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Synthesis of New 1-[5-(Substituted Phenoxymethyl)-1,3,4-oxadiazol-2-yl]-5-(substituted benzylidene)hydantoins as Potential Anthelminthic Agents

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Various 1-[5-(substituted phenoxymethyl)-1,3,4-oxadiazol-2-yl]5-(substituted benzylidene)hydantoins have been synthesized. Their activities against Hymenolepis nana infection in rats were tested. Compound **27** was found to be the most active showing 78.0 % clearance of infection at a dose of 250 mg/kg for 3 days.

Synthese neuer 1-[5-(substituierter Phenoxymethyl)-1,3,4-oxadiazol-2-yl]-5-(substituierter benzyliden)hydantoine als potentielle Anthelminthika

Verschiedene 1-[5-(substituierte Phenoxymethyl)-1,3,4-oxadiazol-2-yl]-5-(substituierte benzyliden)hydantoine wurden synthetisiert und auf ihre Wirksamkeit gegen Hymenolepis-nana-Infektion an Ratten geprüft. Die Verbindung **27** war am wirksamsten. Sie zeigt 78.0 % Wirksamkeit bei einer Dosierung von 250 mg/kg an 3 Tagen.

Despite the wide acceptance of 2-amino-1,3,4-oxadiazole[1-5] as versatile nucleus for building active anticestodicidal agents, comparatively less attention has been paid towards designing oxadiazoles fused with various pharmacologically active hydantoins[6-10] moiety. In a further exploration in this direction the synthesis of various 1-(5′-substituted phenoxymethyl-1′,3′,4′-oxadiazol-2′-yl)-5-substituted benzylidenehydantoins have been carried out.

The starting 2-amino-5-substituted phenoxymethyl-1,3,4-oxadiazoles **1–4** were prepared by cyclodehydration of substituted phenoxyacetic acid and semicarbazide hydrochloride in presence of conc. sulphuric acid which on reaction with potassium cyanate and acetic acid yields the corresponding ureas **5–8**. 5-substituted phenoxymethyl-1,3,4-oxadiazolylureas undergo cyclization in the presence of chloroacetic acid and pyridine to give the 1-(5′-substituted phenoxymethyl-1′,3′,4′-oxadiazol-2′-yl) hydantoins **8–12** which on condensation with appropriate aldehydes give 1-(5′-substituted phenoxymethyl-1′,3′,4′-oxadiazol-2′-yl)-5-substituted benzylidenehydantoins (Scheme 1).

Experimental Part

MP: open capillary, uncorr. *IR spectra* (KBr): Perkin-Elmer 157 infracord spectro photometer (v max cm^{-1}). *PMR spectra* ($CDCl_3$): Varian A60-D instrument, TMS int. ref. (chemical shifts in δ (ppm). *MS*: JEOL-JMS-D300 instrument. The purity of all compounds were checked on silica gel-'G' plates.

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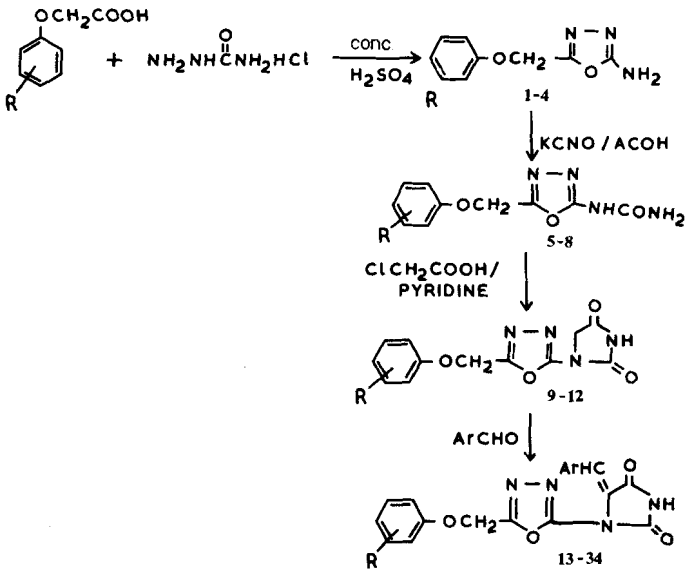

Synthesis of 2-amino-5-substituted methyl-1,3,4-oxadiazoles **1–4**

0.01 mole semicarbazide hydrochloride, 0.01 mole substituted phenoxyacetic acid and 10 ml (0.01 mole) conc. sulphuric acid were heated at 60–80° for 4 h. The resulting mixture was allowed to stand at room temp., then poured into ice cold water and neutralized with aqueous ammonia. The solid thus obtained was recrystallized from ethanol. The results are shown in table 1.

Synthesis of 2-(5-substituted phenoxymethyl-1,3,4-oxadiazolyl)-ureas **4–8**

0.01 mole 2-amino 5-substituted phenoxymethyl-1,3,4-oxadiazole was gradually added in 50 ml of glacial acetic acid with continuous shaking. The solution was diluted with 150 ml of water and after adding slowly 25 ml of an 0,4 M- an aqueous solution of potassium cyanate, the entire solution was stirred for 1 h. It was then allowed to stand for 30 min at room temp. A thick pasty mass thus obtained was agitated for another 30 min. The crude mass separated was washed with cold water. It was dried and recrystallized from water. The results are shown in table 1.

Synthesis of 1-(5'-substituted phenoxymethyl-1',3',4'-oxadiazol-2-yl)hydantoins **9–12**

On warming a mixture of 0.01 mole 2-(5-substituted phenoxymethyl-1,3,4-oxadiazolyl)urea and 0.01 mole chloroacetic acid in 20 ml of dry pyridine on a water bath, an exothermic reaction took place. The reaction mixture was cooled. When a viscous liquid was obtained 20 ml of absol. alcohol was added to this liquid and the resulting mixture was refluxed for 1 h. On subsequent cooling, a crystalline solid separated out. It was crystallized from ethyl acetate. The results are shown in table 1.

Synthesis of 1-(5'-substituted phenoxymethyl-1',3',4'-oxadiazol-2'-yl)-5-substituted benzylidenehydantoins **13–34**

A mixture consisting of 0.01 mole 1-(5-substituted phenoxymethyl-1',3',4'-oxadiazol-2'-yl)hydantoin, 0.01 mole appropriate aldehyde, 20 ml glacial acetic acid, 1 g fused sodium acetate and a few drops

Table 1: *Compounds* **1–12**

No.	R[c]	Mol. Formula[a,b]	m.p. °C	% N Analyses	
				Calc.	Found
1	p-Cl	$C_9H_8ClN_3O_2$	250	18.6	18.4
2	o-Cl	$C_9H_8ClN_3O_2$	248	18.6	18.5
3	p-Cl-m-CH_3	$C_{10}H_{10}ClN_3O_2$	232	17.5	17.3
4	p-CH_3	$C_{10}H_{11}N_3O_2$	270	20.5	20.6
5	p-Cl	$C_{10}H_9ClN_4O_3$	>288	20.9	20.6
6	o-Cl	$C_{10}H_9ClN_4O_3$	132	20.9	20.5
7	p-Cl-m-CH_3	$C_{11}H_{11}ClN_4O_3$	282	19.8	19.6
8	p-CH_3	$C_{11}H_{12}N_4O_3$	>286	22.6	22.4
9	p-Cl	$C_{12}H_9ClN_4O_4$	180	18.2	18.6
10	o-Cl	$C_{12}H_9ClN_4O_4$	192	18.2	18.5
11	p-Cl-m-CH_3	$C_{13}H_{11}ClN_4O_4$	198	17.4	17.6
12	p-CH_3	$C_{13}H_{12}N_4O_4$	150	19.4	19.3

[a] The elemental analyses (C,H) are within the range of ± 0.5 %.

[b] The compounds were obtained in about 70 % yield.

[c] *Spectroscopic data*

IR (KBr νmax cm^{-1}: 3300–3200 (NH); 1260, 1040 (C-O-C), 1615–1630 (C-N cyclic), 1715–1720 (=C=O cyclic).

1: PMR ($CDCl_3$): δ (ppm) = 7.2–8.0 (s, NH), 6.2–7.6 (m, Ar-H), 4.9–5.9 (s, 2H, OCH_2)
Mass: M^+ at m/z = 225.

5: PMR ($CDCl_3$): δ (ppm) = 8.0–9.0 (s, NH), 6.6–7.6 (m, Ar-H), 5.0–5.8 (s, 2H, OCH_2)
Mass: M^+ at m/z = 268

9: PMR ($CDCl_3$): δ (ppm) = 7.1–8.0 (s, NH), 6.8–7.9 (m, Ar-H), 4.2–5.5 (s, 2H, OCH_2)
Mass: M^+ at m/z = 308.

of acetic anhydride was refluxed in an oil bath at 140–150 °C for 8 h. The reaction mixture was then cooled and desiccated for 24 h where upon shining needle-shaped crystals separated out. These were crystallized from n-hexane or ethyl acetate. Physical data of the compounds **13–34** are reported in table 2.

Biological Assay

The compounds were screened for their in vivo cestodicidal and nematodicidal activity against H. nana and N. brasiliensis infection in rats. The screening was carried out by the technique of *Steward*[11] and *Whitlock*[12] with slight modification, and the compounds were given orally at dosage 500, 400 and 250 mg/kg using three rats per experimental group. Niclosamide was used as the standard drug in all the control experiments and it cleared 100 % of the above infection at a single oral dose of 50 mg/kg.

Determination of anthelminthic activity against H. nana infection

A number of male albino mice were infected with 200 viable ova of H. nana. On 15th day after infection faecal smears were collected from each animal and were examined under microscope for the

Table 2: *Compounds* **13–34**

Compd.[c] No.	R	Ar	m.p. °C	Molecular[a,b] formula	% N Analysis Calc.	Found	% cestodicidal activity against H. nana Dose mg/kg	% Efficacy
13	p-Cl	p-ClC_6H_4	> 280	$C_{19}H_{12}Cl_2N_4O_4$	13,0	12.8	250	59.0
14	p-Cl	p-$OCH_3C_6H_4$	> 280	$C_{20}H_{15}ClN_4O_5$	13.1	13.5	400	12.5
15	p-Cl	p-$N(CH_3)_2C_6H_4$	> 280	$C_{21}H_{18}ClN_5O_4$	15.9	15.7	250	28.0
16	p-Cl	o-$NO_2C_6H_4$	> 280	$C_{19}H_{12}ClN_5O_6$	15.9	15.4	250	46.0
17	p-Cl	C_6H_5	282	$C_{19}H_{13}ClN_4O_4$	14.1	14.5	250	–
18	p-Cl	m-$NO_2C_6H_4$	285	$C_{19}H_{12}ClN_5O_6$	15.9	15.6	250	48.0
19	o-Cl	p-ClC_6H_4	192	$C_{19}H_{12}Cl_2N_4O_4$	13.0	12.6	250	Inactive
20	o-Cl	p-$OCH_3C_6H_4$	238	$C_{20}H_{15}ClN_4O_5$	13.1	13.4	400	18.0
21	o-Cl	p-$N(CH_3)_2C_6H_4$	212	$C_{21}H_{18}ClN_5O_4$	15.9	15.8	500	–
22	o-Cl	p-$NO_2C_6H_4$	> 280	$C_{19}H_{12}ClN_5O_6$	15.9	16.0	250	68.0
23	o-Cl	o-$NO_2C_6H_4$	> 280	$C_{19}H_{12}ClN_5O_6$	15.9	15.4	250	–
24	p-Cl-m-CH_3	p-$OCH_3C_6H_4$	280	$C_{21}H_{17}ClN_4O_5$	12.7	12.9	250	30.0
25	p-Cl-m-CH_3	p-$N(CH_3)_2C_6H_4$	148	$C_{22}H_{20}ClN_5O_4$	15.4	15.7	250	48.5
26	p-Cl-m-CH_3	p-ClC_6H_4	270	$C_{20}H_{14}Cl_2N_4O_4$	12.6	12.7	250	55.0
27	p-Cl-m-CH_3	p-$NO_2C_6H_4$	238	$C_{20}H_{14}ClN_5O_6$	15.4	15.6	250	78.0
28	p-Cl-m-CH_3	m-$NO_2C_6H_4$	> 280	$C_{20}H_{14}ClN_5O_6$	15.4	15.8	400	28.0
29	p-Cl-m-CH_3	o-$NO_2C_6H_4$	> 280	$C_{20}H_{14}ClN_5O_6$	15.4	15.5	400	20.8
30	p-CH_3	p-$OCH_3C_6H_4$	> 280	$C_{21}H_{18}N_4O_5$	13.8	14.0	500	11.2
31	p-CH_3	p-$N(CH_3)_2C_6H_4$	> 280	$C_{22}H_{21}N_5O_4$	16.7	16.3	400	Inactive
32	p-CH_3	p-ClC_6H_4	> 280	$C_{20}H_{15}ClN_4O_4$	13.6	13.3	250	65.0
33	p-CH_3	p-$NO_2C_6H_4$	> 280	$C_{20}H_{15}N_5O_6$	16.6	17.0	250	72.0
34	p-CH_3	p-$NHCOCH_3C_6H_4$	> 280	$C_{22}H_{19}N_5O_5$	16.2	16.5	400	–

[a] The elemental analyses (C,H) are within the range of ± 0.4 %.

[b] The compounds were obtained in about 65 % yield.

[c] *Spectroscopic data*

IR (KBr) vmax cm^{-1}: 1630 (C-N), 1260 (C-O-C), 1715–1720 (=C=O cyclic), 3050 (C=CH), 3300–3250 (NH).

13: PMR ($CDCl_3$): δ (ppm) = 6.7–7.34 (m, Ar-H), 8.1–8.6 (s, NH), 3.83–5.4 (s,2,OCH_2), 7.1 (s, 1H, CH=C).

Mass: M^+ at m/z = 431

18: PMR ($CDCl_3$): δ (ppm) = 6.5–7.9 (m, Ar-H), 7.9–8.7 (s, NH), 3.52–5.38 (s,2,OCH_2), 6.9 (s, 1H, CH=C).

Mass: M^+ at m/z = 442

24: PMR ($CDCl_3$): δ (ppm) = 6.3–7.5 (m, Ar-H), 7.8–8.2 (s, NH), 3.75–5.1 (s,2,OCH_2), 7.5 (s, 1H, CH=C), (s,3H,CH_3).

Mass: M^+ at m/z = 440.

30: PMR ($CDCl_3$) δ (ppm) =: 6.2–7.8 (m, Ar-H), 7.9–8.5 (s, NH), 3.85–5.54 (s,2,OCH_2), 7.4 (s, 1H, CH=C).

Mass: M^+ at m/z = 405.

presence of ova of H. nana. All the animals were color marked, weighed and divided into groups of four animals. These were fasted on 17th day and tested with a large single oral dose of the test compound on 18th day. A group of four animals was left untreated as control. For establishing the initial dose a preliminary oral toxicity test was carried out. All the animals including control were

again fasted for 24 h on 19th day and were sacrified on 20th day. The worms from the small intestine were collected and the chemotherapeutic evaluation was done on the bases of the number of mice cleared of infection.

Determination of anthelminthic activity against N. brasiliensis infection in rats

The just waened male rats were incubated with 500 infected larvae of N. brasiliensis. On the 18th day of infection, random samples of faeces from different rats were examined for the presence of ova. Only positive rats were taken for experiments. The infected rats were divided in groups of three and starved for 24 h. A group of 3 animals was left untreated as control. On the 9th day the test compounds were administered to the rest of the rats of each group at a dose of 250 mg/kg × 3. The rats including the control were starved on the 10th day. They were then sacrified on the next day and the worm loads of both the treated and untreated rats were compared.

Results and Discussions

In preliminary screening compounds **22, 27, 33** were found to posses 68.0–78.0 % activity at 250 mg/kg while compounds **13, 14–16, 18, 24,26, 28, 29, 32, 33** also exhibited activity showing inhibition of worm population from 28.0–65.0 % at a dose of 250 mg/kg for 3 days. The rest of the tested compounds were either found to be inactive or showed insignificant activity at a dose of 500 and 400 mg/kg.

The cestodicidal activity against H. nana reported in this paper clearly demonstrates that the presence of a nitro group at para position of the benzene ring at R^1 position increases the activity with respect to the unsubstituted benzene ring. Introduction of the chloro substituent also increases the activity while methyl group substitution does not increase activity to a large extend.

The compounds when tested for their in vivo nematodicidal activity against N. brasiliensis were either found to be inactive or exhibited feeble or insignificant activity.

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Elektronenstoßinduzierter Verlust der Substituenten an C-5 und C-8 bei 1,2,3,4-Tetrahydroisochinolinen, 2. Mitt.[1)]

Synthese C-8-substituierter 1,2,3,4-Tetrahydroisochinoline

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Die Herstellung verschiedener C-8-substituierter 1,2,3,4-Tetrahydroisochinoline wird beschrieben.

Electron-Impact Induced Loss of C-5/C-8 Substituents in the Molecular Ions of 1,2,3,4-Tetrahydroisoquinolines, II: Synthesis of C-8 Substituted 1,2,3,4-Tetrahydroisoquinolines

The synthesis of various C-8 substituted 1,2,3,4-tetrahydroisoquinolines is described.

In der 1. Mitt.[1)] haben wir verschiedene Hexahydro-pyrrolo[1,2-b]isochinoline (Typ **1**) als Modellsubstanzen des Alkaloidderivates Dihydrovinceten (**2**) beschrieben. Die beim Dihydrovinceten beobachteten ungewöhnlichen ms Fragmentierungen treten auch bei **1a** auf, das zugleich die Partialstruktur eines C-8-substituierten 1,2,3,4-Tetrahydroisochinolins enthält. Wir vereinfachten daher unsere Modelle durch Weglassen des Pyrrolidin-Bausteins und synthetisierten C-8-substituierte 1,2,3,4-Tetrahydroisochinoline.

In der Lit. fanden wir einige C-8-substituierte 1,2,3,4-Tetrahydroisochinoline, die für die Einführung der Hydroxybutyl-Seitenkette geeignet sind: *Tomita* und *Watanabe*[2)] haben 8-Brom-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisochinolin hergestellt, *Mathison* et al.[3)] formylierten 5-Methoxy-2-methyl-1,2,3,4-tetrahydroisochinolin zum entspr. C-8-Aldehyd, *Haworth*[4)] beschreibt die Synthese von 5,6-Dimethoxy-2-methyl-8-nitro-1,2,3,4-tetrahydroisochinolin.

** Aus der Dissertation *G. Stöber*, Regensburg 1981.

*** Herrn Prof. Dr. *O.-E. Schultz* zum 75. Geburtstag in Verehrung gewidmet.

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