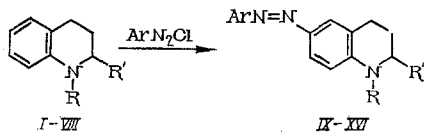
SYNTHESIS AND BIOLOGICAL ACTIVITY OF 6-ARYLAZO DERIVATIVES OF SUBSTITUTED 1,2,3,4-TETRAHYDRO-QUINOLINE

V. F. Vasil'eva, R. A. Zagrutdinova,
M. N. Shchukina, G. N. Pershin,
and T. N. Zykova

UDC 615.281.221.1:547.547.831.6

Arylazo derivatives of substituted tetrahydronaphthalene proved to be active with respect to inducers of $H_{37}Rv$ tuberculosis and leprosy [1]. It appeared of interest to synthesize and study the biological activity of arylazo derivatives of 1,2,3,4-tetrahydroquinoline as aza analogs of tetrahydronaphthalene. For this purpose the 1-alkyl- (from C_1 to C_4) and 1-benzyl-1,2,3,4-tetrahydroquinolines (I-V) were synthesized by the reduction of the iodide or bromide salts of the appropriate 1-substituted quinoline with anhydrous formic acid [2]; 1-(γ-dimethylaminopropyl)-2-benzyl-1,2,3,4-tetrahydroquinoline (VI) was synthesized by the reduction of 2-benzylquinoline with metallic sodium in butanol to the corresponding tetrahydro derivative (VII) and subsequent condensation with γ-dimethylaminopropyl chloride. 1-Benzoyl-2-benzyl-1,2,3,4-tetrahydroquinoline (VIII) was prepared from VII. Compounds I-VIII were subjected to the azo-coupling reaction previously carried out in the case of 1-methyl-1,2,3,4-tetrahydroquinoline and occurring at position 6 of the ring [3].



I-VIII IX-XVI

The azo coupling was carried out with phenyldiazonium, p-chlorophenyldiazonium, and p-nitrophenyldiazonium salts in acidic aqueous solutions. In all cases the appropriate 6-arylazo derivatives IX-XVI were isolated (see Table 1). In the reaction of VIII with phenyldiazonium chloride 93% of unchanged starting material was isolated. This is in keeping with the literature data that other electrophilic substitution reactions were unsuccessful in the case of acyl derivatives of 1,2,3,4-tetrahydroquinoline [4, 5].

All the synthesized arylazo derivatives were brightly colored crystalline substances with sharp melting points. 6-Phenylazo-1-(γ-dimethylaminopropyl)-2-benzyl-1,2,3,4-tetrahydroquinoline (XV) in contrast to the other compounds was successfully isolated only as a hydrochloride.

The bacteriostatic activity of the prepared arylazo compounds with respect to the $H_{37}Rv$ strain of tubercle bacillus was studied in Soton medium in which Asparate replaced casein hydrolyzate. An expressed tuberculostatic activity is observed for compounds XIV, XV, and XVI. Their activity falls sharply on adding 10% of blood serum to the medium (horse serum was used; see Table 1). The hydrochloride of XV was studied in experimental tuberculosis in white mice and proved to be inactive.

EXPERIMENTAL

2-Benzyl-1,2,3,4-tetrahydroquinoline (VII). To a solution of 7.9 g of 2-benzylquinoline [6] in 150 ml of anhydrous butyl alcohol 12.5 g of metallic sodium was added gradually. At the end of the addition the

S. Ordzhonikidze All-Union Pharmaceutical Chemistry Scientific-Research Institute, Moscow. Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 7, No. 9, pp. 19-21, September, 1973. Original article submitted August 18, 1972.

TABLE 1. 6-Arylazo Derivatives of Substituted 1,2,3,4-Tetrahydroquinolines

Compound	R	R′	Ar	Yield (%)	Mp (deg)[1]	Found (%)			Empirical formula	Calc. (%)			Tuberculostatic activity for $H_{37}Rv$ strain, Soton med. (μg/ml)	
						C	H	Cl		C	H	Cl	without serum	with serum
IX	CH_3	H	$n = ClC_6H_4$	57,6	95—97	67,67	5,52	12,51	$C_{16}H_{16}ClN_3$	67,24	5,64	12,40	125	>1000
X	C_2H_5	H	$n = ClC_6H_4$	45,2	66,5—68	67,90	6,02	11,44	$C_{17}H_{18}ClN_3$	68,10	6,05	11,82	250	500
XI	C_3H_7	H	$n = ClC_6H_4$	37,6	54,5—55	68,80	6,21	11,21	$C_{18}H_{20}ClN_3$	68,88	6,42	11,29	250	1000
XII	C_4H_9	H	$n = ClC_6H_4$	53,6	87—90	69,29	6,71	10,68	$C_{19}H_{22}ClN_3$	69,60	6,76	10,81	1000	>1000
XIII	$C_6H_5CH_2$	H	$n = ClC_6H_4$	56,3	113—5	73,43	5,62	9,64	$C_{22}H_{20}ClN_3$	73,01	5,57	9,79	250	1000
XIV	H	$C_6H_5CH_2$	C_6H_5	57,5	116—8	81,02	6,61	—	$C_{23}H_{21}N_3^2$	80,70	6,46	—	16	1000
XV	$(CH_3)_2N(CH_2)_3$	$C_6H_5CH_2$	C_6H_5	—	196	72,41	7,38	7,31	$C_{27}H_{33}N_4 \cdot HCl$	72,21	7,40	7,89	0,5—0,12	125—30
XVI	$(CH_3)_2N(CH_2)_3$	$C_6H_5CH_2$	$n = NO_2C_6H_4$	60,3	107—110	70,49	6,64	—	$C_{27}H_{31}N_5O_3^3$	70,87	6,82	—	4	250

[1]Compounds IX and XIII-XVI were crystallized from absolute alcohol, X was crystallized from rectified spirit, XI from methanol, and XII from hexane.

[2]Found %: N 12.70. Calculated %: N 12.83.

[3]Found %: N 15.26. Calculated %: N 15.30.

mixture was heated, and a further 100 ml of butyl alcohol was run in to complete the solution of the sodium. The butyl alcohol was distilled off with steam, the aqueous residue was extracted with ether, and after drying the extract with magnesium sulfate distillation yielded 6.9 g (85.5%) of VII, bp 165-167° (0.4 mm). Found, %: C 85.60; H 7.90; N 6.11. $C_{16}H_{17}N$. Calculated, %: C 86.05; H 7.67; N 6.27.

Hydrochloride. This was prepared by the addition of an ethereal solution of hydrogen chloride to a solution of VII in absolute ether and had mp 188-193°C (decomp., in a sealed capillary; from absolute alcohol). Found, %: C 73.83; H 6.79; Cl 13.69. $C_{16}H_{17}N \cdot HCl$. Calculated, %: C 73.97; H 6.98; Cl 13.65.

1-(γ-Dimethylaminopropyl)-2-benzyl-1,2,3,4-Tetrahydroquinoline (VI). A solution of 9 g of VII in 5 ml of absolute toluene was added to a suspension of an equimolar quantity of sodamide in 20 ml of toluene and heated at 80-100° for 1.5 h. The reaction mixture was cooled somewhat, and a solution of 9.8 g of γ-dimethylaminopropyl chloride in 10 ml of absolute toluene was added, the mixture was heated at 125° with stirring for 22 h, and then poured into water. The toluene layer was treated wtih dilute hydrochloric acid, and the hydrochloric acid layer was separated and cooled with ice. During this the hydrochloride of the starting material VII precipitated and was filtered off. The weight of dry substance was 1.8 g and the mp was 187-193° (decomp., in a sealed capillary tube). The hydrochloric acid mother liquor was basified with 20% sodium hydroxide solution and extracted with ether. The extract was dried and distilled. This gave 5.9 g of VI with bp 171-173° (0.4 mm), n_D^{25} 1.5800. The yield was 58% taking into account the recovered VII. Found, %: C 81.87; H 9.02; N 9.16. $C_{21}H_{28}N_2$. Calculated, %: C 81.76; H 9.15; N 9.08.

Dipicrate. This was prepared by adding an ethereal solution of picric acid to VI in ether and had mp 152.5-153° (from absolute alcohol). Found, %: C 51.70; H 4.48; N 14.85. $C_{21}H_{28}N_2 \cdot 2C_6H_2N_2O_7$. Calculated, %: C 51.69; H 4.47; N 14.61.

1-Benzoyl-2-benzyl-1,2,3,4-tetrahydroquinoline (VIII). To a solution of 2 g of VII in 5 ml of anhydrous pyridine 2 ml of benzoyl chloride was added with stirring, and the mixture was heated on a water bath for 10 min, cooled, and poured into dilute hydrochloric acid. The precipitate was washed with water and recrystallized from absolute alcohol. This gave 2.4 g (82.3%) of VIII with mp 123-124°. Found, %: C 83.94; H 6.48; N 4.25. $C_{23}H_{21}NO$. Calculated, %: C 84.37; H 6.46; N 4.27.

6-(p-Chlorophenylazo)-1-alkyl(or benzyl)-1,2,3,4-tetrahydroquinolines (IX-XIII). The diazo solution prepared from 0.01 mole of p-chloroaniline in 15 ml of hydrochloric acid (2:1) and 0.01 mole of sodium nitrite in 5 ml of water was added dropwise at 0° to 0.01 mole of I-V dis-

solved in a minimum quantity of hydrochloric acid (1:1).* The mixture was stirred at 0-5° for 3 h, sodium chloride was added,† and the mixture was left over night in a refrigerator. The dark-colored precipitate was filtered off, suspended in a small quantity of water, neutralized with ammonia solution or sodium hydroxide, and extracted with ether. The dried extract was evaporated in vacuum and on cooling and treatment with a small quantity of hexane or alcohol gave XI and XIII. For the isolation of IX, X, and XII the precipitate obtained on salting out was dried, dissolved in the minimum quantity of absolute alcohol; the solution was neutralized with an alcoholic solution of sodium hydroxide, and after separating the sodium chloride evaporated in vacuum.

6-Phenylazo-2-benzyl-1,2,3,4-tetrahydroquinoline (XIV). A solution of phenyldiazonium chloride prepared from 0.85 g of aniline, 2.5 ml of concentrated hydrochloric acid, 15 ml of water, and 0.6 g of sodium nitrite was added dropwise to 2 g of VII in 70 ml of 50% alcohol while stirring at 0°. The stirring and cooling was continued for 3 h, and the mixture was left in the refrigerator until the following day. The precipitate obtained was treated analogously as for the preparation of XIII. The yield was 1.69 g of XIV.

6-Phenylazo-1-(λ-dimethylaminopropyl)-2-benzyl-1,2,3,4-tetrahydroquinoline (XV) Hydrochloride. The reaction of VI with phenyldiazonium chloride was carried out analogously to the preparation of XIII. The dark cerise-colored precipitate obtained during this was filtered off and ground in a mortar with dilute ammonia solution (1:3). The oily substance was dried in a desiccator and recrystallized from absolute alcohol.

6-(p-Nitrophenylazo)-1-(γ-dimethylaminopropyl)-2-benzyl-1,2,3,4-tetrahydroquinoline (XVI). This was prepared from VI and p-nitrophenyldiazonium chloride analogously to XIII. Chloroform was used for the extraction of the reaction product. From 1.26 g of VI in 5 ml of hydrochloric acid (1:1) and the diazo solution prepared from 0.56 g of p-nitroaniline in 6 ml of hydrochloric acid (2:1) and 0.28 g of sodium nitrite in 3 ml of water was obtained 1.12 g of XVI.

LITERATURE CITED

1. L. M. Werbel, E. F. Elslager, and M. W. Fischer, J. Med. Chem., 11, 411 (1968).
2. A. N. Kost and L. G. Yudin, Zh. Obshch. Khim., 26, 1720 (1956).
3. J. Braun and J. Seeman, Ber. Dtsch. Chem. Ges., 56, 2161 (1923).
4. A. N. Kost, A. K. Sheinkman, and A. N. Prilepskaya, Khim. Geterotsikl. Soedin., 248 (1967).
5. H. de Diesbach, A. Pugin, F. Morard et al., Helv. Chim. Acta, 35, 2322 (1952).
6. W. Borsche and O. Vorbach, Justus Liebigs Ann. Chem., 537, 22 (1938).

*In the case of V a suspension in 5% hydrochloric acid was prepared.
†In the case of V sodium chloride was not added.