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SYNTHESES BASED ON β-ETHYLAMINES. VIII. SYNTHESIS OF SUBSTITUTED 2-BENZYLTETRAHYDROISOQUINOLINES AND THEIR INFLUENCE ON BILE SECRETION

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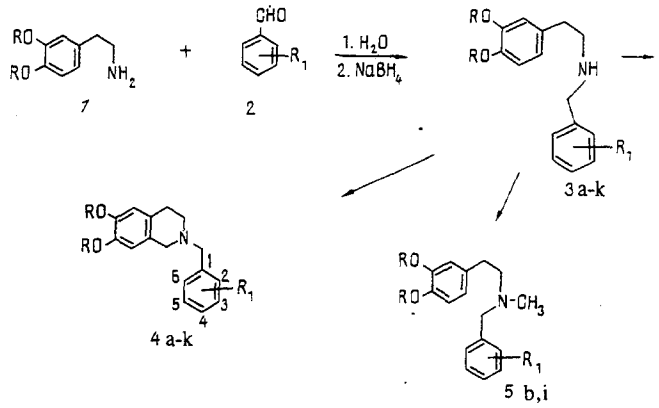
The search for pharmacologically active compounds among substituted 2-benzyl-1,2,3,4-tetrahydroisoquinolines has been continued, and compounds possessing bile-stimulating activity have been found.

The literature contains reports on the search for drugs among the N-benzyltetrahydroisoquinolines and their precursor phenylalkylamines [1, 2]. On performing a preliminary screening of a number of compounds that we had obtained previously (**4a,b** and the methiodides of N-2-hydroxybenzyl-N-methyl- and N-2-methoxy-N-methyl-3,4-methylenedioxyphenylethylamines) [3], we found that the hydrochlorides of substances belonging to the N-benzyltetrahydroisoquinoline series possessed bile-stimulating activity. We have therefore continued the search for active substances in this series by introducing various substituents into both the benzene and the isoquinoline parts of the molecule. The initial compounds for the synthesis of derivatives of this group were homoveratryl- or homopiperonylamines [4] and substituted benzaldehydes, the condensation of which, followed by reduction with lithium tetrahydroborate, gave the amines (**3a-k**). The latter were converted by the Pictet–Spengler reaction into the 2-benzyl-1,2,3,4-tetrahydroisoquinolines (**4a-k**)



RR=CH_2 (3, 4, 5b,d,f)
R_1 a,b—2-OH
c—3-Br; 4-OCH_3
d—2-OCH_3; 5-Br
e—3,4-OCH_2O; 6-Cl
f—3,4-OCH_2O; 5-Br
g—3,4-OCH_2O; 6-NO_2

R=CH_3 (3, 4 a, c, e, g-k
h—3,4-$(OCH_3)_2$; 6-Br
i—3,4-$(OCH_3)_2$; 6-NO_2
j—2-Br; 3-OH; 4-OCH_3
k—3-$OCH_2C_6H_5$; 4-OCH_3
l—4-OCH_3

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TABLE 1. Physicochemical Characteristics of the 2-(R_1-Benzyl)-1,2,3,4-tetrahydroisoquinolines (**4a-k**)

Compound	Yield, %	mp of the hydrochloride, °C	Empirical formula	*m/z*, %
4a	62	137*	$C_{18}H_{21}O_3N$	299($M^{+\bullet}$, 57) 284 (33) 192 (57) 176 (16) 164 (100) 149 (15) 121 (14) 107 (21)
b	55	155*	$C_{17}H_{17}O_3N$	283 ($M^{+\bullet}$) 190, 176, 161, 162, 148 (100) 107
c	78	203	$C_{19}H_{22}NO_3Br$	393/391 ($M^{+\bullet}$,26), 392/390 (30) 312 (22) 201/199, (30), 182 (37), 164 (100), 121 (37)
d	75	198 (decomp.)	$C_{18}H_{18}NO_3Br$	377/375 ($M^{+\bullet}$, 45), 376/374 (55), 199/201 (28), 176 (63), 148 (100), 121 (12), 91 (18)
e	72	204	$C_{19}H_{20}NO_4Cl$	363/361 ($M^{+\bullet}$; 17/49), 192 (43) 169/1 1 (62/19), 164 (100), 135 (12)
f	61	201 (decomp.)	$C_{19}H_{20}NO_4Br$	405/407 ($M^{+\bullet}$;30), 327, 326 (41), 214/212 (37), 192 (80), 164 (100), 135 (50)
g	64	187	$C_{19}H_{20}N_2O_6$	372 ($M^{+\bullet}$), 355 (26), 192 (100), 164 (70), 149 (33), 121 (22)
h	73	210	$C_{20}H_{24}NO_4Br$	423/421 ($M^{+\bullet}$, 33) 422/420 (44), 342 (35), 229/231 (56), 215/217 (18), 192 (93) 164 (100), 151/38
i	66	193	$C_{20}H_{24}N_2O_6$	388 ($M^{+\bullet}$, 3) 371 (27), 353 (19), 192 (100) 164 (55), 152 (28), 151 (24), 149 (17), 121 (16), 69 (18)
j	51	150	$C_{19}H_{22}NO_4Br$	409/407 ($M^{+\bullet}$)
k	77	208	$C_{26}H_{29}NO_4$	419 ($M^{+\bullet}$, 9), 328 (51), 227 (50), 192 (100), 164 (48), 137 (55), 91 (50)

The structures of the substancs obtained were confirmed by their mass and PMR spectra. The study of the mass-spectrometric breakdown of the amines synthesized (**4a-k**) showed that the introduction of bromine or a nitro group into the benzyl part of the molecule had no appreciable influence on the nature of breakdown, which included the cleavage of the −N−C-benzyl bond and the appearance of two directions of fragmentation with the localization of the charge on the benzene ring or on the nitrogen atom (Table 1). The retrodiene decomposition of the isoquinoline ring led to formation of an intense peak of an ion with *m/z* 164 or 148 (for (**4b, d**).

The PMR spectra of the bases (**4**) contained singlets of the protons of methoxy groups at (ppm) 3.75-3.85, of a methylenedioxy groups at 5.86-5.96 (**4b, d, g, f**), and of the methylene protons of the benzyl moiety and those at C-1 at 3.55-3.60 and 3.60-3.65, and also multiplets from the methylene protons at C-3 and C-4 and the signals of the aromatic protons of the benzyl nucleus at 6.70-7.30 ppm, the chemical shift and multiplicity of which depended on the substituents present.

We studied the action of 17 of the compounds synthesized − (**3c, i, j, *l*), (4a-k**), and (**5b, i**) on the secretion of bile.

The action of the substances on the secretion of bile was studied on rats weighing 180-220 g by a procedure described previously [4]. The substances were injected into the animals duodenally in a dose of 5 mg/kg after a control collection of bile. The results of the experiments were compared with those from control animals injected with the same volume of water.

The experiments showed that the introduction of the substances synthesized into rats caused changes of the bile-secreting processes in the directions both of enhancement and of suppression. The secretory reaction to the administration of compounds (**3c, *l*), (4a-c, e, g, h, j**) and (**5**) was expressed in a stable secretion of bile. The most significant, at $p < 0.05$, rise in the rate of secretion of bile was brought about by compounds (**4c**), (**4h**), (**4e**), and (**3c**), which, 1 h after injection, raised this index by 51.8, 43, 37.5, and 25.9%, respectively. The increase in the total volume of bile determined at the 4th hour of the experiment amounted to 23.3, 17.8, 28.5, and 11.8%, respectively. The bile-stimulating activity fell in the direction from (**4e**), (**4c**), (**4a**), (**4h**), (**4g**), (**3c**), (**4c**), (**5i**), and (**3*l***) to (**4j**), amounting to increases of 28.5-4.0%.

On injection into rats, substances (**4i**), (**4f**), and (**3i**) and the methiodide of (**5b**) exhibited inconstant effects. While some of them (**4f, i**) stimulated the rate of secretion in the first hour after administration by 6-13%, they then suppressed the choleretic reaction.

The injection of compounds (**4d**), (**4k**), and (**3j**) in individual hours of the experiment caused suppression of the intensity of bile secretion in the animals, which was 30, 24, and 40% lower than in the controls. While the falls in the total volume of bile in the experiment 4 h after the administration of compounds (**4d**) and (**4k**) were about 10 and 14.7%, compound (**3j**) caused a sharp fall in the amount of bile secreted (by 36.8%). These effects indicate a toxic action of these compounds on the exocrine function of the liver. Thus, bile-stimulating actions have been found for some of the amines investigated (**3c, *l*; 4a-c, e, g, h, j; 5i**), which gives grounds for a search for potential cholegogic agents in this series of compounds.

EXPERIMENTAL

^{1}H NMR spectra of the compounds synthesized were recorded on a Tesla BS-567 A (100 MHz) instrument in $CDCl_3$ (standard: HMDS). Mass spectra were obtained on on a MKh-1310 instrument at an energy of the ionizing radiation of 70 eV.

Preparation of the Amines (4). A solution of a substituted phenylethylamine (**1**) (0.021 mole) in 100 ml of benzene was treated with 0.02 mole of a substituted benzaldehyde (**2a-j**), and the mixture was boiled with the azeotropic distillation of water. After the benzene had been distilled off, the imine obtained was dissolved in methanol (200-300 ml) and was reduced with sodium tetrahydroborate (0.15 mole) with vigorous stirring at 0-5°C. The solvent was evaporated off, and the residue was dissolved in water and extracted with ether (or chloroform). The organic layer was washed with water and dried with sodium sulfate. After the solvent had been distilled off, the technical amine (**3**) obtained was dissolved in acetone, and the solution was acidified with conc. HCl. The precipitate of the hydrochloride of the amine (**3**) was filtered off. A mixture of this hydrochloride (0.02 mole), 50 ml of methanol, 20 ml of 30% formalin, and a few drops of conc. HCl (pH 2) was boiled under reflux for 2-4 h. The solvent was distilled off, the pH of the residue was brought to 9-10 with conc. NH_4OH, and the product was extracted with ether (chloroform). The solvent was evaporated off, the products was dissolved in acetone, and conc. HCl was added. The resulting precipitate of the hydrochloride of an amine (**4**) was filtered off. Some characteristics of the compounds obtained are given in Table 1.

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