DIHYDRO-1,2-DIAZAPHENAZINE DERIVATIVES

G. S. Predvoditeleva, T. V. Kartseva,
T. N. Zykova, M. N. Shchukina,
and G. N. Pershin

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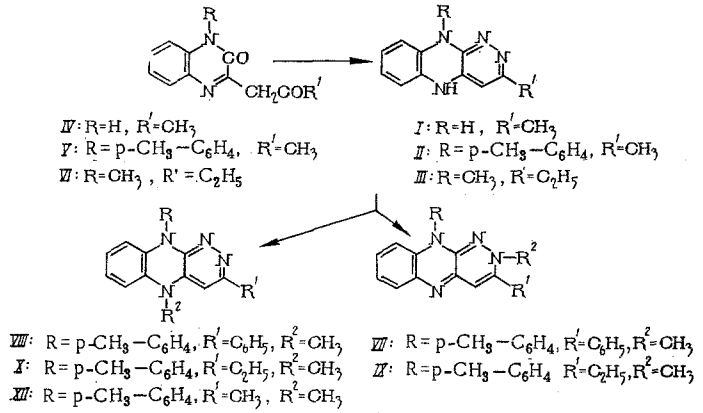
In our previous communication [1] we reported the synthesis of a series of dihydro-1,2-diazophenazine (pyridazino[3,4-b]quinoxaline) derivatives carrying various substituents in positions 2, 3, 5, and 10. The compounds obtained had been screened for their bacteriostatic action against Mycobacterium tuberculosis, and in some cases marked activity in vitro had been observed. It may be noted that the most interesting of these compounds were those carrying a methyl or p-tolyl group in position 10, and that the activity of 3-phenyl derivatives was enhanced by replacing the phenyl group by ethyl. Methylation of 10-methyl-3-phenyldihydro-1,2-diazaphenazine produced a significant rise in activity, provided the entering methyl group went into the 2 position of the system; whereas if the molecule underwent methylation at the 5 position instead, then the resulting product had the same activity as the original unmethylated compound.

Guided by these data, we have now made an attempt to increase the activity of dihydrodiazaphenazine derivatives by replacing the ethyl group in 3-ethyl derivatives by methyl, by introducing a methyl group in the 10 position, and by methylating the active 10-tolyl derivatives described in our previous paper [1].

Accordingly, the following compounds: 3-methyl- (I), 3-methyl-10-p-tolyl- (II), and 3-ethyl-10-methyldihydro-1,2-diazaphenazine (III) have now been prepared, using the method previously developed, viz., by condensing o-phenylenediamine [for (I)] or its appropriate mono-N-substituted derivative [p-tolyl for (II), methyl for (III)] with an ester of the appropriate acyl-[acetyl for (I) and (II), propionyl for (III)]-pyruvic acid, followed by the interaction of the resulting products, 3-acetylmethyl- (IV), 3-acetylmethyl-1-p-tolyl- (V), and 3-propionylmethyl-1-methyl- 1,2-dihydro-2-quinoxalone (VI), respectively, with hydrazine hydrate.



Treatment with methyl iodide of 3-phenyl- and 3-ethyl- (described in [1]), as well of as 3-methyl-10-p-tolyldihydro-1,2-diazaphenazine (II) (described in the present communication), has given rise in each case to a mixture of methylation products, and thin-layer chromatography on aluminum oxide has revealed the presence of three components in each such mixture. On a basis of earlier experience [1], and by analogy with the compounds then described, it is possible to put forward the following structures for the individual compounds actually isolated from these mixtures: 2-methyl-3-phenyl- (VII), 5-methyl-3-phenyl- (VIII),

S. Ordzhonikidze All-Union Pharmaceutical Chemistry Scientific-Research Institute, Moscow. Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 6, No. 10, pp. 3-5, October, 1972. Original article submitted July 13, 1971.

TABLE 1. Dihydro-1,2-Diazaphenazine Derivatives

Compound	Mp (°C)[1]	R_f[2]	Found (%)			Empirical formula	Calculated (%)			Tuberculostatic action (in μg/ml)	
										strain: H-37 Rv	
			C	H	N		C	H	N	in absence of serum	in presence of serum
I	308—10		66,22	5,18	28,53	$C_{11}H_{10}N_4$	66,60	5,09	28,31	60	>1000
II	256—8	0,2 (A)	74,70	5,45	19,37	$C_{18}H_{16}N_4$	74,98	5,59	19,44	100	>100
III	146—8	0,443 (B)	68,98	6,34	24,68	$C_{13}H_{14}N_4$	69,00	6,24	24,76	8	60
VII	126—8	0,535 (A)	72,04	5,48	14,96	$C_{24}H_{20}N_4$	72,20	5,51	15,40	4	60
VIII	160—1,5	0,677 (A)	78,80	5,58	15,53	$C_{24}H_{20}N_4$	79,20	5,51	15,40	500	1000
IX	84—6	0,180 (C)	76,01	6,27	17,53	$C_{20}H_{20}N_4$	76,40	6,44	17,80	4	30
X	93—6	0,293 (C)	76,16	6,17	7,83	$C_{20}H_{20}N_4$	76,40	6,44	17,80	60	250
XI[3]	244—6	—	54,88	4,90	12,21	$C_{21}H_{23}N_4I$	55,02	5,06	12,23	8	30
XII	172—4	0,555 (A)	75,72	5,90	18,62	$C_{19}H_{18}N_4$	75,50	5,95	18,55	1000	1000

[1]Compounds (I), (II), (VII), and (VIII) were crystallized from alcohol; (III) from 75% alcohol; (XI) from absolute ethanol; and (IX) from a mixture of benzene and petroleum ether.

[2](A): in chloroform–methanol (99 : 1); (B): in chloroform–methanol (98 : 2); (C): in chloroform.

[3]Found %: I 27.63. Calculated %: I 27.70.

2-methyl-3-ethyl- (IX), 5-methyl-3-ethyl- 10-p-tolyldihydro-1,2-diazaphenazine (X), a methiodide of (IX) or (X) (XI), and 3,5-dimethyl-10-p-tolyldihydro-1,2-diazaphenazine (XII).

The dihydrodiazaphenazines so obtained were screened for their bacteriostatic action against Mycobacterium tuberculosis, var. hominis, using a deep-culture H-37 Rv strain of the organism. Some of the compounds showed pronounced activity, but this was depressed in the presence of serum.

By comparing the biological results now obtained with those previously described [1], we have been able to draw the following conclusions. While in 3-phenyldihydrodiazaphenazines, unsubstituted in positions 2, 5, and 10, replacement of the phenyl group by ethyl or methyl tends to increase the activity to some extent, e. g., from 1000 to 60 μg/ml, no such tendency is retained when a substituent is introduced in position 10. Introduction of a methyl group in the 5 position does not affect activity, but a methyl group in the 2 position, i.e., at one of the nitrogen atoms of the pyridazine ring, markedly increases it, e.g., up to 1-4 μg/ml, and in this case the effect is independent of the presence of other substituent groups elsewhere in the molecule. This high activity of 2-methyldihydrodiazaphenazines is reduced by the presence of serum down to a value of 16-60 μg/ml.

The physical constants and biological action of the compounds we have prepared are set forth in Table 1.

EXPERIMENTAL

3-Acetylmethyl-1,2-dihydro-2-quinoxalone (IV). The ethyl ester (5 g) of acetylpyruvic acid was added to a solution of o-phenylenediamine (3.4 g) in alcohol (50 ml) and the mixture boiled for 30 min. A precipitate of (IV) separated on cooling. Yield, 4.3 g (67.5%), mp 258-260°C (from acetic acid). Found %: C 65.64; H 5.03; N 14.07. $C_{11}H_{10}N_2O_2$. Calculated %: C 65.40; H 4.98; N 13.85.

Compounds (V) and (VI) were obtained in an analogous manner. Compound (V): mp 252-254° (from alcohol). Found %: N 9.51. $C_{18}H_{16}N_2O_2$. Calculated %: N 9.27. Compound (VI): yield, 3.4 g (22.5%), mp 148-150° (from alcohol). Found %: C 68.02; H 6.37; N 12.00. $C_{13}H_{14}N_2O_2$. Calculated %: C 67.70; H 6.07; N 12.20.

3-Ethyl-10-methyldihydro-1,2-diazaphenazine (III). A mixture of (VI) (3.4 g), ethanol (100 ml), 98% hydrazine hydrate (5 ml), and acetic acid (8 ml) was boiled for 18 h. After driving off the solvent, the oily residue was triturated with water and recrystallized from 75% alcohol. This gave 2.48 g of (III), the compounds (I) and (II) being obtained in an analogous manner.

Methylation of 3-Phenyl-10-p-tolyldihydro-1,2-diazaphenazine. 3-Phenyl-10-p-tolyldihydro-1,2-diazaphenazine (9.6 g) was dissolved in alcoholic potash (2 g of potassium hydroxide in 125 ml of alcohol). The solution was treated with methyl iodide (2 ml), warmed for 30 min, and then allowed to stand at 20-25° for 24 h. The resulting precipitate was filtered off and washed with water. This gave 5.3 g of (VIII). The mother liquor deposited on concentration a precipitate which was triturated with water; the remaining insoluble solid was filtered off giving 2 g of (VII).

Methylation of 3-Ethyl-10-p-tolyldihydro-1,2-diazaphenazine. 3-Ethyl-10-p-tolyldihydro-1,2-diazaphenazine (7.5 g) was dissolved in alcoholic potash (2 g of potassium hydroxide in 200 ml of alcohol). The solution was treated with methyl iodide (3.5 ml), warmed for 30 min, and then allowed to stand for 48 h at 20-25°. Potassium iodide was filtered off, the filtrate evaporated to dryness, and the residue triturated with water. The resulting material (8.4 g) was a mixture giving three spots on a chromatogram. It was warmed with benzene, and the solution so obtained decolorized with charcoal and filtered. A crop of crystals separated on cooling, and this consisted of a methiodide, (XI), of one of the isomeric methylation products. Yield, 2.4 g. The mother liquor from this furnished on concentration 6 g of a mixture giving three spots on a chromatogram. The material was introduced into a column of aluminum oxide whence, on elution with benzene, 4.3 g of (X) was obtained, and with chloroform, 0.42 g of (IX).

3,5-Dimethyl-10-p-tolyldihydro-1,2-diazaphenazine (XII). 3-Methyl-10-p-tolyldihydro-1,2-diazaphenazine (II) (1.95 g) was dissolved in alcoholic potash (10.5 g of potassium hydroxide in 30 ml of alcohol). The solution was treated with methyl iodide (1 ml) and allowed to stand at 20-25° for 10 days. The potassium iodide which separated was filtered off, and the filtrate evaporated to dryness. The residue was triturated with water and the remaining insoluble solid filtered off giving 2.17 g of material. This was a mixture giving two spots on a chromatogram. Recrystallization from alcohol furnished 1 g of (XII), mp 172-174°, but the second component, a compound having mp 230-232°, could not be isolated in a pure state.

LITERATURE CITED

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