SYNTHESIS AND PHARMACOLOGICAL STUDY OF AZAPHENE ANALOGS – 2,11-DISUBSTITUTED DERIVATIVES OF 10,11-DIHYDRO-11H-PYRIDAZINO[3,4-b]-1,4-BENZOAZEPINE

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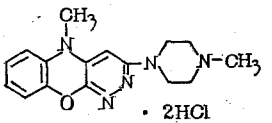
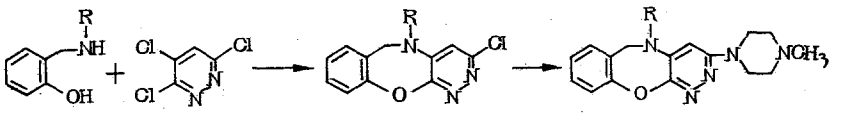
Tricyclic compounds with a central seven-membered ring have recently been widely used in medicine as antidepressants, neuroleptics, and for other pharmaceutical purposes.

Derivatives of 3,4-diazaphenoxazine have been shown to have antidepressant properties [1, 2]; the most active of these compounds was the dihydrochloride of 2-(4'-methylpiperazinyl-1)-10-methyl-3,4-diazaphenoxazine (I), which, under the name of "azaphene," has been used as an antidepressant having both a thymoleptic and a sedative action [3].



I

In the present work, azaphene analogs with a central seven-membered ring have been prepared by the following reaction scheme:

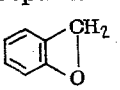


IIa-h IIIa-h IVa-d

where a) R = 4-$CH_3C_6H_4$; b) R = 4-$CH_3OC_6H_4$; c) R = furfuryl; d) R = 2-thiazolyl; e) R = 3,4-xylyl; f) R = C_6H_5; g) R = 4-$NO_2C_6H_4$; h) R = 2-pyridyl

The 2,11-disubstituted derivatives of the new heterocyclic system 10,11-dihydro-11H-pyridazino[3,4-b]-1,4-benzoxazepine (IIIa-h) were prepared by the reaction of the 2-hydroxybenzylamine derivatives (IIa-h) with 3,4,6-trichloropyridazine and potash.

The N-aryl [4-6] or N-heteryl derivatives [7] of 2-hydroxybenzylamine (IIa-h) were obtained by the treatment of salicylic aldehyde with the appropriate amine followed by reduction of the Schiff's base with sodium borohydride [7].

The structure of the dihydropyridazinobenzoxazepines (IIIa-h) was confirmed by mass spectroscopy. The intensities of the principle peaks in the mass spectra of compounds IIIa-h (M : M+2) were in the ratio of 3 : 1, indicating the presence of one chlorine atom. The derivatives IIIa-h were very stable to electronic bombardment and in most cases the most intense peak was that produced by the molecular ion; the exception was compound IIIb which gives a stable ion with a quinoid structure by the loss of a methyl group and this gives rise to a peak at M = 15 in the mass spectrum. With the exception of IIIc and g, all the compounds were characterized by the presence in the mass spectra of the particles  and RN = CH_2, formed by the splitting of the

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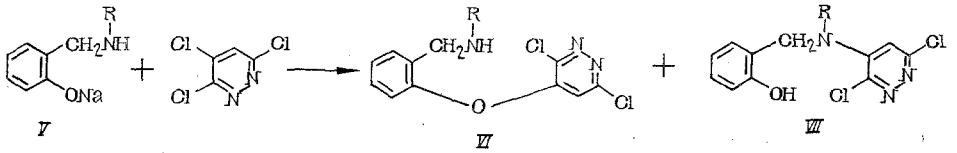
molecular ion. In compound IIIc, the fragment giving the most intense peak is M−R, and in compound IIIg, M−NO. These data indicate that the condensation of derivatives of 2-hydroxybenzylamine (IIa-h) with 3,4,6-trichloropyridazine gives the tricyclic compounds (IIIa-h) which have a central seven-membered oxazepine ring. To confirm the position of the nitrogen atoms in the pyridazine compounds (IIIa-h), compound IIIa was synthesized from the sodium salt of N-tolyl-o-hydroxybenzylamine (V, R-p-$CH_3C_6H_4$) and 3,4,6-trichloropyridazine in which the chlorine atom in position 4 is the most reactive [8-10].

The reaction between compound V and 3,4,6-trichloropyridazine at room temperature gave a mixture consisting of 56% of 3,6-dichloro-4-[2-(p-toluidinomethyl)phenoxy]pyridazine (VI) and 15% of 3,6-dichloro-4-(2-hydroxybenzyl-p-toluidino)pyridazine (VII):



On boiling with potash in alcohol, compounds VI and VII were both converted to 2-chloro-11-p-tolyl-11H-pyridazino[3,4-b]-1,4-benzoxazepine (IIIa) . For compound VI this reaction indicates that an intramolecular rearrangement (VI → VII) of the heterocyclic system IIIa has occurred and that the nitrogen atoms in the pyridazine ring are in positions 3 and 4. The rearrangement of compounds VI and VII was carried out by heating compound VI in pyridine; the reaction did not take place on heating in triethylamine.

The acetyl derivatives (VIII and IX) were obtained from compounds VI and VII. The structures of 3,6-dichloropyridazine derivatives (VI-XIII) were confirmed by IR spectra.

The condensation of IIa with 3,4,6-trichloropyridazine in the presence of triethylamine yielded two products: IIIa and VII. Under the same conditions, compound IIb gave IIIb and 3,6-dichloro-4(2-hydroxybenzyl-p-anisidino)pyridazine (X); from IIf-h was isolated only the corresponding N-substituted 3,6-dichloro-4(2-hydroxybenzylamino)pyridazine (XI-XIII), which, when heated with potash in alcohol or at 160-170° with triethylamine, was converted to IIIf-h.

The reaction between compounds IIIa-e and N-methylpiperazine gave 11-substituted 2-(4'-methylpiperazinyl-1)-10,11-dihydro-11H-pyridazino[3,4-b]-1,4-benzoxazepines (IVa-e). Compound IVc and e could not be isolated as the base.

CHEMICAL EXPERIMENTAL SECTION

IR spectra were taken on an IR-10 spectrophotometer, UV spectra on a Hitachi apparatus, and mass spectra on an MAT spectrometer at 50 eV.

2-Chloro-11-p-tolyl-10,11-dihydro-11H-pyridazino[3,4-b]-1,4-benzoxazepine (IIIa). A mixture of 15.3 g (0.072 mole) of IIa, 13.2 g (0.072 mole) of 3,4,6-trichloropyridazine, 15 g (0.108 mole) of calcined potash, and 100 ml of absolute alcohol was refluxed for 6 h, cooled, the precipitate filtered off, washed with water, and dried to give 12 g of compound IIIa.

UV spectrum, λ_{max} (log ε), nm: 280 (3.95); 300-314 (3.84).

Compounds IIIb-h (see Table 1) were prepared by the same method.

2-(4'-Methylpiperazinyl-1)-11-p-tolyl-10,11-dihydro-11H-pyridazino[3,4-b]-1,4-benzoxazepine (IVa). A mixture of 4.86 g (0.015 mole) of IIIa, 14.5 g (0.045 mole) of methylpiperazine, 30 ml of cyclohexanol, and 0.1 g of potassium iodide was refluxed for 17 h, the cyclohexanol evaporated, the residue triturated with aqueous sodium bicarbonate, filtered, washed with water, and dried. Recrystallization from ethyl acetate gave 3.1 g of IVa.

Compounds IVb-e were obtained by the same method (see Table 1).

Maleate of Compound IVa. A hot solution of 2 g of IVa in ethyl acetate was treated with a hot solution of 1.6 g of maleic acid in ethyl acetate, left for 30 min at room temperature, cooled, and the precipitate filtered off and recrystallized from absolute alcohol to give 2.4 g (68.5%) of the maleate of compound IVa.

The maleates of compounds IVb, d-e were prepared in the same way (see Table 1).

TABLE 1. 2,11-Disubstituted 10,11-Dihydro-11H-pyridazino[3,4-b]-1,4-benzoxazepines

Compound	Yield, %	mp,* °C	Found, %					Empirical formula	Calculated, %					Molecular weight †
			C	H	Cl	N	S		C	H	Cl	N	S	
IIIa	44,7	199—200	66,58	4,10	10,70	12,88	—	$C_{18}H_{14}ClN_3O$	66,77	4,36	10,95	12,98	—	323
IIIb	54,3	206—7	63,29	4,40	10,05	12,29	—	$C_{18}H_{14}ClN_3O_2$	63,63	4,15	10,43	12,37	—	339
IIIc	56	166—7	61,35	4,09	11,25	12,90	—	$C_{16}H_{12}ClN_3O_2$	61,24	3,85	11,30	13,39	—	313
IIId	23,7	186	53,43	2,87	11,03	18,07	10,22	$C_{14}H_9ClN_4OS$	53,08	2,87	11,19	17,69	10,12	316
IIIe	43,2	175—6	67,15	4,90	10,56	12,10	—	$C_{19}H_{16}ClN_3O$	67,55	4,77	10,49	12,44	—	337
IIIf	28,7	203—5	65,67	3,96	11,38	13,60	—	$C_{17}H_{12}ClN_3O$	65,92	3,96	11,45	13,57	—	309
IIIg	48,85	193—5	57,13	3,32	9,72	15,67	—	$C_{17}H_{11}ClN_4O_3$	57,55	3,10	9,99	15,79	—	354
IIIh	37,85	164—5	61,65	3,69	11,79	17,93	—	$C_{16}H_{11}ClN_4O$	61,81	3,57	11,41	18,03	—	310
IVa	53,3	190—2	71,20	6,29	—	18,40	—	$C_{23}H_{25}N_5O$	71,29	6,47	—	18,08	—	—
		149—50 (decomp.)	58,43	5,13	—	10,90	—	$C_{23}H_{25}N_5O \cdot 2{,}5\ C_4H_4O_4$	58,48	5,20	—	10,33	—	—
IVb	72	120—2	68,43	6,40	—	16,88	—	$C_{23}H_{25}N_5O_2$	68,46	6,25	—	17,36	—	—
		154—6	57,41	5,26	—	10,63	—	$C_{23}H_{25}N_5O_2 \cdot 2{,}5\ C_4H_4O_4$	57,13	5,09	—	10,10	—	—
IVc	35	235 (decomp.)	52,52	6,10	14,68	14,11	—	$C_{21}H_{23}N_5O_2 \cdot 2HCl \cdot 13/4\ H_2O$‡	52,32	5,96	14,71	14,54	—	—
IVd	48,8	152,5—3,5	59,97	5,55	—	22,13	8,61	$C_{19}H_{20}N_6OS$	59,98	5,30	—	22,09	8,43	—
		186—7 (decomp.)	55,52	4,90	—	16,37	6,18	$C_{19}H_{20}N_6OS \cdot 1{,}1\ C_4H_4O_4$	55,30	4,84	—	16,54	6,31	—
IVe	48,9	187,5—8,5 (decomp.)	64,80	6,38	—	13,44	—	$C_{24}H_{27}N_5O \cdot C_4H_4O_4$	64,97	6,04	—	13,53	—	—
		198 (decomp.)	—	—	13,89	—	—	$C_{24}H_{27}N_5O \cdot 2HCl \cdot 3H_2O$‡	—	—	13,42	—	—	—
VI	56	101—1,5	60,03	4,08	19,82	12,04	—	$C_{18}H_{15}Cl_2N_3O$	60,01	4,19	19,68	11,67	—	—
VII	15,3	152,5—3	60,10	4,48	19,89	11,67	—	$C_{18}H_{15}Cl_2N_3O$	60,01	4,19	19,68	11,67	—	—
VIII	90	123—4	59,66	4,47	17,18	10,55	—	$C_{20}H_{17}Cl_2N_3O_2$	59,71	4,26	17,62	10,44	—	—
IX	80	93—6	59,62	4,17	17,15	10,24	—	$C_{20}H_{17}Cl_2N_3O_2$	59,71	4,26	17,62	10,44	—	—
X	26,4	158—9	57,40	3,95	18,76	11,06	—	$C_{18}H_{15}Cl_2N_3O_2$	57,46	4,02	18,85	11,17	—	—
XI	37,2	173—5	58,82	3,67	20,06	12,14	—	$C_{17}H_{13}Cl_2N_3O$	58,97	3,78	20,48	12,14	—	—
XII	51,94	181—3	52,30	3,09	17,94	14,25	—	$C_{17}H_{12}Cl_2N_4O_3$	52,38	3,07	18,12	14,32	—	—
XIII	50,2	140—1	55,34	3,38	—	16,29	—	$C_{16}H_{12}Cl_2N_4O$	55,36	3,46	—	16,14	—	—

* Compounds IIIa-c, IIIe, IIIh, VI, VII, IVd-e, X, XIII were recrystallized from alcohol, IIId, IIIf-g, XII from a mixture of dimethylformamide and alcohol, VIII, IX, and IVc from aqueous alcohol, IVa and XI from ethyl acetate, and IVb from hexane.

† Molecular weights were determined mass spectrometrically. Calculated values are given for ions containing isotopes ^{12}C, ^{1}H, ^{16}O, ^{14}N, ^{32}S, and ^{35}Cl.

‡ Quantity of water was obtained from analytical data.

2-(4'-Methylpiperazinyl-1)-11-furfuryl-10,11-dihydro-11H-pyridazino[3,4-b]-1,4-benzoazepine (IVc). This compound was prepared from 5 g (0.159 mole) of IIIc, 4.8 g (0.048 mole) of methylpiperazine, 0.1 g of potassium iodide, and 30 ml of cyclohexanol, using the method employed for the preparation of compound IVa except that the residue after removal of the cyclohexanol was treated with 10% hydrochloric acid and the precipitate filtered off and recrystallized from absolute alcohol to give 2.7 g of the dihydrochloride of IVc (see Table 1).

3,6-Dichloro-4-[2-(p-toluidinomethyl)phenoxy]pyridazine (VI) and 3,6-dichloro-4-(2-hydroxybenzyl-p-toluidino)pyridazine (VII). To a solution of 5.5 g (0.03 mole) of 3,4,6-trichloropyridazine in 25 ml of absolute alcohol was gradually added a solution of compound V, obtained by the reaction of 6.4 g (0.03 mole) of compound IIa with sodium alcoholate [obtained from 0.69 g (0.03 mole) of metallic sodium and 24 ml of absolute alcohol]. The reaction mixture was mixed for 3 h at 20°, the precipitate was filtered off, washed with alcohol, and the filtrate evaporated in vacuum at 20°. The oily residue was triturated with benzene, the precipitate filtered off, and dried to give 1.66 g of compound VII. IR spectrum (chloroform), cm^{-1}: 3590 (ν_{OH}). The benzene solution was evaporated at 20°, the residue triturated with a small quantity of absolute alcohol to give 6.2 g of compound VI. IR spectrum (chloroform), cm^{-1}: 3440 (ν_{NH}).

3,6-Dichloro-4-[2-(p-acetotoluidinomethyl)phenoxy]pyridazine (VIII). A mixture of 1 g of compound VI, 10 ml of acetic anhydride, and 0.5 ml of pyridine was shaken for several minutes and after the solid had dissolved, the solution was left at room temperature for 2 h, and then poured onto ice. The precipitate was filtered off, washed with water, and dried to give 1 g of compound VIII. IR spectrum (mineral oil, cm^{-1}: 1655 (ν_{CON}).

3,6-Dichloro-4-(2-acetoxybenzyl-p-toluidino)pyridine (IX). Compound VIII was dissolved in 3 ml of acetic anhydride at room temperature, two drops of pyridine added, and the mixture allowed to stand for 2 h and then poured onto ice. The precipitated material was filtered off, washed, and dried to give 2.7 g of compound IX.

IR spectrum (mineral oil), cm^{-1}: 1755 (ν_{COOR}: carbonyl).

Conversion of Compound VI to Compound IIIa. A mixture of 1.1 g of compound VI, 0.41 g of calcined potash, and 8 ml of absolute alcohol was refluxed for 5 h, cooled, and the precipitate filtered off. After washing and drying, 0.63 g (63.5%) of compound IIIa mp 194-196° was obtained and there was no depression of melting point on admixture with a sample of IIIa obtained by the method given above.

Rearrangement of Compound VI to Compound VII. A solution of 0.2 g of compound VI in 2.5 ml of dry pyridine was refluxed for 40 min, cooled, and poured onto ice. The precipitated material was filtered off and yielded 0.12 g of compound VII mp 150-151° (from alcohol), and there was no depression of melting point on admixture with a sample of VII obtained as described above.

Conversion of Compound VII to Compound IIIa. A mixture of 0.5 g of VI, 0.5 g of potash, and 5 ml of absolute alcohol was refluxed for 5 h. After cooling, the precipitate was filtered off, washed with water, and dried to give 0.3 g of compound IIIa mp 191-196°. Recrystallization from alcohol raised the mp to 198-199° and there was no depression of melting point on admixture with a sample of compound IIIa obtained as described above.

Reaction of Compounds IIa, b, and f-h with 3,4,6-Trichloropyridazine in the Presence of Triethylamine. A. A mixture of 8 g (0.038 mole) of compound IIa, 7 g (0.038 mole) of 3,4,6-trichloropyridazine, 50 ml of alcohol, and 21 ml of triethylamine was refluxed for 10 h, cooled, and the triethylamine and alcohol distilled off. The precipitate was filtered off, washed with water, and dried. Recrystallization from alcohol yielded 2.5 g of compound VII mp 151-153°; there was no depression of melting point on admixture with a sample of IIIa prepared as described above. B. Using the same method, 9.2 g (0.04 mole) of compound IIb, 7.3 g (0.04 mole) of 3,4,6-trichloropyridazine, 40 ml of alcohol, and 22 ml of triethylamine gave 7 g of X and 1.47 g of IIIb, mp 199-203°; the melting point was not depressed on admixture with a sample of IIIb prepared as described above. IR spectrum of compound X (chloroform), cm^{-1}: 3590 (ν_{OH}).

C. A mixture of 17.42 g (0.07 mole) of compound IIe, 12.9 g (0.07 mole) of 3,4,6-trichloropyridazine, 29 ml of triethylamine, and 200 ml of alcohol was refluxed for 7 h. When cool, the precipitate was filtered off, washed with water and dried to give 14.3 g of compound XI (see Table 1). IR spectrum (chloroform), cm^{-1}: 3590 (ν_{OH}).

Compounds XII and XIII were obtained by the same method (see Table 1).

Cyclization of Compounds XI-XIII to Compounds IIIf-h. A. A mixture of 5 g of compound XI, 5.4 ml of triethylamine, and 20 ml of alcohol was heated at 160-170° for 7 h and cooled. The precipitate was filtered off,

washed with water, and dried to give 2.29 g (50.6%) of compound IIIf, mp 202-204°; there was no depression of melting point on admixture with a sample of IIIf prepared as described above. UV spectrum, λ_{max}, log ε, nm: 280 (3.93); 313 (3.85).

Compounds IIIg and h were obtained in the same way.

B. A mixture of 0.5 g of compound XI and 0.5 g of calcined potash in 10 ml of alcohol was refluxed for 7 h. After cooling, the precipitate was filtered off, washed with water, dried, and recrystallized from a mixture of dimethylformamide and alcohol to give compound IIIf mp 203-205°; there was no depression of melting point on admixture with a sample of IIIf obtained as described above.

Compounds IIIg and h were obtained in the same way.

PHARMACOLOGICAL EXPERIMENTAL SECTION

As the compounds under investigation have a tricyclic structure, they were tested for properties characteristic of neuroleptic and antidepressive substances.

Mice and rats were used to study the effect of the compounds on the following: phenamine-induced hyperthermia (10 mg/kg, subcutaneously), toxicity (2.5, 5, 7.5 mg/kg subcutaneously), hypothermia and blepharoptosis caused by reserpine (2 mg/kg), the hypothermic action of L-dopa (200 mg/kg intraperitoneally), apomorphine-caused stereotopy (10 mg/kg subcutaneously), catalepsy caused by triftazin (6 mg/kg intraperitoneally), the analgesic action of promedol (2 mg/kg subcutaneously), and the soporific action of hexenal (50 mg/kg intravenously).

Urethane-narcotized cats were used to study the effect on blood pressure and the peripheral adreno- and cholinoreactive systems.

It was found that none of the test compounds caused hypothermia, blepharoptosis, a decrease in motor activity, or catalepsy, i.e., phenomena characteristic of neuroleptic substances. The compounds also displayed little antidepressant activity.

Only compounds IVc and d increased the hyperthermic action of phenamine. In mice of the control group, phenamine (10 mg/kg subcutaneously) caused an increase in body temperature from 37.5° (37.2-37.8°) to 38.2° (38.0-38.4°); after injection of compound IVc (25 mg/kg) the body temperature increased from 37.7° to 39.1° (38.3-39.4°), and an approximately equal increase in body temperature was produced by injection of 15 mg/kg of compound IVe. Compounds IVc and e (25 mg/kg) increased the toxicity of phenamine. Thus, phenamine (7.5 mg/kg subcutaneously) destroyed 10% of the mice, whereas injection of phenamine together with compound IVc or e destroyed 40-50% of the animals. Compounds IVa, b, and d did not display this activity.

The compounds showed no significant activity in the remaining tests.

The LD_{50} on subcutaneous injection was 255 mg/kg for compound IVa, 255 for IVb, 350 for IVc, 217 for IVd, and 155 for IVe.

Some of the tricyclic compounds that we studied earlier – derivatives of 3,4-diazaphenoxazine containing a methylpiperazine group – displayed antidepressant activity [11].

The tests carried out showed that pyridazino[3,4-b]benzoxazepine derivatives containing a methylpiperazine group (IVa-e) do not display properties characteristic of psychotropic and other neurotropic preparations.

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