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REACTION OF 1-AMINOMETHYL-1,2,3,4-TETRAHYDRO-ISOQUINOLINE WITH DIETHYL FUMARATE

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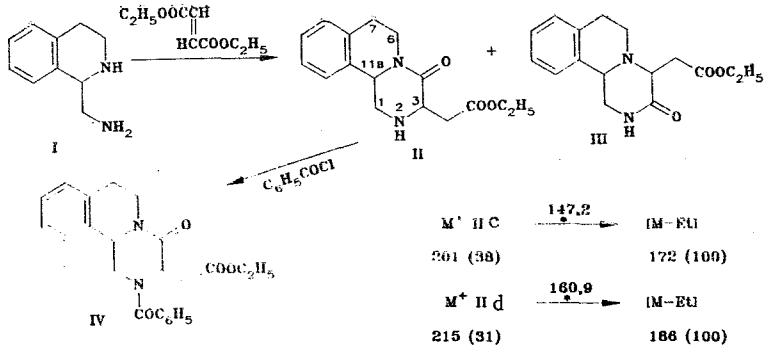
The reaction of 1-aminomethyl-1,2,3,4-tetrahydroisoquinoline with diethyl fumarate goes by two possible paths, to form a mixture of 3-carbethoxymethyl-4-oxo-1,2,3,6,7,11b-hexahydro-4H-pyrazino[2,1-a]isoquinoline and its isomer 4-carboxymethyl-3-oxo-1,2,3,6,7-11b-hexahydro-4H-pyrazino[2,1-a]isoquinoline.

The most outstanding achievement in the chemotherapy of helminthiasis in recent years has been the development of the highly efficient preparation Prasiquantel, which is an acyl derivative of the tricyclic system 4-oxo-1,2,3,6,7,11b-hexahydro-4H-pyrazino[2,1,-a]isoqunioline [1]. Judging from the patent data [2], other derivatives of this system also have anthelmintic activity. In the patented syntheses of these compounds the starting material is 1-aminomethyl-1,2,3,4-tetrahydroisoquinoline (I), which is converted in several steps to the corresponding pyrazinoisoquinolines [2, 3].

It was of interest to study the reaction of I with diethyl fumarate in order to obtain this tricyclic system. It is known [4] that some N-substituted ethylene diamines are converted by reaction with maleic or fumaric diesters or monoamides to the corresponding carbethoxy- or aminocarbonylmethylpiperazinones in high yield; the Michael addition, which is the first step in the formation of these compounds, proceeds selectively at the primary amino group. If we consider I to be a substituted ethylene diamine, we might expect it to react with diethyl fumarate to give compound II exclusively. But we find that when this reaction is carried out in absolute alcohol, it forms a mixture of isomers, viz., 3-carbethoxymethyl-4-oxo-1,2,3,6,7,11b-hexahydro-4H-pyrazino[2,1-a]isoquinoline (II) and 4-carbethoxymethyl-3-oxo-1,2,3,6,7,11b-hexahydro-4H-pyrazino[2,1-a]isoquinoline (III), 1.5:1, with ∿80% overall yield. When the solvent was anhydrous ether, as described in [4, 5] for substituted ethylene diamines, the mixture of II and III was also obtained, but the overall yield was no more than 40%. These substances, which are very similar in polarity, were separated by repeated recrystallization of the hydrochlorides from absolute alcohol.



Since II is a secondary amine while III is a tertiary amine, the product mixture of hydrochlorides was also separated by the standard method, benzoylation. Secondary amine II is converted to the benzoyl derivative IV, whereas benzoylation of the amide nitrogen $N_{(a)}$ in III does not occur, and III is easily separated from the reaction mixture.

The structures of pyrazinoisoquinolines II and III were confirmed by elemental analysis and IR and PMR spectroscopy; that of III also by mass spectrometry.

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The IR spectra of II and III contain ester carbonyl bands (1730 and 1735 cm^{-1}, respectively), amide bands (1670 and 1648 cm^{-1} respectively), and NH bands (3370 and 3340 cm^{-1}, respectively).

The PMR spectrum of II shows signals of: aromatic protons (multiplet 6.9-7.15 ppm); methylene protons: $-OCH_2CH_3$ (quartet at 3.95 ppm, J = 7 Hz), at $C_{(1)}$, $_{(6)}$, $_{(7)}$ and also α to the ester group (multiplet at 2.35-3.15 ppm); protons at $C_{(11b)}$ and $C_{(3)}$ (multiplets at 3.6-3.75 and 3.1-3.335 ppm, respectively); methyl protons (triplet at 1.1 ppm); and finally, the proton at nitrogen (broad singlet at 4.6 ppm). Along with these signals the PMR spectrum of III also contains the signal of the amide proton in the downfield region (broad singlet at 7.6 ppm), but has no signal for an amino proton.

In the mass spectrum of III the most intense peak belongs to the ion $[M - CH_2COOC_2H_5 - CONH]^+$ with m/z 158. Elimination from the molecular ion, m/z 288, of $COOC_2H_5$ gives a fragment with m/z 215; detachment of $CH_2COOC_2H_5$ gives m/z 201. The other decomposition path is the elimination of CH_2NHCO with proton capture to form a peak with m/z 230.

Thus, in contrast to the N-substituted ethylene diamines compound I react with diethyl fumarate by two possible mechanisms. In our opinion this difference is to be explained by the much larger steric hindrance of the secondary amino group in the N-substituted ethylene diamines than in the derivatives of I. Therefore in the condensation of the latter with diethyl fumarate, Michael addition takes place at both the primary and secondary amino groups, so that the mixture of isomers II and III is formed.

EXPERIMENTAL

IR spectra were obtained on a UR-20 instrument in KBR tablets. PMR spectra were obtained on a Tesla Bs-467A spectrometer (60 MHz) in $CDCl_3$, with TMS internal standard. Mass spectra were measured on Varian MAT-112 (West Germany) instrument with direct introduction of sample into the source. Electron ionization energy was 70 eV; temperature of ionizing chamber, 180°. The course of the reaction and the purity of the products was monitored by TLC on Silufol plates in 20:1 chloroform–methanol.

Reaction of 1-aminomethyl-1,2,3,4-tetrahydroisoquinoline with diethyl fumarate. To a solution of 4.5 g (28 mmole) of I in 15 ml of abs. alcohol was added a solution of 4.8 g (28 mmole) of diethyl fumarate in 10 ml of abs alcohol. The mixture was held at 20° for 48 h; the alcohol was distilled off in vacuum, and the residue was dissolved in 20 ml of ether and extracted with three 20-ml portions of 5% hydrochloric acid. The combined acid extracts were neutralized with sodium bicarbonate to pH 7 and extracted with three 10-ml portions of ether. The ether extract was washed with water and dried over Na_2SO_4. The solvent was distilled off. To the residue (which by TLC contained a mixture of esters II and III) was added 15 ml of 9 N HCl in alcohol. The precipitate of II and III hydrochlorides was filtered off and treated by method A or B.

A. The hydrochloride mixture was recrystallized 3-4 times from abs. alcohol. There was obtained 4.1 g (45%) of the hydrochloride of 3-carbethoxymethyl-4-oxo-1,2,3,6,7,11b-hexahydro-4H-pyrazino[2,1-a]isoquinoline (II). Mp 198-200°. IR spectrum: 1670 (amide CO), 1730 cm^{-1} (ester CO). Found: C 59.2; H 6.5; Cl 10.6; N 8.2%. $C_{16}H_{21}ClN_2O_3$. Calculated: C 59.2; H 6.5; Cl 10.9; N 8.6%. II base, mp 84-85° (from alcohol). R_f 0.6. IR spectrum: 1658 (amide CO), 1730 (ester CO), 3370 cm^{-1} (NH). PMR spectrum ($CDCl_3$): 6.9-7.15 (m, 4H, arom.); 4.6 (br s, 1H, NH); 3.95 (q, J = 7 Hz, 2H, OCH_2CH_3); 3.6-3.75 (m, 1H, 11b-H); 3.1-3.35 (m, 1H, 3-H); 2.35-3.05 (m, 8H, 1-H, 6-H, 7-H, CH_2COOC–); 1.1 ppm (t, 3H, CH_2CH_3). Found: C 66.9; H 6.9; N 10.1%. $C_{16}H_{20}N_2O_3$. Calculated: C 66.6; H 7.0; N 9.7%.

The combined mother liquors left after recrystallization of II hydrochloride were evaporated in vacuum. The residue was recrystallized from alcohol to give 2.9 g (32%) of the hydrochloride of 4-carbethoxymethyl-3-oxo-1,2,3,6,7,11b-hexahydro-4H-pyrazino-[2,1-a]isoquinoline (III). Mp 225-228°. Found: Cl 10.5; N 8.4%. $C_{16}H_{20}ClN_2O_3$. Calculated: Cl 10.9; N 8.6%. III base, mp 92-94° (from 1:1 chloroform–hexane). R_f 0.5. IR spectrum: 1648 (amide CO), 1735 (ester CO), 3340 cm^{-1} (NH). PMR spectrum ($CDCl_3$): 7.7 (br. s, 1H, NH); 6.95-7.12 (m, 4H, arom.); 4.05 (q, J = 7 Hz, 2H, OCH_2CH_3); 3.6-3.75 (m, 1H, 11b-H); 2.6-3.5 (m, 9H, 1-H, 6-H, 7-H, CH_2COOC, 4-H); 1.1 ppm (t, 3H, CH_2CH_3). Mass spectrum, m/z (relative intensity, %): 288 (28.5); 230 (28.5); 215 (28.5); 201 (42.8), 158 (100). Found: C 66.4; H 7.1; N 9.9%. $C_{16}H_{20}N_2O_3$. Calculated: C 66.6; H 7.0; N 9.7%.

B. A mixture of II and III hydrochlorides was recrystallized once from abs. alcohol. Then it was converted to the free base mixture by treatment with sodium bicarbonate to yield 4.8 g (60%). The mixture was dissolved in 30 ml of methylene chloride, 1.7 g of triethylamine was added, then with stirring, a solution of 2.4 g of benzoyl chloride in 5 ml of methylene chloride. The mixture was stirred for 2 h at room temperature, then extracted with three 20-ml portions of 5% hydrochloric acid, then with 20 ml of water. The combined extracts were used for the isolation of III. The organic phase was dried over Na_2SO_4, and the solvent was evaporated in vacuum to give 4.3 g (64%) of 2-benzoyl-3-carbethoxymethyl-4-oxo1,2,3,6,7,11b-hexahydro-4H-pyrazino[2,1-a]-isoquinoline (IV). Mp 100-102° (from ethyl acetate). R_f 0.9. IR spectrum: 1628, 1660 (amide CO), 1742 cm^{-1} (ester CO). Found: C 70.6; H 6.4; N 7.4%. $C_{23}H_{24}N_2O_4$. Calculated: C 70.4; H 6.2; N 7.1%.

The hydrochloric acid solution was neutralized with sodium bicarbonate to pH 7 and the precipitate was extracted with 20 ml of methylene chloride and dried over Na_2SO_4. After distillation of the solvent, 0.9 g (17%) of base III was obtained. After recrystallization from chloroform-hexane mixture it was identical in mp, TLC, and IR spectrum with the sample obtained by procedure A.

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DUAL REACTIVITY OF 1,2-DISUBSTITUTED DIHYDRO-N-HETEROAROMATIC SYSTEMS.

6.* ELECTROCHEMICAL OXIDATION OF N-ACYL DERIVATIVES OF 2-PHENYL-1,2-DIHYDROQUINOLINES

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In the electrochemical oxidation of 1-acyl-2-phenyl-1,2-dihydroquinolines, first the radical cations of the starting compounds form; these then lose a benzoyl radical and go over to the 2-arylquinoline cations.

The oxidation of substituted dihydroheteroaromatic compounds can proceed via a monomolecular mechanism [2], in which there first forms an ion pair of heteroaromatic cation and substituent anion [1], which then reacts with the aromatizing agent (the so-called nucleophilic alkylation [3]). An alternative is the bimolecular aromatization mechanism, in which the aromatizing agent first oxidizes the starting compound to a radical cation, then (depending on the electron density distribution) removes either hydrogen or a geminal substituent [2]. The direct removal of substituent or hydrogen with an electron pair is also not excluded in those cases where the aromatizing agent is a strong electrophile but its reduction potential is lower than the oxidation potential of the dihydro derivative. The behavior of dihydroheteroaromatic compounds in oxidations can be predicted when their electrochemical oxidation has first been studied at a rotating platinum disk electrode with a ring [4].

Thus we have previously shown [4] that in the electrochemical oxidation of N-acyl derivatives of α-(γ)-(indolyl-3)-1,2-dihydroheteroaromatic compounds an unstable radical

*For Communication No. 5, see [1].

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