5-STYRYL-2-BENZIMIDAZOLYLURETHANES AS POTENTIAL ANTHELMINTHICS

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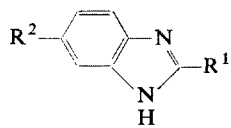
Reactions of benzaldehyde, *p*-chloro- and *p*-methoxybenzaldehyde and 2-thiophenaldehyde with 3-acetamido-4-nitrotoluene were used to prepare stilbenes *VIa*— *VIc* and 2-(3-acetamido--4-nitrostyryl)thiophene (*VId*). The 3,4-diamino derivatives obtained then by reduction (*VIIa* to *VIId*) were condensed with 3-ethoxycarbonyl-2-methylisothiourea, giving rise to 2-benzimidazolylurethanes substituted in position 5 with styryl, *p*-chlorostyryl, *p*-methoxystyryl and 2-(2-thienyl)-vinyl groups (*VIIIa*— *VIIId*). With compound *VIIIc* a pronounced effect on the tapeworm *Hymenolepis nana* was observed.

Modern anthelminthics, particularly the veterinary ones, are required to possess a broad activity spectrum, to be active against gastrointestinal parasites as well as against pulmonary worms. A number of effective drugs have been derived from benzimidazole: thiabendazole (*I*), lobendazole (*II*), parbendazole (*III*), cambendazole (*IV*), mebendazole (*V*).

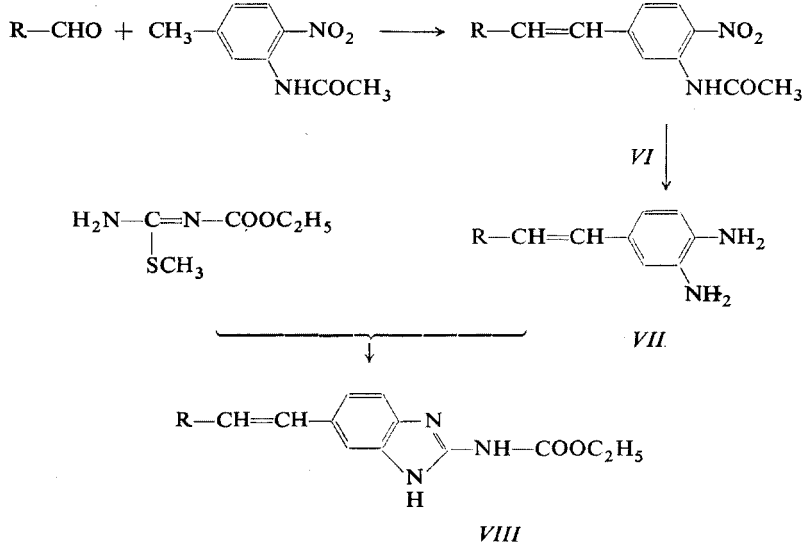


I, R^1 = 4-thiazolyl, R^2 = H
II, R^1 = $NHCOOC_2H_5$, R^2 = H
III, R^1 = $NHCOOCH_3$, R^2 = n-C_4H_9
IV, R^1 = 4-thiazolyl, R^2 = $COOCH(CH_3)_2$
V, R^1 = $NHCOOCH_3$, R^2 = COC_6H_5

It being known that compounds containing a double bond are usually more potent biologically than analogous saturated compounds, we were interested in the effect of the vinyl group in position 5 of 2-benzimidazolylurethanes on anthelminthic activity. The only suitable way of preparing these compounds is cyclization of the *o*-phenylenediamines correspondingly substituted in position 4. We focussed our attention on the synthesis of 3,4-diaminostilbene and some of its 4′-substituted

derivatives. Of asymmetric diaminostilbenes only 2,4-diaminostilbene is known, prepared by reduction of the 2,4-dinitro derivative[1]. This 2,4-dinitrostilbene was obtained by Knoevenagel's condensation of benzaldehyde with 2,4-dinitrotoluene. The same method was used to prepare most of the mononitrostilbenes. The prerequisite for this reaction is the activation of α-carbon of toluene by directly bound carboxyl (phenylacetic acid) or nitro group in *ortho* or *para* position. 4-Nitrotoluene reacts with benzaldehyde under catalysis with piperidine rather reluctantly. By using more drastic conditions[2] one can attain satisfactory results. After 22 h of heating of benzaldehyde with 4-nitrotoluene in the presence of sodium *4*-toluenesulfonamide and triethanolamine we were able to prepare 4-nitrostilbene in a 28% yield. It was attempted to reduce this compound to the 4-amino derivative with iron under conditions of Béchamp's reduction, with zinc in acetone in the presence of ammonium chloride, with hydrogen on Raney nickel but all without success. Only ferrous sulfate in ethanolic ammonia led to the amine in a 56% yield. After conversion to 4-acetamidostilbene, it was attempted to nitrate it. Even when using 100% nitric acid, a solution of potassium nitrate in sulfuric acid and a mixture of nitric and acetic acids, the nitration was impossible.

This preparatory path being unusable, we thought of carrying out Knoevenagel's condensation with such starting compounds as would contain a preformed 3,4-diamino grouping. The starting compound used was *p*-chlorobenzaldehyde which was nitrated to 4-chloro-3-nitrobenzaldehyde and then employed for condensation with



a, R = C_6H_5; *b*, R = *p*-Cl.C_6H_4; *c*, R = *p*-$CH_3O.C_6H_4$; *d*, R = 2-thienyl.

4-nitrophenylacetic acid but without success. If nonsubstituted phenylacetic acid was used in this trial, α-phenyl-4-chloro-3-nitrocinnamic acid was obtained in a 41% yield but the acid could not be decarboxylated by heating it either alone or in the presence of copper powder in quinoline to 290°C. Equally unsuccessful was an attempt to aminate and decarboxylate simultaneously by heating under pressure with copper powder in ammonia to 200°C.

Likewise, it was not possible to prepare 4-chloro-3-nitrostilbene by Meerwein's method[3], *i.e.* by a reaction of benzenediazonium chloride with 4-chloro-3-nitrocin-

TABLE I
List of Prepared Compounds

Compound (yield, %)	M.p., °C solvent	Formula m.w.	Calculated/Found % C	% H	% N	% S(Cl)
VIIb	202·9—203·9	$C_{14}H_{11}ClN_2O_2$	61·21	4·04	10·19	(12·91)
(48·0)	ethanol	274·7	60·99	4·26	10·15	(12·75)
VIIc	207·7—208·1	$C_{15}H_{14}N_2O_3$	66·65	5·22	10·37	—
(52·2)	ethanol	270·3	66·69	5·49	10·33	—
VIId	144·5—145·6	$C_{14}H_{12}O_3S$	58·32	4·20	9·72	11·12
(35·3)	ethanol	260·4	58·47	4·23	9·67	10·99
VIIIa	151·8—153·2	$C_{14}H_{14}N_2$	79·96	6·71	13·33	—
(76·2)	ethanol	210·3	80·36	6·78	13·22	—
VIIIb	195·1—196·0	$C_{14}H_{13}ClN_2$	68·71	5·35	11·45	(14·49)
(68·7)	benzene	244·7	67·93	5·21	11·34	(14·31)
VIIIc	174·1—175·0	$C_{15}H_{16}N_2O$	74·97	6·71	11·66	—
(83·5)	ethanol	240·3	75·12	6·67	11·68	—
VIIId	161·0—163·2	$C_{12}H_{12}N_2S$	66·63	5·59	12·95	14·83
(80·5)	ethanol	216·3	66·70	5·96	12·68	14·34
IXa	330—333	$C_{18}H_{17}N_3O_2$	70·34	5·58	13·67	—
(41·9)	90% dimethylformamide	307·3	70·11	5·60	13·64	—
IXb	333—335	$C_{18}H_{16}ClN_3O_2$	63·25	4·72	12·30	(10·37)
(87·6)	80% dimethylformamide	341·8	63·23	4·74	12·19	(10·45)
IXc	326—328	$C_{19}H_{19}N_3O_3$	67·64	5·68	12·45	—
(51·5)	80% dimethylformamide	337·4	67·80	5·74	12·59	—
IXd	317—318	$C_{16}H_{15}N_3O_2S$	61·32	4·83	13·41	10·23
(46·3)	80% dimethylformamide	313·4	61·58	5·06	13·72	10·18

namic acid which was prepared for this purpose by Perkin's reaction of 4-chloro-3-nitrobenzaldehyde either with acetic anhydride (44% yield) or with malonic acid (67% yield).

It was mentioned before that 3-chloro-4-nitrotoluene does not condense with benzaldehyde. Hence we assumed that chlorine in position 3 counteracts through its +M effect the −M effect of the nitro group. Therefore, 3-acetamido-4-nitrotoluene was used for further experiments and, for greater stability, benzaldehyde was replaced with *p*-chlorobenzaldehyde. Heating of these two compounds with sodium *p*-toluenesulfonamide and triethanolamine in ethanol for 47 h under a reflux condenser produced 3-acetamido-4'-chloro-4-nitro-stilbene (*VIb*) in a 2·9% yield. Using a potassium salt as catalyst and dimethylformamide or hexamethylphosphorus triamide as solvent the yields increased to 48 and 53·8%, respectively. The *VIb* thus obtained was reduced with zinc in an aqueous–ethanolic solution of sodium hydroxide to 3,4-diamino-4'-chlorostilbene (*VIIb*). For the final cyclization we used the procedure of Loux[4], its principle being in a reaction of *o*-phenylenediamine with 3-ethoxycarbonyl-2-methylisothiourea. Using this method, we prepared 5-(*p*-chlorostyryl)-2-benzimidazolylurethane (*VIIIb*) from the diamine *VIIb*. Urethanes *VIIIa*, *VIIIc* and *VIIId* were synthesized in the same way from the corresponding aldehydes.

The screening for anthelminthic effectivity was done in a model experiment with rats invaded subcutaneously with third-instar larvae of the parasite *Nippostrongylus brasiliensis* as a representative of *Nemathelminthes*, and with mice invaded *per os* with eggs of the tapeworm *Hymenolepis nana* (a representative of *Platyhelminthes*). Eight days after invasion in the first case and 15 days after invasion in the second case the animals were given *per os* the tested compound in an amount of 200 mg/kg body weight. The efficiency was evaluated by comparing the number of adult individuals of *N. brasiliensis* or *H. nana* found in helminthological autopsy in the small intestine of experimental and control animals (*i.e.* invaded but not treated). In this test, the efficiency of *VIIIa*—*VIIId* and *IX* against the first parasite was rather slight, at best 17% with *VIIIc*. Against the second parasite it was better, 44% with *VIIId* and 100% with *VIIIc*.

The five derivatives of 2-benzimidazolylurethane tested represent a small array to permit definite conclusions to be drawn on the relationship between structure and anthelminthic activity. One may merely observe that replacement of the benzoyl group in the molecule of mebendazol (*V*) diminishes the efficiency against the roundworms but a new effect against the tapeworm appears.

EXPERIMENTAL

The melting points were determined in a Mettler FP 2 apparatus (up to 300°C), or in a Kofler block (above 300°C).

α-Phenyl-4-chloro-3-nitrocinnamic Acid

A mixture of phenylacetic acid (13·6 g, 0·1 mol), 4-chloro-3-nitrobenzaldehyde (18·6 g, 0·1 mol), triethylamine (10 ml, 0·07 mol) and acetic anhydride (20 ml) was refluxed for 1 h. The volatile fractions were removed by steam-distillation (800 ml distillate), the residue was cooled, the aque-

ous layer decanted and the residue crystallized from 80% ethanol. Yield: 11·7 g (38·6%) yellow compound, melting at 226·1—227·8°C. For $C_{15}H_{10}ClNO_4$ (303·7) calculated: 59·32% C, 3·32% H, 4·61% N, 11·68% Cl; found: 59·74% C, 3·94% H, 4·72% N, 11·82% Cl.

3-Amino-4-nitrostilbenes *VIa—VId*

A suspension of potassium *p*-toluenesulfonamide (20·9 g, 0·1 mol) in dimethylformamide (80 ml) was combined with the corresponding aldehyde (0·2 mol) and 3-acetamido-4-nitrotoluene (38·8 g, 0·2 mol) and the mixture was refluxed for 21 h. Dimethylformamide was then distilled away at reduced pressure and the residue stirred with acetic acid (20 ml) and methanol (150 ml). On the following day the product was filtered, washed with methanol and dried.

With the exception of the chloro derivative *VIb* which was obtained as a free amine, the products had to be deacetylated. The corresponding 3-acetamido-4-nitrostilbene (0·1 mol) was refluxed for 1 h in a mixture of ethanol (160 ml) and 20% aqueous solution of sodium hydroxide (40 ml). After cooling, the precipitated compound was filtered, washed with ethanol and dried. The yields, melting points and results of elementary analysis are shown in Table I.

3,4-Diaminostilbenes *VIIa—VIId*

Zinc powder (30 g) was added under stirring to a boiling mixture of the corresponding 3-amino-4-nitrostilbene (0·1 mol), 240 ml ethanol and 24 ml 20% aqueous solution of sodium hydroxide. After 3 h of refluxing, dimethylformamide was added dropwise to the reaction mixture until the precipitated product dissolved. The nonreacted zinc was then filtered off, washed with hot ethanol (200 ml) and the combined filtrates left to crystallize. The precipitate was then filtered, washed with ethanol and dried. The yields, melting points and results of elementary analysis are shown in Table I.

5-Styryl-2-benzimidazolylurethanes *VIIIa—VIId*

The compounds were prepared according to Loux[4]. Ethyl chloroformate (1·9 ml, 0·018 mol) was added dropwise under stirring to a suspension of powdered S-methylisothiourea sulfate (1·40 g, 0·01 mol) in 8 ml water precooled to −3°C. This was followed under external cooling by 25% solution of sodium hydroxide (over 10 min, 2·9 ml, 0·023 mol) to bring the pH to 7—8. Over the following five min glacial acetic acid was added dropwise (1·2 ml, 0·02 mol) and the mixture formed (pH 6) was combined with a solution of the corresponding 3,4-diaminostilbene (0·01 mol) in 20 ml dimethylformamide. The mixture was stirred for 90 min on a boiling-water bath, then it was cooled and poured into cold water (250 ml). The brown-red precipitate formed was filtered, washed with ethanol and dried. The yields, melting points and elementary analyses are shown in Table I.

Methyl Ester of 5-(*p*-Methoxystyryl)-2-benzimidazolylcarbamic Acid (*IX*)

A solution of 0·1 g Na in 50 ml methanol was combined with urethane *IXc* (1·69 g, 0·005 mol) and dimethylformamide. The mixture was refluxed for 8 h, filtered while hot and diluted with hot water (20 ml). After cooling, the crystals were filtered, washed with methanol and dried. Yield: 1·00 g (61·4%) of a brown powder, m.p. 317—318°C. After crystallization from 80% dimethylformamide the m.p. rose to 318—320°C. For $C_{18}H_{17}N_3O_3$ (323·3) calculated: 66·86% C, 5·30% H, 13·00% N; found: 66·76% C, 5·39% H, 13·40% N.

The elementary analyses were done by Mrs J. Komancová and Mrs A. Slavíková of the analytical department of this Institute.

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