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SUBSTITUTED PYRIDINES
5-Methyl-2-formylpyridine and 5-Methyl-4-phenyl-2-formylpyridine

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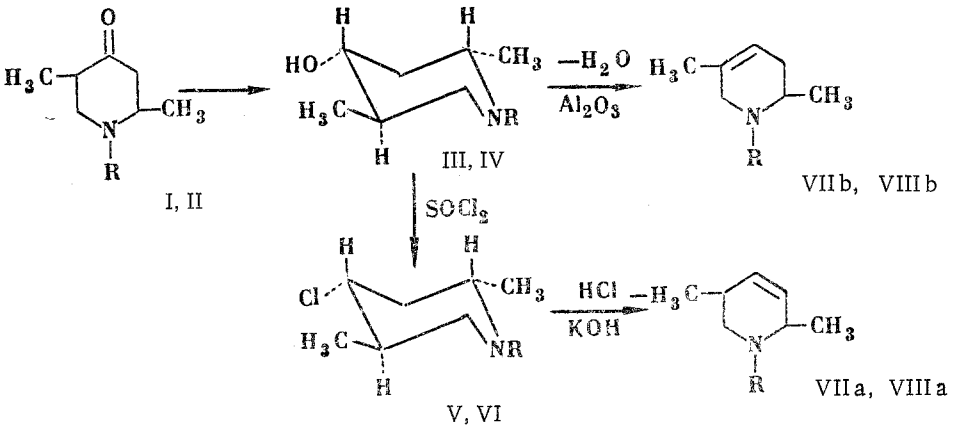
2, 5-Dimethylpiperidol-4, 1,2,5-trimethylpiperidol-4, and the gamma isomer of 1,2,5-trimethyl-4-phenylpiperidol-4 are dehydrated by various methods. The secondary piperidols mentioned are used to synthesize 5-methyl-2-formylpyridine and 5-methyl-4-phenyl-2-formylpyridine.

The starting materials used for preparing 5-methyl-2-formylpyridine were 2, 5-dimethylpiperidol-4 (III) and 1,2,5-trimethylpiperidol-4 (IV), while the gammer isomer of 1,2,5-trimethyl-4-phenylpiperidol-4 was used to synthesize 5-methyl-4-phenyl-2-formylpyridine.

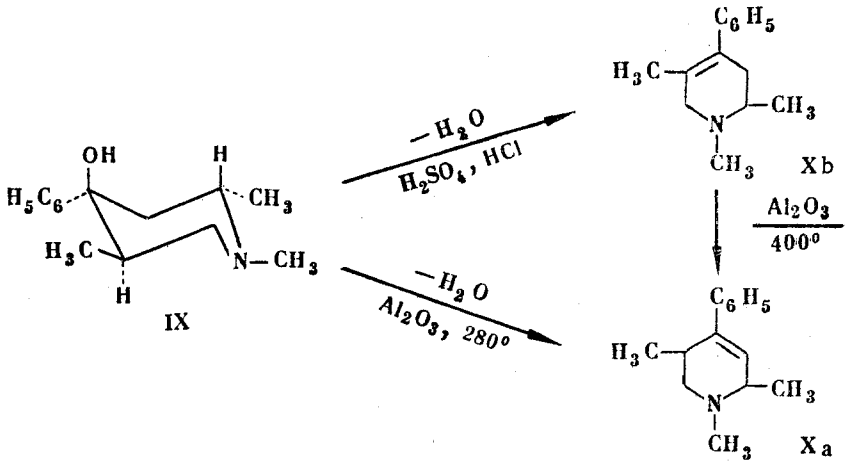
The piperidols III and IV are prepared by sodium-alcohol reduction of, respectively, 2,5-dimethyl-(I) and 1,2,5-trimethyl-(II) piperidone-4 [1]. However, that method of reducing cyclic ketones usually gives mainly alcohols with an equatorial hydroxyl group. Taking into account that the most thermodynamically favored structures of the starting piperidones I and II are those with C_2 and C_5 methyl groups with trans-equatorial configurations, the same configurations are to be expected for the C_4 hydroxyl and C_5 methyl groups in piperidols III and IV. Two ways of dehydrating III and IV were investigated in connection with the synthetic route mentioned. In one case the piperidols were first converted respectively to 2,5-dimethyl-(V), and 1,2,5-trimethyl-(VI) -4-chloropiperidine, and then dehydrochlorinated. Reaction of the piperidols with thionyl chloride does not lead to change in configuration at C_4, and the halogen in the derivatives V and VI is in the equatorial position, as is particularly indicated by the relatively stable characters of the chlorides [2]. Subsequent dehydrochlorination with alcoholic potassium hydroxide involves trans elimination of hydrogen chloride, so that formation of the didehydropiperidines VIIA and VIIIA respectively is to be expected.

In the other case the piperdols III and IV were catalytically dehydrated over aluminum oxide. As cis-elimination of water is mainly involved in catalytic dehydration, formation of didehydropiperidines with the double bond at a different position is to be expected, and obviously the didehydropiperidines should have the structure shown for VIIb and VIIIb. It was found experimentally that application of the different dehydration methods to 2,5-dimethylpiperidol-4, and also to 1,2,5-trimethylpiperidol-4 gives different didehydropiperidines.



R = H: I, III, V, VIIa, VIIb
R = CH_3: II, IV, VI, VIIIa, VIIIb

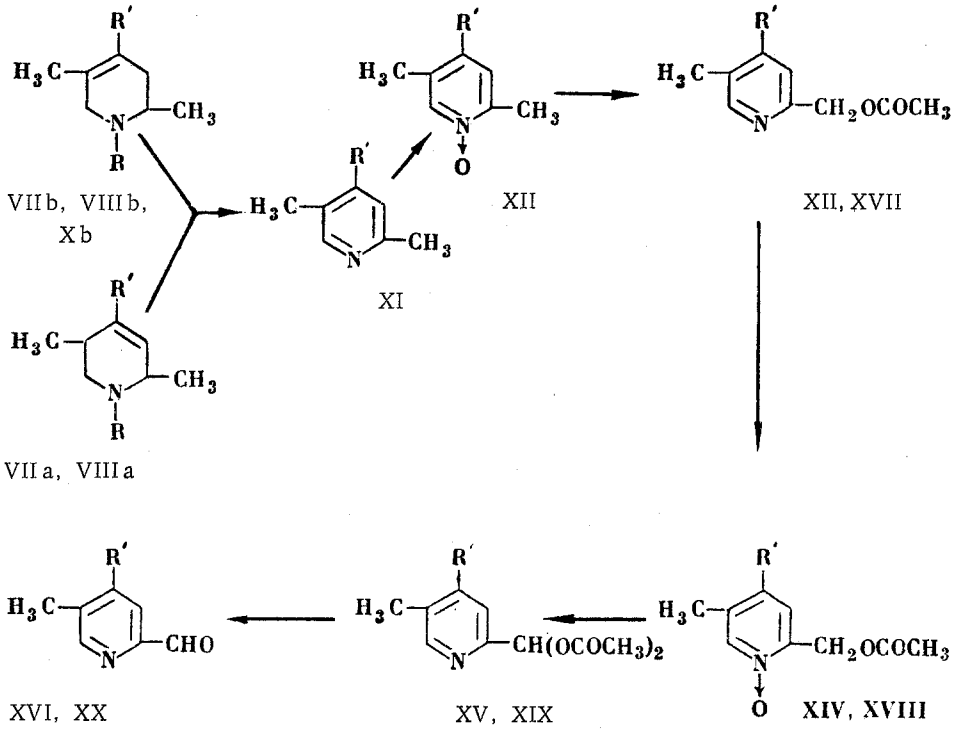
Similar results are obtained when dehydrating tertiary γ-piperidols. The C_5 methyl and the C_4 hydroxyl in the gamma isomer of 1,2,5-trimethyl-4-phenylpiperidol-4 (IX) are cis [3]. So catalytic dehydration, and dehydration with sulfuric and hydrochloric acids can all be expected to take place in two ways.



In view of the above, acid dehydration of the gamma isomer of 1,2,5-trimethyl-4-phenylpiperidol-4 can be expected to lead to formation of 1,2,5-trimethyl-4-phenyl-Δ^4-didehydropiperidine (Xb) (trans-elimination), and dehydration over aluminum oxide at 280° to formation of 1,2,5-trimethyl-4-phenyl-Δ^3-didehydropiperidine (Xa) (cis-elimination). It is also found that Xb isomerizes over aluminum oxide at 400°, to Xa.

By means of a method previously described by the present authors and coworkers [4, 5], didehydropiperidines VIIa, b and VIIIa, b were used to perpare α, β'-lutidine (XI), which latter subsequently served for carrying out the following reactions: preparation of α, β-lutidine N-oxide (XII), and conversion of this to 5-methyl-2-acetoxymethylpyridine (XIII) [6], oxidation of XIII to N-oxide (XIV), conversion of the latter to 5-methyl-2-diacetoxymethylpyridine (XV), and acid hydrolysis of this to 5-methyl-2-formylpyridine (XVI).

5-Methyl-4-phenyl-2-acetoxymethylpyridine (XVII), previously described [7], was used to synthesize, by a similar route, 5-methyl-4-phenyl-2-formylpyridine (XX). The N-oxide (XVIII) of XVII was obtained by oxidation of the latter, and acetic anhydride converted it into 5-methyl-4-phenyl-2-diacetoxymethylpyridine (XIX), acid hydrolysis of which gave 5-methyl-4-phenyl-2-formylpyridine (XX).



R = H: VIIa, VIIb; R = CH_3: VIIIa, VIIIb, Xb;
R' = H: XI XVI; R' = C_6H_5: Xb, XVII XX.

Experimental

Dehydration of 2,5-dimethylpiperidol-4. a) 31 ml thionyl chloride in 35 ml benzene was slowly added to a solution of 20 g, 2,5-dimethylpiperidol-4 (III) in 150 ml benzene. The mixture was stirred for 1 hr at room temperature, and then for 2 hr at 60-70°. The benzene and excess thionyl chloride were evaporated under reduced pressure. 120 ml 30% alcoholic potassium hydroxide was added to the residue, the mixture refluxed for 4 hr, made acid to congo red with 18% hydrochloric acid, the alcohol distilled off, the residue treated with sodium hydroxide and extracted with ether. The ether solution gave 8.4 g 2,5-dimethyldidehydropiperidine (VIIa), 49-50.5° (20 mm); n_D^{20} 1.4693; d_4^{20} 0.8724; MR_D 35.10. Calculated for $C_7H_{13}N$: 35.66. Picrate mp 161.5-163° (from alcohol). Found: N 16.58, 16.42%. Calculated for $C_7H_{13}N \cdot C_6H_2(NO_2)_3OH$: N 16.47%.

b) A reactor tube connected to a Claisen flask was packed with 100 ml aluminum oxide, and at 50 mm pressure, with the catalyst zone at 350°, 30 g 2,5-dimethylpiperidol-4 (III) passed in from the flask in 45 min. The reaction products were made acid to congo red with 18% hydrochloric acid. Neutrals were extracted with ether, and after drying, distilled to give 2 g yellow liquid bp 50-98° (5 mm), which very rapidly darkened in contact with air. The water layer was treated with sodium hydroxide and extracted with ether, and distillation of the extract gave 6.4 g 2,5-dimethyldidehydropiperidine (VIIb), 49-51.5° (22-25 mm), n_D^{20} 1.4748; d_4^{20} 0.8758; MR_D 35.71. Calculated for $C_7H_{13}N$: 35.66.

Picrate mp 161-163° (from alcohol). Found: N 16.14, 16.30%. Calculated for $C_7H_{13}N \cdot C_6H_2(NO_2)_3OH$: N 16.47%. Mixed mp of picrates obtained in experiments a and b 133-135°.

Dehydration of 1,2,5-trimethylpiperidol-4 (IV). a) Dehydration was effected via 1,2,5-trimethyl-4-chloropiperidine (VI), as described in experiment (a) above. The quantities used were 75 g piperidol IV, 530 ml benzene, 116 ml thionyl chloride. 350 ml 30% alcoholic potassium hydroxide solution was used for dehydrochlorination. Yield 42.6 g 1,2,5-trimethyldidehydropiperidine (VIIIa) bp 56° (13 mm), n_D^{20} 1.4600; d_4^{20} 0.8523; MR_D 40.18. Calculated for C_8H_{15}: 40.50.

b) A solution of 61 g 1,2,5-trimethylpiperidol-4 (IV) in 120 ml benzene was passed at a constant rate and in 3 hr through a reactor (Al_2O_3 – 100 ml) at 325°. The products were treated with 18% hydrochloric acid, and washed with ether. The aqueous layer was saturated with sodium hydroxide. The organic base was extracted with ether. The ethereal extract gave 19.8 g 1,2,5-trimethyldidehydropiperidine (VIIIb) bp 45-47° (15 mm) n_D^{20} 1.4672; d_4^{20} 0.8553; MR_D 40.58. Calculated for $C_8H_{15}N$; 40.50.

Picrate – mp 167-168° (from alcohol). Found: N 16.05, 16.15%. Calculated for $C_8H_{15}N \cdot C_6H_2(NO_2)_3OH$: N 15.82%. Mixed mp of the products from experiments (a) and (b), 111-116°.

Dehydration of 1,2,5-trimethyl-4-phenylpiperidol-4 (IX). a) 116 g γ-isomer IX (mp 107-108°) [9] and 250 g 80% sulfuric acid were heated together for 5 hr. After cooling 1.5 *l* water was added, and the solution neutralized with soda. Then a further 100 g soda was added, and the mixture heated for 1 hr at 100°. The organic bases were extracted with ether, and the extract distilled to give 96.6 g 1,2,5-trimethyl-4-phenyldidehydropiperidine (Xb), bp 103-105° (2.5 mm), n_D^{20} 1.5445. Picrate mp 127-129° (from alcohol) [8].

b) A Claisen flask was attached to a reactor packed with 100 ml Al_2O_3 held at 280°, the pressure inside the apparatus being 14 mm, and 30 g of the gamma isomer of IX distilled through it. The condensate was made acid to Congo Red with 18% hydrochloric acid, neutrals extracted with ether, and the aqueous solution saturated with potassium hydroxide. The organic base which separated was extracted with ether, and the extract distilled, to give 17 g 1,2,5-trimethyl-4-phenyldidehydropiperidine (Xa), bp 106-108° (4 mm), n_D^{20} 1.5334. Picrate mp 167-170° (from alcohol). Found: N 13.48, 13.42%. Calculated for $C_{13}H_{19}N \cdot C_6H_2(NO_2)_3OH$: 13.02%.

c) 96 g 1,2,5-trimethyl-4-phenyldidehydropiperidine (Xb) was prepared by sulfuric acid dehydration of the piperidol IX, and over a period of 2 hr passed through a reactor packed with 100 ml Al_2O_3 maintained at 400°. The gaseous products observed to be formed were trapped in acetic acid. The condensate was worked up for organic bases as described in experiment (b) above, and gave: 1st fraction bp 102-110° (2 mm), 9.54 g; 2nd fraction bp 110-120° (2 mm) 5.45 g; 3rd fraction bp 120-130° (2 mm), 4.56 g. Picrates obtained in quantitative yields from all three fractions, melted at 153-165° (from alcohol), mixed mp with the picrate prepared in experiment (b) above, undepressed.

2,5-Dimethylpyridine N-oxide (XII). 60 ml 30% hydrogen peroxide was added in 15 min, with stirring, to 19.9 g 2,5-dimethylpyridine and 210 ml acetic acid, and the mixture then heated for 10 hr at 80-90°, a further 25 ml 30% hydrogen peroxide being added after the first 5 hr heating. The acetic acid was distilled off, the residue saturated with soda, and extracted with chloroform. From the extract was isolated 12 g XII mp 55-57° (from acetone). Picrate mp 122.5-124° (from alcohol). Found: N 16.31, 16.37%. Calculated for $C_7H_9NO \cdot C_6H_2(NO_2)_3OH$: 15.91%.

5-Methyl-2-acetoxymethylpyridine (XIII). A mixture of 2,5-dimethylpyridine and 60 ml acetic anhydride was heated for 2 hr at 70-80°, and then distilled to give 10.5 g XIII, bp 133-136° (14 mm), n_D^{20} 1.4952. Picrate – mp 122-125° [6].

5-Methyl-2-acetoxymethylpyridine N-oxide (XIV). 52 ml 30% hydrogen was added in 15 min, with stirring, to 18.5 g 5-methyl-2-acetoxymethylpyridine in 193 ml acetic acid, and the whole then heated to 80-90° for 10 hr, a further 24 ml 30% hydrogen peroxide being added at half-time. The acetic acid was distilled off, the residue saturated with soda, and extracted with chloroform. 9.5 g XIV was isolated from the extract. Picrate mp 113-116° (from alcohol). Found: N 13.02, 13.14%. Calculated for $C_9H_{11}NO_3 \cdot C_6H_2(NO_2)_3OH$: 13.66%.

5-Methyl-2-diacetoxypyridine (XV). A mixture of 9.3 g 5-methyl-2-acetoxymethylpyridine N-oxide and 60 ml acetic anhydride was heated for 4 hr at 70-80°. Excess acetic anhydride was distilled off under reduced pressure. 5-methyl-2-diacetoxymethylpyridine was isolated from the residue (6.3 g) as its picrate mp 137-140° (from alcohol). Found: N 12.41, 12.69%. Calculated for $C_{11}H_{13}NO_4 \cdot C_6H_2(NO_2)_3OH$: N 12.39%.

5-Methyl-2-formylpyridine (XVI). 6 g 5-methyl-2-diacetoxymethylpyridine and 79 ml concentrated hydrochloric acid were heated together for 1 hr at 100°, after which the acid was distilled off under reduced pressure. The residue was dissolved in 60 ml water, treated with sodium hydroxide, and extracted with ether. Distillation of the ether extract gave 1.8 g 5-methyl-2-formylpyridine (XVI) bp 126-130° (17 mm). Picrate – mp 165-167° (from alcohol). Found: N 15.85, 15.66%. Calculated for $C_7H_7NO \cdot C_6H_2(NO_2)_3OH$: 16.00%.

5-Methyl-4-phenyl-2-formylpyridine (XX). 34.8 g 5-methyl-4-phenyl-2-acetoxymethylpyridine (XVII) [7], 247 ml acetic acid, and 44 ml 30% hydrogen peroxide were heated together for 5 hr, 11 ml hydrogen peroxide added, and heating continued for 5 hr longer. The acetic acid was distilled off (to secure more complete removal of the acetic acid an amount of water equal to double the amount of reaction mixture was added), and the residue treated with soda and chloroform, the chloroform extract dried, and the chloroform distilled off, leaving 37.3 g impure 5-methyl-4-phenyl-2-acetoxymethylpyridine N-oxide (XVIII). To this was added 95 ml acetic anhydride, the mixture heated for 4 hr at 80°, and acetic anhydride distilled off, leaving a residue of 5-methyl-4-phenyl-2-diacetoxymethylpyridine (XIX), from which was prepared the picrate mp 144-147°. Found: N 10.78, 10.76%. Calculated for $C_{17}H_{17}NO_4 \cdot C_6H_2(NO_2)_3OH$: N 10.60%.

148 ml concentrated hydrochloric acid was added to the crude XIX obtained above, the mixture heated for 1 hr at 100°, the acid distilled off, the residue dissolved in water, treated with sodium hydroxide, and extracted with ether. The extract was distilled to give the following fractions: 1st – bp 144-155° (5 mm), 2.31 g; 2nd – bp 155-180° (5 mm) 8.2 g. The second fraction was recrystallized. Recrystallization from petrol ether gave 5-methyl-4-phenyl-2-formylpyridine (XX) mp 64-66°. Found: N 6.57, 6.66%. Calculated for $C_{13}H_{11}NO$: N 7.10%.

Picrate – mp 128-130° (from alcohol). Found: N 13.14, 12.86%. Calculated for $C_{13}H_{11}NO \cdot C_6H_2(NO_2)_3OH$: N 12.91%.

Oxime – mp 206-207°; oxime methiodide – mp 199-201°.

REFERENCES

1. I. N. Nazarov and V. A. Rudenko, ZhOKh, 22, 829, 1952.
2. I. N. Nazarov, N. S. Prostakov, N. N. Mikheeva, and N. A. Fradkina, ZhOKh, 29, 2609, 1959.
3. N. S. Prostakov and N. N. Mikheeva, Usp. Khim., 31, 1191, 1962.
4. N. S. Prostakov and K. S. Kvasnevskaya, ZhPKh, 32, 2820, 1959.
5. N. S. Prostakov, L. A. Gaivoronskaya, N. N. Mikheeva, and N. P. Filippova, ZhOKh, 33, 2926, 1963.
6. Arata and Achiwa, J. Pharm. Soc. Japan, 79, 108, 1959.
7. N. S. Protakov, L. A. Gaivoronskaya, N. M. Mikhailova, and L. M. Kirillova, ZhOKh, 33, 2573, 1963.
8. I. N. Nazarov, N. S. Prostakov, Zh. A. Krasnaya, and N. N. Mikheeva, ZhOKh, 26, 2820, 1956.
9. I. N. Nazarov, N. S. Prostakov, and N. I. Shvetsov, ZhOKh, 26, 2798, 1956.

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