8. G. T. Pilyugin, P. V. Prisyazhnyuk, and E. P. Opanasenko, Zh. Obschch. Khim., 44, 2256-2260 (1974).
9. J. W. Ashley, W. H. Perkin, and R. Robinson, J. Chem. Soc., 382-395 (1930).
10. S. Gabriel, Ber. Dtsch. Chem. Ges., 51, 1508 (1918).
11. H. Dahn and A. Donzel, Helv. Chim. Acta, 50, 1911-1917 (1967).

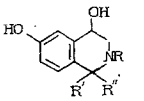
SYNTHESIS AND RADIOPROTECTANT PROPERTIES OF SOME 6-HYDROXY-1,2,3,4-TETRAHYDROISOQUINOLINES

T. V. Alpatova, A. D. Klimova,
V. I. Kulinskii, V. S. Mirzoyan,
A. T. Mirzoyan, and V. G. Yashunskii

UDC 615.31:547.831].012.1

It has previously been shown [1, 2] that the radioprotectant effects (RPE) of derivatives of 1-(3-hydroxyphenyl)-2-aminoethanol (I) are highly dependent on structural factors. It was of interest to determine the effect on the RPE of locking the aminoalkanol chain in a definite position with respect to the benzene ring in these compounds. It has quite recently been shown [3] in the case of 1-(2,5-dimethoxyphenyl)-2-aminopropanol that incorporation of the aminoalkyl chain in a cyclic structure increases adrenomimetic activity.

Cyclic derivatives of (I) include substituted 4,6-dihydroxy-1,2,3,4-tetrahydroisoquinolines, which can be obtained by reacting (I) with carbonyl compounds. We have previously [4] described the preparation of some similar compounds (II-VI). We here describe the synthesis of other derivatives of (II) (VII-XIX), and present the results of studies of the toxicity and RPE of these compounds.



II-XIX (

II: $R = R' = R'' = H$; III: $R = R' = H$, $R'' = 3\text{-}CH_3O\text{-}4\text{-}HOC_6H_3$; IV: $R = R' = H$, $R'' = 3,4,5\text{-}(CH_3O)_3C_6H_2$; V: $R = C_6H_5CH_2$, $R' = R'' = H$; VI: $R = C_6H_5CH_2$, $R' = H$, $R'' = 3,4,5\text{-}(CH_3O)_3C_6H_2$; VII: $R = C_6H_5CH_2$, $R' = H$, $R'' = CH_3$; VIII: $R = C_6H_5CH_2$, $R' = H$, $R'' = 2\text{-}HOC_6H_4$; IX: $R = C_6H_5CH_2$, $R' = H$, $R'' = 4\text{-}HOC_6H_4$; X: $R = C_6H_5CH_2$, $R' = H$, R'' = pyridyl-4; XI: $R = R' = H$, $R'' = CH_3$; XII: $R = R' = H$, $R'' = 2\text{-}HOC_6H_4$; XIII: $R = R' = H$, $R'' = 4\text{-}HOC_6H_4$; XIV: $R = R' = H$, $R'' = 4\text{-}CH_3OC_6H_4$; XV: $R = R' = H$, $R'' = 3,4\text{-}(CH_3O)_2C_6H_3$; XVI: $R = H$, $R' = R'' = CH_3$; XVII: $R = CH_3$, $R' = R'' = H$; XVIII: $R = CH_3$, $R' = H$, $R'' = 2\text{-}HOC_6H_4$; XIX: $R = CH_3$, $R' = H$, $R'' = 4\text{-}CH_3OC_6H_4$.

As in [4], starting from N-benzyl-(I) (XX) [2] and the appropriate aldehydes, there were obtained 1-methyl-(VII), 1-(2-hydroxyphenyl)-(VIII), 1-(4-hydroxyphenyl)-(IX), and 1-(4-pyridyl)-(X) derivatives of 2-benzyl-4,6-dihydroxy-1,2,3,4-tetrahydroisoquinoline. Compounds (VII-IX) were converted by debenzylation into 1-methyl-(XI), 1-(2-hydroxyphenyl)-(XII), and 1-(4-hydroxyphenyl)-(XIII)-4,6-dihydroxy-1,2,3,4-tetrahydroisoquinolines respectively. Known methods were used to prepare 1-(4-methoxyphenyl)-(XIV) [5], 1-(3,4-dimethoxyphenyl)-(XV) [5], and 1,1-dimethyl-(XVI) derivatives of (II) [6]. Condensation of N-methyl-(I) (XXI) with aldehydes afforded 2-methyl-4,6-dihydroxy-1,2,3,4-tetrahydroisoquinoline (XVII) and its 1-(2-hydroxyphenyl)-(XVIII) and 1-(4-methoxyphenyl)-(XIX) derivatives. Treatment of (VIII) with $SOCl_2$ gave 1-(2-hydroxyphenyl)-2-benzyl-4-chloro-6-hydroxy-1,2,3,4-tetrahydroisoquinoline (XXII), which was catalytically dechlorinated and debenzylated to 1-(2-hydroxyphenyl)-6-hydroxy-1,2,3,4-tetrahydroisoquinoline (XXIII), and similarly from the 2-benzyl derivative of

Institute of Biophysics, Ministry of Health of the USSR, Moscow. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 18, No. 4, pp. 444-449, April, 1984. Original article submitted April 22, 1983.

 0091-150X/84/1804-0262$08.50

TABLE 1. Mass Spectra*

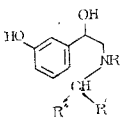
Compound	m/z (relative intensity, %)
II	166 (10), 165 (54), 164 (20), 148 (10), 147 (16), 146 (10), 137 (15), 136 (100), 135 (16), 108 (10), 107 (23), 30 (8)
XI	179 (18), 178 (22), 164 (100), 163 (6), 150 (20), 149 (10), 148 (8), 135 (20), 121 (11)
XIV	272 (24), 271 (100), 270 (50), 254 (10), 253 (24), 252 (20), 251 (18), 250 (8), 243 (16), 242 (64), 241 (24), 240 (16), 228 (12), 227 (12), 226 (28), 225 (82), 224 (41), 212 (20), 211 (33), 210 (25), 209 (16), 197 (10), 196 (28), 195 (10), 181 (26), 165 (14), 164 (76), 163 (24), 162 (10), 148 (10), 146 (28), 137 (10), 136 (12), 135 (26), 121 (20), 120 (8), 108 (8), 106 (25)
XVI	179 (8), 178 (100), 177 (6), 160 (20), 149 (16), 45 (6), 44 (12)
XVII	180 (4), 179 (70), 178 (18), 161 (6), 160 (10), 136 (60), 135 (20), 134 (6), 108 (8), 107 (16), 44 (100)
XXI	182 (3), 168 (8), 167 (27), 148 (6), 124 (10), 123 (8), 122 (6), 95 (10), 77 (7), 44 (100)
XXVII	181 (15), 163 (7), 162 (6), 148 (6), 123 (6), 122 (7), 121 (7), 59 (24), 58 (100), 44 (8), 30 (30)
XXVIII	181 (9), 180 (7), 163 (12), 150 (13), 149 (9), 148 (12), 147 (22), 122 (6), 121 (13), 120 (16), 107 (12), 95 (8), 91 (8), 77 (9), 59 (12), 58 (100), 44 (12), 42 (10), 30 (10)
XXIX	195 (8), 176 (12), 162 (28), 134 (12), 123 (8), 121 (13), 107 (14), 95 (17), 94 (8), 91 (7), 77 (21), 73 (14), 72 (100), 65 (7), 56 (10), 43 (15), 41 (10), 30 (25)
XXX	273 (12), 151 (10), 150 (98), 124 (10), 122 (12), 121 (100)

*Peaks with intensities >5% shown.

(XIV) (XXIV) there was obtained 1-(4-methoxyphenyl)-6-hydroxy-1,2,3,4-tetrahydroisoquinoline (XXV). For purposes of comparison, the structurally similar known bronchodilator trimetoxinol [7] [1-(2,3,4-trimethoxybenzyl)-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline (XXVI) was also prepared. Most of the compounds were isolated as their hydrochlorides.

In order to study the structural features and possible differences in metabolism of some derivatives of (II) as compared with (I), the behavior of some similarly-substituted pairs of cyclic (II, XI, XVI, XVII, XIV) and straight-chain (XXI, XXVII, XXVIII, XXIX, XXX) compounds under electron impact was examined.

It follows from the mass spectra of these compounds (Table 1) that in the case of the noncyclic compounds the molecular ion peaks (M^+) are of medium intensity. The highest peaks are those for ions formed by α-fission of the chain with localization of charge at the amine moiety of the molecule.



XXI, XXVII - XXX

XXI: R = R′ = R″ = H; XXVII: R = R′ = H, R″ = CH_3; XXVIII: R = CH_3, R′ = R″ = H;
XXIX: R = H, R′ = R″ = CH_3; XXX: R = R′, R″ = 4-$CH_3OC_6H_4$

From the metastable transitions and the shifts in the corresponding peaks in the spectra, the following general scheme for the breakdown of (XXI, XXVII-XXX) under electron impact may be written:

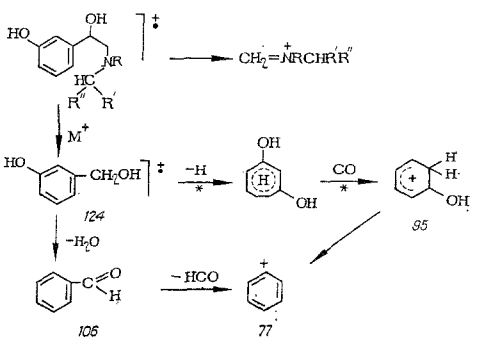
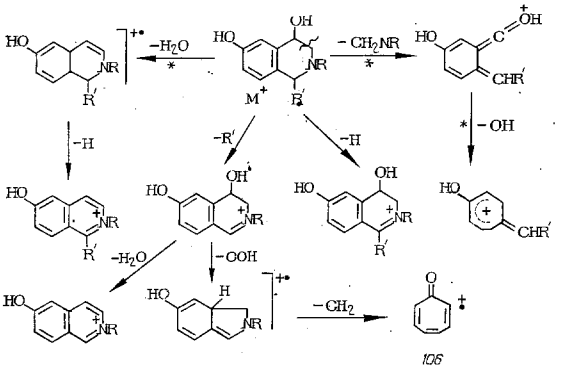


TABLE 2. Properties of Compounds (VII-XIII), (XVII-XIX), and (XXII-XXV)

Compound	Yield, %	mp, °C	Found, %				Empirical formula	Calculated, %			
			C	H	Cl	N		C	H	Cl	N
VII*	80	Indistinct mp	63,2	6,9	10,7	4,2	$C_{17}H_{19}NO_2HCl \cdot H_2O$	63,1	6,8	10,9	4,3
VIII*	88	218—20	68,6	6,0	9,0	3,8	$C_{22}H_{21}NO_3 \cdot HCl$	68,8	5,8	9,2	3,6
IX*	88	212—4	68,6	5,8	9,2	3,7	$C_{22}H_{21}NO_3 \cdot HCl$	68,8	5,8	9,2	3,6
X	36,5	110—16	75,5	6,1	—	8,8	$C_{21}H_{20}N_2O_2$	75,8	6,1	—	8,4
XI*	63	218—20	55,7	6,6	16,4	6,5	$C_{10}H_{13}NO_2 \cdot HCl$	55,7	6,5	16,5	6,5
XII	76	193—4	69,9	5,9	—	5,6	$C_{15}H_{15}NO_3$	70,0	5,9	—	5,4
XIII†	47	218—9	62,4	6,6	—	3,6	$C_{15}H_{15}NO_3 \cdot C_6H_{10}O_4$	62,5	6,3	—	3,5
XVII*	30	200—2	55,5	6,6	16,2	6,8	$C_{10}H_{13}NO_2 \cdot HCl$	55,6	6,5	16,5	6,5
XVIII*	50	Indistinct mp	57,7	6,5	10,0	4,3	$C_{16}H_{17}NO_3 \cdot HCl \cdot 1,5H_2O$	57,4	6,3	10,6	4,2
XIX*	49	150	61,9	6,5	10,3	4,2	$C_{17}H_{19}NO_3 \cdot HCl \cdot 0,5H_2O$	61,9	6,4	10,7	4,2
XXII	79	167—9	72,3	5,6	9,3	3,8	$C_{22}H_{19}NO_2 \cdot HCl$	72,2	5,5	9,7	3,8
XXIII*	79	243—5	64,7	6,7	12,7	5,0	$C_{15}H_{15}NO_2 \cdot HCl$	64,9	5,9	12,8	5,0
XXIV	60	170—3	76,2	6,4	—	4,2	$C_{22}H_{23}NO_3$	76,4	6,4	—	3,9
XXV*	44	252—3	65,7	6,4	12,1	...	$C_{16}H_{17}NO_2 \cdot HCl$	65,9	6,2	12,2	...

*Hydrochlorides.
†Adipate.

Quite intense M^+ ion peaks are also present in the spectra of the tetrahydroisoquinolines (Table 1) at high mass numbers. As in the case of their noncyclic analogs, the most characteristic feature of the mass spectra is the clearly-marked tendency to α-fission and elimination of the CH_2NR group. In this series of compounds, other routes of fragmentation of M^+ are more apparent, involving loss of a molecule of water or elimination of a proton, as in the proposed scheme of breakdown:



It will be seen that the principal fragmentation route of cyclic and straight-chain structures is α-fission of the ring or the chain.

EXPERIMENTAL CHEMISTRY

Mass spectra were obtained on an MX-1303 instrument (USSR), with direct introduction of the sample into the ion source at an ionizing voltage of 30 eV, and a temperature 50-60°C below the melting points of the compounds.

1-(3-Hydroxyphenyl)-2-aminoethanol Hydrochloride (I). A mixture of 30 g of 1-(3-hydroxyphenyl)-2-benzylaminoethanol [2] and 11 ml of conc. hydrochloric acid in 300 ml of alcohol was hydrogenated over Pd black at 55°C until hydrogen uptake ceased. The catalyst was filtered off, and the alcohol evaporated to give (I), yield 98.3%, mp 162-163.5°C (from alcohol). Literature value, mp 159°C [8].

Under the same conditions, (XI) was obtained from (VII), (XII) from (VIII), (XIII) from (IX), and (XXIII) from (XXII). Debenzylation of (X) was unsuccessful.

1-(4-Hydroxyphenyl)-2-benzyl-4,6-dihydroxy-1,2,3,4-tetrahydroisoquinoline Hydrochloride (IX). A solution of 12.15 g (0.042 mole) of 1-(3-hydroxyphenyl)-2-benzylaminoethanol and 6.1 g (0.05 mole) of p-hydroxybenzaldehyde in 150 ml of ethanol was boiled for 10 h, evaporated, the residue dissolved in ether, acidified with ethereal hydrogen chloride, and (IX) isolated. Similarly obtained were (VII-X), (XIV-XIX), and (XIV) (Table 2). The mp of (XIV) was 220-223°C, [5] 218-221°C, that of (XV) was 238-240°C, [5] 247-250°C, and of (XVI) 221-222°C, [6] 228-230°C.

TABLE 3. Toxicity and Radioprotectant Activity of 1,2,3,4-Tetrahydroisoquinolines

Compound	LD_{50}, μmoles/kg	% survival		
		control	dose, μmole/kg	
			50	500
II	>15 000	6±2,0	0±12	12±12
III	2 741	6±2,0	10±10	5±5
IV	~670	6±2,0	0±10	5±5
V	1885±247	3,8±1,4	20±13	19±10
VI	6200	6±2,0	10±10	0±6
VII	3521±56	5,6±1,3	13±6	17±7
VIII	1595±162	3,8±1,4	0±10	20±9
IX	9156±2,6	3,8±1,4	0±6	6±6
X	9550±127	5,6±1,3	25±10	25±10
XI	—	3,7±1,5	0±10	0±10
XII	6141±622	3,8±1,4	25±11	25±8
XIII	6519±556	3,8±1,4	18±8	21±7
XIV	4402±140	3,8±1,4	10±7	33±9
XV	~2 200	6±2,0	12±12	0±12
XVI	~5 565	11±4,0	10±10	20±13
XVII	~16 000	3±3,0	0±10	8±5
XVIII	4600±140	3,8±1,4	0±10[a]	0±10[b]
XIX	2600±317	3±3,0	0±10	25±11
XXI	5290±746	5,9±1,8	82±3,1[c]	
XXII	~6 800	3,8±1,4	5±5	7±5
XXIII	1584±84	3,8±1,4	10±7[d]	5±5[e]
XXV	1714±66	5,6±1,3	3±3	33±9
XXVI	1257±86	3,7±1,5	32±8	29±8[f]
XXVII	6570±59	5,9±1,8	82±8[c]	
XXVIII	400±23	5,6±1,3	0±5,6[g]	0±5,6
XXIX	3240±354	3,7±1,5	20±7,0[g]	0±10
XXX	2161±116	9,6±2,9	0±10[g]	0±10

[a]Dose 553 μmole/kg.
[b]Dose 2133 μmole/kg.
[c]cf [1].
[d]Dose 171 μmole/kg.
[e]Dose 684 μmole/kg.
[f]Dose 413 μmole/kg.
[g]cf. [2].

1-(2-Hydroxyphenyl)-2-benzyl-4-chloro-6-hydroxy-1,2,3,4-tetrahydroisoquinoline (XXII). The base (VIII) (9.7 g) was added gradually to 11 ml of $SOCl_2$, the mixture kept at ambient temperature for 2 h, and evaporated to give (XXII).

Similarly, from (XXIV) there was obtained 1-(4-methoxyphenyl)-2-benzyl-4-chloro-6-hydroxy-1,2,3,4-tetrahydroisoquinoline, which was converted without isolation, as described above, into (XXV) (Table 2).

EXPERIMENTAL BIOLOGY

Acute toxicities and RPE were studied in female mice of strains CBA and (CBA × C57Bl)F_1, aged 3-5 months. The compounds were administered in a volume of 10 ml/kg in aqueous solution subcutaneously, or in the case of insoluble compounds, as a suspension in 1% starch mucilage intraperitoneally. The LD_{50} values were determined by the Litchfield–Wilkinson–Rot method [9].

Fifteen minutes after administration of the compound (usually in two doses, 50 and 500 μmole/kg), x-irradiation was carried out in a dose of 8 Gy. The methods of irradiation and chemical dosimetry have been described [10]. Survival of the mice was determined on the 30th day following irradiation.

The results presented in Table 3* show that none of the new compounds are effective radioprotectants. They are generally of low toxicity, and display weak RPE, the percentage survival of the mice being no greater than 20-30. It is therefore evident that when derivatives of type (I) include a bicyclic tetrahydroisoquinoline structure, the RPE falls sharply,

*For comparison, Table 3 includes previously-published data for (XXI), (XXVII), and (XXX).

sometimes to zero. Low protection is also seen in trimetoxinol (XXVI), which has β-adrenomimetic activity.

Comparison of the RPE data with the mass spectra leads to the conclusion that there are no fundamental differences in behavior on electron impact between the noncyclic compounds (XXI) and (XXVII), which have high RPE, and noncyclic and cyclic analogs of low activity.

LITERATURE CITED

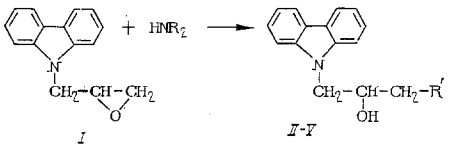
1. V. I. Kulinskii and V. G. Yashchunskii, Byull. Eksp. Biol., No. 3, 232-233 (1979).
2. T. V. Alpatova, V. I. Kulinskii, and V. G. Yashchunskii, Khim.-farm. Zh., No. 8, 922-925 (1983).
3. R. M. De Marinis, W. M. Bryan, D. H. Shan, et al., J. Med. Chem., 24, 1432-1437 (1981).
4. T. V. Alpatova and V. G. Yashchunskii, Khim. Geterotsikl. Soedin., 1084-1087 (1981).
5. S. N. Quessy and L. R. Williams, Aust. J. Chem., 32, 1317-1329 (1979).
6. T. Kametani, K. Fukumoto, H. Agui, et al., J. Chem. Soc. (C), 112-118 (1968).
7. E. Yamato, M. Hirakura, and S. Sugasawa, Tetrahedron, 22, Suppl. 8, Pt. 1, 129 (1966).
8. M. L. Belen'kii, Elements of the Quantitative Measurement of Pharmacological Effects [in Russian], 2nd edn., Leningrad (1963), pp. 81-107.
9. V. I. Kulinskii, Radiobiologiya, No. 2, 178-182 (1978).
10. A. D'Amico, L. Bertolini, and C. Monreale, Chim. Indust., 38, 93-98 (1965).

SYNTHESIS AND PHARMACOLOGICAL ACTIVITY OF N-SUBSTITUTED DERIVATIVES OF 9-(3-AMINO-2-HYDROXYPROPYL)CARBAZOLES

D. D. Mysyk, A. T. Dolzhenko, R. E. Kononova, O. V. Charfas, and V. F. Galat

UDC 615.214.012.1.038

A new psychotropic agent, a derivative of 9-propylcarbazole with a 3,5-dimethylpiperazinyl radical in the propyl substituent, has been described in [1]. To study the pharmacological activity of carbazole derivatives, we synthesized N-substituted derivatives of 9-(3-amino-2-hydroxypropyl)carbazoles (II-V) according to the following scheme:



II: $R' = N(C_2H_5)_2$; III: $R' = N(CH_2)_5$; IV: $R' = N(CH_2)_6$; V: $R' = N(CH_2)_4O$.

Diethylamine, piperidine, hexamethylenediimine, and morpholine are added to 9-(2,3-epoxypropyl)carbazole (I), when the components are heated in boiling ethanol. The oxirane ring is opened with cleavage of the C–O bond at the primary atom, which corresponds to the direction of opening of the oxirane ring in the nucleophilic addition of the carbazolyl anion to I [2] and was confirmed by the study of compounds II-V by NMR spectroscopy.

To confirm the assignment of compounds II-V to the class of secondary alcohols, we obtained their PMR spectra in tetrachloromethane and dimethyl sulfoxide (Table 1). As the result of rapid chemical exchange in tetrachloromethane, the hydroxyl proton signal of compounds II-V is represented by a somewhat broadened singlet. With increase in temperature, it is shifted to the stronger field region, so that its position could be found in the PMR spectrum. The chemical exchange is appreciably slowed down in dimethyl sulfoxide: The hydroxyl proton signal of compounds II-V is represented by a broadened doublet, which is shifted by more than 1 ppm to a weak field region, compared with the spectrum in tetrachloromethane, and is characteristic of secondary alcohols [3].

Donetsk Polytechnical Institute. M. Gorkii Donetsk Medicinal Institute.

Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 18, No. 4, pp. 449-451, April, 1984. Original article submitted February 23, 1983.

0091-150X/84/1804-0266$08.50