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Heterocyclic Analogues of Pinosylvin

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Stilbazole-3-derivatives have been prepared by condensation of 3-pyridylacetic acid with methoxylated benzaldehydes followed by decarboxylation and demethylation. The synthetic procedures have been studied in some detail.

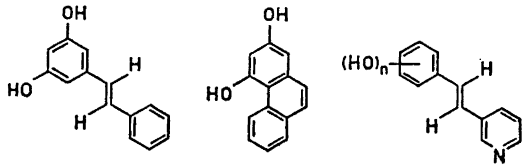
None of the hydroxylated stilbazoles showed any significant fungicidal activity as compared with pinosylvin.

The well-known durability of pine heartwood [1] is essentially due to the presence of pinosylvin (I) and its monomethyl ether. These phenolic stilbene derivatives are toxic to bacteria [2,28] as well as to wood decaying fungi [3–12] and inhibit the germination of fungal spores even in low concentrations.[8] They are also toxic to fish [13] and mice [2] and repel termites [14–16] and other insects.

Pinosylvin dimethyl ether itself exhibits little or no toxicity towards fungi but, like dihydropinosylvin monomethyl ether, several nitro- and chloro-stilbenes, various benzalanilines and azobenzene, it repels termites.[15]

Structural changes in the pinosylvin molecule generally lead to products of decreased fungi-toxic properties. Dihydropinosylvin [8] and the phenanthrene derivative II are less active than pinosylvin.[7,17] This is of some interest since the 9,10-dihydrophenanthrenes orchinol and hircinol function as regulators of mycorrhiza growth in certain orchids.[18–20]

Pinosylvin is sparingly soluble in water but soluble in many lipids. For this reason it was of some interest to prepare and investigate the fungicidal properties of hydrophilic analogues of pinosylvin. The present paper describes a series of aza-analogues of pinosylvin of the type III.



I II III

These stilbazoles were prepared by condensing the appropriate methoxylated benzaldehydes with 3-pyridylacetic acid to give the corresponding stilbazole carboxylic acids which were then decarboxylated and demethylated.

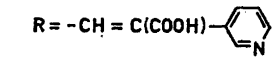
Initially the condensations caused some trouble due to the formation of tars. This made the isolation of the desired compounds difficult and gave low yields which varied considerably according to the method and reaction conditions used. A series of experiments were therefore carried out to find optimal conditions.

The following methods were used:

1. Condensation using a mixture of pyridine and piperidine.
2. Condensation using lead(II) oxide and acetic anhydride.
3. Condensation using a mixture of acetic anhydride and triethyl amine.

Typical examples of these condensations are described in the experimental part and a comparison of the yields of the condensation products obtained is given in Table 1. The physical constants of the stilbazole carboxylic acids *etc.* are given in Table 2.

Table 1. Yields of stilbazole carboxylic acids obtained by condensation of aromatic aldehydes with 3-pyridylacetic acid.



Compound No.	Condensation product	Yield %		
		Method		
		1	2	3
1	C_6H_5-R	28	22	—
2	$4\text{-}(CH_3O)-C_6H_4-R$	64	42	24
3	$3,4\text{-}(CH_3O)_2-C_6H_3-R$	55	30	47
4	$3,4\text{-}(CH_2O_2)-C_6H_3-R$	27	21	[a]
5	$3,5\text{-}(CH_3O)_2-C_6H_3-R$	40	[a]	52
6	$3,4,5\text{-}(CH_3O)_3-C_6H_2-R$	[a]	72	[a]
7	3-pyridyl-R	20	—	—

[a] Excessive tar formation.

Table 2. Physical constants and analyses of compounds 1—7 in Table 1.

Compound No.	m.p. °C	C found	C calc.	H found	H calc.	N found	N calc.
1	236—238 [a]						
2	221—222	70.8	70.6	5.2	5.1	5.6	5.5
3	190—191	67.6	67.4	5.2	5.3	5.1	4.9
4	240—241	67.0	66.9	4.1	4.1	5.2	5.2
5	163—164	67.4	67.4	5.5	5.3	5.4	4.9
6	175—176	65.0	64.8	5.8	5.4	4.5	4.4
7	253—254	69.0	69.1	4.4	4.5	12.2	12.4

[a] Lit.[21] m.p. 235—236°.

The decarboxylation of the stilbazole carboxylic acids could be effected: 1, by heating them to 180—210° in liquid paraffin in the presence of copper powder and copper(I) chloride according to Nilsson,[22] or 2, by heating the acids with copper powder in a vacuum with subsequent distillation of the stilbazoles formed. The yields (Table 3) were in both cases excellent, and typical examples are given in the experimental part. The physical constants of the stilbazoles and some of their derivatives are given in Table 4.

Demethylation and decarboxylation could be accomplished in one step by heating the stilbazole carboxylic acid with pyridine hydrochloride.[24] The yields (Table 5) were in some cases acceptable but particularly when methoxyl

Table 3. Yields of stilbazoles obtained by decarboxylation of the corresponding carboxylic acids.

Reaction product	Method 1 % yield	Method 2 crude product
Stilbazole-3	95	0 [a]
4′-Methoxystilbazole-3	76	84
3′,4′-Dimethoxystilbazole-3	91	96
3′,4′-Methylenedioxystilbazole-3	—	80
3′,5′-Dimethoxystilbazole-3	92	94
3′,4′,5′-Trimethoxystilbazole-3	91	96

[a] The acid distilled unchanged.

Table 4. Physical constants and analyses of stilbazoles and their derivatives.

Coumpound	m.p. °C	C found	C calc.	H found	H calc.	N found	N calc.
Stilbazole-3 [a]	81— 82	86.1	86.2	6.1	6.1	7.7	7.7
4′-Methoxystilbazole-3 [b]	102—103	79.5	79.6	6.3	6.2	6.0	6.6
N-methyl iodide	221—222	50.9	51.0	4.6	4.6	4.3	4.0
3′,4′-Dimethoxystilbazole-3	77— 79	74.8	74.7	6.4	6.3	5.4	5.8
Hydrobromide	218—220	55.9	55.9	5.0	5.0		
N-methyl iodide	225—228	49.6	50.1	4.8	4.7		
3′,5′-Dimethoxystilbazole-3	64— 65	74.3	74.7	6.3	6.3	5.9	5.8
Hydrobromide	235—242	55.9	55.9	5.1	5.0	4.6	4.4
Picrate	200—202	53.6	53.6	3.8	3.9		
N-methyl iodide	210—211	50.5	50.1	4.6	4.7		
3′,4′,5′-Trimethoxystilbazole-3	106—108	70.8	70.8	6.3	6.3	5.1	5.2
Hydrobromide	223—230						
Picrate	182—184					11.3	11.2
N-methyl iodide	190—192	49.2	49.4	5.3	4.9	3.4	3.4
3′,4′-Methylenedioxystilbazole-3							
Hydrochloride	223—225						

Lit. [a] m.p. 72—73° [21]; [b] m.p. 103° [23]

Table 5. % Yields of hydroxy stilbazoles obtained from methoxylated stilbazole carboxylic acids with pyridine hydrochloride (1) and from methoxylated stilbazoles with boron tribromide (2).

Reaction product	Method 1	Method 2
4′-Hydroxystilbazole-3	78	58
3′,4′-Dihydroxystilbazole-3	48	—
3′,5′-Dihydroxystilbazole-3	0	64
3′,4′,5′-Trihydroxystilbazole-3	24	56

Table 6. Physical constants and analyses of hydroxy stilbazoles and their derivatives.

Compound	m.p. °C	C found	C calc.	H found	H calc.	N found	N calc.
4′-Hydroxystilbazole-3	236—237	79.1	79.2	5.7	5.6	7.1	7.1
Acetate	100—102	75.2	75.3	5.4	5.5	—	—
N-methyl iodide	219—221	49.8	49.6	4.4	4.2	4.4	4.1
3′,4′-Dihydroxystilbazole-3	220—222	73.3	73.2	5.7	5.2	6.4	6.6
Diacetate	110—112	68.6	68.7	5.1	5.1	—	—
N-methyl iodide	233—235	47.7	47.3	4.1	4.0	4.1	3.9
3′,5′-Dihydroxystilbazole-3	225—227	73.2	73.2	5.3	5.2	6.6	6.6
Diacetate	112—114	68.6	68.7	5.2	5.1	—	—
3′,4′,5′-Trihydroxystilbazole-3	230° (decomp.)	67.9	68.1	4.8	4.8	6.0	6.1
Triacetate	139—141	64.0	64.2	4.9	4.8	—	—

Table 7. Physical constants and analyses of stilbazole hydrogenation products and their derivatives.

Compound	b.p. °C 1 mm Hg	m.p. °C	C found	C calc.	H found	H calc.	N found	N calc.
3′,4′-Dimethoxydihydrostilbazole-3	170—175							
Picrate		143—144	53.4	53.4	4.3	4.3	11.6	11.9
N-methyl iodide		194—196	49.7	49.9	5.3	5.2	3.5	3.6
3′,4′,5′-Trimethoxydihydrostilbazole-3	170—172							
Picrate		143—145	52.4	52.6	4.5	4.4	11.2	11.2
3′,4′-Dimethoxystilbazoline-3 [a]								
Picrate		182—184	52.6	52.7	5.6	5.5	12.2	11.7

[a] Prepared by reduction of 3′,4′-dimethoxystilbazole-3 with sodium and ethanol.

Table 8. The activity of various stilbene and stilbazole derivatives against some decay fungi.

+++: No visible growth; —: No inhibition of growth

Substances tested	Organisms tested [a]							
	1	2	3	4	5	6	7	8
Stilbene	++	++	+	(+)	(+)	+	+	++
Pinosylvin	+++	++	++	+++	+++	++	++	++
Dihydropinosylvin	+++		+++	++	+++			
Pinosylvin monomethyl ether	+	+	—	—	(+)	—	—	
3,4,3′,5′-Tetrahydroxy-stilbene	++	++	+	—	(+)	+	+	++
2,4-Dibromo-3,5-dihydroxy-stilbene	+	+						
2,4,6-Tribromo-3,5-dihydroxystilbene	(+)	—						
4′-Hydroxystilbazole-3	—	—	(+)	(+)	—	(+)	—	—
3′,4′-Dihydroxystilbazole-3	—	—	(+)	—	—	(+)	(+)	—
3′,5′-Dihydroxystilbazole-3	—	—	(+)	—	—	—	(+)	—
3′,4′,5′-Trihydroxystilbazole-3	—	—	—	—	—	(+)	—	—

[a] Organisms tested 1) *Sporotrichum termophile.* 2) *Chrysosporium pruinosum.* 3) *Fomes pinicola.* 4) *Peniphora gigantea.* 5) *Trametes cinnabarina.* 6) *Lenzites betulina.* 7) *Irpex lacteus.* 8) *Pullularia pullulans.*

groups were present in the 3′,5′-positions the yields of hydroxy-stilbazoles were low. In these cases higher yields were obtained by demethylation with boron tribromide at low temperatures.[25] In Table 6 the physical constants of the hydroxy-stilbazoles are given as well as of some of their derivatives.

Catalytic hydrogenation of the methoxy stilbazoles with Pd on charcoal in ethanol proceeded smoothly. Some of the hydrogenation products are listed in Table 7.

Docent M. Johansson, The Royal School of Forestry, Stockholm 50, Sweden, has kindly tested the fungicidal properties of the hydroxy-stilbazoles and some pinosylvin derivatives using the method of Rennerfelt and Nacht.[7] As can be seen from Table 8 none of the stilbazoles showed any significant activity. The pharmacological properties of these compounds are now under investigation at AB Astra.

EXPERIMENTAL

A. *Condensations.* A_1. Using piperidine and pyridine. A synthesis of β-phenyl-α-(3-pyridyl)-acrylic acid has been reported by Beard and Katritzky.[21] They heated a mixture of benzaldehyde, 3-pyridylacetic acid, piperidine, and pyridine to 120° for 72 h and obtained, after removal of the bases by steam distillation, a 34 % yield of the condensation product. We have found that this method was less successful with alkoxylated benzaldehydes, owing to formation of large amounts of tars. However, the yields were improved when the time of reaction was lowered to 48 h and the reaction product not subjected to distillation with steam but extracted as described in example 1.

A_2. Using lead(II) oxide and acetic anhydride. The condensations were carried out essentially according to Kuhn and Winterstein.[26] In some cases an insoluble lead salt crystallized on cooling and this was collected and dissolved in glacial acetic acid and the lead removed with hydrogen sulphide or, preferably, sulphuric acid. In other cases sirups were formed which were boiled with small amounts of ethanol until crystallization occurred or otherwise until the product did not improve. The alcohol insoluble material was then decomposed with sulphuric acid as described in example 2.

A_3. Using triethylamine and acetic anhydride. These condensations were carried out as described by Buckles and Hausman [27] but the time of reaction could be reduced. Optimal yields were obtained after 30 min boiling under reflux (*cf.* example 3).

Example 1, (Compound 5, Table 1). A mixture of 3,5-dimethoxybenzaldehyde (16.6 g, 0.1 mole), 3-pyridylacetic acid (18 g, 0.13 mole), piperidine (3 ml), and pyridine (150 ml) was boiled under reflux for 48 h. The bases were then removed by distillation (rotating evaporator) under reduced pressure. Sodium hydroxide (10 g) in water (150 ml) was added and the mixture extracted with ether. The aqueous phase was neutralized with acetic acid and the precipitate collected and washed with water and a little ethanol. The crude product was recrystallized from ethanol.

Example 2, (Compound 6, Table 1). A mixture of 3,4,5-trimethoxybenzaldehyde (1.5 g, 0.075 mole), 3-pyridylacetic acid (20.5 g, 0.15 mole), lead(II) oxide (33.5 g, 0.15 mole), and acetic anhydride (70 ml) was heated for 4 h (reflux). The reaction mixture was stored overnight in a refrigerator when crystallization occurred. The crystals were collected, washed with methanol and dried. The product was dissolved in acetic acid (600 ml) and sulphuric acid (17 ml) added dropwise while stirring. The lead sulphate was removed by centrifugation and washed with acetic acid. Evaporation (rotating evaporator) gave an oil which, on addition of sodium hydroxide until neutral reaction, crystallized. The product was recrystallized from ethanol.

Example 3, (Compound 5, Table 1). 3,5-Dimethoxybenzaldehyde (26.6 g, 0.16 mole) and 3-pyridylacetic acid (27.4 g, 0,2 mole) in acetic anhydride (400 ml) were treated with triethylamine (30 ml). The mixture was boiled for 30 min (reflux) and then evaporated to dryness in a rotating evaporator. The residue was neutralized with acetic acid and the resulting precipitate collected and washed with water and a little ethanol. The crude product was recrystallized from ethanol.

B. *Decarboxylations.* B_1. The stilbazole carboxylic acid (0.05 mole), copper powder, copper(I) chloride (both 0.05 mole),[22] and liquid paraffin (130 ml) were heated in an atmosphere of oxygen-free nitrogen until evolution of carbon dioxide started(180—210°) and kept at this temperature until reaction was complete (1—7 h). The reaction mixture was diluted with ether (300 ml), filtered and the filtrate extracted with dilute hydrochloric acid. The aqueous phase was then made alkaline and the base recovered by extraction with ether. The yield of crude product was usually about 90 % (*cf.* Table 3).

B_2. The stilbazole carboxylic acid (4 g) was mixed with copper powder (1.5 g) and heated in an evacuated (1 mm Hg) flask fitted with a receiver. Carbon dioxide evolution started at about 170° and the decarboxylated product distilled at about 200—210°. Heating was continued for about 1 h, when the temperature had reached 240°. The procedure was then repeated by adding further batches of acid to the same apparatus. The stilbazoles obtained were mostly sufficiently pure for the demethylation step, but could be purified by passing hydrogen bromide through a solution in ether. The precipitated salt was collected and recrystallized from methanol and finally decomposed with alkali. The yields varied between 80 and 95 % (*cf.* Table 3).

The method B_2, however, could not be used for decarboxylation of β-phenyl-α-(3-pyridyl)-acrylic acid since it distilled without decarboxylation, but with method B_1 a 95 % yield of decarboxylation product was obtained. Decarboxylation in liquid paraffin without the use of the copper/copper(I)chloride catalyst gives only about 12 % yield.[21]

C. *Simultaneous decarboxylation and demethylation* of the stilbazole carboxylic acids: The stilbazole carboxylic acid (0.01 mole) and freshly distilled pyridine hydrochloride (0.065 mole) were heated in a dry, oxygen-free nitrogen atmosphere. Demethylation started at about 160° and decarboxylation at about 170°. The temperature was kept at 180° for 3.5 h. About 50 ml water was then added to the cooled reaction mixture and aqueous ammonia was added until the solution had pH 6.5. The yellowish precipitate was collected, washed with cold water and recrystallized from ethanol. (Yields are given in Table 5.)

D. *Demethylation* of the stilbazoles with boron tribromide: Freshly distilled boron tribromide (1.5 g) in dry dichloromethane (30 ml) was added slowly (30 min) with stirring to 3′,5′-dimethoxystilbazole-3 (4.8 g) in dry dichloromethane (30 ml) in a distillation apparatus at a temperature of −78°. A yellowish-red precipitate was formed. The reaction mixture was allowed to reach room temperature and absolute methanol containing a few drops of sulphuric acid was added very slowly (vigorous exothermic reaction!). Distillation commenced during the addition of the methanol, which was continued until the distillate no longer gave a green flame reaction (approx. 200 ml of reagent). The non-volatile material was dissolved in water (250 ml) and a solution of sodium acetate added until the pH was 6.0. The precipitate formed was collected, recrystallized from methanol and sublimed under reduced pressure. (Yields are given in Table 5.)

E. *Hydrogenation* of the 3′,4′- and 3′,4′,5′-methoxystilbazoles to the corresponding dihydro-derivatives were carried out in the usual way (ethanol, 10 % Pd on charcoal). 3′,4′-Dimethoxystilbazole-3 was also reduced to the corresponding stilbazoline with sodium and ethanol (see Table 7).

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