SYNTHESIS AND BIOLOGICAL ACTIVITY OF 1-SUBSTITUTED BENZIMIDAZOLES AND BENZOTRIAZOLES

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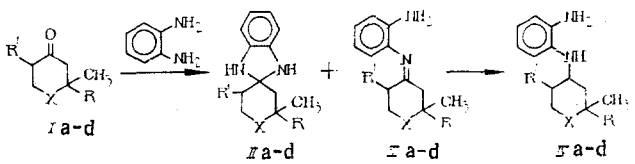
Benzimidazoles are known to display a wide range of biological activity [1].

It was of interest to prepare new benzimidazoles, and the structurally related benzotriazoles, carrying in the 1-position 4-tetrahydropyranyl, 4-tetrahydrothiopyran, or 4-piperidinyl radicals. Similar benzimidazoles, carrying the 4-piperidinyl substituent, have found extensive application in medicine [2].

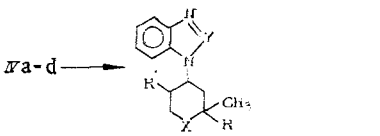
The starting materials for these biheterocyles were the N-(4-heteryl)-2-aminoanilines (IVa-d), which were synthesized as follows:



Ia-d IIa-d IIIa-d IVa-d

a) X = O, R = CH_3, R' = H c) X = N-CH_3, R = H, R' = CH_3
b) X = S, R = CH_3, R' = H d) X = N-CH_2-C_6H_5, R = H, R' = CH_3

Condensation of o-phenylenediamine with the heterocyclic 4-ketones (Ia-d) gave two types of compound, namely the spirocycles (IIa-d) and the Schiff's bases (IIIa-d). Hydrogenation of either (IIa-d) or (IIIa-d) with sodium borohydride gave the substituted o-phenylenediamines (IVa-d). Reaction of the latter with nitrous acid, formamide or formic acid or mesityl oxide [3] or acetic acid gave the corresponding benzotriazoles (Va-d) and benzimidazoles (VIa-d) and (VIIa-d).



IVa-d Va-d-VIIa-d

Va-d Y = N, VIa-d Y = CH, VIIa-d Y = CCH_3

The expected values for the molecular ions were found in the mass spectra of (Va-d-VIIa-d).

EXPERIMENTAL CHEMICAL SECTION

GLC analyses were carried out on a Chrom-4 instrument using columns packed with 5% silicone XE-60 on Chromatone P-A silanized with HMDS. PMR spectra were recorded on a UR-20 instrument, and mass spectra on an MX-1303 with direct introduction of the sample into the ionization zone.

Ketones (Ia-d) were obtained by known methods [4-6].

Condensation of o-Phenylenediamine with Ketones (Ia-d). To a solution of 10.8 g (0.1 mole) of o-phenylenediamine and 0.01 g of p-toluenesulfonic acid in 300 ml of boiling benzene was added slowly, dropwise, 0.1 mole of the ketone (over approximately 4 h). Boiling was

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TABLE 1. Properties of Products of Condensation of o-Phenylenediamine with Ketones, (IIa-d) and (IIIa-d)

Compound	Yield, %	mp or bp, °C/mm	Found, %			Molecular formula	Calculated, %			PMR spectra (δ, ppm)
			C	H	N		C	H	N	
IIa	40	131	71,56	8,28	12,84	$C_{13}H_{18}N_2O$	71,60	8,20	12,80	1,32 s [$OC(CH_3)_2$] 1,82 m and 2,00 m ($20CCH_2$); 3,81 m (OCH_2); 3,94 s (NH); 6,62 m (C_6H_4).
IIb	3	68	66,66	7,69	11,96	$C_{13}H_{18}N_2S$	66,70	7,70	12,00	1,30 s [$SC(CH_3)_2$]; 1,63 m and 1,81 m ($2S\ CCH_2$); 3,60 m (SCH_2); 3,92 s (NH); 6,60 m (C_6H_4).
IIc	5	74	72,22	9,09	18,18	$C_{14}H_{21}N_3$	72,17	9,00	18,20	0,80—1,20 m ($NCCH_3$ and $NCCCH_3$); 2,20 s (NCH_3); 3,40 s (NH); 6,70 m (C_6H_4).
IIIa	20	150/2	71,56	8,28	12,84	$C_{13}H_{18}N_2O$	71,64	8,19	12,91	1,32 [$OC(CH_3)_2$]; 2,20—2,40 m ($20CCH_2$); 3,80 m (OCH_2); 3,90 s (NH_2); 6,62 (C_6H_4).
IIIb	49	180/2	66,60	7,69	11,96	$C_{13}H_{18}N_2S$	66,70	7,61	12,00	1,30 [$SC(CH_3)_2$]; 2,00—2,20 m ($2S\ CCH_2$); 3,60 m (SCH_2); 3,82 s (NH_2); 6,61 m (C_6H_4).
IIIc	50	162/2	72,72	9,09	17,98	$C_{14}H_{21}N_3$	72,80	9,00	18,20	0,80—1,20 m ($NCCH_3$ and $NCCCH_3$); 2,20 s (NCH_3); 3,42 s (NH_2) 6,73 m (C_6H_4).
IIId	34	191/2	78,50	8,41	13,08	$C_{21}H_{27}N_3$	78,55	8,38	13,00	0,80—1,20 m ($NCCH_3$ and $NCCH_3$) 2,20—2,80 m (NCH_2CH_2); 3,40 s (NH_2) 6,71—7,20 m (C_6H_4 and C_6H_5).

TABLE 2. Properties of 1-(4-Heterocyclyl)-2-aminoanilines (IVa-d)

Compound	Yield, %	bp, °C/mm, or mp	Found, %			Molecular formula	Calculated, %			PMR spectra (δ, ppm)
			C	H	N		C	H	N	
IVa	53	124	70,91	9,09	12,72	$C_{18}H_{20}N_2O$	71,00	9,10	12,80	1,32 s [$OC(CH_3)_2$]; 1,80—2,00 m ($2OCCH_2$) 3,80 m (OCH_2), 3,55 s (NH and NH_2), 6,64 m (C_6H_4).
IVb	50	130	66,10	8,47	11,86	$C_{13}H_{20}N_2S$*	66,18	8,41	11,90	1,30 s [$SC(CH_3)_2$]; 1,60—1,80 m ($2SCCH_2$); 3,40 m (SCH_2); 3,60 s (NH and NH_2); 6,60 m (C_6H_4).
IVc	55	155/1	72,10	9,87	18,02	$C_{14}H_{23}N_3$	72,17	9,81	18,00	1,00—1,20 m ($NCCH_3$ and $NCCCH_3$); 2,20 s (NCH_3); 3,60 s (NH and NH_2); 6,88 m (C_6H_4).
IVd	48	201/1	78,02	8,98	13,00	$C_{21}H_{29}N_3$	78,00	8,88	13,04	0,80—1,20 m ($NCCH_3$ and $NCCCH_3$); 2,20—2,80 m (NCH_2CH_2); 3,55 s (NH and NH_2), 6,80—7,20 m (C_6H_5 and C_6H_4).

*Found, %: S 13.56. Calculated, %: S 13.49.

TABLE 3. Properties of Biheterocyclic Compounds (V, VI, and VII)

Compound	Yield, %		mp, °C	mp of picrate, °C	Found, %			Molecular formula	Calculated, %			PMR spectra (δ, ppm)
	A	B			C	H	N		C	H	N	
Va	72	—	72	—	67,53	7,36	18,18	$C_{13}H_{17}H_3O$	67,58	7,30	18,20	1,32s [$OC(CH_3)_2$]; 5,45m(NCH); 7,20—8,00m(C_6H_4)
VIa	48	70	62	60	73,04	7,83	12,17	$C_{14}H_{18}N_2O$	73,10	7,88	12,21	1,32s [$OC(CH_3)_2$]; 4,40m(NCH), 7,80s (N=CH).
VIIa	15	65	109	68	73,47	8,57	11,43	$C_{15}H_{21}N_2O$	73,50	8,60	11,41	1,32s [$OC(CH_3)_2$]; 2,60s (N=HCCH_3); 4,40m (NCH).
Vb	52	—	85	—	63,16	6,88	17,00	$C_{13}H_{17}N_3S$	63,20	6,84	17,06	1,28s [$SC(CH_3)_2$]; 5,00m(NCH); 7,20—8,00m(C_6H_4).
VIb	50	70	80	76	68,29	7,32	11,38	$C_{14}H_{18}N_2S$	68,31	7,35	11,40	1,28s [$SC(CH_3)_2$]; 4,40m(NCH); 7,80s (N=CH).
VIIb	25	60	98	93	68,96	8,05	10,73	$C_{15}H_{21}N_2S$	68,88	8,00	10,70	1,28s [$SC(CH_3)_2$]; 2,60s (N=CCH_3); 4,40m(NCH).
Vc	48	—	—	53	68,85	8,19	22,95	$C_{14}H_{20}N_4$	68,90	8,20	22,91	2,20s (NCH_3); 5,00m(NCH); 7,20—8,00m(C_6H_4).
VIc	54	65	—	83	74,07	8,64	17,28	$C_{15}H_{21}N_3$	74,00	8,60	17,30	2,20s (NCH_3); 4,40m (NCH); 7,80s (N=CH).
VIIc	30	50	—	96	74,70	8,95	16,34	$C_{16}H_{23}N_3$	74,61	8,90	16,38	2,20s (NCH_3); 2,60s (N=CCH_3); 4,40m(NCH).
Vd	42	—	—	80	75,45	7,78	16,76	$C_{21}H_{26}N_4$	75,50	7,80	16,80	0,80—1,20m (NCCH_3 and NCCCH_3); 5,00m(NCH); 7,20—8,00m(C_6H_4 and C_6H_5).
VId	32	60	—	70	79,28	8,11	12,61	$C_{22}H_{27}N_3$	79,30	8,16	12,68	0,80—1,20m(NCCH_3 and NCCCH_3); 4,30m (NCH); 7,80s (N=CH).
VIId	27	45	—	83	79,31	8,62	12,07	$C_{23}H_{30}N_3$	79,37	8,66	12,10	0,80—1,20 (NCCH_3 and NCCCH_3); 2,60s (N=CCH_3), 4,40m (NCH).

continued until no more water was removed (1.8 ml). The cooled solution was washed with 10% sodium bicarbonate and water, and dried over magnesium sulfate. The solvent was distilled off and the crystals which separated (IIIa-d) were filtered off and washed with ether. Distillation of the filtrate gave (IIIa-d) (Table 1). IR spectra, ν, cm^{-1}: IIa-d, 3400 (N–H); (IIIa-d), 1640 (N=C).

1-(4-Heteryl)-2-aminoanilines (IVa-d). To a solution of 0.1 mole of (IIa-d) in 100 ml of methanol at 35-40°C was added over 1 h 0.2 mole (7.6 g) of sodium borohydride. The mixture was then stirred for a further 30 min, and the methanol distilled off. A 3 N solution of sodium hydroxide (10 ml) was then added, the mixture extracted with ether, and the ether extract dried over magnesium sulfate (Table 2).

1-(4-Heteryl)benzotriazoles (Va-d). To a solution of 0.1 mole of (IVa-d) in 12 ml (0.2 mole) of glacial acetic acid and 30 ml of water was added at room temperature a solution of 7.52 g (0.109 mole) of sodium nitrite in 12 ml of water, whereupon the temperature rose to 50°C. When the mixture had reached room temperature, it was basified with ammonium hydroxide, extracted with benzene, and the extract dried over magnesium sulfate. The solvent was distilled off, and the product crystallized from hexane (Table 3).

1-(4-Heteryl)benzimidazoles (VIa-d). *A*. A solution of 0.1 mole of (Ia-d) in 100 ml of formamide was heated for 16 h at 135°C. Water (200 ml) was added to the cooled solution, and the mixture extracted with chloroform. The extract was dried over calcium chloride, the solvent removed, and the product recrystallized from hexane.

B. A solution of 0.05 mole of (IVa-d) and 3.4 ml of 90% formic acid was heated on the water bath for 4 h. The mixture was cooled, neutralized with 10% sodium hydroxide, and extracted with chloroform. The extract was dried over calcium chloride, the solvent distilled off, and the product crystallized from hexane (Table 3).

1-(4-Heteryl)-2-methylbenzimidazoles (VIIIa-d). *A*. A solution of 0.2 mole of (IVa-d) in 100 ml of mesityl oxide was heated in an autoclave for 48 h at 150°C. The excess of mesityl oxide was then distilled off, and the residue crystallized from hexane.

B. A solution of 0.1 mole of (IVa-d) in 10 ml of glacial acetic acid was heated for 4 h on the water bath, cooled, neutralized with 10% sodium hydroxide solution, and extracted with chloroform. The extract was dried over calcium chloride, the solvent distilled off, and the product crystallized from hexane (Table 3).

EXPERIMENTAL BIOLOGICAL PART

The pharmacological properties of the citrates of the compounds were studied using analgesimetric tests (the hot plate test on white mice [7], and mechanical irritation of the tail in rats [8]). In the experiments on white mice (hot plate), the antagonistic properties of the compounds toward opiates were examined [9]. The range of doses employed was 5–30–60 mg/kg intraperitoneally. The standard drugs used were morphine and the antagonist to narcotic analgesics, nalorphine. No activity was observed in tests with these compounds.

The local anesthethic properties of the compounds were measured by means of a test for conductive anesthesia on isolated frog nerves [10], and superficial anesthesia on the rabbit eye cornea [2]. The compounds were tested in concentrations of 0.25% (frog nerves) and 0.2% (cornea). The standards used were novocaine and dicaine. The results were treated statistically.

The anesthesometric results showed that the test compounds possessed anesthetic effects in the conductive anesthesia test. The citrates of (VId) and (VIIc) were the most active of the group, and in comparison with novocaine in equieffective concentrations their activities were 70 and 60% respectively (novocaine, 90%). It is therefore desirable to continue the search for compounds with local anesthetic activity in the 1-substituted benzimidazole and benzotriazole series.

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SYNTHESIS AND PHARMACOLOGICAL ACTIVITY OF SOME 3-HYDRAZINO-2,3-DIHYDRO-1,4-BENZODIAZEPIN-2-ONES

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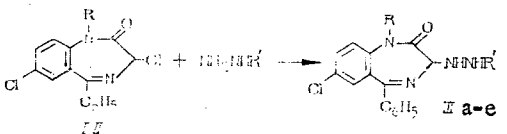
Benzodiazepines have found broad applications in medical practice as tranquillizers and antispasmodic drugs [1, 2]. During the last decade, there have been reports of the high tranquillizing activity of 2-hydrazino[1,4]benzodiazepine and its derivatives, in particular triazolo[4,3-a][1,4]- and triazino[4,3-a][1,4]benzodiazepines [3-8].

We have obtained a number of new 3-hydrazino-2,3-dihydro-1,4-benzodiazepin-2-ones, and studied their biological activity.

Reactions of 3,7-dichloro-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepin-2-one (I) and its 1-methyl derivative (II) with acetyl- and benzoylhydrazines in dioxane gave the 3-acylhydrazino benzodiazepin-2-ones (IIIa-d).



II IIIa-e

I: R = H;
II: R = CH_3;
IIIa: R = H, R' = COC_6H_5;
IIIb: R = H, R' = $COCH_3$;
IIIc: R = CH_3, R' = COC_6H_5;
IIId: R = CH_3, R' = $COCH_3$;
IIIe: R = R' = H.

The structures of (IIIa-d) were confirmed by their IR spectra and elemental analyses. The IR spectra of (IIIa, b) contained two bands in the carbonyl stretching region, at 1675-1695 cm^{-1} (ν C=O in the side chain) and 1698-1712 cm^{-1} (ν C=O in the ring). In compounds with a methyl group on the ring nitrogen (IIIc, d), the frequencies of the stretching vibrations of the carbonyl groups were similar, and their spectra showed only one band, at 1690 and 1680 cm^{-1} respectively. A few bands at 3100-3440 cm^{-1} were assigned to stretching vibrations of the N-H bonds. Ring C=N bond vibrations appeared at 1610-1620 cm^{-1}, which is typical of 2,3-dihydro-1H-1,4-benzodiazepines [9].

3-Acylhydrazinobenzodiazepin-2-ones unsubstituted at nitrogen of the seven-membered ring undergo rearrangement in acid media to the 6-chloro-4-phenylquinazolin-2-aldehyde acylhydrazones (IV), confirmed by direct synthesis in the case of 6-chloro-4-phenylquinazolin-2-aldehyde benzoylhydrazone. Rearrangement to quinazolines has been observed previously in some 3-substituted benzodiazepin-2-ones [10].

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