FORMATION OF 1-ARYL-2-CHLOROMETHYLENE-1,2,3,4-TETRAHYDROPYRIDINES AND ISOMERIZATION TO 1,4-DIHYDROPYRIDINES

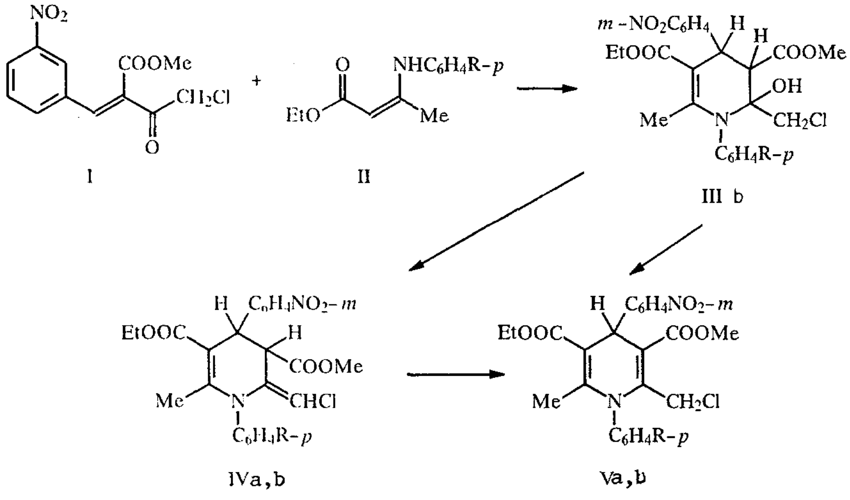
B. S. Chekavichus, I. S. Birgele, A. É. Sausin'sh,
and G. Ya. Dubur

4-Chloro-2-arylideneacetoacetic acid esters of the I type and 3-aminocrotonic acid esters form 2-chloromethylene-1,2,3,4-tetrahydropyridines, which even at room temperature in chloroform undergo isomerization to the more stable 2-chloromethyl-1,4-dihydropyridines [1].

We have established that atypical products of the Hantzsch cyclization, viz., 1-aryl-2-chloromethylene-1,2,3,4-tetrahydropyridines IV, which are more stable substances than their 1-unsubstituted analogs, are formed when 3-arylaminocrotonic acid esters II are used as the enamine components. Compounds IV undergo isomerization to the corresponding 2-chloromethyl-1,4-dihydropyridines V in an acidic medium.

If the Michael addition proceeds at room temperature or with brief heating, one can isolate an intermediate, viz., 1-(p-ethoxyphenyl)-2-hydroxy-1,2,3,4-tetrahydropyridine (IIIb).

Only one maximum at 312 nm, in contrast to dihydropyridines Va, b, appears in the UV spectra of IVa, b; the absorption of carbonyl groups at 1742 and 1658 cm^{-1} is observed in the IR spectra. Signals of C=CHCl protons at 4.95 ppm are identified unambiguously in the PMR spectra, while 3-H and 4-H signals are identified unequivocally in the form of doublets (J = 2.0 Hz) at 4.21 and 4.87 ppm, respectively. Signals of a 2-methylene group in the form of a quartet show up in the PMR spectra of dihydropyridines Va, b.



II—V a R = OMe; b R = OEt

The structure of intermediate IIIb was confirmed by the ^{1}H and ^{13}C NMR spectra. Two signals in the ^{13}C NMR spectrum at 83.93 and 52.22 ppm correspond to the $C_{(2)}$ and $C_{(3)}$ ring carbon atoms, respectively. A doublet of quartets at 4.38 ppm (the region characteristic for the 4-H proton)) with spin–spin coupling constants (SSCC) $^3J = 11.4$ Hz and $^5J = 1.8$ Hz was detected in the ^{1}H NMR spectrum. The long-range coupling between the protons of the 6-CH$_3$ group and the 4-H proton is due to the presence of a $C_{(5)}=C_{(6)}$ double bond in the molecule.

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1-(p-Ethoxyphenyl)-2-hydroxy-1,2,3,4-tetrahydropyridine IIIb was obtained by heating 0.01 mole of starting I and II in methanol for 20 min or by stirring the reaction mixture for 4 h at room temperature.

To obtain **1-(p-alkoxyphenyl)-4-(m-nitrophenyl)-2-chloromethylene-1,2,3,4-tetrahydropyridines IVa, b**, 6 mmole of starting I and II was dissolved in methanol, and the mixtures were heated for 2 h. Compounds IVa, b were yellowish crystals (from methanol).

1-(p-Alkoxyphenyl)-4-(m-nitrophenyl)-2-chloromethyl-1,4-dihydropyridines Va, b were obtained from the reaction mixtures without isolation of IVa, b with the subsequent addition of a few drops of hydrochloric acid and refluxing for 30 min.

The following data were obtained [compound, yield (%), mp (°C), ^{1}H and ^{13}C NMR data ($CDCl_3$), δ (ppm) given]: IIIb: 38, 136-137, 0.75 (3H, t, CH_3), 1.44 (3H, t, CH_3), 2.02 (3H, d, $^5J = 1.8$ Hz, CH_3), 3.25 and 3.16 (2H, d and d, $J = 12.3$ Hz, CH_2Cl), 3.47 (3H, s, OCH_3), 3.49 (1H, d, $^5J = 11.4$ Hz, 3-H), 3.74 and 4.07 (4H, q and q, OCH_2), 4.38 (1H, dq, $^3J = 11.4$ Hz and $^3J = 1.8$ Hz, 4-H), 4.58 (1H, s, OH), 6.91 (2H, m, aromatic H_0), 7.2-8.2 (6H, m, aromatic), 13.61, 14.63, 19.38 (CH_3), 42.24 (CH_2Cl), 46.19 (4-C), 52.06 (OCH_3), 52.22 (3-C), 59.12 (OCH_2), 63.55 (OCH_2), 83.93 (2-C), 100.07 (5-C), N—C_6H_4, 131.53 (C_i), 132.10, 133.32 (C_0), 114.00, 114.68 (C_m), 158.71 (C_p), 4-C_6H_4, 146.29 (C_i), 122.19 and 132.10 (C_0), 129.18 (C_m), 148.31 [$C_m(NO_2)$], 121.61 (C_p), 152.36 (6-C), 167.34 (5-C=O), 174.89 (3-C=O); IVa: 51, 140-142, 4.22 (1H, d, $J = 2.0$ Hz, 3-H), 4.88 (1H, d, $J = 2.0$ Hz, 4-H), 4.95 (1H, s, =CHCl); IVb: 55, 108-110, 4.20 (1H, d, $J = 2.0$ Hz, 3-H), 4.86 (1H, d, $J = 2.0$ Hz, 4-H), 4.95 (1H, s, =CHCl); Va, 49, 135-136, 4.02 and 4.91 (2H, AB-q, $J = 11.4$ Hz, CH_2Cl); Vb: 54, 125-127, 4.08 and 4.91 (2H, AB-q, $J = 11.4$ Hz, CH_2Cl).

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