8. B. Z. Gorbunov and Yu. I. Naberukhin, Zh. Struk. Khim., 15, 8 (1974).
9. R. S. Mulliken, J. Am. Chem. Soc., 91, 1237 (1969).
10. D. G. Lister and J. K. Tyler, Chem. Commun., 152 (1966).
11. R. Stewart and M. G. Harris, J. Org. Chem., 43, 3123 (1978).
12. A. Weisstuch, P. Neidig, and A. C. Testa, J. Luminescence., 10, 137 (1975).
13. A. R. Katritzky (editor), Physical Methods in the Chemistry of Heterocyclic Compounds, Academic Press (1963).
14. The Chemist's Handbook [in Russian], Vol. 3, Khimiya, Moscow (1964).
15. O. A. Osipov, V. I. Minkin, and A. D. Garnovskii, Handbook of Dipole Moments [in Russian], Vysshaya Shkola, Moscow (1971).

UTILIZATION OF A BENZYL PROTECTIVE GROUP IN THE SYNTHESIS OF TETRAHYDROISOQUINOLINE DERIVATIVES

T. V. Alpatova and V. G. Yashunskii

UDC 547.833.3.6.9.07

The corresponding N-benzyl-1,2,3,4-tetrahydroisoquinolines, the debenzylation of which is realized by hydrogenation in the presence of Pd black, were synthesized by the reaction of 1-(3-hydroxyphenyl)-2-benzylaminoethanol with aldehydes.

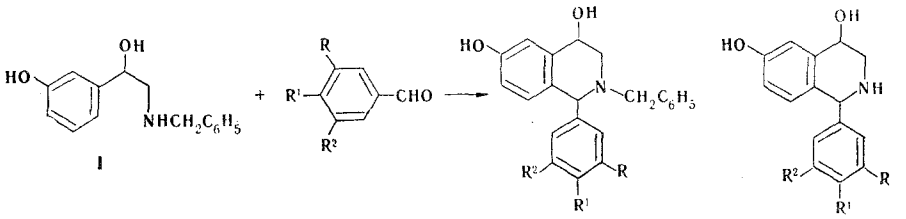
The modification of the Pictet—Spengler reaction proposed by Kametani and Fukumoto [1] has proved to be a convenient method for the synthesis of hydroxy-containing derivatives of tetrahydroisoquinoline that are of interest as potential biologically active and medicinal substances. However, in a number of cases, particularly when primary hydroxyphenylethylamines are used as the starting substances, the yields of the desired products are low because of the necessity for thorough purification to remove significant amounts of impurities. To avoid this, it was recently proposed [2] that the intermediates, viz., the Schiff bases of the hydroxyphenylethylamines with carbonyl compounds, be isolated prior to cyclization; however, this cannot always be accomplished, and this method does not always give positive results.

The utilization of a benzyl group to protect the amino group in the starting hydroxyphenylethylamine, which can be easily removed after the cyclization step, may serve as one of the possible ways to simplify this reaction. Thus the corresponding 1-aryl-2-benzyl-1,2,3,4-tetrahydroisoquinoline-4,6-diones (IIa-c) were synthesized by the reaction of 1-(3-hydroxyphenyl)-2-benzylaminoethanol (I) with vanillin, 3,4,5-trimethoxybenzaldehyde, and 4-dimethylaminobenzaldehyde.

The debenzylation of IIa-c was carried out by hydrogenation over palladium black without pressure at room temperature in aqueous alcohol in, where necessary, an acidic or alkaline medium.

Institute of Biophysics, Ministry of Public Health of the USSR, Moscow 123182. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 8, pp. 1084-1087, August, 1981. Original article submitted September 15, 1980.

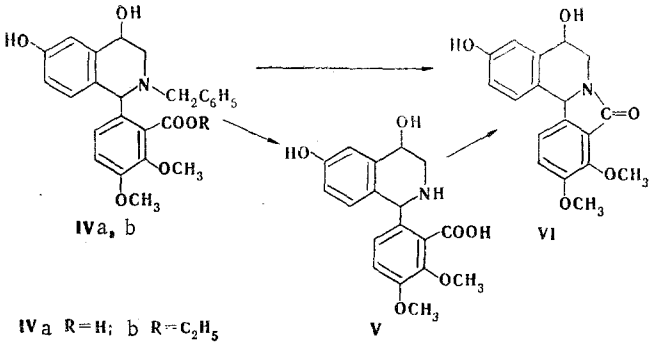
0009-3122/81/1708-0804$07.50



II, III a $R=CH_3O$, $R^1=HO$, $R^2=H$; b $R=R^1=R^2=CH_3O$; c $R=R^2=H$, $R^1=N(CH_3)_2$

The reaction of I with opianic acid proceeds smoothly and gives tetrahydroisoquinoline IVa. When we used the unsubstituted amine, we were unable to isolate an individual substance from the reaction mixture.

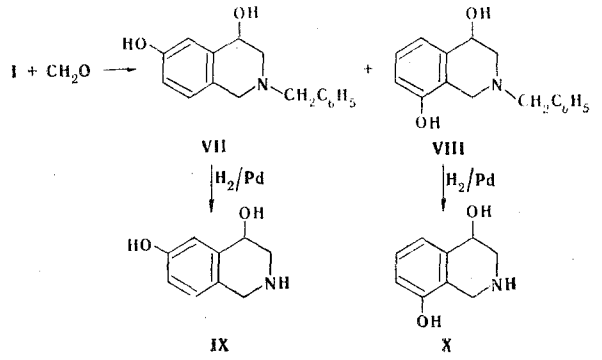
Lactam VI was obtained instead of the expected acid V in the debenzylation of acid IVa in an aqueous alcohol medium. Removal of the benzyl protective group by catalytic hydrogenation in the presence of sodium bicarbonate led to acid V, which was converted to lactam VI by heating with hydrochloric acid. The formation of a lactam was also observed in the catalytic debenzylation of the hydrochloride of ethyl ester IVb, which was obtained by condensation of amine I with ethyl opianate or by esterification of acid IVa in the presence of dicyclohexylcarbodiimide.



IVa $R=H$; b $R=C_2H_5$

The UV spectrum of VI differs substantially from the spectrum of starting acid IVa: instead of the maximum at 285 nm, one observes three absorption maxima at 278, 288, and 303 nm; this can be explained by the greater planarity of resulting lactam VI as compared with IVa. The IR spectrum of lactam contains an intense absorption band of a carbonyl group at 1668 cm^{-1}, which differs appreciably from the analogous bands of acid IVa (1610 cm^{-1}), which has a betaine structure, and the hydrochloride of IVa (1710 cm^{-1}). The ease of formation of a lactam ring in tetrahydroisoquinolines was previously observed in the reaction of 3-hydroxyphenylethylamine with levulinic or ketoglutaric acid [3].

As a consequence of the low solubility of lactam VI in organic solvents, attempts to reduce it by means of diborane and lithium aluminum hydride were unsuccessful.



In the case of the reaction with formaldehyde we demonstrated that benzylated amine I also reacts smoothly with aliphatic aldehydes. In this case we isolated two isomers that are products of ortho and para cyclization (with respect to the phenolic hydroxy group), via., 2-benzyl-1,2,3,4-tetrahydroisoquinoline-4,6-diol (VII) and 2-benzyl-1,2,3,4-tetrahy-

TABLE 1. Properties of the Compounds Obtained

Compound	mp*, °C	R_f (system)	Found, %				Empirical formula †	Calculated, %				Yield, %
			C	H	Cl	N		C	H	Cl	N	
IIb	222—224	0,85 (C)	64,8	6,2	7,4		$C_{25}H_{27}NO_5 \cdot HCl \cdot 1/3H_2O$	64,7	6,2	7,64	7,3	65
IIc	182—185	0,76 (D)	75,3	7,5		7,0	$C_{24}H_{26}N_2O_2 \cdot 1/2H_2O$	75,2	7,1		3,8	33
IIIa	215—217	0,34 (C)	62,4	6,2		3,8	$C_{16}H_{17}NO_4 \cdot 1/2C_6H_{10}O_4 \times \times 1/4H_2O$	62,6	6,2			50
IIIb	237—238		58,0	6,0	9,2		$C_{18}H_{21}NO_5 \cdot HCl \cdot 1/3H_2O$	57,8	6,1	9,5		60
IIIc	209—211	0,18 (D)	55,9	6,6	19,4	7,7	$C_{17}H_{19}N_2O_2 \cdot 2HCl \cdot 1/2H_2O$	55,7	6,3	19,4	7,6	45
IVa	230—232	0,63 (B)	68,7	5,8		3,4	$C_{25}H_{25}NO_6$	68,9	5,8		3,2	69
IVb	182—184		69,5	6,5		3,1	$C_{27}H_{29}NO_6$	70,0	6,3		3,0	25
V	210—211	0,34 (B)	61,1	5,9			$C_{18}H_{19}NO_6 \cdot 1/2H_2O$	61,0	5,7			71
VI	214—216	0,93 (B)	66,2	5,3		4,4	$C_{18}H_{17}NO_5$	66,0	5,2		4,3	78
VII	208—209	0,60 (E)	65,7	6,4	11,9		$C_{16}H_{17}NO_2 \cdot HCl$	65,9	6,2	12,1	4,8	30
VIII	213—215	0,69 (E)	65,6	6,4	12,1	5,0	$C_{16}H_{17}NO_2 \cdot HCl$	65,9	6,2	12,1	4,8	35
IX	208—210	0,44 (A)	53,8	5,9	17,8	7,1	$C_9H_{11}NO_2 \cdot HCl$	53,6	6,0	17,6	6,9	69
X	219—220	0,51 (A)	53,9	5,9	17,6	7,1	$C_9H_{11}NO_2 \cdot HCl$	53,6	6,0	17,6	6,9	87

*Compounds IIb and VII-X were obtained in the form of the hydrochlorides, IIIc was obtained in the form of the dihydrochloride, and IIIa was obtained in the form of the adipate. †Compound IIb was crystallized from aqueous methanol, IIc was crystallized from propanol, IIIb was crystallized from alcohol—ether, and IIIa, c, IVa, and VII-X were crystallized from absolute ethanol.

droisoquinoline-4,8-diol (VIII). In analogy with the data in [4], the isomers were identified on the basis of a comparison of their UV spectra with the spectra of 3,4-dimethylphenol (λ_{max} 281 nm) and 2,3-dimethylphenol (λ_{max} 275 nm). The spectra of VII and VIII contain absorption maxima at 284 (log ε 3.24) and 280 nm (log ε 3.41), respectively.

By removal of the benzyl protective group in an acidic medium over Pd black from VII and VIII we obtained tetrahydroisoquinolines IX and X, the structures of which were confirmed by the PMR spectra and a comparison of their constants with recently published data for these compounds, which were synthesized directly from 1-(3-hydroxyphenyl)-2-aminoethanol and formaldehyde [2].

EXPERIMENTAL

The purity of the compounds obtained was monitored on Silufol UV-254 plates in the following systems: ethanol—water—concentrated ammonium hydroxide (24:9:1) (system A), ethanol—chloroform—water—concentrated ammonium hydroxide (20:16:4:1) (system B), ethyl acetate—methanol—concentrated ammonium hydroxide (17:2:1) (system C), chloroform—acetone—concentrated ammonium hydroxide (17:10:1) (system D), and n-butanol—acetic acid—water (5:4:1) (system E). The IR spectra of KBr pellets of the compounds were recorded with a Pye-Unicam SP 1100 spectrometer. The UV spectra of solutions of the compounds in alcohol were recorded with a Shimadzu spectrophotometer in a quartz cuvette (l = 1 cm). The PMR spectra of solutions of the compounds in D_2O were recorded with a Varian-100 spectrometer with hexamethyldisiloxane as the external standard.

1-Aryl-2-benzyl-1,2,3,4-tetrahydroisoquinoline-4,6-diols. A solution of 0.01 mole of I and 0.01 mole of the corresponding aldehyde in 50 ml of absolute ethanol was refluxed for 6 h, after which the solution was cooled, and IIc and IVa precipitated. In the case of IIa, b the mixtures were evaporated to dryness, and the residue was treated with ether to give IIa (R_f 0.74 in system D), which was used without purification in the debenzylation step; IIb was isolated in the form of the hydrochloride by treatment of the residue with alcoholic HCl. Data on IIa-c and IVa are presented in Table 1.

Ethyl 6-(4,6-Dihydroxy-1,2,3,4-tetrahydroisoquinolin-1-yl)-2,3-dimethoxybenzoate (IVb). A solution of 4.86 g (0.02 mole) of I and 4.76 g (0.02 mole) of ethyl opianate in 60 ml of ethanol was refluxed for 8 h, after which it was evaporated to dryness, and ether was added.

The mixture was filtered to remove 2 g of the insoluble precipitate of acid IVa, and ethanol saturated with HCl was added to the ether solution. The resulting precipitate was removed by filtration, washed with ether, and dissolved in water. The aqueous solution was treated with a dilute solution of ammonium hydroxide, ester IVb was removed by filtration and purified with a column filled with L 40/100 μ silica gel (elution with ethyl acetate) to give pure ester IVb. IR spectrum: 1730 cm^{-1} (C=O).

2-Benzyl-1,2,3,4-tetrahydroisoquinoline-4,6-diol (VII) and 2-Benzyl-1,2,3,4-tetrahydroisoquinoline-4,8-diol (VIII). A 3.2-ml sample of a 33% solution of formaldehyde was added to a suspension of 8.9 g (36.7 mmole) of I in 12 ml of absolute ethanol, and the mixture was maintained at room temperature for 48 h. Compound VIII was removed by filtration and dissolved in absolute ethanol. An ether solution of HCl was added to the ethanol solution to isolate the hydrochloride of VIII. The filtrate was evaporated to dryness, and the residue was dissolved in chloroform and chromatographed with a column filled with L 40/100 μ silica gel [elution with chloroform–isopropyl alcohol (2:1)] to give VII, which, like VIII, was converted to the hydrochloride. Data on VII and VIII are presented in Table 1.

Debenzylation of N-Benzyl-1,2,3,4-tetrahydroisoquinolines. A solution of 0.01 mole of IIa, c in 150 ml of methanol was hydrogenated over Pd black until hydrogen absorption ceased, after which the catalyst was removed by filtration, and the filtrate was evaporated to dryness. 1-(3-Methoxy-4-hydroxyphenyl)-1,2,3,4-tetrahydroisoquinoline-4,6-diol (IIIa) was isolated in the form of the adipate by treatment of a solution of the residue in ethanol with adipic acid. 1-(4-Dimethylaminophenyl)-1,2,3,4-tetrahydroisoquinoline-4,6-diol (IIIc) was obtained in the form of the dihydrochloride by the action of an ether solution of HCl on a solution of the residue in ethanol. The hydrochlorides of IIb, VII, VIII, and IVa were similarly debenzylated by the addition of an equimolar amount of concentrated HCl to give the hydrochlorides of, respectively, 1-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydroisoquinoline-4,6-diol (IIIb), 1,2,3,4-tetrahydroisoquinoline-4,6-diol (IX), 1,2,3,4-tetrahydroisoquinoline-4,8-diol (X) and the lactam (VI) of 6-(4,6-dihydroxy-1,2,3,4-tetrahydroisoquinolin-1-yl)-2,3-dimethoxybenzoic acid. PMR spectrum of IX: 7.47 (d, $J_{7,8}$ = 7.6 Hz, 7-H), 7.22 (d, $J_{7,8}$ = 7.6 Hz, 8-H), 7.27 ($J_{5,7}$ = 2 Hz, 5-H), 5.26 (4-H), 4.71 (J_{gem} = 16.5 Hz, 1-H), 4.49 (J_{gem} = 16.5 Hz, 1-H), and 3.76 ppm ($J_{3,4}$ = 4 Hz, J_{gem} = 12.5 Hz, 3-H). PMR spectrum of X: 7.55 (t, $J_{6,7}$ = 7.6 Hz, 6-H), 7.28 (d, $J_{6,7}$ = 7.6 Hz, 7-H), 7.17 (d, $J_{5,6}$ = 7.6 Hz, 5-H), 5.25 (4-H), 4.65 (d, J_{gem} = 17 Hz, 1-H), 4.38 (d, J_{gem} = 17 Hz, 1-H), 3.85 (q, $J_{3,4}$ = 3.75 Hz, J_{gem} = 12 Hz, 3-H), and 3.68 ppm (q, $J_{3,4}$ = 3.0 Hz, J_{gem} = 12 Hz, 3-H).

A solution of 0.03 g of sodium bicarbonate in 5 ml of water was added to a suspension of 0.35 g (0.008 mole) of acid IVa in 100 ml of methanol, and hydrogenation was carried out over Pd black until hydrogen absorption ceased. The catalyst was removed by filtration, the reaction mixture was evaporated to a volume of 5 ml, and the concentrate was acidified to pH 6 with dilute HCl to give 6-(4,6-dihydroxy-1,2,3,4-tetrahydroisoquinolin-1-yl)-2,3-dimethoxybenzoic acid (V).

LITERATURE CITED

1. T. Kametani and K. Fukumoto, Heterocycles, 3, 311 (1975).
2. S. N. Quessy and L. R. Williams, Aust. J. Chem., 32, 1317 (1979).
3. T. Kametani, K. Kigasawa, M. Hiiragi, H. Ishimaru, and S. Haga, J. Heterocycl. Chem., 11, 1023 (1974).
4. T. Kametani, F. Satoh, H. Agui, K. Ueki, K. Kigasawa, M. Hiiragi, H. Ishimaru, and S. Horie, Chem. Pharm. Bull., 18, 1161 (1970).