63. *Studies of the Coal-tar Bases. Part VI.* A New Synthesis of* 3 : 5-*Lutidine.*

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3 : 5-Lutidine has been prepared from diethyl acetonedicarboxylate by a five-stage process in an overall 43% yield.

Of the six dimethyl derivatives of pyridine the 3 : 5-isomer is the least accessible and has been the least studied. It has been identified in the bases from coal-tar,[1] shale-oil and petroleum [2] but is not plentiful therein.[3] For the measurement of its salient physical or physicochemical properties in extension of work already reported [4] we needed considerable amounts of the pure base and turned our attention to its synthesis.

The base has been secured as a by-product or main product from the thermal treatment of propionaldehyde–ammonia with or without formaldehyde.[5] Oparina introduced the use of a catalyst (Al_2O_3) but the most favourable claim appears to be that by Hearne and Buls [6] of 31% conversion of α-methylacraldehyde into 3 : 5-lutidine by passage with ammonia over boron phosphate at 350—370°. Nevertheless the thermal products are all complex mixtures containing both basic and non-basic materials.

A recent method of obtaining 3 : 5-dimethylpiperidine *via* dimethylglutarimide [7] might have been tried had the method we chose first not been effective.

A projected synthesis of pyridine, never brought to completion, by Stokes and von Pechmann,[8] appeared capable of development into a general one for introducing alkyl groups into the 3- and/or 5-position of the pyridine ring. By interaction of diethyl acetonedicarboxylate (I; R = H) and ammonia they obtained the ethyl ester of β-amino-β-hydroxyglutaromonoamide (II) which yielded glutazine (β-aminoglutaconimide) (III;

* Part V, *J. Appl. Chem.*, 1952, **2**, 236.

[1] Ahrens and Gorkow, *Ber.*, 1904, **37**, 2062.

[2] Hackmann and Wibaut, *Rec. Trav. chim.*, 1943, **62**, 229; Bratton and Bailey, *J. Amer. Chem. Soc.*, 1937, **59**, 175; Eguchi, *Bull. Chem. Soc. Japan*, 1928, **3**, 227; Benzie, Milne and Nisbet, Proc. 2nd Oil Shale and Cannel Coal Conf., Glasgow, 1950.

[3] Coulson, Hales, Holt, and Ditcham, *J. Appl. Chem.*, 1952, **2**, 71.

[4] Biddiscombe, Coulson, Handley, and Herington, *J.*, 1954, 1957.

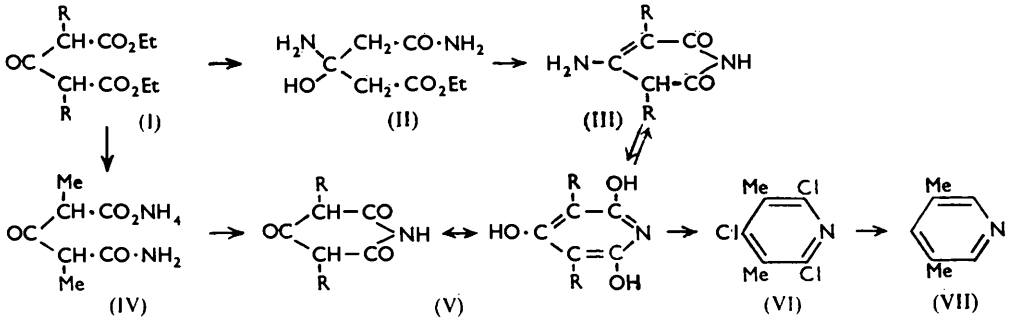
[5] Dürkopf and Göttsch, *Ber.*, 1890, **23**, 685, 1114; Tschitschibabin and Oparina, *J. prakt. Chem.*, 1924, [2], **107**, 138, 145; Oparina, *J. Russ. Phys. Chem. Soc.*, 1929, **61**, 2002.

[6] Hearne and Buls, B.P. 654,443/1948.

[7] Hoch and Karrer, *Helv. Chim. Acta*, 1954, **37**, 397.

[8] Stokes and von Pechmann, *Ber.*, 1886, **19**, 2694.

R = H) when boiled with sodium carbonate solution. Glutazine yields 2 : 4 : 6-trihydroxypyridine (V; R = H) when boiled with strong acid. This trihydroxypyridine gave no more than a smell of pyridine when it was heated with zinc dust.



Our intention was to use the αα'-dimethyl derivative (I; R = Me), replace the hydroxyl groups of 2 : 4 : 6-trihydroxy-3 : 5-dimethylpyridine (V; R = Me) by chlorine, and reduce the trichloropyridine derivative (VI) catalytically to 3 : 5-lutidine (VII). However, the reactions took a different course. Diethyl αα'-dimethylacetone-αα'-dicarboxylate (I; R = Me) with ammonia gave the ammonium salt (IV) of the monoamide and this was transformed into 2 : 4 : 6-trihydroxy-3 : 5-dimethylpyridine (V; R = Me) when treated with either sodium carbonate solution or hydrochloric acid. The final stages of the synthesis were completed according to plan and gave a 43% overall yield of 3 : 5-lutidine (VII) by this five-stage route.

The ammonium salt (IV) of the monoamide is unstable, being rapidly converted at its m. p. into dimethylglutazine (III; R = Me). Presumably the parent compound, unsubstituted by methyl groups, is even more unstable since it was not isolated as an intermediate product in the formation of glutazine either by Stokes and von Pechmann [8] or by von Niematowski and Sucharda.[9]

The compounds formulated as 2 : 4 : 6-trihydroxypyridine and 2 : 4 : 6-trihydroxy-3 : 5-dimethylpyridine possess so much ketonic character that it is questionable whether they should not be regarded as the cyclic imides of acetone- and dimethylacetone-dicarboxylic acid. When titrated in aqueous solution both show three inflexions in the pH curve, which appear to indicate the presence of one basic and two acidic functional groups.[10] However, whereas von Niematowski and Sucharda [9] report that boiling 2 : 4 : 6-trihydroxypyridine with excess of acetic anhydride gives a diacetyl derivative we find that 2 : 4 : 6-trihydroxy-3 : 5-dimethylpyridine gives, to some extent at least, the triacetyl compound, which implies the existence of three potentially acidic groups. The unacetylated compound (in potassium chloride discs) shows infrared absorption bands typical of a cyclic imide (amide-CO at 1650 cm.$^{-1}$; cyclic C=O at 1708 cm.$^{-1}$; bonded NH at 3260 cm.$^{-1}$), but the triacetyl compound shows a single band due to ester –C=O (1770 cm.$^{-1}$) as well as the strong ester-C–O band (1182 cm.$^{-1}$), but no absorption band between 3100 and 3400 cm.$^{-1}$ due to bonded NH, and clearly (unlike the unacetylated compound) has the character of a trihydroxypyridine derivative.

The infrared absorption spectrum of the compound formulated as β-amino-αα'-dimethylglutaconimide (dimethylglutazine) does not offer unambiguous evidence of structure and although there is some indication that the preferred structure is the most important component other obvious variations are not excluded.

[9] Von Niematowski and Sucharda, *J. prakt. Chem.*, 1916, **94**, 203.
[10] Albert and Phillips, *J.*, 1956, 1294.

Experimental

Diethyl Acetonedicarboxylate.—The ester was obtained in 46% yield (b. p. 118—121°/3·5 mm.) from citric acid.[11] The reaction is more difficult to control than published directions indicate and a bigger flask should be used.

Diethyl αα'-Dimethylacetone-αα'-dicarboxylate (I; R = Me).—The published method of preparation [12] was somewhat modified. To diethyl acetonedicarboxylate (337 g.) mixed with methyl iodide (478 g.) and absolute alcohol (337 g.) a solution of sodium (77 g.) in absolute alcohol (1400 ml.) was slowly added with slight warming on a steam-bath. After 2 hr. at room temperature the excess of alcohol was removed at 14 mm. Towards the end sodium iodide separated. Sufficient water was added to dissolve the salt, and the aqueous solution was separated. The ester was washed with water which was added to the sodium iodide solution, and the combined aqueous solution was extracted with ether, the ethereal extract being added to the ester. Drying ($CaSO_4$) and distillation *in vacuo* gave 335 g. (87%) of diethyl 3-oxopentane-2 : 4-dicarboxylate, b. p. 119—122°/4·5 mm.

Ammonium 4-Carbamoyl-2-methyl-3-oxopentanoate (IV).—The preceding ester (335 g.) was mixed with aqueous ammonia (*d* 0·88; 335 ml.), cooled in ice, and saturated with gaseous ammonia. The ester did not dissolve at this stage and the mixture was shaken for 100 hr. Needle-like crystals slowly separated, were filtered off, pressed dry, washed with ether, and dried *in vacuo*. The product (175 g.) melted at 135—140° (gas evolution), resolidified, and melted again between 220° and 255°. A further 39 g. were obtained by resaturation of the filtrate with ammonia and reshaking (total yield, 77·3%). The *product* is essentially the *ammonium salt* of the monoamide although its composition is somewhat variable since it contains absorbed water and ammonia which cannot be removed without causing further change of composition (Found: C, 41·7; H, 8·0; N, 15·4. $C_7H_{14}O_4N_2,0·4H_2O,0·2NH_3$ requires C, 41·9; H, 7·7; N, 15·4%). After further washing with ether and drying at 100° more than the excess of ammonia and water had been removed and the composition approximated that of the ammonium salt admixed with 2 : 4 : 6-trihydroxy-3 : 5-dimethylpyridine (which it forms with great ease by loss of constitutional water and ammonia) (Found: C, 45·9; H, 7·1; N, 14·2. Calc. for $9C_7H_{14}O_4N_2,2C_7H_9O_3N$: C, 45·7; H, 7·1; N, 13·9%). It was not possible to separate the constituents by crystallisation and obtain a pure specimen of the ammonium salt; the unpurified product is extremely soluble in water or alcohol, with development of a deep red colour, resulting, it seems, from oxidation by air.

2 : 4 : 6-*Trihydroxy-3 : 5-dimethylpyridine* (V; R = Me).—(*a*) The preceding ammonium salt (100 g.) was heated with anhydrous sodium carbonate (32 g.) in water (300 ml.) under reflux in nitrogen. The ammonium salt quickly dissolved, and the solution, at first deep red, became finally pink, ammonia being evolved. After 20 minutes' boiling the mixture was cooled in ice and neutralised with acetic acid. 2 : 4 : 6-*Trihydroxy-3 : 5-dimethylpyridine* which was slowly precipitated was filtered off, washed with a little water (yield 61·2 g., 86%), and recrystallised from boiling water (in which it is moderately soluble) as pale pink rhombic prisms, m. p. 231° (Found: C, 54·1; H, 5·7; N, 9·1. $C_7H_9O_3N$ requires C, 54·2; H, 5·8; N, 9·0%).

(*b*) The ammonium salt (25 g.) was boiled in concentrated hydrochloric acid (30 ml.) and water (50 ml.) under reflux in nitrogen. The salt rapidly dissolved giving a clear pink solution which after 15 min. was cooled and brought to pH 5 with 25% aqueous sodium hydroxide. The precipitated 2 : 4 : 6-trihydroxy-3 : 5-dimethylpyridine (16 g., 90%; m. p. 225°) crystallised from water whereupon the m. p. rose to 231° alone or mixed with the specimen from (*a*) above.

The extreme instability of the ammonium salt is shown by its reaction with no more than an equivalent of hydrochloric acid. When the salt (10 g.) was mixed with concentrated hydrochloric acid (5·3 ml.) and water (3 ml.) and stirred, a little heat was evolved. After 10 min. the crystalline solid reaction product was filtered off and washed with a little water to remove ammonium chloride. The yield was 6·1 g. (86%) of 2 : 4 : 6-trihydroxy-3 : 5-dimethylpyridine, m. p. 215—216°. It was purified by crystallisation from water and then melted at 231° alone or admixed with a previous specimen.

2 : 4 : 6-Trihydroxy-3 : 5-dimethylpyridine (1·5 g.) was boiled under reflux for 1½ hr. with

[11] *Org. Synth.*, Coll. Vol. I, 2nd Edn., pp. 10, 237.
[12] Schroeter, *Ber.*, 1916, **49**, 2711.

acetic anhydride (4 g.), then poured on crushed ice. The acetylated product (2·3 g.) so precipitated was crystallised from acetic acid. Mother-liquors from this crystallisation contained lower-melting material which was probably incompletely acetylated. 2 : 4 : 6-*Triacetoxy*-3 : 5-*dimethylpyridine* forms minute colourless rhombic plates, m. p. 198° (Found : C, 55·0; H, 5·3; N, 5·0%. $C_{13}H_{15}O_6N$ requires C, 55·1; H, 5·3; N, 5·0%).

0·1M-Aqueous 2 : 4 : 6-trihydroxy-3 : 5-dimethylpyridine, when titrated with 0·1N-hydrochloric acid and with 0·1N-sodium hydroxide, showed inflexions in the curve of pH against titre at pH 3·2 (basic function), 7, and 11. This seems to indicate that only two of the hydroxyl groups are sufficiently acidic to form sodium salts under these conditions.

β-*Amino-αα'-dimethylglutaconimide* (III; R = Me).—(*a*) The ammonium salt (IV) was heated in a metal-bath and began to melt and evolve gas at 140°. The colour darkened and after 10 min., the bath-temperature being 185°, no further change ensued. The loss of weight was about 25%. The residual *imide* recrystallised from boiling water (charcoal) as straw-coloured needles, m. p. 250° (decomp.) (Found : C, 54·3; H, 6·4; N, 18·3. $C_7H_{10}O_2N_2$ requires C, 54·6; H, 6·5; N, 18·2%).

(*b*) 2 : 4 : 6-Trihydroxy-3 : 5-dimethylpyridine was heated with twice its weight of anhydrous ammonium acetate at 155° for 5 min. The mixture liquefied but solidified again after excess of ammonium acetate had been driven off. The residue, crystallised from water, melted at 250° alone or mixed with a specimen from (*a*) above.

2 : 4 : 6-*Trichloro*-3 : 5-*dimethylpyridine* (VI).—2 : 4 : 6-Trihydroxy-3 : 5-dimethylpyridine (72·2 g.) and phosphorus oxychloride (151 ml.) were heated for 1½ hr. in an autoclave at 190°. The product was treated with crushed ice. Crude trichloro-compound separated from the aqueous solution, with some charred impurity, and was removed and dissolved in ether. The aqueous filtrate held some trichloro-compound which was extracted with ether. The combined ethereal solution was shaken with dilute aqueous sodium carbonate and with water and evaporated. The residue of 2 : 4 : 6-*trichloro*-3 : 5-*dimethylpyridine* (90 g., 91·7%; m. p. 77°) crystallised from alcohol as colourless or pale straw, square or octagonal leaflets, m. p. 78° (Found : C, 39·8; H, 2·8; N, 6·7; Cl, 50·5. $C_7H_6Cl_3N$ requires C, 39·9; H, 2·85; N, 6·65; Cl, 50·6%).

3 : 5-*Lutidine* (VII).—The trichloro-compound (96 g.) and potassium acetate (150 g.) were dissolved in warm methanol (1200 ml.); then allowed to cool, giving a fine suspension. Palladium chloride (8 g.) was added and the whole shaken in hydrogen at slightly >1 atm. After absorption of 24·4 l. (6 hr.) a further 8 g. of palladium chloride were added and the reduction continued till a further 11·5 l. (6 hr.) had been taken up. More palladium chloride (4 g.) caused a final absorption of 3·6 l. in 12 hr. Potassium chloride and palladium were filtered off and washed with hot methanol, and the methanol solution and washings reduced to small bulk by distillation through a fractionating column. The residue was treated with concentrated sulphuric acid (56 ml.) in water (300 ml.), extracted with ether, made strongly alkaline, and steam-distilled. The 3 : 5-lutidine was salted out of the aqueous distillate with sodium sulphate, separated, and dried (NaOH). A small amount of lutidine was extracted by ether from the saturated sodium sulphate solution and added to the main portion. The dried base was distilled to yield 45·5 g. (93%) of base, b. p. 169—170°/767 mm. The infrared absorption spectrum of this specimen was identical with that of a specimen isolated from shale bases and purified through the picrate, also with that of a specimen made by purification of a commercial sample (this contained aldehyde suggesting that it had been made by thermal treatment of propionaldehyde).

The above method of catalytic reduction was ineffective when applied to 2 : 4 : 6-trihydroxy-3 : 5-dimethylpyridine.

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