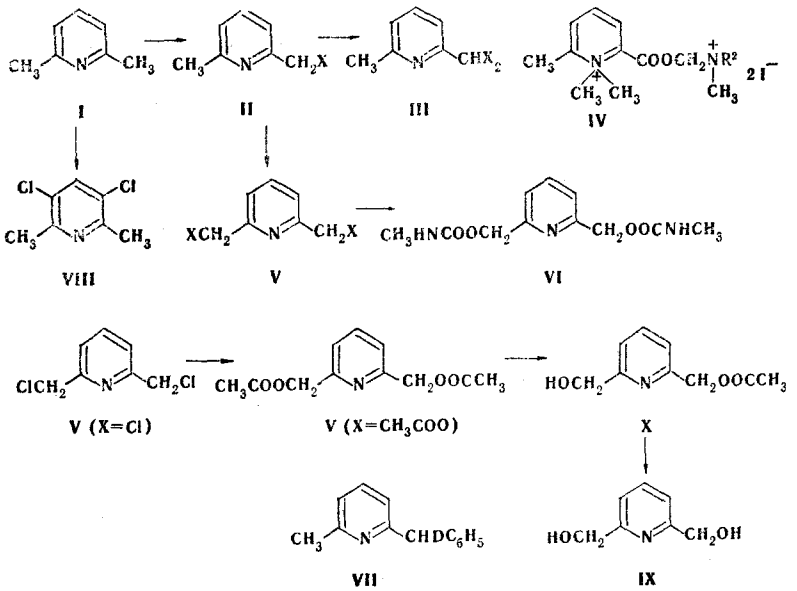
SEQUENCE OF REPLACEMENT OF HYDROGEN IN 2,6-DIMETHYLPYRIDINE BY LITHIUM OR HALOGEN

Ya. S. Karpman, V. A. Azimov,
O. S. Anisimova, and L. N. Yakhontov

UDC 546.823/824

It is shown that, according to the results of chromatographic mass spectrometry, the reaction of 2,6-dimethylpyridine with phenyllithium leads only to the monolithium derivative. The chlorination and bromination of 2,6-dimethylpyridine with various reagents were studied systematically. A method for the conversion of 2,6-bis(chloromethyl)pyridine to 2,6-bis(hydroxymethyl)pyridine is given.

The problem of the sequence of replacement of hydrogen by lithium or halogen in the 2,6-dimethylpyridine (2,6-lutidine) (I) molecule is of both scientific and practical interest. 2-Substituted 6-methylpyridines (III), which may serve as intermediates in the synthesis of the original ganglion-blocking preparations dicolin (IV, R = (C_2H_5) and dimecolin (IV, R = CH_3), which are being produced by the pharmaceutical-chemistry industry and are being used in medical practice, are formed in the replacement of the hydrogen atoms in one methyl group via the pathway I → II → III. A new pathway for the preparation of 2,6-bis-(hydroxymethyl)pyridine (V, X = OH), which is the intermediate in the industrial synthesis of the antisclerotic preparation parmidin (VI), is opened up in the case of replacement of one hydrogen atom in the methyl groups in the 2 and 6 positions (I → II → V).



The literature data on the sequence of replacement of the hydrogen atoms in 2,6-lutidine are contradictory and not sufficiently systematic. Yong and Wibaut [1] obtained III (X = $CH_2C_6H_5$) in 25% yield and II (X = $CH_2C_6H_5$) in 17% yield, as well as the product of replacement of hydrogen by a benzyl group in the pyridine ring, by successive treatment of lutidine I with two equivalents of phenyllithium and excess benzyl chloride. Compound V (X = $CH_2C_6H_5$) was not detected in the reaction products, and the authors concluded that the reaction of lutidine I with phenyllithium is realized via the scheme I → II → III (X = Li). On the other hand, Bergman and Pinchas [2] obtained a series of 2,6-disubstituted pyridines of the V type in the analogous reaction of 2,6-lutidine with phenyllithium and reaction of the product with

S. Ordzhonikidze All-Union Scientific-Research Institute of Pharmaceutical Chemistry, Moscow 119021. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 1, pp. 105-110, January, 1980. Original article submitted May 3, 1979.

0009-3122/80/1601-0089$07.50

carbonyl compounds and postulated that the process takes place via the scheme I → II → V through symmetrical dilithium derivative V (X = Li). Barnes and Fales [3], who investigated the bromination of the products of the reaction of 2,6-lutidine with phenyllithium and described the preparation of 2,6-bis(bromomethyl)pyridine (V, X = Br) in 1% yield, also arrived at the same conclusions.

To determine the sequence of replacement of the hydrogen atoms in 2,6-lutidine or its transformation products by lithium we used the highly sensitive method of chromatographic mass spectrometry. To exclude the effect of the introduced substituents and the participation of intermediate products of the organolithium synthesis on the reaction pathway we determined the number and position of the lithium atoms in the investigated substances by treatment of the reaction mass with deuterium oxide rather than with halo or carbonyl derivatives. Treatment with deuterium oxide converted the lithium compounds to the corresponding deutero derivatives, the number and positions of the deuterium atoms in which also characterized the structures of the organolithium products.

The reaction of 2,6-lutidine with phenyllithium was carried out in ether at a reagent ratio of 1:8 under various temperature conditions. It was found that dilithium derivatives III and V (X = Li) are not formed either at room temperature or in refluxing ether: not even traces of dideuterolutidines are present in the reaction products. The ratio of monodeutero-2,6-lutidine (II, X = D), with m/e 108, and nondeuterated product I, with m/e 107, ranged from 65:35 (at room temperature) to 55:45 (in refluxing ether). The certain decrease in the amount of the lithium derivative when the reaction is carried out in refluxing ether is evidently associated with its partial decomposition due to side processes that take place under these conditions.

2-Benzyl-6-methylpyridine (II, X = C_6H_5), with m/e 183, and its monodeutero derivative, with m/e 184, in a ratio of 1:1 were detected in the reaction mixtures in less than 1% amounts (based on the starting 2,6-lutidine) in both cases. The same intensity ratio is also retained in the mass spectra for the peaks with m/e 168 and 169. This provides a basis for the assumptions that the peak with m/e 169 is due to $[M-CH_3]^+$ ions, that detachment of a CH_2D fragment from the molecular ion of the deutero derivative does not occur, and that the substance consequently has structure VII. This structure is also confirmed by the presence in the mass spectrum of VII of a peak of a fragment with m/e 92, which is related to $C_6H_5CHD^+$ ions.

The formation of VII and the absence of dideuterated compounds of the III and V type (X = D) constitute evidence that the formation of the "disubstitution" products described in [1, 2] is evidently due to reaction of the monolithium compounds with the halo or carbonyl derivatives added to the reaction mixture, subsequent replacement of the hydrogen in these products by lithium, and reaction of the new lithium derivatives with the halogen- or carbonyl-containing compounds; depending on the structure and reactivity of the resulting intermediate, replacement of hydrogen by lithium takes place either at the same group or at the second methyl residue. The higher reactivities of the lithium derivatives of 2,6-lutidine as compared with phenyllithium and the low yields of the "disubstitution" products are in agreement with this point of view.

At the same time, from theoretical considerations (the strong electron-donor effect of lithium should hinder the detachment of a second proton), it is difficult to expect the formation of a dilithium derivative in the case of replacement of hydrogen atoms in 2,6-lutidine by lithium; the situation is even more complex in the case of analogous replacement of hydrogen atoms by halogen.

The reaction of 2,6-lutidine with N-bromosuccinimide (NBS) and the formation of monobromo derivatives II (X = Br) in low yield have been described [4]; dibromo derivative V (X = Br) was obtained in 2% yield when the reaction was carried out in CCl_4 and in 20% yield when it was carried out in benzene [5]. It has been reported [6] that lutidine I reacts with chlorine in concentrated sulfuric acid at 90-110°C to give a mixture of mono- and dichloro derivatives (II and V, X = Cl) in a ratio of 3:5. The rate of conversion of monochloro derivative II (X = Cl) to dichloro derivative V (X = Cl) in the case of chlorination in CCl_4 at 60°C with added sodium carbonate and water is higher by a factor of 3.7 than in the case of dichloro derivative III (X = Cl) [7]. Data on the conversion of lutidine I to 2,6-bis(trichloromethyl)pyridine in the reaction with chlorine with UV irradiation at 50-180°C [8] or with thionyl chloride after 20 h at 180°C [9] are available.

The formation of 3-chloro-2,6-dimethylpyridine [10] in 45% yield in the reaction of 2,6-lutidine with chlorine in the presence of aluminum chloride at 110°C has also been described. Products of substitution in the 3 and in the 3 and 5 positions are formed in yields of 52 and 69%, respectively, in the reaction of 2,6-lutidinesulfotrioxide with bromine [11]. The reaction of 2,6-lutidine with a mixture of phosphorus oxychloride and phosphorus pentachloride by heating to give a mixture of 2-monochloromethyl- and 2-trichloromethyl-6-methylpyridines and 4-chloro-2,6-dimethylpyridine is known [12].

In our study of the processes involved in the chlorination and bromination of 2,6-lutidine we used gas-chromatographic analysis with a quantitative estimate of the amounts of products by comparison of the areas of the peaks with the corresponding data for genuinely pure samples of 2,6-lutidine and its mono- and dichloro and bromo derivatives. It was shown that 2,6-lutidine does not react with bromine (2.5 moles per mole of lutidine I) in glacial acetic acid at 80-100°C (5 h) either without a catalyst or in the presence of zinc chloride or excess sodium acetate. Analogous reactions also do not occur in dimethylformamide (DMF). In all cases starting I was recovered quantitatively. 2,6-Lutidine did not undergo chlorination when it was refluxed with a fivefold molar amount of sulfuryl chloride (for 2 h with UV irradiation) or when chlorine was passed through a solution of 2,6-lutidine in 100% sulfuric acid in the presence of Porofor N and phosphorus trichloride (for 5.5 h at 110°C or for 6.5 h at 140°C). In the latter case the recovered 2,6-lutidine contained ∿2% monochloro derivative II (X = Cl), according to the GLC data. Up to 20% monobromo derivative II (X = Br) is formed in the reaction of excess (2.5 moles) bromine with 2,6-lutidine in a mixture of DMF with methylene chloride in the presence of anhydrous sodium acetate, which neutralizes the reaction mixture. This compound was obtained in higher yield (up to 70%) when 2,6-lutidine was heated with excess (2 moles) N-bromosuccinimide (NBS) in the presence of benzoyl peroxide. A further increase in the amount of NBS leads to the formation of polybromo compounds. More profound halogenation processes are also observed in the chlorination of 2,6-lutidine in glacial acetic acid in the presence of excess anhydrous sodium acetate. Primarily dichloro derivative III (X = Cl) is formed in this case at 20°C (for 4.5 h), according to the GLC and PMR spectral data, whereas the trichloro derivative is primarily formed at 80°C (for 3 h). In the case of the reaction of 2,6-lutidine with chlorine in carbon tetrachloride in the presence of powdered sodium carbonate and small amounts of water with the periodic addition of fresh portions of Porophor N and monitoring of the process by GLC it was found that at 60°C a mixture of chlorinated products that contains primarily (60%) monochloro derivative II (X = Cl) is obtained after the starting lutidine disappears in the reaction mixture. Further chlorination leads to a mixture of polychloro products, from which dichloro derivatives (in 10% yields) with a ratio of the symmetrical and unsymmetrical products (V and III, X = Cl) of 3:7 were isolated. Raising the temperature to the boiling point of carbon tetrachloride or lowering it to 40°C does not have a substantial effect on the ratio of the chlorination products. However, when we carried out the reaction with chlorine in carbon tetrachloride at 5°C, we obtained a pure dichloro derivative, which, on the basis of the results of elementary analysis and the PMR and mass spectra, had the 2,6-dimethyl-3,5-chloropyridine structure (VIII), in good yield (60%). The formation of 3,5-dichloro-substituted 2,6-lutidine in the reaction of I with chlorine has not been previously described.

Compound VIII is more stable than halo derivatives of the II, III, and V type, the instability of which hinders their isolation and conversion to hydroxy derivatives.

As noted in [3], 2,6-bis(halomethyl)pyridines are easily converted to polymeric quaternary derivatives through intermolecular quaternization processes, and attempts to obtain 2,6-bis(hydroxymethyl)pyridine (IX) from them by hydrolysis in aqueous alcohol with subsequent treatment with moist silver oxide or other alkaline agents do not give positive results. The attempted hydrolysis of these substances in acidic media (by refluxing with dilute hydrochloric or sulfuric acid) was also unsuccessful.

The unexpectedly easy conversion of 2,6-bis(halomethyl)pyridines to the corresponding diol IX by heating with anhydrous sodium acetate in absolute alcohol therefore seems of interest. Analysis of this process with respect to time by GLC showed that 2,6-bis(halomethyl)pyridines (V, X = a halogen) are initially converted to 2,6-bis(acetoxymethyl)pyridine (V, X = CH_3COO). However, 2-hydroxymethyl-6-acetoxymethylpyridine (X) begins to form during the first hour of refluxing, and 2,6-bis(hydroxymethyl)pyridine (IX) is subsequently formed from it. The addition of sodium hydroxide at the instant that all of the dichloro derivative (V, X = Cl) has reacted (i.e., 1 h after the start of the reaction) intensifies

the process. However, the process can be brought to completion by more prolonged refluxing (for 30 h instead of 2 h) and without the addition of sodium hydroxide. The recrystallized diol (IX) was obtained in 70% yield. It should be noted that the use of absolute ethanol is necessary for a successful reaction and that the addition of even small amounts of water slows down the process markedly and lowers the yield of the product. In the case of monoacetoxy derivative II (X = CH_3COO) the ester group is retained under similar experimental

EXPERIMENTAL

The PMR spectra of the compounds were obtained with a Varian XL-100A spectrometer with tetramethylsilane as the internal standard. The mass spectra were obtained with a Varian MAT-112 chromatographic mass spectrometer; the ionizing-electron energy was 70 eV, the ionization-chamber temperature was 200°C, and the chromatographic column was filled with SE-30. Analysis by GLC was accomplished with a Pye-Unicam Series 104 chromatograph with a catharometer as the detector; the carrier gas was helium, the flow rate was 30 ml/min, the column dimensions were 2100 by 4 mm, and the stationary phase was SE-30 silicone elastomer (10%) on silanized diatomaceous earth S (100-120 mesh). The retention times in seconds at 150°C were as follows: I 58, VIII 130, II (X = Cl) 158, III (X = Cl) 245, II (X = Br) 331, and V (X = Cl) 403. The retention times in seconds at 200°C were as follows: II (X = OH) 72, V (X = OH) 158, V (X = Br) 303, and V (X = CH_3COO) 460. The V (X = Br) and V (X = CH_3COO) that were used as reference compounds for GLC were synthesized from V (X = OH) by the method described in [13].

Reaction of 2,6-Lutidine (I) with Phenyllithium. A solution of 1.07 g (10 mmole) of 2,6-lutidine (I) in 15 ml of ether was added at 20°C to a solution of phenyllithium in 25 ml of ether, prepared from 0.55 g (80 mmole) of lithium and 6.3 g (40 mmole) of bromobenzene, and the mixture was stirred at 20°C for 1 h. A 2.5-g sample of D_2O was added dropwise. After 1 h, the precipitated LiOD was removed by filtration, and the filtrate was analyzed with a chromatographic mass spectrometer.

The experiment was carried out similarly in refluxing ether for 1 h. The results of chromatographic mass-spectral analysis were discussed in the general section of this paper.

Reaction of 2,6-Lutidine with N-Bromosuccinimide (NBS). A mixture of 8.7 g (81 mmole) of 2,6-lutidine and 26.57 g (162 mmole) of NBS was refluxed for 7 h in 130 ml of CCl_4 with the addition of 20 mg of benzoyl peroxide every hour. The precipitated succinimide was removed by filtration, the filtrate was evaporated in vacuo, and the residue was refluxed for 2 h with 24 g (290 mmole) of freshly fused sodium acetate in 150 ml of absolute ethanol. The precipitated sodium bromide was removed by filtration, and the filtrate was evaporated in vacuo. The residue was refluxed for 2.5 h with 100 ml of 10% HCl, after which the mixture was made alkaline with sodium hydroxide and extracted with methylene chloride. The extract was dried with magnesium sulfate and evaporated in vacuo, and the residue was distilled. The fraction with bp 117-120°C (21 mm) [13] was collected. The yield of 2-hydroxymethyl-6-methylpyridine (II, X = OH) was 4 g (40%). The picrate had mp 141-142°C [13] (obtained by precipitation from ether solution). Found: C 44.1; H 3.4; N 15.8%. $C_7H_9NO \cdot C_6H_3N_3O_7$. Calculated: C 44.3; H 3.4; N 15.9%.

The initially formed 2-bromomethyl-6-methylpyridine (II, X = Br) was not isolated, since this compound was unstable even when it was stored in a refrigerator.

2-Chloromethyl-6-methylpyridine (II, X = Cl). Chlorine was bubbled at 60°C into a reaction mixture containing 24.5 g (0.23 mole) of 2,6-lutidine, 70 g of sodium carbonate, 250 ml of CCl_4, and 3 ml of water with the addition of 20 mg of Porofor N every 30 min. The composition of the reaction mixture was monitored every hour by GLC; chlorine was bubbled into the mixture until the chromatographic peak of starting I disappeared completely (9 h). The sodium chloride was removed by filtration and washed with 200 ml of CCl_4. The filtrate was dried with $MgSO_4$, and dry hydrogen chloride was passed into it until precipitation of the hydrochloride was complete. Workup gave 24.6 g (60%) of the hydrochloride of 2-chloromethyl-6-methylpyridine (II, X = Cl) as colorless crystals with mp 157-158°C. PMR spectrum (in CD_3OD): 2.93 (s, CH_3), 5.15 (s, CH_2Cl), 8.04 (t, 3-H and 5-H), and 8.59 ppm (t, 4-H). Treatment of the hydrochloride of II (X = Cl) with aqueous sodium carbonate solution and methylene chloride and subsequent distillation of the organic layer in vacuo gave 14.6 g (45%) of base II (X = Cl) with bp 75-78°C (5.5 mm) and n_D^{20} 1.5325 (1.5315 [14]).

In a similar experiment with passage of chlorine into the reaction mixture until not only I but also 2-chloromethyl-6-chloropyridine (II, X = Cl) had reacted completely (according

to GLC), a total of 10 g (25%) of 2,6-bis(chloromethyl)pyridine (V, X = Cl) and 2-bis(chloromethyl)-6-methylpyridine (III, X = Cl) in the form of a light-yellow oil, with bp 160-183°C (20 mm), was obtained. According to the GLC data the ratio of III to V (X = Cl) was 79:21, as compared with 80:20 according to the PMR spectral data. PMR spectrum (in CCl_4): 2.52 (s, CH_3), 4.60 (s, CH_2Cl), 6.65 (s, $CHCl_2$), and 6.95-8.00 ppm (m, protons of the pyridine ring).

2,6-Dimethyl-3,5-dichloropyridine (VIII). Chlorine was bubbled into a mixture of 24.5 g (0.23 mole) of 2,6-lutidine, 100 g of sodium carbonate, 3 ml of water, and 300 ml of CCl_4 at 5°C, during which the chlorination was monitored by GLC until the peak of the I in the mixture vanished. After 6 h, the reaction was complete. The reaction mixture was filtered, and the filtrate was dried with magnesium sulfate and distilled in vacuo. The fraction with bp 95-100°C (20 mm) was collected to give 24.3 g (60%) of 2,6-dimethyl-3,5-dichloropyridine (VIII). The hydrochloride was obtained as colorless crystals with mp 183-184°C. PMR spectrum (in $CDCl_3$): 3.04 (s, 6H, two CH_3); 8.25 ppm (s, 1H attached to C_4). The molecular weight of VIII was 176 (by mass spectrometry). Found: C 39.9; H 3.9; N 6.5%. $C_7H_7Cl_2N \cdot HCl$. Calculated: C 39.6; H 3.8; N 6.5%. The picrate had mp 157-158°C (from absolute alcohol). Found: C 38.5; H 2.5; Cl 17.5; N 13.9%. $C_7H_7Cl_2N \cdot C_6H_3N_3O_7$. Calculated: C 38.6; H 2.5; Cl 17.5; N 13.8%. Similar results were obtained when the reaction was carried out with the addition of Porofor N.

2,6-Bis(hydroxymethyl)pyridine (IX). A) A mixture of 12.2 g (69 mmole) of 2,6-bis-(chloromethyl)pyridine (V, X = Cl), 15 g (153 mmole) of anhydrous potassium acetate, and 200 ml of absolute alcohol was refluxed for 2 h, after which 5.5 g (138 mmole) of sodium hydroxide was added, and the mixture was refluxed for another hour. It was then evaporated to dryness, and the residue was recrystallized from ethyl acetate to give 6.3 g (70%) of 2,6-bis(hydroxymethyl)pyridine (IX) with mp 120-121°C (119-120°C [13]). No melting-point depression was observed for a mixture of this product with a genuine sample of IX. The IR spectra of the two samples were identical.

B) A mixture of 12.2 g (69 mmole) of V (X = Cl), 15 g (153 mmole) of anhydrous potassium acetate, and 200 ml of absolute alcohol was refluxed for 30 h, after which the alcohol was removed by vacuum distillation, and the residue was recrystallized from ethyl acetate to give 6 g (66.7%) of 2,6-bis(hydroxymethyl)pyridine (IX), which was identical to an authentic sample.

LITERATURE CITED

1. Y. I. Yong and Y. P. Wibaut, Rec. Trav. Chim., 70, 962 (1951).
2. E. D. Bergman and S. Pinchas, J. Org. Chem., 15, 1184 (1950).
3. R. A. Barnes and H. M. Fales, J. Am. Chem. Soc., 75, 3830 (1953).
4. Hasegawa, Pharm. Bull. Jpn., 47, 293 (1953).
5. W. Offermann and F. Vögtle, Synthesis, 272 (1977).
6. French Patent No. 1394362 (1965); Chem. Abstr., 63, 8326 (1965).
7. T. Hattory, Japan Kokai, 74127977 (1974); Chem. Abstr., 84, 121665 (1976).
8. E. T. McBee, H. B. Hass, and E. M. Hodnett, Ind. Eng. Chem., 39, 389 (1947).
9. R. Graf and H. Zete, J. Prakt. Chem., 147, 188 (1935).
10. L. Does and H. J. Hertog, Rec. Trav. Chim., 91, 1403 (1972).
11. J. Abblard, C. Decoret, and L. Cronenberger, Bull. Soc. Chim. Fr., 2466 (1972).
12. T. Kato, H. Hayashi, and T. Anzai, Yakugaku Zasshi, 87, 387 (1967).
13. W. Baker, K. M. Buggle, and McOmie, J. Chem. Soc., 3594 (1958).
14. W. Mathes and H. Shülz, Angew. Chem., 75, 235 (1963).