4-Nitro-2,6-lutidine 1-Oxide

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4-Nitro-2,6-lutidine 1-oxide is as versatile as its parent 4-nitropyridine 1-oxide in its reactions. The nitro group is reduced by a variety of agents and may be replaced by halogen atoms which in turn are also replaceable by other groups.

Particularly striking is the ease with which pyridine 1-oxide is nitrated compared with pyridine itself.[3] The 4-nitropyridine 1-oxide thus obtained has been an immense boon to pyridine chemists, for through its reactions, almost any grouping can be introduced into the 4-position of the pyridine nucleus. The higher homologs of 4-nitropyridine 1-oxide have not attracted as much attention as the parent compound itself. We were interested in preparing 4-amino-2,6-lutidine (II) by a route that gave better yields than the forced amination of 2,6-lutidine. It seemed to us that the reduction of 4-nitro-2,6-lutidine 1-oxide (I) offered a reasonable alternative.

As anticipated, the introduction of two methyl groups into the pyridine molecule facilitated electrophilic substitution and rendered nucleophilic substitution more difficult. Thus 2,6-lutidine 1-oxide was nitrated in better yield (88%) and at a lower temperature (100°) than pyridine 1-oxide itself (66% and 117°, respectively), while replacement by chlorine of the nitro group in 4-nitro-2,6-lutidine 1-oxide using hydrochloric acid required a much higher temperature (190–200°) than did the analogous reaction with 4-nitropyridine 1-oxide (110°).[4]

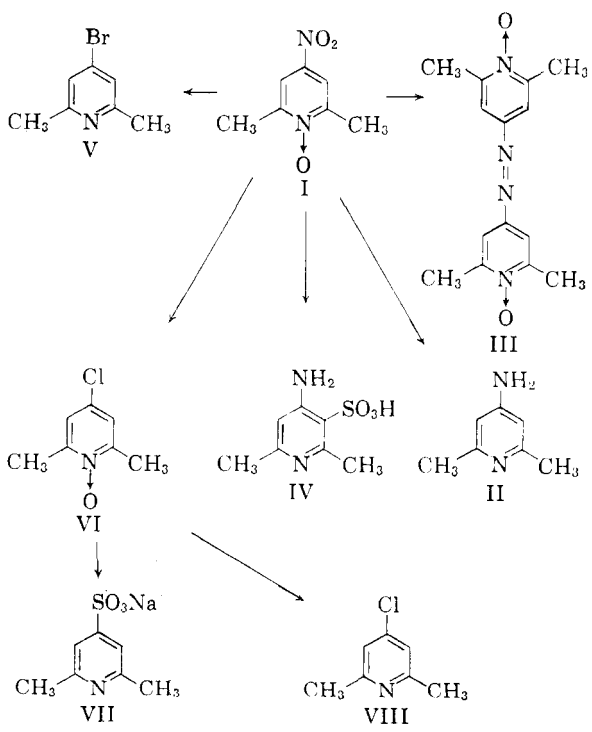
The nitro group in (I) was activated by the *N*-oxide linkage to such an extent that it was reduced by sodium borohydride, a reagent which usually does not attack nitro groups, giving 4,4′-azo-2,6-lutidine 1,1′-dioxide (III). Hydrogen in the presence of palladized charcoal and hydrochloric acid reduced the nitro derivative to the same substance, but in acetic anhydride, 4-amino-2,6-lutidine (II) was obtained.

Sodium hydrosulfite, sulfite, or bisulfite yielded 4-amino-2,6-lutidine but a side reaction, probably analogous to the Piria reaction,[5] caused the formation of some 4-amino-2,6-lutidine-3-sulfonic acid (IV).

Concentrated hydrobromic acid caused replacement by bromine, but the reaction in this case went further, and the *N*-oxide linkage was also reduced. 4-Bromo-2,6-lutidine (V) was isolated and identified as its picrate.

The activation of the chlorine atom in 4-chloro-2,6-lutidine 1-oxide (VI) by the *N*-oxide linkage promoted its replacement by—SO_3Na when heated with aqueous sodium sulfite. At the high temperature of the reaction, reduction of the *N*-oxide linkage also occurred (VII). Iron and acetic acid, phosphorus trichloride, and sodium borohydride in the presence of aluminum chloride were successfully used for deoxygenating 4-chloro-2,6-lutidine 1-oxide to 4-chloro-2,6-lutidine (VIII).

Reaction Scheme



Experimental

4-Nitro-2,6-lutidine 1-Oxide.—A mixture of 208 g. (1.24 moles) of 2,6-lutidine 1-oxide[6] with 480 ml. of concd. sulfuric acid (*d* 1.84) and 167 ml. of concd. nitric acid was heated under reflux on the steam bath for 7 hr. The mixture was

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(3) E. Ochiai, *J. Org. Chem.*, **18**, 534 (1953).

(4) H. J. den Hertog and W. P. Combé, *Rec. trav. chim.*, **70**, 581 (1951).

(5) W. M. Lauer, M. M. Sprung and C. M. Langkammerer, *J. Am. Chem. Soc.*, **58**, 225 (1936).

(6) R. F. Evans and H. C. Brown, *J. Org. Chem.*, **27**, 1329 (1962).

poured into a large excess of ice, and the precipitate was separated and dissolved in chloroform. The aqueous acidic mixture was then continuously extracted with chloroform. The combined chloroform extracts were washed with aqueous sodium hydroxide and dried over magnesium sulfate. Removal of the chloroform furnished 246 g. (87%) of 4-nitro-2,6-lutidine 1-oxide m.p. 151–153° (lit.,[3] m.p. 163°) after two crystallizations from alcohol.

Anal. Calcd. for $C_7H_8N_2O_3$: C, 49.99; H, 4.79; N, 16.66. Found: C, 50.14; H, 4.99; N, 16.40.

Reduction Experiments. (1) **With Sodium Borohydride.**—Twelve and five-tenths milliliters (0.015 mole) of a 1.2 *M* solution of sodium borohydride in diglyme was cautiously run onto 0.8062 g. (0.0048 mole) of nitro compound, with external cooling of the flask. The mixture was allowed to stand at room temperature in a stoppered flask for 3 hr. An exothermic reaction set in after 45 min. but was checked by cooling in ice. The color of the solution changed from yellow to deep brown during the period. A blank experiment with the same amount of borohydride, but no nitro compound was also run simultaneously under the same conditions. Both solutions were now separately and cautiously decomposed with 2 *N* hydrochloric acid and the volumes of hydrogen evolved in both cases were measured in a wet flow meter. The difference in the two values was equivalent to the quantity of borohydride that had reacted with the nitro compound. It was calculated that 1 mole of nitro compound had reacted with 1 mole of borohydride.

The reaction mixture was made alkaline and extracted with chloroform. After drying over magnesium sulfate, the chloroform extract was distilled on the steam bath and the residue recrystallized from acetone to yield orange 4,4′-azo-2,6-lutidine 1,1′-dioxide m.p. 246–247° dec. (lit.,[7] m.p. 248°).

(2) **With Palladized Charcoal in Hydrochloric Acid.**—A suspension of 2 g. of 4-nitro-2,6-lutidine 1-oxide in 10 ml. of concd. hydrochloric acid and 25 ml. of water was shaken with 0.8 g. of palladized charcoal (60% palladium) and hydrogen at 30 p.s.i. for 4 hr. The mixture was filtered, the filtrate was made alkaline with aqueous sodium hydroxide, and the brown precipitate was extracted with chloroform. After drying over magnesium sulfate, the chloroform was removed and the residue, following two recrystallizations from acetone was identified as 4,4′-azo-2,6-lutidine 1,1′-dioxide by m.p. and mixed m.p.

(3) **Reduction with Palladized Charcoal in Acetic Anhydride.**—A mixture of 2 g. of the nitro compound with 30 ml. of acetic anhydride containing a little glacial acetic acid was shaken with 0.8 g. of palladized charcoal (60% palladium) and hydrogen at 35 p.s.i. for 3 hr. After filtration, the filtrate was evaporated at 100° under reduced pressure. The residue was boiled for 1.5 hr. with 5 g. of potassium hydroxide in 5 ml. of water and 30 ml. of alcohol. The major portion of the alcohol was removed by distillation on the steam bath and the residue, after dilution with water, was continuously extracted with chloroform. Evaporation of the chloroform extract afforded 1 g. (69%) of residue which, after sublimation at 130°/2 mm. followed by crystallization from acetone was identified as 4-amino-2,6-lutidine by m.p.[6] (188–190°) and mixed m.p.

(4) **With Sodium Hydrosulfite.**—Forty-five grams (0.26 mole) of powdered sodium hydrosulfite was cautiously added in portions with swirling, to 20 g. (0.12 mole) of nitro compound in 150 ml. of 95% alcohol and 50 ml. of water. After standing for 1.5 hr., the mixture was refluxed on the steam bath for 0.5 hr. and the alcohol then distilled. The mixture was refluxed for a further 0.5 hr. with 50 ml. of concd. hydrochloric acid and then made alkaline with 30 g. of sodium hydroxide in 30 ml. of water. The extracts from several chloroform extractions of the aqueous solution, after drying with magnesium sulfate, were distilled on the steam bath. The residue (8.5 g., 65%), after sublimation *in vacuo* and recrystallization from acetone was identified as 4-amino-2,6-lutidine by m.p. and mixed m.p.

The aqueous mother liquor was acidified with concd. hydrochloric acid, evaporated to dryness, and the solid residue continuously extracted with alcohol in a Soxhlet apparatus. Evaporation of the alcoholic extract gave 10.9 g. of a resinous solid. This was dissolved in the minimum quantity of water, filtered, and acidified with twice its volume of concd. hydrochloric acid. After cooling to 0° and filtering, the filtrate was concentrated *in vacuo* to half its bulk and again filtered. The new filtrate was evaporated to dryness and the residue recrystallized from methyl alcohol, affording 4-amino-2,6-lutidine-3-sulfonic acid, m.p. 293–295°.

Anal. Calcd. for $C_7H_{10}N_2O_3S$: C, 41.57; H, 4.98; S, 15.86. Found: C, 41.10; H, 5.29; S, 15.71. Its identity was confirmed by the similarity of its infrared spectrum in Nujol mull, (Table I) with that of 2,6-lutidine-3-sulfonic acid.

TABLE I

ABSORPTION BANDS IN INFRARED SPECTRA OF PRODUCT M.P. 293–295° (A) AND 2,6-LUTIDINE-3-SULFONIC ACID (B)[a]

A	B
6.05 vs	6.09
6.25 vs	6.24
6.75	7.06
7.30	7.18 s
7.71	7.41
8.17 vs	8.00 vs
8.45 vs	8.35 vs
	8.70
9.10	9.07 vs
9.42	
9.80 vs	9.67 vs
10.24 w	10.15
11.61 s	11.72
13.30	13.88 s
14.69 vs	14.71 vs

[a] Values are wave lengths in μ; vs = very strong, s = strong, w = weak.

(5) **With Sodium Bisulfite.** A mixture of 8.4 g. (0.05 mole) of nitro compound, 39 g. (0.375 mole) of sodium bisulfite, 4 g. (0.1 mole) of sodium hydroxide, and 150 ml. of water was refluxed for 8 hr. Following the procedure outlined under (3), 2.2 g. (36%) of 4-amino-2,6-lutidine and 9.6 g. of residue were obtained and from the latter 1.6 g. (16%) of 4-amino-2,6-lutidine-3-sulfonic acid were isolated.

(6) **With Sodium Sulfite.**—A mixture of 31.5 g. (0.25 mole) of sodium sulfite, 8.4 g. (0.05 mole) of nitro compound and 1.35 ml. of water was refluxed for 8 hr. The orange-colored solution was treated as under (3) and yielded 1.2 g. (20%) of 4-amino-2,6-lutidine and some 4-amino-2,6-lutidine-3-sulfonic acid.

Replacement Reactions. (1) **By Chlorine.**—A mixture of 19 g. (1.1 mole) of 4-nitro-2,6-lutidine 1-oxide and 210 ml. of concd. hydrochloric acid was heated for 24 hr. in a sealed tube at 200°. The yellow solution was evaporated to dryness under reduced pressure, the white residue dissolved in the minimum amount of water, and the solution cautiously decomposed with 10 g. of sodium hydroxide in 10 ml. water. The cloudy solution was then continuously extracted with chloroform for 8 hr. and the chloroform extract, on evaporation, gave 4-chloro-2,6-lutidine 1-oxide, 14.6 g. (82%). The picrate had m.p. 144.5–146°.

Anal. Calcd. for $C_{13}H_{11}ClN_4O_8$: C, 40.37; H, 2.86; N, 14.49. Found: C, 40.30; H, 2.99; N, 14.22.

No replacement occurred when the reaction was carried out in constant boiling hydrochloric acid solution at 110°.

(2) **By Bromine.**—A mixture of 5 g. (0.03 mole) of nitro compound and 42 ml. of 42% hydrobromic acid was heated

(7) T. Kato and F. Hamaguchi, *Pharm. Bull.* (Tokyo), **4**, 174 (1956); *Chem. Abstr.*, **51**, 7367 (1957).

at 180° in a sealed tube for 24 hr., and then treated as described under (1) above. The chloroform extract, on evaporation, furnished 1.4 g. (23%) of an oil; this was converted into a yellow picrate which was identified as 4-bromo-2,6-lutidine picrate[6] by m.p. and mixed m.p. (183.5–185°).

Reactions of 4-Chloro-2,6-lutidine 1-Oxide. (1) With Sodium Sulfite.—A mixture of 8 g. (0.064 mole) of sodium sulfite, 5 g. (0.032 mole) of chloro compound, 20 ml. of water, and 25 ml. of 95% alcohol was heated at 180° in a sealed tube for 12 hr. The red reaction mixture was evaporated to dryness and the resinous material was extracted four times with boiling methyl alcohol. Evaporation of the extract furnished 6.6 g. (92%) of resinous material which was dissolved in the minimum quantity of water and acidified with three times its volume of concd. hydrochloric acid. After cooling and filtration, the solution was evaporated to dryness and the residue fractionally recrystallized from methyl alcohol to yield a product identified as 2,6-lutidine-4-sulfonic acid (VII) by equiv. wt., and its ultraviolet spectrum in 0.1 *N* HCl (λ_{max} 278 mμ, ϵ_{max} 9,200). The expected 2,6-lutidine-4-sulfonic acid 1-oxide had a different ultraviolet spectrum in 0.1 *N* hydrochloric acid (λ_{max} 217 mμ, ϵ_{max} 13,390; λ_{max} 268 mμ, ϵ_{max} 9700).

(2) With Phosphorus Trichloride.—A solution of 7 g. (0.044 mole) of 4-chloro-2,6-lutidine 1-oxide in 100 ml. of ice-cold chloroform was slowly treated with 12 ml. (1.12 mole) of phosphorus trichloride. The solution was allowed to warm up to room temperature over 2 hr. and then refluxed on the steam bath for 1 hr. The cold solution was decomposed with ice, made alkaline with aqueous sodium hydroxide, and extracted three times with chloroform. The chloroform extract, after drying over magnesium sulfate, furnished 6.6 g. (100%) of oil on evaporation; this was quantitatively converted into a picrate m.p. 160.5–162° alone or when mixed with authentic 4-chloro-2,6-lutidine picrate.[6]

(3) With Sodium Borohydride–Aluminum Chloride.[8]—Three and three-tenths milliliters of 1.0 *M* aluminum chloride in diglyme was cautiously added to an ice cold mixture of 0.8845 g. (0.0056 mole) of chloro compound and 10 ml. of 1.0 *M* (0.01 mole) sodium borohydride also in diglyme. After standing at room temperature for 3 hr., the reaction mixture was decomposed with 2 *N* hydrochloric acid. Five hundred and sixty milliliters of hydrogen was evolved at 33.5° and 735 mm. compared with 1080 ml. for a blank experiment run without chloro compound under similar conditions, indicating that 1 mole of compound had required 0.9 mole of borohydride for reaction. The acidic solution was evaporated to dryness and the residue extracted with hot alcohol. Picric acid precipitated from the alcoholic extract 4-chloro-2,6-lutidine picrate, identified by m.p. and mixed m.p.

(4) With Iron and Acetic Acid.—The 4-chloro-2,6-lutidine 1-oxide hydrochloride obtained from a sealed tube reaction of 5 g. (0.03 mole) of 4-nitro-2,6-lutidine 1-oxide with hydrochloric acid was suspended in 25 ml. of hot (100°) glacial acetic acid and 3 g. of iron powder was cautiously added down the reflux condenser. After 2 hr. heating at 100°, the mixture was diluted with water, made alkaline with aqueous sodium hydroxide, and steam distilled. Chloroform extraction of the distillate furnished 0.5 g. (12%) of liquid which was converted by picric acid into 4-chloro-2,6-lutidine picrate again identified by m.p. and mixed m.p.

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(8) H. C. Brown and B. C. Subba Rao, *J. Am. Chem. Soc.*, **78**, 2582 (1956).

The Alkylation and Arylation of 2-Thienyllithium and the Reactions of 3-Methylthiophene with Organometallic Compounds[1]

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2-Thienyllithium has been alkylated and arylated to give 2-substituted thiophene derivatives in 45–65% yield. 3-Methylthiophene on metalation with *n*-butyllithium or phenyllithium and carbonation gave 4-methylthiophene-2-carboxylic acid (61–68%) and 3-methylthiophene-2-carboxylic acid (19%), while phenylsodium led to 4-methylthiophene-2-carboxylic acid (58%) and 3-methylthiophene-2,5-dicarboxylic acid (11%).

The methods which are used for preparing alkylthiophenes can be divided into two types. The first involves the ring closure of either a hydrocarbon with sulfur or of a γ-dicarbonyl compound with phosphorus sulfides. The second starts with the thiophene nucleus and proceeds through the preparation of carbonyl derivatives and their reduction by any of the standard procedures.[2] The direct introduction of alkyl substituents into the thiophene ring by means of metal halides or other acidic catalysts has been studied by some workers.[2]

Both 2-thienylmagnesium iodide[3] and 2-thienylsodium[2] react with allyl bromide to give 2-allylthiophene. 2-Thienylsodium, obtained by the action of sodium amide in liquid ammonia on thiophene, can be alkylated with alkyl bromides to give monoalkyl compounds in 50–70% yields.[4] However, side reactions such as the dialkylation of the thiophene ring—*i.e.*, the formation of 2,5-dialkylthiophene—also take place.

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(2) H. D. Hartough, "Thiophene and Its Derivatives," Interscience Publishers, Inc., New York, 1952.

(3) Grischewitsch-Trochimovski, *J. Russ. Phys. Chem. Soc.*, **43**, 201 (1911).

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