# REACTION OF 1-PYRIDYL-1,3-BUTANEDIONES AND 1,3-DIPYRIDYL-1,3-PROPANEDIONES*

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Reduction of diketones *I* with zinc and formic acid gives monoketones *II*. Diketones *Ia, IIIb, IIIc* are converted with hydrazines to pyrazoles *VIa, IVa, IVb, V*. Methiodides *VII* are reduced with sodium borohydride to derivatives of 1-methyl-3-piperideine *VIII—X*.

Both triads of 1-pyridyl-1,3-butanediones and 1,3-dipyridyl-1,3-propanediones, easily accessible by Claisen condensation, inspired us to the study of some reactions. In the first place we were interested in the reductions of diketones *I* with zinc and formic acid. We already had some experience with this reaction in the pyridine series[1].

It was found that in the mentioned reduction of all three 1-pyridyl-1,3-butanediones (*I*) only the attack on one keto group takes place, precisely that one which is conjugated with the pyridine nucleus. The structure of the ketones formed (*II*) was confirmed by means of $^1$H-NMR spectra.

In addition to the reductions mentioned we also prepared by condensation of diketones *IIIb, IIIc* with hydrazine or phenylhydrazine new derivatives of pyrazole, *i.e.* 3,5-di(3-pyridyl)pyrazole (*IVa*), 1-phenyl-3,5-di(3-pyridyl)pyrazole (*IVb*), and 1-phenyl-3,5-di(4-pyridyl)pyrazole (*V*).

The 1-phenyl-dipyridylpyrazoles *IVb, V* obtained differ conspicuously from the derivatives with the hydrogen atom on nitrogen (*IVa*). While in the NMR spectrum of *IVa* both pyridine rings are equivalent, in the case of N-phenylderivatives *IVb, V* distinct differences in chemical shifts are observed. The pyridine nucleus is evidently affected sterically by the neighbourhood of the benzene ring on the nitrogen atom, which becomes apparent in the shifts of protons in the positions vicinal to the positions of the junction of the pyridine ring to the pyrazole ring, *i.e.* in the positions 2 and 4 in *IVb*, and 3 and 5 in compound *V*. The values of the chemical shifts of these protons are considerably higher than the corresponding values of the second pyridine ring.

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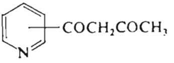
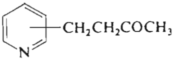
* Part LIV in the series Studies in the Pyridine Series; Part LIII: This Journal *44*, 3137 (1979).

Finally we prepared methiodides *VII* of all three known 3-methyl-5-pyridylpyrazoles *VI* (ref.[2,3]) which were reduced with sodium borohydride. According to our expectation we obtained derivatives of 1-methyl-3-piperideine *VIII*–*X*. In these products the orientation of the double bond is analogous to that in the products of similar reduction of methiodides of corresponding methylpyridine[4].



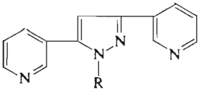
*I*



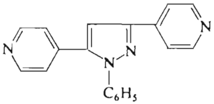
*II*

In formulae *I*, *II*, *III*, *VI*, *VII*: *a* 2-pyridyl, *b* 3-pyridyl, *c* 4-pyridyl

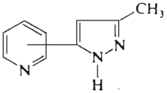
*III*



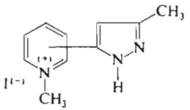
*IVa*, R = H
*IVb*, R = $C_6H_5$



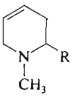
*V*



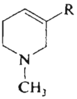
*VI*



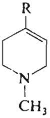
*VII*



*VIII*



*IX*



*X*

In formulae *VIII*—*X*: R = 5-methyl-3-pyrazolyl

## EXPERIMENTAL

The temperature data are not corrected. The infrared spectra were measured on a Perkin-Elmer spectrophotometer, Model 325, the $^1$H-NMR spectra were recorded on a Varian XL-100-15 (100·1 MHz) instrument at 37°C, using tetramethylsilane as internal standard, if an organic solvent was used for the dissolution of the sample, or $(CH_3)_3Si(CH_2)_3SO_3Na$, if $D_2O$ was used as solvent. Thin-layer chromatography was carried out on Silufol UV 254, detection was carried out under a Universal UV-Lampe Camag (Muttenz — Switzerland) with the 254 and 366 nm wave-length ranges.

### Reduction of 1-(2-Pyridyl)-1,3-butanedione (*Ia*) with Zinc and Formic Acid

A mixture of 8·2 g (0·05 mol) of *Ia* (ref.[5]), 53·2 g (1·0 mol) of formic acid (85%) and 16·3 g (0·25 mol) of zinc dust was refluxed at 120°C for 6·5 h (until reaction with $FeCl_3$ was negative). After dilution with water the unreacted zinc was filtered off under suction and washed with hot water. The filtrate was alkalized with sodium carbonate and the precipitate of zinc carbonate was filtered off and washed with hot water. The filtrate was extracted with chloroform, the extract dried over magnesium sulfate and evaporated. The residue (6 g) was distilled, b.p. 59°C/2·7 Pa, Yield 4·7 g (62·7%) of *IIa*. For $C_9H_{11}NO$ (149·2) calculated: 72·46% C, 7·43% H, 9·39% N; found: 72·50% C, 7·70% H, 9·43% N. $^1$H-NMR spectrum ($CCl_4$) ppm: 2·08 (s, 3 H) $CH_3$; 2·68—3·10 (m, 4 H) $CH_2CH_2$; 6·86—7·16 (m, 2 H) protons in the positions 3 and 5 of the pyridine ring; 7·45 (td, 1 H, $J = 8$ Hz) H in the position 4; 8·37 (d, 1 H, $J = 5$ Hz) H in the position 6. IR spectrum ($CCl_4$): 1 720 $cm^{-1}$ $\nu(C{=}O)$.

Reduction of 1-(3-pyridyl)-1,2-butanedione[6] (*Ib*) was carried out analogously as the reduction of *Ia*. Yield 23·5% of *IIb*, b.p. 72°C/8 Pa. For $C_9H_{11}NO$ (149·2) calculated: 72·46% C, 7·43% H, 9·39% N; found: 72·65% C, 7·67% H, 9·44% N. $^1$H-NMR spectrum ($CDCl_3$) and IR spectrum ($CHCl_3$) are in agreement with the literature data[7].

*Picrate* IIb, m.p. 106·5—107·5°C (ethanol). For $C_{15}H_{14}N_4O_8$ (378·3) calculated: 47·62% C, 3·73% H, 14·81% N; found: 47·91% C, 3·99% H, 15·08% N.

Reduction of 1-(4-pyridyl)-1,3-butanedione[6] (*Ic*) was carried out as the reduction of *Ia*. Yield, 62·7% of 4-(4-pyridyl)-2-butanone (*IIc*), b.p. 75°C/3 Pa. Lit.[8] gives b.p. 143—144°C/14 Torr For $C_9H_{11}NO$ (149·2) calculated: 72·46% C, 7·43% H, 9·39% N; found: 72·41% C, 7·55% H, 9·44% N. $^1$H-NMR ($CDCl_3$), ppm: 2·17 (s, 3 H) $CH_3$; 2·85 (m, 4 H) $CH_2CH_2$; 7·11 (d, 2 H, $J = 5$ Hz) protons in the positions 3 and 5 of the pyridine nucleus; 8·48 (d, 2 H, $J = 5$ Hz) protons in the positions 2 and 6 of the pyridine ring. IR spectrum ($CHCl_3$), $cm^{-1}$: 1 720 $\nu(C{=}O)$.

*Picrate* IIc, m.p. 120°C (ethanol). For $C_{15}H_{14}N_4O_8$ (378·3) calculated: 47·62% C, 3·73% H, 14·81% N; found: 47·64% C, 3·86% H, 14·63% N.

### 1,3-Di(3-pyridyl)-1,3-propanedione (*IIIb*)

3-Acetylpyridine[9] (12·1 g; 0·1 mol) in 25 ml of diethyl ether was added dropwise over 15 min and under nitrogen to a stirred suspension of 4·8 g (0·2 mol) of sodium hydride, 30·2 g (0·2 mol) of ethyl nicotinate and 5 ml of diethyl ether. The mixture became hot spontaneously and hydrogen was set free. It was then diluted with 100 ml of diethyl ether and refluxed for 30 min until the development of hydrogen ceased. Ethanol (12 ml) was then added dropwise under nitrogen, followed by ice and 200 ml of water. The ethereal layer was separated and the aqueous layer was extracted with a small amount of ether. The aqueous layer was then neutralized with 13 ml of acetic acid and the voluminous precipitate of the diketone formed was filtered off under suction and washed with cold water. Crystallization from ethanol gave 16·05 g (71%) of *IIIb*, m.p. 199—201°C, lit.[10] gives m.p. 198°C.

### 3,5-Di(3-pyridyl)pyrazole (*IVa*)

A mixture of 6 g (0·026 mol) of *IIIb*, 125 ml of ethanol and 21 ml of 80% hydrazine hydrate was stirred for 10 min at room temperature and then refluxed for 30 min. After standing overnight the separated crystals were filtered off under suction and the mother liquors were concentrated; yield, 5·3 g (89%) of *IVa*, m.p. 230·5—232°C (2-propanol). For $C_{13}H_{10}N_4$(222·5) calculated: 70·26% C, 4·54% H, 25·20% N; found: 70·29% C, 4·79% H, 25·27% N. $^1$H-NMR spectrum ($CD_3OD$), ppm: 7·19 (s, 1 H) proton in the position 4 of the pyrazole ring; 7·36—7·58 (m, 2 H) protons in the position 5 of the pyridine rings; 8·20 (d, 2 H, $J = 8$ Hz) and 8·45 (d, 2 H, $J = 5$ Hz) protons in the positions 4 and 2 of the pyridine rings; 8·96 (s, 2 H) protons in the position 6 of the pyridine rings. IR spectrum (KBr pellet): 3430 cm$^{-1}$ $\nu$NH.

*Dihydrochloride* IVa, m.p. 251—254°C (methanol). For $C_{13}H_{12}Cl_2N_4$ (295·2) calculated: 52·90% C, 4·10% H, 24·02% Cl, 18·98% N; found: 52·79% C, 4·41% H, 23·54% Cl, 18·69% N.

### 1-Phenyl-3,5-di(3-pyridyl)pyrazole (*IVb*)

Freshly distilled phenylhydrazine (3·3 g; 0·03 mol) and 6 drops of acetic acid were added to a hot solution of 6·8 g (0·03 mol) of *IIIb* in 200 ml of an ethanol-chloroform mixture (1 : 1) and refluxed on a water bath for 30 h. Since *IIIb* was still present in the reaction mixture (according to TLC) an additional 3·3 g of phenylhydrazine were added and the mixture refluxed for 2 h. The solvents were evaporated in a vacuum and the residue extracted three times with boiling cyclohexane. The extract gave 2·4 g (27%) of yellow crystals of *IVb*, m.p. 121·5—122·5°C (cyclohexane). For $C_{19}H_{14}N_4$ (298·3) calculated: 76·49% C, 4·72% H, 18·78% N; found: 76·61% C, 4·99% H, 18·89% N. $^1$H-NMR spectrum ($CDCl_3$), ppm: 7·03 (s, 1 H) H of the pyrazole ring; 7·25—7·56 (m) and 7·48 (bs) 7 H of the benzene ring and 3 H of the pyridine ring; 7·64 (dt, 1 H, $J = 8$ Hz) H in the position 4 of the pyridine ring bound in the position 5 of the pyrazole ring; 8·33 (dt, 1 H, $J = 8$ Hz) H in the position 4 of the pyridine ring bound in the position 5; 8·62 to 8·76 (m, 3 H) 2-H of the pyridine rings; 9·24 (d, 1 H, $J = 2·5$ Hz) 2-H of the pyridine ring bound in the position 5.

*Dimethiodide monohydrate* IVb, m.p. 234—237·5°C (methanol-water). For $C_{21}H_{22}I_2N_4O$ (600·25) calculated: 42·02% C, 3·69% H, 42·28% I, 9·33% N; found: 42·32% C, 3·67% H, 42·58% I, 9·17% N.

### 1-Phenyl-3,5-di(4-pyridyl)pyrazole (*V*)

This compound was prepared analogously as *IVb* from 1,3-diketone *IIIc* (ref.[11]) and phenylhydrazine; m.p. 130·5—131·5°C (cyclohexane), after previous separation on a column of Silpearl (in chloroform-ethanol 10 : 1), yield 47%. For $C_{19}H_{14}N_4$ (298·3) calculated: 76·49% C, 4·72% H, 18·78% N; found: 76·58% C, 4·74% H, 18·61% N. $^1$H-NMR spectrum ($CDCl_3$), ppm: 7·20 (s, 1 H) H of the pyrazole ring; 7·58% (bs, 5 H) aromatic H, 7·32 (d, 2 H, $J = 6$ Hz) and 7·95 (d, 2 H, $J = 6$ Hz) 3,5-H of the pyridine rings; 8·66—7·91 (m, 4 H) 2,6-H of the pyridine rings.

### 2-(5-Methyl-3-pyrazolyl)pyridine (*VIa*)

A mixture of 25 g (0·153 mol) of *Ia* (ref.[5]) and 120 ml of 80% hydrazine hydrate was refluxed at 140—150°C (temperature of the bath) for 13 h. After evaporation of the solvents and crystallization of the residue from tetrachloromethane 19·7 g (80·8%) of *VIa* were obtained, m.p. 113—116·5°C. Lit.[2] gives m.p. 115—116°C.

### 1-Methyl-2-(5-methyl-3-pyrazolyl)pyridinium Iodide (*VIIa*)

A mixture of 20 g (0·126 mol) of *VIa* (ref.[2]), 23 g (0·162 mol) of methyl iodide and 200 ml of benzene was refluxed for 30 h. After evaporation of the solvents the residue was washed with acetone and crystallized from acetone and ethanol to yield 5·2 g (13·7%) of *VIIa*, m.p. 181—184°C. Lit.[3] gives m.p. 166—168°C. For $C_{10}H_{12}IN_3$ (301·14) calculated: 39·89% C, 4·02% H, 42·14% I, 13·95% N; found: 39·93% C, 3·77% H, 42·12% I, 13·82% N. $^1$H-NMR spectrum ($^2H_2O$), ppm: 2·41 (s, 3 H) C—$CH_3$: 4·40 (s, 3 H) N—$CH_3$; 6·70 (s, 1 H) H in the position 4 of the pyrazole ring; 7·96 (t, 1 H, $J = 7$ Hz) H in the position 5 of the pyridine ring; 8·20 (d, 1 H, $J = 7$ Hz) H in the position 3; 8·56 (t, 1 H, $J = 7$ Hz) H in the position 4; 8·83 (d, 1 H, $J = 7$ Hz) H in the position 6.

### 1-Methyl-2-(5-methyl-3-pyrazolyl)-1,2,3,6-tetrahydropyridine (*VIII*)

Sodium borohydride (2·27 g, 0·06 mol) was added to a stirred solution of 9·03 g (0·03 mol) of methiodide *VIIa* in 150 ml of ethanol and 50 ml of water and the mixture was refluxed for 5 h. After evaporation of ethanol ice was added and the mixture extracted with diethyl ether (three 60 ml portions) and chloroform (three 50 ml portions). The combined extracts were dried over $MgSO_4$, filtered and evaporated. Yield 3·9 g (73·6%) of *VIII*, b.p. 165—167°C/1 200 Pa. For $C_{10}H_{15}N_3$ (177·25) calculated: 67·76% C, 8·53% H, 23·71% N; found: 67·85% C, 8·72% H, 23·71% N. $^1$H-NMR spectrum ($CDCl_3$), ppm: 2·17 and 2·39 (s, 3 H) $CH_3$ on both rings; 2·0—2·56 (m, 2 H) H in the position 3 of the pyridine ring; 2·82—3·46 (m, 2 H) H in the position 6; 3·56—3·74 (m, 1 H) H in the position 2 of the pyridine ring; 5·99 (s, 1 H) H in the position 4 of the pyrazole ring.

### 1-Methyl-3-(5-methyl-3-pyrazolyl)pyridinium Iodide (*VIIb*)

A mixture of 4·3 g (0·027 mol) of 3-methyl-5-(3-pyridyl)pyrazole[3] (*VIb*), 3·8 g (0·027 mol) of methyl iodide and 30 ml of methanol was refluxed for 6 h. Yield 6·4 g (70·2%) of yellow crystals of *VIIb*, m.p. 276—279°C (methanol). For $C_{10}H_{12}IN_3$ (301·14) calculated: 39·89% C, 4·02% H, 42·14% I; found: 39·75% C, 4·07% H, 41·76% I.

### 1-Methyl-3-(5-methyl-3-pyrazolyl)-1,2,5,6-tetrahydropyridine (*IX*)

Methiodide *VIIb* (3·01 g; 0·01 mol) was reduced as *VIIa*. Yield, 1·5 g (84·7%) of a product, in two fractions, m.p. 113—116°C (0·95 g) and 124—130°C (0·55 g), respectively. The latter was crystallized from benzene and filtered through alumina, yielding pure *IX*, m.p. 130·5—133°C. For $C_{10}H_{15}N_3$ (177·25) calculated: 67·76% C, 8·53% H, 23·71% N; found: 67·97% C, 8·69% H, 23·71% N. $^1$H-NMR spectrum ($CDCl_3$), ppm: 2·26 (s, 3 H) $CH_3$ on the pyrazole ring; 2·43 (s, 3 H) N—$CH_3$; 2·06—2·70 (m, 10 H) $CH_2$ in positions 5 and 6, overlapping with the signals of both $CH_3$ groups; 3·35 (bs, 2 H) $CH_2$ in position 2; 6·03 (s, 1 H) H in the position 4 of the pyrazole ring; 6·16 (bs, 1 H) H in the position 4 of the pyridine ring. IR spectrum ($CHCl_3$), $cm^{-1}$: 3 470, 3 200 $\nu$(NH).

### 1-Methyl-4-(5-methyl-3-pyrazolyl)-1,2,3,6-tetrahydropyridine (*X*)

1-Methyl-4-(5-methyl-3-pyrazolyl)pyridinium iodide[3] (*VIIc*) was reduced as *VIIb*. Yield, 50·5% of *X*, m.p. 98—100°C (cyclohexane). For $C_{10}H_{15}N_3$ (177·25) calculated: 67·76% C, 8·53% H, 23·71% N; found: 68·00% C, 8·86% H, 23·72% N. $^1$H-NMR spectrum ($CDCl_3$), ppm: 2·23 (s, 3 H) $CH_3$ of the pyrazole ring; 2·39 (s, 3 H) N—$CH_3$; 2·46—2·76 (m, 4 H) H in the position

2 and 3 of the tetrahydropyridine ring; 2·94—3·18 (m, 2 H) H in the position 6 of the tetrahydropyridine ring; 6·00 (s, 1 H) in the position 4 of the pyrazole ring; 5·94—6·15 (m, 1 H) H on the double bond of the tetrahydropyridine ring. The broad band at 11·71, belonging to the NH the pyrazole ring is shifted and broadened on heating at 60°C. IR spectrum ($CHCl_3$), $cm^{-1}$: 3470, 3200 $\nu$(NH).

*The analyses were carried out in our analytical laboratory (head Dr L. Helešic), the* NMR *spectra were recorded under the direction of Dr P. Trška and the* IR *spectra were measured by Dr E. Janečková and Dr A. Kohoutová.*

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