SYNTHESIS OF 2-CYCLOHEXYLCARBONYL-4-OXOPERHYDROPYRAZINO[2,1-a]-ISOQUINOLINE

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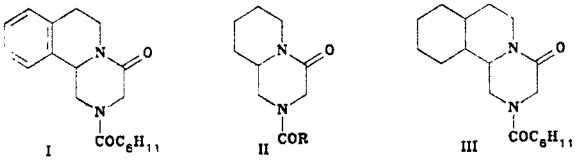
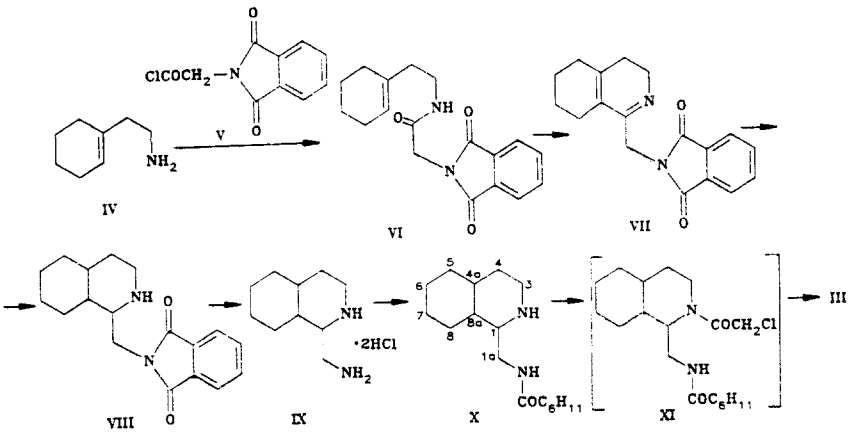
2-Cyclohexylcarbonyl-4-oxoperhydropyrazino[2,1-alisoquinoline, an analog of the highly effective anthelmintic prasiquantel, was synthesized from 2-(cyclohexen-1-yl)-ethylamine.

The discovery of the highly effective anthelmintic prasiquantel (I) [1] with a broad spectrum of activity, entailed a study of a series of its analogs with a mono-, bi-, and tricyclic structure [1-6]. It was found that bicyclic pyridopyrazines II have no noticeable anthelmintic activity [1]. It was of interest to prepare "perhydroprasiquantel" (III) for biological study.



We carried out the synthesis of compound III starting from 2-(cyclohexen-1-yl)ethylamine (IV) according to the following scheme:



We selected this scheme because the cyclization of certain acyl derivatives of amine IV according to Bischler-Napieralski, which proceeds under mild conditions with the formation of the corresponding hexahydroisoquinolines, has been described in the literature [7, 8]. Reaction of compound IV with acid chloride V gave amide VI. Cyclization of this amide by heating with phosphorus oxychloride in xylene gives hexahydroisoquinoline VII in high yield; its structure was confirmed by elemental analysis, IR and PMR spectroscopic data. In the ^1H NMR spectrum of compound VII, as well as the aromatic proton signals, there are also signals of methylene protons of the phthalimidomethyl group, and signals of the $C_{(3)}$-$C_{(8)}$ protons.

During the hydrogenation of compound VII over the Adams catalyst, 1-phthalimidomethyl-perhydroisoquinoline VIII is formed. On acid hydrolysis the latter converts into diamine IX, which is isolated in the form of dihydrochloride. Selective acylation of the primary amino group in compound IX by cyclohexylcarbonyl chloride by a method used in the synthesis

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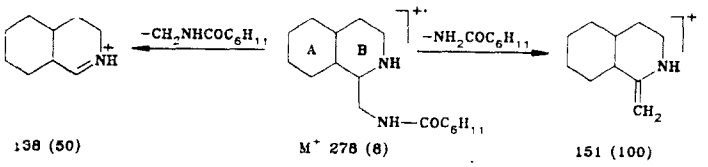
of monoacyl derivatives of 1-aminomethyl-1,2,3,4-tetrahydroisoquinoline [9], leads to 1-cyclohexylcarbonylaminomethylperhydroisoquinoline (X), whose structure was confirmed by elemental analysis, IR, ^{13}C NMR and mass spectroscopy.

In the ^{13}C NMR spectrum of the monoacyl derivative X taken with a total suppression of the ^{13}C-^{1}H spin–spin coupling, in weak field region has a signal of the carbonyl group carbon atom with δ 176.05 ppm. In the strong field region, several signals are observed belonging to the methine and methylene group carbon atoms. Their assignment was based on literature analogies [10, 11] (see the experimental part). The signals of the olefin carbon atoms in the 110...130 ppm region are absent, which confirms the perhydroisoquinoline structure of compound X.

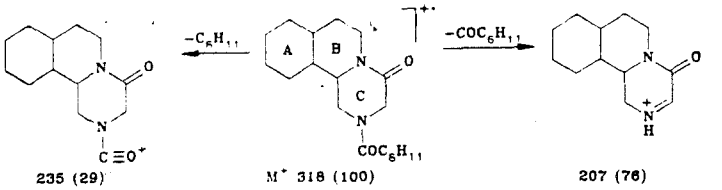
In the mass spectrum of the monoacyl derivative X, a low intensity peak of the molecular ion with m/z 278 is observed. The most intense peaks belong to the ions $[M - CH_2NHCOC_6H_{11}]^+$ (m/z 138) and $[M - NH_2COC_6H_{11}]^+$ (m/z 151):



138 (50) M⁺ 278 (8) 151 (100)

Acylation of the secondary amino group of compound X by chloracetyl chloride leads to the diacyl derivative XI, which cyclizes by the action of potassium tert-butylate into pyrazino[2,1-a]isoquinoline [1] (cf. [2]). The final stages of the synthesis of "perhydroprasiquantel" (III) are carried out in one step without the isolation of compound XI. Its structure was confirmed by the data of elemental analysis, IR and mass spectroscopy.

In the mass spectrum of compound III, an intense peak of the molecular on is observed with m/z 318. The main paths of fragmentation involve the splitting off of the COC_6H_{11} and C_6H_{11} groups:



235 (29) M⁺ 318 (100) 207 (76)

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EXPERIMENTAL

The IR spectra were run in KBr tablets on a UR-20 spectrophotometer. The ^{1}H and ^{13}C NMR spectra (internal standard TMS) were measured in $CDCl_3$ on DA 60-K (60 MHz) and Bruker WM-250 (62.89 MHz) spectrometers, respectively. The mass spectra were obtained on a MAT-112S Varian spectrometer (USA) with direct introduction of the sample into the source. The energy of the ionizing electrons was 70 eV and the temperature of the ionizing chamber 180°C. The course of the reactions and the purity of the compounds obtained were monitored on Silufol plates in a 10:1 chloroform methanol system.

N-Phthaloylglycine 2-(cyclohexen-1-yl)ethylamide (VI). A solution of 8.26 g (66 mmoles) of amine IV [7] in 127 ml of a 3% $NaHCO_3$ solution is added with stirring to a solution of 16.3 g (73 mmoles) of acid chloride V in 150 ml of benzene. The mixture is stirred for 1 h at 20°C, then diluted with 100 ml of water, the precipitate is filtered, and washed with water. Yield, 15.3 g (74%), mp 193...194°C (from ethanol). IR spectrum: 3285 (NH), 1771, 1728 (C=O, imide), 1658 cm^{-1} (C=O, amide). Found: C 69.6; H 6.5; N 9.0%. $C_{18}H_{20}N_2O_3$. Calculated: C 69.2; H 6.5; N 9.0%.

1-Phthalimidomethyl-3,4,5,6,7,8-hexahydroisoquinoline (VII). A mixture of 20 mg (64 mmoles) of compound VI and 29.45 g (192 mmoles) of $POCl_3$ in 90 ml of xylene is boiled for 20 min, then cooled, the precipitate is filtered, and purified by dissolving in an ethanolic solution of HCl and precipitation by ether. Yield, 15 g (70%) of hydrochloride of compound VII, mp 205...207°C. Found: Cl 10.7%. $C_{18}H_{18}N_2O_2 \cdot HCl$. Calculated Cl 10.6%. Base VII:

mp 162...164°C (from isopropanol). IR spectrum: 1770, 1720 (C=O), 1668 cm^{-1} (C=N). ^1H NMR spectrum: 7.5...7.9 (4H, m, arom.); 4.47 (2H, s, CH_2N), 3.2 (2H, t, J = 8 Hz, 3-H_2); 1.3...2.6 ppm (10H, m, 4-H_2...8-H_2). Found: C 73.2; H 6.1; N 9.8%. $C_{18}H_{18}N_2O_2$. Calculated: C 73.4; H 6.2; N 9.5%.

1-Phthalimidomethylperhydroisoquinoline Hydrochloride (VIII). A 1 g portion of platinum oxide is added to a solution of 15 g (45 mmoles) of hydrochloride of compound VII in a mixture of 25 ml of water and 150 ml of acetic acid, and the mixture is hydrogenated at atmospheric pressure and room temperature. At the end of the hydrogen absorption (~3 h), the catalyst is filtered, the filtrate is evaporated to dryness in vacuo, and the residue is recrystallized from an ethanol-ether mixture. Yield, 10.2 g (68%), mp 235-237°C. IR spectrum: 1780, 1720 cm^{-1} (C=O). Found: C 64.8; H 6.9; N 8.2%. $C_{18}H_{22}N_2O_2 \cdot HCl$. Calculated: C 64.6; H 6.9; N 8.4%.

1-Aminomethylperhydroisoquinoline Dihydrochloride (IX). A mixture of 20 g (60 mmoles) of hydrochloride of VIII in 300 ml of 18% hydrochloric acid is boiled for 10 h. The reaction mixture is cooled, the precipitated phthalic acid is filtered, the hydrochloric acid solution is extracted with ether, and the extract is evaporated to dryness. The residue is dried over P_2O_5 and boiled with 150 ml of absolute alcohol. After cooling the precipitate of dihydrochloride IX is filtered. Yield, 7.8 g (54%), mp 262...266°C (from an ethanol-ether mixture). Found: C 50.1; H 9.1; Cl 30.0%. $C_{10}H_{20}N_2 \cdot 2HCl$. Calculated: C 49.8; H 9.2; Cl 29.4%.

1-Cyclohexylcarbonylaminomethylperhydroisoquinoline (X). A 39 ml portion (78 mmoles) of a 2 N NaOH solution and 7.4 g (94 mmoles) of pyridine are added, with stirring, to a suspension of 18.8 g (78 mmoles) of dihydrochloride IX in 150 ml of acetonitrile, and then 13.8 g (94 mmoles) of cyclohexanecarbonyl chloride are added in the course of 1 h. The mixture is stirred for 3 h at 20°C, acetonitrile is distilled off in vacuo, 250 ml of water are added to the residue, and the mixture is acidified with a 25% solution of hydrochloric acid to pH 4. The solution obtained is extracted with benzene, the organic layer is separated, the aqueous layer is made alkali with a 25% NaOH solution and the precipitate is filtered. Yield 17.9 g (82.4%), mp 149...150°C (from an ethyl acetate-hexane mixture). IR spectrum: 3321 (NH), 1646 cm^{-1} (C=O). ^{13}C NMR spectrum: 60.05 ($C_{(1)}$); 45.46 ($C_{(3)}$) 38.88 ($C_{(4)}$); 42.55 ($C_{(4a)}$); 35.78 ($C_{(5)}$); 47.19 ($C_{(8a)}$); 29.66 ($C_{(1a)}$); 176.05 ppm (C=O). Found: C 73.5; H 10.6; N 9.8%; M^+ 278. $C_{17}H_{30}N_2O$. Calculated: C 73.3; H 10.9; N 10.1%; M 278.

2-Cyclohexylcarbonyl-4-oxoperhydropyrazino[2,1-a]isoquinoline (III). A solution of 4.97 g (44 mmoles) of chloroacetyl chloride in 50 ml of benzene is added gradually to a suspension of 11.1 g (40 mmoles) of compound VIII in 100 ml of benzene, and a solution of potassium tert-butylate, obtained from 3.44 g (88 mmoles) of potassium and 120 ml of tert-butanol is then added. The mixture is stirred for 1 h at 20°C and for 3 h at the boiling point. After cooling, the mixture is diluted with water, the organic layer is separated, washed with water, 5% solution of hydrochloric acid, with water again, and dried over Na_2SO_4. The solvent is distilled off, and the residue is recrystallized from an ethyl acetate-hexane mixture. Yield, 7.6 g (60%), mp 149...151°C. IR spectrum: 1660, 1640 sh cm^{-1} (C=O). Found: C 71.9; H 9.1; N 9.1%; M^+ 318. $C_{19}H_{30}N_2O_2$. Calculated: C 71.7; H 9.5; N 8.8%; M 318.

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