A NEW SYNTHESIS OF SUBSTITUTED 1,4,5,6-TETRAHYDROPYRIDINES

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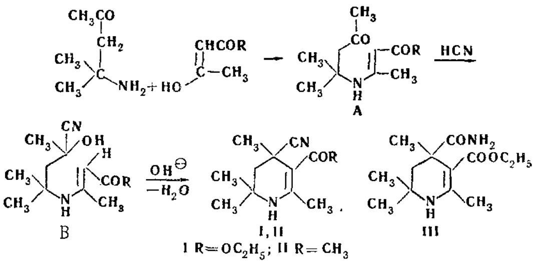
3-Ethoxycarbonyl- and 3-acetyl-4-cyano-2, 4, 6, 6-tetramethyl-1, 4, 5, 6-tetrahydropyridines have been obtained by the reaction of diacetoneamine with acetoacetic ester (or acetylacetone), the conversion of the amino ketones so obtained into the corresponding cyanohydrins, and the cyclization of the latter under the influence of alkali.

Tetrahydropyridines, particularly those which contain a number of functional groups, are attracting attention as intermediates and as subjects for theoretical study. We have found a new method of preparing substituted tetrahydropyridines [1] using as examples 4-cyano-3-ethoxycarbonyl-2,4,6,6-tetramethyl-1,4,5,6-tetrahydropyridine (I) and 3-acetyl-4-cyano-2,4,6,6-tetramethyl-1,4,5,6-tetrahydropyridine (II) in accordance with the following scheme:

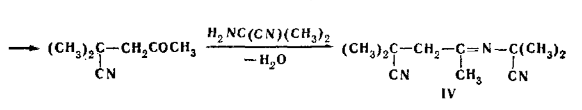


In the first stage, diacetoneamine reacts with acetoacetic ester or acetylacetone giving the enamines A ($R = OC_2H_5$ and CH_3), which form viscous oils that cannot be distilled in vacuum without decomposition. Without purification, these are treated with a strong acid, and are converted into the corresponding cyanohydrins (B). Again without isolation and purification, the latter are cyclized to the tetrahydropyridines (I, II) under the influence of alkali. In the first series of experiments, equimolar amounts of alkali were used, but then it was found that catalytic amounts of caustic soda or caustic potash were sufficient for cyclization.

The structure of substances I and II is confirmed by their UV, IR, and NMR spectra. In their UV spectra, substances I and II (ethanol, c 10^{-4}–10^{-3} M) have λ_{max} 278 nm (log ε 4.45) and 298 nm (log ε 4.41), respectively. In the IR spectrum [taken by V. S. Troitskaya, to whom the authors express their deep gratitude], substance I (Fig. 1, curve 1) has bands at 3440 cm^{-1} (NH), 2230 cm^{-1} ($C\equiv N$), and 1680 cm^{-1} (conjugated carbonyl group in $COOC_2H_5$). The spectrum of compound II (Fig. 1, curve 2) has bands of NH and $C\equiv N$ groups at 3430 and 2230 cm^{-1}. The frequencies of the carbonyl ketone group in the 1700 cm^{-1} region are not present, which is characteristic for the system of β-aminovinyl ketones.

In the NMR spectrum of substance II (Fig. 2, curve 1) the signal of the proton of an amino group appears at δ 5.60 ppm. The singlet signals with an area of three proton units each at 2.37, 2.25, and 1.60 are evidently due to the methyl groups in position 3 adjacent to the keto group, in position 2 on the double bond, and in position 4, respectively. The two singlets with δ 1.36 and 1.25 ppm must be ascribed to the signals of the two gem-methyl groups in position 6. The nonequivalence of these methyl groups in the NMR spectrum may be explained by the difference in their positions in the fairly conformationally stable molecule of a substituted tetrahydropyridine having anisotropic groupings. For the same reasons, the protons of the methylene group proved to be nonequivalent, giving details in the 1.8–2.4 ppm region. In substance I, in addition to the broad signal with δ 4.97 ppm caused by the NH group and also the quartet at 4.20 ppm and the triplet at 1.30 ppm relating to the signals of the $O{-}CH_2 \cdot CH_3$ group, there are singlet signals of the two methyl groups in positions 2 and 4 with δ 2.20 and 1.60, of the two gem-methyl groups with δ 1.36 and 1.23 ppm, and of the protons of the methylene group of the heterocycle in the 1.8–2.1 ppm region. It does not appear possible to draw definite conclusions concerning the nature of the splitting of the signals due to the spin-spin interaction of the nonequivalent gem-protons of the CH_2 groups in compounds I and II on the basis of the curve obtained. By acid hydrolysis of the nitrile I it was possible to obtain the corresponding amide (III). In the preparation of substance I, a side product of the reaction is formed from which it can be freed either by heating with metallic sodium, whereupon this substance is converted into a sparingly soluble resin, or by fractional crystallization. The substance corresponds to the empirical formula $C_{11}H_{17}N_3$ and its IR spectrum lacks bands of $C{=}O$ and NH groups and has bands with the frequency 2230 cm^{-1} of a $C\equiv N$ group and a very weak band at 1670 cm^{-1}.

On the basis of these data, we ascribe to it the formula (IV) and explain its formation in the following way:



$$(CH_3)_2C{=}CHCOCH_3 + HCN \rightarrow$$

$$\rightarrow (CH_3)_2\underset{\displaystyle CN}{C}{-}CH_2COCH_3 \xrightarrow[-H_2O]{H_2NC(CN)(CH_3)_2} (CH_3)_2\underset{\displaystyle CN}{C}{-}CH_2{-}\underset{\displaystyle CH_3}{C}{=}N{-}\underset{\displaystyle CN}{C}(CH_3)_2$$

IV

EXPERIMENTAL

4-Cyano-3-ethoxycarbonyl-2, 4, 6, 6-tetramethyl-1, 4, 5, 6-tetrahydropyridine (I). The superfluous ammonia was eliminated from a mixture of 49 g of mesityl oxide and 70 ml of 27% aqueous ammonia, and 65 g of acetoacetic ester was added to the resulting solution of diacetoneamine. After ~16 hr, the oil that had separated out was re-

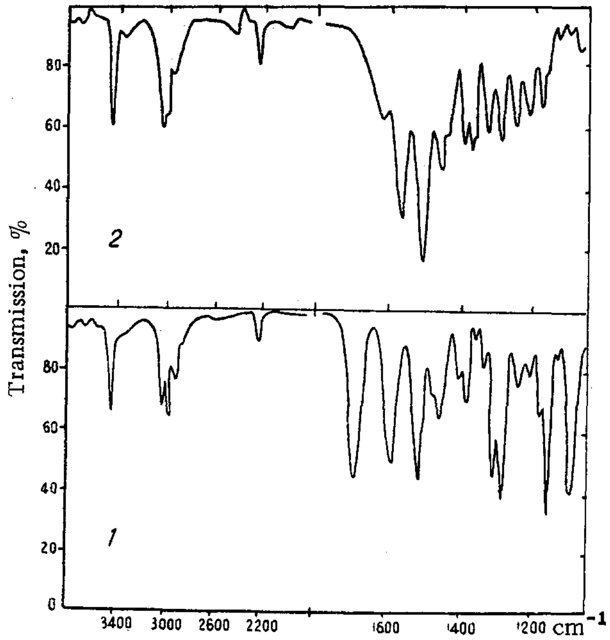


Fig. 1. IR spectra: 1) 4-cyano-3-ethoxycarbonyl-2,4,6,6-tetramethyl-1,4,5,6-tetrahydropyridine (I); 2) 3-acetyl-4-cyano-2,4,6,6-tetramethyl-1,4,5,6-tetrahydropyridine (II) (UR-10 instrument; c 0.1 M in chloroform, d 0.1 mm).

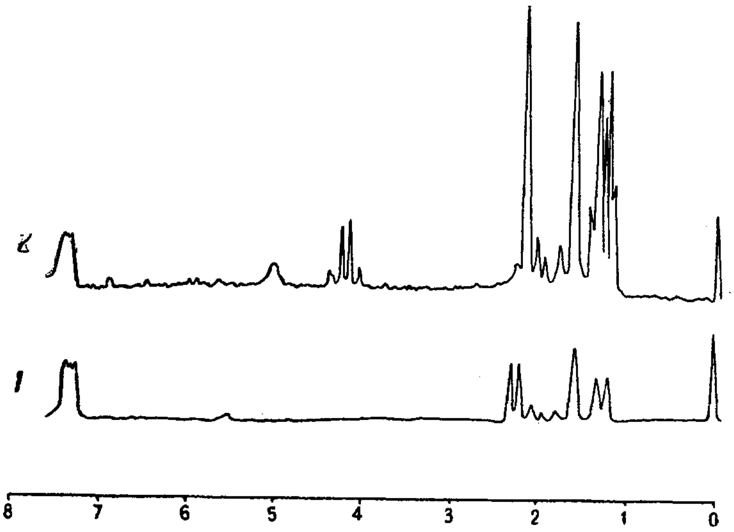


Fig. 2. NMR spectra: 1) 3-acetyl-4-cyano-2,4,6,6-tetramethyl-1,4,5,6-tetrahydropyridine (II); 2) 4-cyano-3-ethoxycarbonyl-2,4,6,6-tetramethyl-1,4,5,6-tetrahydropyridine (I) ("Hitachi" instrument—H-60, with a working frequency of 60 MHz; in chloroform, δ-scale; standard—hexamethyldisiloxane).

moved from the aqueous layer, dried over 20 g of anhydrous magnesium sulfate (~16 hr) and decanted from the desiccant. The aqueous layer separated off previously was added to this desiccant, leading to the separation of a further small amount of oily product which was dried as before with the corresponding amount of magnesium sulfate and added to the bulk of the reaction product. The crude substance **A** (R = OC_2H_5) obtained in this way, amounting to 105.1 g, was treated with a solution of 13.5 g of hydrocyanic acid in 50 ml of methanol and a solution of 1 g of potassium cyanide in 10 ml of methanol and the mixture was stirred at ~20° C for about 2 hr. Then 2 g of solid potassium hydroxide was added to it with stirring and the mixture was left for ~16 hr, after which the addition of an equal volume of water precipitated 19.5 g (16.5%, calculated on the mesityl oxide) of fairly pure I. It was washed with petroleum ether and recrystallized from a mixture of benzene and petroleum ether, mp 132–134° C. Found, %: C 66.03, 66.10; H 8.54, 8.50; N 11.47, 12.03. Calculated for $C_{13}H_{20}N_2O_2$, %: C 66.07; H 8.53; N 11.86.

4-Carbamoyl-3-ethoxycarbonyl-2,4,6,6-tetramethyl-1,4,5,6-tetrahydropyridine (III). A solution of 2.36 g of the nitrile I in 12 ml of concentrated H_2SO_4 was stirred for ~16 hr, poured into ice water, and neutralized with ammonia. This gave 1.04 g (41%) of the amide III, mp 151–153° C (from ethanol). Found, %: C 61.46, 61.48; H 8.81, 8.79; N 11.20, 11.17. Calculated for $C_{13}H_{22}N_2O_3$, %: C 61.39; H 8.73; N 11.01. IR spectrum (in oil): series of bands in the 3170–3420 cm^{-1} region (amino group), 1680 cm^{-1} (C=O) in $COOC_2H_5$), 1655 cm^{-1} (C=O in $CONH_2$), 1560 cm^{-1} (second amide band).

3-Acetyl-4-cyano-2,4,6,6-tetramethyl-1,4,5,6-tetrahydropyridine (II). Fifty grams of acetylacetone was added to an aqueous solution of the diacetoneamine from 49 g of mesityl oxide and the mixture was treated as in the preparation of I. The crude product **A** (R= $=CH_3$; 71 g) was also treated in a similar manner to the preceding case. The solid product obtained after dilution with water was washed with petroleum ether and recrystallized from ethanol. For purification, the product after drying was heated with 0.5 g of metallic sodium in boiling xylene, the resinous impurities were separated off, the xylene was evaporated in vacuum, and the residue was recrystallized from benzene. This gave 20 g (~10%, calculated on the mesityl oxide) of substance II, mp 167–168° C. Found, %: C 70.08, 70.25; H 8.76, 8.79; N 13.97, 13.85. Calculated for $C_{12}H_{18}N_2O$, %: C 69.87; H 8.79; N 13.58.

If the cyclization product was not treated with metallic sodium as described above but was crystallized from acetone (100 ml of acetone for 40 g of mixture), 15.9 g of the tetrahydropyridine II with mp 168–169° C was obtained. By evaporating the acetonic mother liquor to 1/4 of its volume, another 7.8 g of less pure II with mp 152–162° C was obtained. The residual mother liquor was evaporated to dryness. The resinous residue (14 g) crystallized, and this was recrystallized first from ethanol and then from ethyl acetate, to give 4.7 g of substance IV, mp 150–152° C. Found, %: C 68.84, 68.77; H 9.19, 9.04; N 22.22, 22.37. Calculated for $C_{11}H_{17}N_3$, %: C 69.07; H 8.95; N 21.97.

REFERENCES

1. I. A. Zaitsev, M. M. Shestaeva, and V. A. Zagorevskii, USSR patent, no. 172804; Byull. izobr., no. 14, 1965.

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