$ (177·2) calculated: 67·78% C, 6·26% H; found: 68·05% C, 6·12% H. Mass spectrum: *m/e* 177 (M^+; r.i. 44·4%); *m/e* 162 (M^+—CH_3; 77·8%); *m/e* 134 (M^+—CH_3CO; 35·0%); *m/e* 92 (5·9%); *m/e* 43 (CH_3CO^+; 100%). Mass spectrum of 4-methyl isomer *XI*: *m/e* 177 (M^+; r.i. 95·7%); *m/e* 162 (M^+—15; 90·7%); *m/e* 134 (M^+—43; 56·4%); *m/e* 92 (24·2%); *m/e* 43 (CH_3CO^+; 100%).

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