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SYNTHESIS OF PIPERIDINES AND DECAHYDROQUINOLINES, AND THEIR ANALGESIC AND PSYCHOTROPIC PROPERTIES.

XI. 1-[3'-PHENYL-2'-PROPYNYL]-2,4-DIPHENYL-3-METHYL-4-HYDROXYPIPERIDINE AND ITS DERIVATIVES

K. D. Praliev, B. T. Sydykov, D. V. Sokolov, V. M. Kurilenko, and Zh. N. Khlienko

UDC 615.211+615.214.22]:[547.822.3+547.565.2].012.1

It has recently been found that N-alkyl(alkenyl, arylalkyl)-substituted 4-phenyl-1,2,3,6-tetrahydropyridines and their salts possess analgesic, spasmolytic, and psychosedative activity [1, 2]. There are, however, no reports in the literature on the synthesis and pharmacological activity of tetrahydropyridines with mixed aliphatic—aromatic radicals in the heterocyclic ring. It was therefore of interest to synthesize and examine the pharmacological activity of 1-(3'-phenyl-2'-propynyl)-2,4-diphenyl-3-methyl-4-hydroxypiperidine (III) and its derivatives.

The starting material used was trans-2-phenyl-3-methyl-4-oxopiperidine (I) [3], which on reaction with phenylacetylene and paraformaldehyde gave the N-substituted piperidone (II) [4]. Reaction of (II) with phenyllithium, obtained from bromobenzene and lithium, in dry ether under dry argon, followed by decomposition of the resulting lithium alkoxide with water, afforded high yields of the single isomer (III), mp 151-152°C.

Institute of Chemical Sciences of the Kazakh SSR, Alma-Ata; Novokuznetsk Scientific-Research Chemical-Pharmaceutical Institute. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 17, No. 9, pp. 1053-1055, September, 1983. Original article submitted February 16, 1983.

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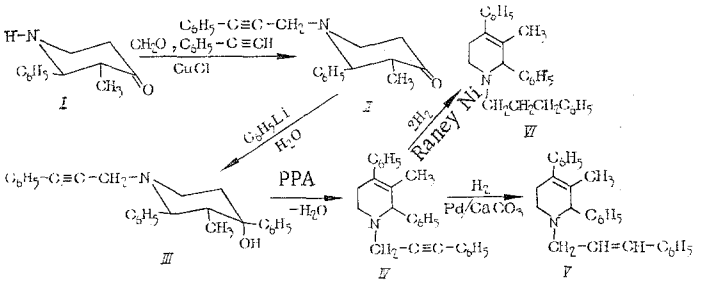

It is known [5] that bulky radicals on the nitrogen atom of 4-oxopiperidines in the equatorial position screen the axial region, and direct phenyllithium to the oxo group preferentially from the axial region, with the formation of axial alcohols only, with an equatorial phenyl at C_4. Hence, our isomer (III) must exist in the chair form, with diequatorial substituents at C_2 and C_3, and with axial hydroxyl.

Attempts to acylate the hydroxyl group in (III) by widely used methods were unsuccessful. Acylation with propionic anhydride in the presence of polyphosphoric acid at room temperature gave, instead of the expected acyl derivative, the dehydration product of the alcohol (III), 1-(3'-phenyl-2'-propynyl)-2,4-diphenyl-3-methyl-1,2,5,6-tetrahydropyridine (IV), in quantitative yield. This finding confirmed that the hydroxyl group in (III) occupies the axial position. As a result of trans-diaxial elimination in the acidic dehydration of alcohols, according to the literature [6], a double bond is formed in the Δ^3-position.

Selective hydrogenation of the acetylenic bond in (IV) over palladium, and total hydrogenation over Raney nickel, gave high yields of the N-substituted tetrahydropyridines (V) and (VI), respectively.

To confirm the structures of the latter compounds, their IR spectra were examined. The IR spectrum of (III) contained a band for the hydroxyl group (3400 cm^{-1}) which was absent in the tetrahydropyridines (IV-VI). In all the latter, a band was present for stretching vibrations of the C=C bond in the ring at 1660-1665 cm^{-1}, confirming the proposed structures.

EXPERIMENTAL CHEMISTRY

IR spectra were recorded on a UR-20 instrument (East Germany) over the frequency range 3600-600 cm^{-1}, in KBr disks or CCl_4 solutions. The purities of the compounds were checked by chromatography on unbound thin layers of alumina, grade III activity. The eluent was ether–light petroleum (1:2), and the developer iodine vapor.

1-(3'-Phenyl-2'-propynyl)-2,4-diphenyl-3-methyl-4-hydroxypiperidine (III). To a solution of phenyllithium, obtained from 0.56 g (0.081 g-atom) of lithium and 6.9 g (0.044 mole) of bromobenzene in 35 ml of dry ether was added dropwise at 5°C with continuous stirring in a stream of argon over 2 h a solution of 9.1 g (0.03 mole) of (II) (mp 88-89°C) in 35 ml of dry ether. The reaction mixture was kept for a day at ambient temperature, then cooled to −5°C and hydrolyzed with 50 ml of water. The ether layer was separated, the aqueous layer extracted repeatedly with ether, and the combined ether extracts dried over magnesium sulfate. The solution was evaporated and the residue crystallized from ether–light petroleum to give 9.1 g (80%) of (III), mp 151-152°C. R_f 0.50. Found, %: C 84.96, 84.59; H 6.95, 7.00; N 3.40, 3.80. $C_{27}H_{27}NO$. Calculated, %: C 85.00; H 7.13; N 3.67.

Hydrochloride (III). This was a finely crystalline, colorless solid, mp 245-246°C (acetone–ether). Found, %: N 3.47, 3.72. $C_{27}H_{28}ClNO$. Calculated, %: N 3.36.

1-(3'-Phenyl-2'-propynyl)-2,4-diphenyl-3-methyl-1,2,5,6-tetrahydropyridine (IV). A mixture of 5.78 g (0.015 mole) of (III), 11.6 g (0.09 mole) of propionic anhydride, 11.6 g (0.156 mole) of propionic acid, and 48 g of polyphosphoric acid was kept for 12 h at ambient temperature. Thin-layer chromatography showed that the spot for the starting material (III) had disappeared, and a new spot with R_f 0.72 appeared. The mixture was poured onto crushed ice, treated with saturated sodium hydroxide solution, and the base extracted with ether (3 × 100 ml) and dried over potassium carbonate. Removal of the ether left 5.26 g (95%) of (IV) as a yellow oil with a characteristic pyridine odor.

Hydrochloride (IV). This was obtained in 92% yield by treating the base wtih ethereal hydrogen chloride; small, colorless crystals, mp 150-151°C (from acetone–ether). Found, %: C 80.79, 80.98; H 6.89, 7.00; N 4.04, 3.97; Cl 9.17, 8.85. $C_{27}H_{26}ClN$. Calculated, %: C 81.07; H 6.65; N 3.50; Cl 8.86.

1-Cinnamyl-2,4-diphenyl-3-methyl-1,2,5,6-tetrahydropyridine (V). In a hydrogenation flask containing 0.5 g of 5% $Pd/CaCO_3$ saturated with hydrogen in 25 ml of anhydrous alcohol was placed 1.66 g of (IV) in 100 ml of absolute ethanol. When one mole of hydrogen had been taken up (102 ml), hydrogenation was stopped, the catalyst filtered off, washed with hot ethanol, and the alcoholic solution evaporated under water pump vacuum to give 1.4 g (84%) of (V) as an oil, R_f 0.80.

Hydrochloride (V). This was obtained in quantitative yield as described above: white powder, mp 102-104°C (from acetone—ether). Found, %: N 3.33, 3.52. $C_{27}H_{28}ClN$. Calculated, %: N 3.48.

1-(3'-Phenylpropyl)-2,4-diphenyl-3-methyl-1,2,5,6-tetrahydropyridine (VI). This compound (1.66 g) dissolved in 150 ml of anhydrous alcohol was hydrogenated in a catalytic flask in the usual manner in the presence of 1.7 g of Raney nickel. When 2 moles (205 ml, 2 h 20 min) of hydrogen had been taken up, the catalyst was filtered off, washed with hot alcohol, and the alcoholic solution evaporated *in vacuo* to give 1.63 g (97%) of (VI) as an oil, R_f 0.84.

Hydrochloride (IV). This was obtained in quantitative yield; white powder, mp 179-180°C (from ethanol—ether). Found, %: N 3.44, 3.62. $C_{27}H_{30}ClN$. Calculated, %: N 3.47.

EXPERIMENTAL PHARMACOLOGY

Using white mice, the toxicities and mode of action on the central nervous system of compounds (IV-VI) administered intraperitoneally were examined. Standard methods were used for the pharmacological studies [7]; effects on body temperature, motor coordination, orientational reactions, chloral hydrate sleep, ineraction with convulsive poisons (corazole, 100-120 mg/kg), antiserotonin and antireserpine effects were studied. The analgesic effects of the compounds were examined in mice using electrical [8] and thermal [9] stimuli, and in rats using mechanical stimuli [10].

It was found that the toxicities of the compounds increased with saturation of the phenylpropargyl radical C≡C bond. Thus, (IV) was of very low toxicity, its daily LD_{50} being greater than 1000 mg/kg. In (V) and (VI), which possess cinnamyl and γ-phenylpropyl substituents on nitrogen, the acute toxicites were much greater, being 250 and 200 mg/kg respectively.

The neurotropic activity of the compounds was slight. In a dose of 1/5 of the LD_{50}, (IV) caused slight hypothermia and inhibited orientational reactions, and (VI) slightly increased the convulsive effects of corazole. Of greatest interest were (V) and (VI), which had pronounced peripheral antiserotonin effects, preventing diarrhea induced by the serotonin precursor 5-hydroxytryptophan. By this test, the ED_{50} values were for (V) 17 (10.3-28) mg/kg, and for (VI), 18 (10.3-31.5) mg/kg.

Studies of the analgesic activity of the compounds showed that none of them, in doses of 1/5 of the LD_{50}, had a significant effect on the pain sensitivity threshold, i.e., they possessed no analgesic activity.

Comparison of the chemical structures of (IV)-(VI) and ring-unsubstituted-tetrahydropyridines [1, 2] with their pharmacological activity showed that the introduction of araliphatic substituents into the heterocycle led to a reduction in analgesic activity.

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