PYRIDINE DERIVATIVES

PART VI*. MALONATIONS OF SUBSTITUTED NITROPYRIDINES[1]

By W. Gruber

ABSTRACT

5-Hydroxy-2-alkylpyridines (VII) were prepared by a sequence of reactions starting with the malonation of 2-chloro-5-nitropyridine with diethyl alkylmalonates. Malonation failed with 4-methoxy-3-nitropyridine (VIII) and 2-chloro-3-nitropyridine (XII), yielding decomposition products only. Reactivity of the methoxyl groups in 4-methoxy-3-nitropyridine (VIII) and in 2-methoxy-3-nitropyridine (XV) was compared with respect to the rearrangement to N-methylpyridone, the reaction with aromatic amines, and hydrolysis with dilute acids. Methylation of 2-hydroxy-3-nitropyridine yields either 2-methoxy-3-nitropyridine (XV) or N-methyl-3-nitro-2-pyridone (XVI) as can be expected.

In Part I of this series (5) it was shown that malonation of 2-chloro-5-nitropyridine gives in good yields diethyl(5-nitropyridyl-2)-ethylmalonate (I, R = Et). This compound was the intermediate for a synthesis of *d*-pseudoconhydrine (II), thus proving the structure of (II). In Part IV (4) the isomeric 3-hydroxy-2-alkylpyridines (III) have been synthesized by rearrangement of 2-acylfuranes with ammonia. This paper reports further applications of the malonation reaction on 2,5-, 2,3-, and 3,4-substituted pyridine derivatives.

The reaction was studied first with 2-chloro-5-nitropyridine. The best yields of (I) were obtained by heating the components without a solvent. At 80–100°C. a violent reaction took place which was moderated by gentle cooling. After the first reaction subsided the dark brown mixture was heated for one hour at 150°C. to complete the reaction. The cooled mixture was poured into water and extracted with ether. The solvent was evaporated and the residue distilled *in vacuo* so as to remove the starting material and also to distill the end product, provided its boiling point was not too high. (5-Nitropyridyl-2)-alkylmalonesters are highly viscous, yellow oils which did not crystallize. During hydrolysis of these malonesters with sulphuric acid (50% v/v) or 20% hydrochloric acid, complete decarboxylation occurred. The intermediate, (5-nitropyridyl-2)-alkylacetic acid (IV) is still more unstable than pyridyl-2-acetic acid (6,12), the nitro group in the 5-position increasing the lability. The 2-alkyl-5-nitro-pyridines (V) do not give picrates, having not enough base-strength, but some of them have been characterized as chloroplatinates.

The nitro group was reduced either with stannous chloride or by catalytical hydrogenation. Both methods yielded the 5-amino-2-alkylpyridines almost quantitatively. Except 5-amino-2-benzylpyridine (VI, R = $CH_2C_6H_5$) all of them were oils and were therefore characterized as monopicrates (Table I). By diazotization and hydrolysis of the diazoniumsulphate, the amines were converted into the 5-hydroxy-2-alkylpyridines (VII, R_1 = alkyl, R_2 = H), which showed the normal properties of aromatic phenols: Color reaction with

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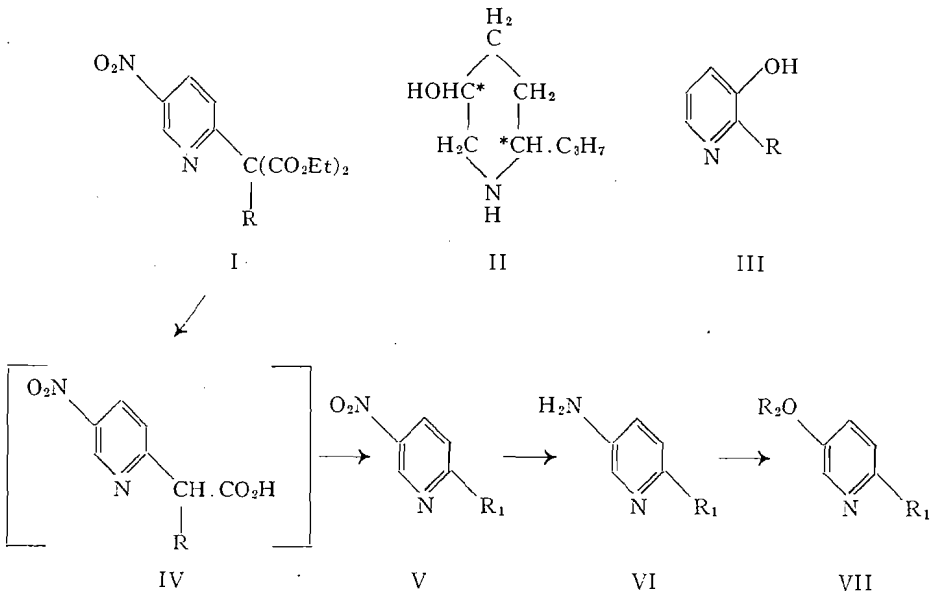


TABLE I

5-Amino-2-alkylpyridines VI	M.p., °C.	Analytical figures	
		Calc., %	Found, %
Picrate of 5-amino-2-ethylpyridine ($R_1 = C_2H_5$)	189–191	$C_7H_{10}N_2.C_6H_3N_3O_7$ N 19.94	20.12
Picrate of 5-amino-2-*n*-propylpyridine ($R_1 = n$-C_3H_7) (5)	163–165		
Picrate of 5-amino-2-*n*-butylpyridine ($R_1 = n$-C_4H_9)	142–143	$C_9H_{14}N_2.C_6H_3N_3O_7$ C 47.49 H 4.52	 47.55 4.41
Picrate of 5-amino-2-*sec*-butylpyridine ($R_1 = sec$-C_4H_9)	151–153	$C_9H_{14}N_2.C_6H_3N_3O_7$ C 46.51 H 4.42 N 18.08	 46.74 4.53 18.05
Picrate of 5-amino-2-*n*-amylpyridine ($R_1 = n$-C_5H_{11})	150–152	$C_{10}H_{16}N_2.C_6H_3N_3O_7$ C 48.85 H 4.87 N 17.81	 48.65 4.93 17.65
5-Amino-2-phenylethylpyridine ($R_1 = CH_2CH_2C_6H_5$)	113–115	$C_{13}H_{14}N_2$ C 78.75 H 7.12 N 14.13	 78.55 7.13 14.27

ferric chloride solution produced red to brown complexes, and coupling with *o*- and *p*-nitroanilines gave brown azo dyes.

Compounds of type (VII) are readily soluble in 1 *N* alkali and 1–2 *N* acids (Table II).

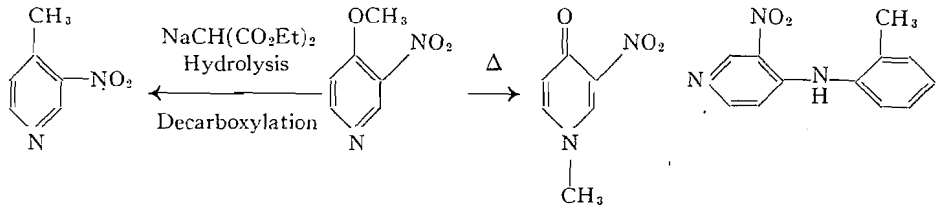
TABLE II

5-Hydroxy-2-alkylpyridines VII	M.p., °C.	Analytical figures	
		Calc., %	Found, %
5-Hydroxy-2-ethylpyridine (R_1 = C_2H_5, R_2 = H)	129–131	C_7H_9NO	
		C 68.27	68.26
		H 7.37	7.36
		N 11.37	11.35
5-Hydroxy-2-*n*-propylpyridine (R_1 = *n*-C_3H_7, R_2 = H) (5)	92–94		
5-Hydroxy-2-*n*-butylpyridine (R_1 = *n*-C_4H_9, R_2 = H)	83–85	$C_9H_{13}NO$	
		C 71.49	71.39
		H 8.67	8.60
		N 9.26	
5-Hydroxy-2-*sec*-butylpyridine (R_1 = *sec*-C_4H_9, R_2 = H)	96–98		71.27
			8.76
3,5-Dinitrobenzoate (R_1 = *sec*-C_4H_9, R_2 = 3,5-$(NO_2)_2C_6H_3CO$-)	133–135	$C_{16}H_{15}N_3O_6$	9.50
		C 55.65	55.44
		H 4.38	4.32
		N 12.17	12.15
5-Hydroxy-2-*n*-amylpyridine, 3,5-Dinitrobenzoate (R_1 = *n*-C_5H_{11}, R_2 = 3,5-$(NO_2)_2C_6H_3CO$-)	98–101	$C_{17}H_{17}N_3O_6$	
		C 56.82	56.75
		H 4.71	4.82
		N 11.70	11.52
5-Hydroxy-2-phenylethylpyridine (R_1 = $CH_2CH_2C_6H_5$, R_2 = H)	148–150	$C_{13}H_{13}NO$	
		C 78.36	78.20
		H 6.58	6.45
		N 7.03	7.14

4-Chloro-3-nitropyridine does not seem to be stable (9) (4-chloropyridine is also unstable according to Wibaut and Broekman (11)). The malonation of "4-chloro-3-nitropyridine hydrochloride with diethyl disodiomalonate" reported by Koenigs and Fulde (7) was almost certainly a malonation of 4-methoxy-3-nitropyridine hydrochloride, in view of a later paper by Bremer (3), who prepared 4-methoxy-3-nitropyridine (VIII) *in situ* by pouring a mixture of 4-hydroxy-3-nitropyridine and phosphorus pentachloride into cooled methanol. The methoxyl group was highly reactive, so that this stable compound could be used as starting material for many reactions instead of the unstable halide. Bremer did perform the malonation of (VIII) with diethyl sodiomalonate, which yielded 4-methyl-3-nitropyridine (IX).

The synthesis of (VIII) was repeated in the hope of establishing a general method for the synthesis of 3-nitro-4-alkylpyridines, but we could not achieve the desired malonation with substituted diethyl malonates. The identity of the starting material was checked by its rearrangement to N-methyl-3-nitro-4-pyridone (X) and by its reaction with *o*-toluidine to yield N-(3-nitropyridyl-4)-*o*-toluidine (XI) quantitatively. Malonation of (VIII) was attempted with diethyl sodiomethylmalonate and diethyl sodio-*i*-propylmalonate using ether,

ethanol, or benzene as a solvent. After reduction of the supposed nitro-compound, the amine, which was obtained as an oil, was characterized as a picrate which was the same in both cases, but identical neither with that of 3-amino-4-hydroxypyridine nor that of 3-aminopyridine. This picrate (Substance P) is now believed to derive from a base generated during the reaction by decomposition of the pyridine nucleus.

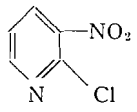


IX VIII X XI

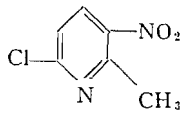
Finally, malonations were tried with 2-chloro-3-nitropyridine (XII). Although the components reacted violently and the reaction mixture gave a positive test for chloride ion, the desired (3-nitropyridyl-2)-alkylmalonate could not be isolated, probably because (XII) decomposed. According to Baumgarten and Chien-Fan Su (1) the reaction of 2-chloro-5-nitropicolin (XIII) with sodium methylate gave 2-methoxy-5-nitropicolin in high yield, whereas the same reaction with the 2,3-isomer (XIV) brought about only decomposition. From these facts it was concluded that all chloro-nitropyridines with substituents in ortho position react in a similar way; however, the reaction of 2-chloro-3-nitropyridine (XII) with sodium methoxide yields the methoxyl compound (m.p. 57–58°C.) almost quantitatively. 2-Methoxy-3-nitropyridine (XV) has been reported in the literature (8) to have a m.p. of 110°C. It was prepared from the silver salt of 2-hydroxy-3-nitropyridine and methyl iodide and it is well known from methylation experiments on 2-hydroxy-5-nitropyridine (2) that this silver salt method gives rise not only to the methyl ethers but also to the N-methyl-nitropyridones. The methylation of 2-hydroxy-3-nitropyridine with methyl iodide via Ag-salt was therefore repeated and 2-methoxy-3-nitropyridine (XV) as well as N-methyl-3-nitro-2-pyridone (XVI) could be separated from the reaction mixture. The methyl ether (XV) from this experiment was identical with the compound prepared by methylation of the halide (XII) with sodium methoxide. The methylation of the potassium salt of 2-hydroxy-3-nitropyridine with methyl sulphate produced mainly the pyridone (XVI), which again was identical with the compound, prepared by methylation of the silver salt.

The reaction of (XII) with aliphatic and aromatic amines proceeds normally.

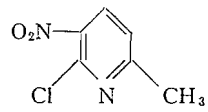
To compare the reactivity of the methoxyl groups in (VIII) and (XV) attempts were made to rearrange 2-methoxy-3-nitropyridine (XV) to N-methyl-3-nitro-2-pyridone by heating *in vacuo* in a sealed tube. Such a rearrangement would be expected by analogy with XVII → XVIII, (10), but the reaction failed. Unlike (VIII) the 2-methoxyl group in (XV) would react



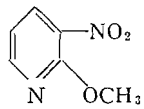
XII



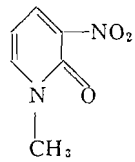
XIII



XIV

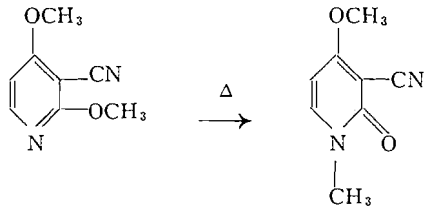


XV



XVI

neither with *o*-toluidine nor piperidine at 130°C., but could be hydrolyzed easily even with 0.5 *N* acid at the steam bath for two hours.



XVII XVIII

EXPERIMENTAL*

The following are a few typical examples of the malonation reaction and of subsequent steps.

Diethyl (5-nitropyridyl-2)-methylmalonate (I, $R = CH_3$)

Diethyl sodiomethylmalonate was prepared by refluxing a mixture of 1.2 gm. of finely powdered sodium and 8.7 gm. of diethyl methylmalonate in 100 ml. of absolute ether. After complete dissolution of the sodium sand (10 hr.) the solvent was evaporated, the residue dried overnight in a desiccator, intimately mixed with 8 gm. of 2-chloro-5-nitropyridine, and cautiously heated on the steam bath. At 90°C. (thermometer in the mixture) a violent reaction set in and the content of the flask darkened. After the reaction subsided the mixture was heated to 150°C. (oil bath) for one hour, cooled, and 200 ml. of water added. The solution was extracted exhaustively with ether, the solvent evaporated and the residue distilled at 1 mm. The fraction above 150°C. (air bath temperature) was collected and redistilled; yield: 8.7 gm. (58%). Calc. for $C_{13}H_{16}N_2O_6$: N, 9.46%; Found: N, 9.70%.

5-Nitro-2-n-amylpyridine (V, $R_1 = n\text{-}C_5H_{11}$)

Diethyl (5-nitropyridyl-2)-*n*-butylmalonate (I, R = n-C_4H_9) (15.5 gm.) was heated to 110–120°C. with 90 ml. of sulphuric acid (1:1) until evolution of gas bubbles ceased (four hours). After cooling, the dark solution was ex-

**Melting points are corrected. Analyses are by A. Bernhardt, MPI, Mühlheim (Ruhr), Germany.*

tracted with ether and the organic layer discarded. The acid layer was diluted and made alkaline and after exhaustive extraction with ether, the ether was evaporated and the residue distilled *in vacuo* (120–130°C. air bath, 2 mm. Hg); Yield, 7.0 gm., i.e. 68%.

Of this base 380 mgm. was dissolved in 2 ml. of 20% hydrochloric acid and added to 3 ml. of a solution containing 350 mgm. H_2PtCl_6. The precipitate was thoroughly washed with very dilute hydrochloric acid and methanol. M.p. 152–155°C. (dec.); Yield, 578 mgm., i.e. 79%. Calc. for $(C_{10}H_{15}N_2O_2)_2$. $PtCl_6$: Pt, 23.89%. Found: Pt, 23.70%.

5-Nitro-2-n-butylpyridine (V, $R_1 = n\text{-}C_4H_9$)

This was synthesized as above. Chloroplatinate: m.p. 181–183°C. (dec.). Calc. for $(C_9H_{13}N_2O_2)_2$ $PtCl_6$: C, 28.06; H, 3.40; Pt, 25.34%. Found: C, 28.07; H, 3.27; Pt, 25.34%.

5-Amino-2-n-butylpyridine (VI, $R_1 = n\text{-}C_4H_9$)

A solution of 1.98 gm. of (V) ($R_1 = n\text{-}C_4H_9$) in 80 ml. of absolute methanol was shaken in a hydrogen atmosphere in the presence of 0.3 gm. of Adams' catalyst. The required amount of three moles of hydrogen (0°C., 760 mm. Hg, 739.2 ml.) was taken up in 15 min. The amine was isolated by filtering off the catalyst and evaporating the solvent and purified by distillation *in vacuo* (0.005 mm. Hg, 90–100°C. air bath). Yield: 1.64 gm. (almost quantitative). The picrate was prepared in ethereal solution from 300 mgm. of the base and 530 mgm. picric acid. Purification by several recrystallizations from methanol; m.p. 142–143°C.

5-Amino-2-phenylethylpyridine (VI, $R_1 = CH_2CH_2C_6H_5$)

A solution of 4.4 gm. of the nitro compound (V) ($R_1 = CH_2CH_2C_6H_5$) in 15 ml. of concentrated hydrochloric acid was added slowly to a cooled solution of 20 gm. of crystalline stannous chloride in 16 ml. of concentrated hydrochloric acid. After standing for one hour a strong sodium hydroxide solution was added in excess and then exhaustively extracted with ether. Purification by recrystallization from ether yielded 3.6 gm., i.e. 95%; m.p. 113–115°C.

5-Hydroxy-2-sec-butylpyridine (VII, $R_1 = sec\text{-}C_4H_9$, $R_2 = H$)

A solution of 1.26 gm. of (VII) ($R_1 = sec\text{-}C_4H_9$) in 90 ml. of 1 *N* sulphuric acid was diazotized with 0.8 gm. of sodium nitrite in 12 ml. of water, the yellow mixture was then heated on the steam for one hour and cooled. After the addition of solid sodium bicarbonate in excess, the solution was extracted with ether, the solvent evaporated, and the residue distilled *in vacuo*, giving a crude yield of 1.10 gm., i.e. 86%. This oil crystallized and was purified by several recrystallizations from ether – petroleum ether; m.p. 96–98°C.

The 3,5-dinitrobenzoate of this phenolic base was prepared by heating a mixture of 0.8 gm. of (VII) ($R_1 = sec\text{-}C_4H_9$, $R_2 = H$) and 1.3 gm. of 3,5-dinitrobenzoyl chloride for one hour on the steam bath. The cooled reaction mixture was taken up in ether, washed with 1 *N* sodium hydroxide and with water, then the solvent was evaporated. The residue was recrystallized twice from ether; m.p. 133–135°C.

N-(3-Nitropyridyl-4)-o-toluidine (XI)

4-Methoxy-3-nitropyridine (1.54 gm.) was heated with 1.07 gm. of *o*-toluidine on the steam bath until the mixture solidified completely (two hours). After cooling the mass was triturated with ether, filtered, and the residue recrystallized from dilute methanol; m.p. 85–87°C. Calc. for $C_{12}H_{13}N_3O_2$: C, 62.87; H, 4.84; N, 18.33. Found: C, 62.76; H, 4.84; N, 18.12%.

2-Methoxy-3-nitropyridine (XV)

A solution of 1.4 gm. of 2-chloro-3-nitropyridine (XII) in 10 ml. of absolute methanol was shaken with sodium methoxide (from 0.3 gm. sodium and 5 ml. of methanol) for eight hours at room temperature, then refluxed for one hour, the solvent evaporated *in vacuo* and after addition of 100 ml. of water, the precipitate filtered with suction. After purification by vacuum distillation and recrystallization from ether – petroleum ether the m.p. was 57–59°C. Yield, 0.9 gm., i.e. 65%. Calc. for $C_6H_6N_2O_3$: C, 46.75; H, 3.93; N, 18.18; OCH_3, 20.13%. Found: C, 46.81; H, 4.05; N, 18.10; OCH_3, 20.05%.

Methylation of 2-Hydroxy-3-nitropyridine (XX)

(*a*) A solution of 0.60 gm. of (XX) in aqueous potassium hydroxide (0.25 gm. potassium hydroxide in 34 ml. of water) was mixed with aqueous silver nitrate solution (0.73 gm. silver nitrate in 2 ml. of water). The silver salt was isolated and dried; 800 mgm. was suspended in 8 ml. of methanol, 0.3 ml. of methyl iodide added, and the mixture refluxed overnight. The solvent was evaporated and the residue extracted twice with 10 ml. of cooled ether. After evaporation of the solvent and vacuum distillation of the residue, the m.p. was 57–58°C., not depressed by admixture of the methyl ether XV. Yield, 88 mgm., i.e. 18%, based on silver salt. The residue from the ether extraction weighed 286 mgm., i.e. 59%, and had a m.p. of 168–171°C. It was recrystallized several times from methanol–ether; m.p. 171–174°C.

(*b*) A mixture of 737 mgm. of (XX), 645 mgm. of potassium hydroxide, 633 mgm. of freshly distilled dimethyl sulphate, and 6 ml. of water was refluxed for six hours, cooled, the precipitate collected on a Büchner funnel and recrystallized twice from water. Yield, of N-methyl-3-nitro-2-pyridone, almost quantitative; m.p. 171–174°C. The mixed m.p. with the same fraction from (*a*) was not depressed. Calc. for $C_6H_6N_2O_3$: C, 46.75; H, 3.93; N, 18.18%. Found: C, 46.29; H, 3.82; N, 18.02%.

Acid Hydrolysis of XV

2-Methoxy-3-nitropyridine (257 mgm.) was heated with 20 ml. of 0.5 *N* hydrochloric acid on the steam bath for three hours. The oil disappeared slowly; cooling precipitated yellow crystals, m.p. 224–226°C.; no depression when mixed with 2-hydroxy-3-nitropyridine.

N-(3-Nitropyridyl-2)-o-toluidine

2-Chloro-3-nitropyridine (XII, 0.9 gm.) and *o*-toluidine (1.0 gm.) were heated at 150°C. for one hour. After removal of the excess of *o*-toluidine as hydrochloride, the residue was recrystallized from dilute methanol; m.p.

124–126°C. Calc. for $C_{12}H_{11}N_3O_2$: C, 62.87; H, 4.84%. Found: C, 62.72; H, 5.00%.

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