A NEW SYNTHESIS OF BENZOFURO[3,2-c]PYRIDINES

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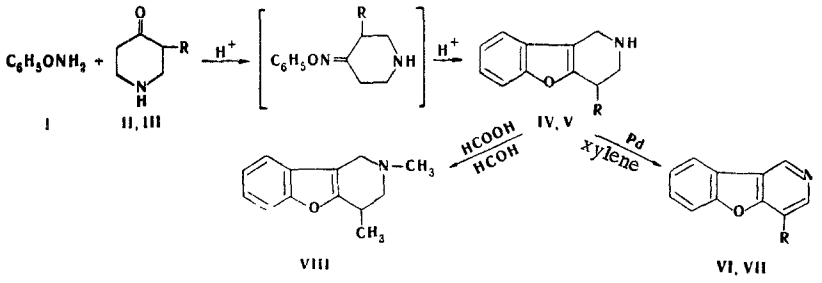
The condensation of O-phenylhydroxylamine with piperidin-4-one and 3-methylpiperidin-4-one has given 1,2,3,4-tetrahydrobenzofuro[3,2-c]pyridine and 4-methyl-1,2,3,4-tetrahydrobenzofuro[3,2-c]pyridine, and these have been dehydrogenated to the corresponding heteroaromatic system of benzofuro[3,2-c]pyridine.

It has been established [1] that the cyclization of 1-methylpiperidin-4-one and 1,2,5-trimethylpiperidin-4-one with O-phenylhydroxylamine (I) in ethanolic solutions of hydrogen chloride takes place smoothly and leads to N-substituted 1,2,3,4-tetrahydrobenzofuro[3,2-c]pyridines. The study of this cyclization with N-unsubstituted piperidin-4-ones may considerably expand the synthetic possibilities of this method for obtaining pharmacologically active compounds among benzofuran derivatives, all the more since N-unsubstituted 1,2,3,4-tetrahydrobenzofuro[3,2-c]pyridines can be dehydrogenated to benzofuro[3,2-c]pyridines. Piperidin-4-one (II) [2] and 3-methylpiperidin-4-one (III) [3] were used as ketonic components. Substance (II) was obtained by the Dieckmann cyclization of N,N-di(β-methoxycarbonylethyl)acetamide with the subsequent hydrolysis of the methoxycarbonyl and acetyl groups; compound (II) was used in the reaction without purification in the form of the hydrochloride.

In the condensation of (I) with (II) and (III) in ethanolic solutions of hydrogen chloride without the isolation of the intermediate oxime ethers the 1,2,3,4-tetrahydrobenzofuro[3,2-c]pyridines (IV and V) were obtained with good yields.



I II, III IV, V VIII VI, VII

II, IV, VI R=H; III, V, VII R=CH3

In the PMR spectrum (in CCl_4) of (IV) at 1.2 ppm there is the singlet signal of the proton of the NH group; a multiplet signal of 3-H_2 is located in the 2.43-2.8-ppm region and the signal of 4-H_2 in the form of a distorted triplet with broadened components is located at 3.08 ppm; the 1-H_2 protons are represented by a triplet signal with δ 3.82 ppm split (J ~ 2 Hz) through long-range coupling with the 4-H_2 protons. On the addition of CD_3OD, the signal with the δ 1.2 ppm disappeared, but the shape of the remaining signals did not change, which is due to a fairly rapid exchange of the NH proton in the nondeuterated sample under the conditions of recording the spectrum. In the PMR spectrum (in CD_3OD) of the hydrochloride (V) there is a doublet signal of 4-CH_3 at 1.5 ppm (J = 6 Hz), the singlet of 2-CH_3 with δ 3.2 ppm, a broadened signal of 1-H_2 at 4.6 ppm, and unresolved signals of the 3-H_2 and 4-H protons in the 3.3-4.0-ppm region.

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Compounds (IV) and (V) were dehydrogenated by boiling in xylene over palladium black to the heteroaromatic system (VI, VII), (VI) being the unsubstituted representative of this system. Some 1,3-disubstituted benzofuro[3,2-c]pyridines have recently been obtained by another method [4]. In the PMR spectrum of (VI) there are only the signals of aromatic protons. In the PMR spectrum of (VII), in addition a singlet signal appears with δ 2.6 ppm of the 4-CH_3 protons. Compound (V) was N-methylated by the Leuckart–Wallach method to form compound (VIII).

EXPERIMENTAL

The PMR spectra were taken on a Varian T-60 instrument (60 MHz, δ scale).

Piperidin-4-one (II). With stirring, a solution of 216 g (0.935 mole) of N,N-di(β-methoxycarbonylethyl)acetamide [3] in 200 ml of absolute benzene was added to a suspension of 41.3 g (1.7 mole) of sodium hydride in 800 ml of absolute benzene, and then 2 ml of absolute ethanol was added and the reaction mixture was boiled for 2 h 30 min. After cooling with ice, 75 ml of acetic acid and 70 ml of water were added, and the benzene layer was separated off and evaporated. The residue was treated with 800 ml of 6 N hydrochloric acid and the mixture was boiled for 4 h and was evaporated in vacuum to dryness. This gave 105 g (82%) of the unpurified hydrochloride of (II).

Hydrochloride of 1,2,3,4-Tetrahydrobenzofuro[3,2-c]pyridine (IV). A mixture of 13 g (0.01 mole) of the hydrochloride of (II) and 8.7 g (0.006 mole) of the hydrochloride of (I) in 75 ml of a 25% solution of hydrogen chloride in absolute ethanol was boiled for 2 h, and the precipitate that deposited on cooling was filtered off to give 9 g (86%) of the hydrochloride of (IV), mp 309-310°C (from water). Found, %: C 63.0; H 5.8; Cl 16.8; N 6.7. $C_{11}H_{11}NO \cdot HCl$. Calculated, %: C 63.0; H 5.8; Cl 16.9; N 6.7.

The base (IV), mp 53-53.5°C (from ether). Found, %: C 76.4; H 6.5; N 8.0. $C_{11}H_{11}NO$. Calculated, %: C 76.2; H 6.4; N 8.1.

Hydrochloride of 4-Methyl-1,2,3,4-tetrahydrobenzofuro[3,2-c]pyridine (V). Similarly, 3 g (2 mmoles) of the hydrochloride of (III) and 3 g (2.3 mmoles) of the hydrochloride of (I), by boiling in 40 ml of ethanolic hydrogen chloride, gave 4 g (87.8%) of the hydrochloride of (V), mp 262-263°C (from absolute ethanol). Found, %: C 64.2; H 6.4; Cl 15.9; N 6.2. $C_{12}H_{13}NO \cdot HCl$. Calculated, %: C 64.4; H 6.3; Cl 15.9; N 6.3.

Benzofuro[3,2-c]pyridine (VI). A mixture of 1.2 g of (IV) and 30 ml of absolute xylene was boiled for 10 h in the presence of palladium black, and then the catalyst was filtered off and the xylene was evaporated in vacuum to give 1 g (85%) of (VI), mp 73-74.5°C (from heptane). Found, %: C 78.0; H 4.4; N 8.2. $C_{11}H_7NO$. Calculated, %: C 78.1; H 4.2; N 8.3. PMR spectrum (CCl_4), ppm: 9.2 (singlet, 1-H), 8.6 (doublet, 3-H, J 6 Hz), 7.8-8.1 (multiplet, one proton of a benzene ring), 7.2-7.7 (overlapping signals of a 4-H doublet with J 6 Hz and multiplets of three protons of a benzene ring).

4-Methylbenzofuro[3,2-c]pyridine (VII). The dehydrogenation of 1.8 g of (V) was performed similarly, giving 1 g (59%) of (VII), mp 118.5-120°C (from heptane). Found, %: C 78.7; H 5.0; N 7.4. $C_{12}H_9NO$. Calculated, %: C 78.7; H 4.9; N 7.6. PMR spectrum (in CCl_4), ppm: 9.0 (singlet, 1-H), 8.4 (singlet, 2-H), 7.8-8.1, and 7.2-7.7 (one and three protons of a C_6H_4 group), and 2.6 (singlet, 4-CH_3).

Hydrochloride, mp > 300°C (decomp.). Found, %: Cl 16.0. $C_{12}H_9NO \cdot HCl$. Calculated, %: Cl 16.1.

Hydrochloride of 2,4-Dimethyl-1,2,3,4-tetrahydrobenzofuro[3,2-c]pyridine (VIII). With ice-water cooling, 5 ml of 85% formic acid and 4 ml of formaldehyde were added through a condenser to 4.4 g of (V). The mixture was heated on the water bath for 13 h and was then acidified with concentrated hydrochloric acid and evaporated to dryness in vacuum. The residue was dissolved in water, made alkaline with 25% caustic soda solution, and extracted with ether. The extract was dried and evaporated. The residue was dissolved in 5 ml of absolute benzene, 1 ml of acetic anhydride was added, and the mixture was boiled for 1 h 30 min and was then extracted with 15% hydrochloric acid. The acid solution was made alkaline with 20% caustic soda solution and extracted with ether. The extract was dried, and a solution of hydrogen chloride in ether precipitated the hydrochloride of (VIII); yield 3.5 g (63.6%), mp 249-250.5°C (purified by reprecipitation). Found, %: C 65.6; H 6.7; Cl 14.9; N 5.9. $C_{13}H_{15}NO \cdot HCl$. Calculated, %: C 65.7; H 6.8; Cl 14.9; N 5.9.

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