Substituted 5-Aryl- or 5-diphenylmethyl-3-alkyl-2-oxazolidones as Anticonvulsants

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Several 5-aryl- or 5-diphenylmethylhydracrylyl hydrazides were synthesized and converted into 5-aryl- or diphenylmethyl-2-oxazolidones. The latter compounds were further alkylated into their corresponding 5-aryl- or 5-diphenylmethyl-3-alkyl-2-oxazolidones as possible anticonvusants.

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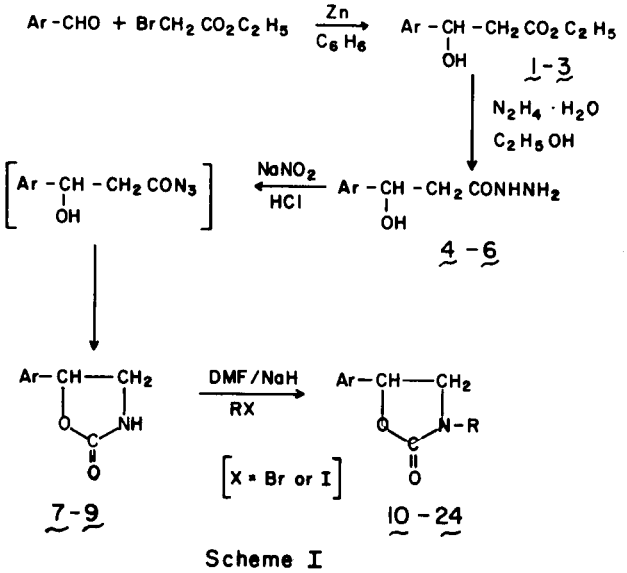
Derivatives of substituted aryl-2-oxazolidones have been reported to possess central nervous system stimulant, antidepressant, analgesic and muscle-relaxant activities (1). Trimethadione, belonging to a group of oxazolidone derivatives, has been found to possess therapeutic usage in the management of petit-mal epilepsy (2). These observations prompted synthesis of 5-aryl- or 5-diphenylmethylhydracrylyl hydrazides (**4-6**) which were converted into 5-aryl- or 5-diphenylmethyl-2-oxazolidones (**7-9**). The latter compounds were further alkylated to obtain the corresponding 5-aryl- or 5-diphenylmethyl-3-alkyl-2-oxazolidones (**10-24**). The various steps used in the synthesis of substituted oxazolidones (**10-24**) are outlined in Scheme I.

Treatment of 3,4-dimethoxybenzaldehyde, 3,4,5-trimethoxybenzaldehyde or diphenylacetaldehyde with ethyl bromoacetate and zinc (Reformatsky reaction) formed ethyl- β-aryl- or β-diphenylmethylhydracrylates **1-3** (4) which were then refluxed in ethanol with hydrazine hydrate to obtain β-aryl- or β-diphenylmethylhydracrylyl hydrazides **4-6**. Reaction of these hydrazides with sodium nitrite resulted in cylization of the corresponding azide (Curtius rearrangement) to form 5-aryl- or 5-diphenylmethyl-2-oxazolidones which were further alkylated by successive treatment with sodium hydride and the appropriate alkyl halide to obtain 5-aryl- or 5-diphenylmethyl-3-alkyl-2-oxazolidones **10-24**.



Scheme I

All 5-aryl- or 5-diphenylmethyl-3-alkyl-2-oxazolidones (**10-24**) have been reported to possess anticonvulsant activity against pentylenetetrazol induced seizures in mice, ability to potentiate pentobarbital sleeping time in mice, and monoamine oxidase inhibitory activity during oxidation of 5-hydroxytyramine, kynuramine and tyramine by rat brain homogenates (3).

EXPERIMENTAL

All compounds were analyzed for their carbon, hydrogen and nitrogen content. Melting points were taken in an open capillary tube with an immersion thermometer and are corrected. Infrared spectra were obtained using Perkin-Elmer 137 spectrophotometer. All 5-aryl- or 5-diphenylmethyl-2-oxazolidones (**7-24**) were examined as suspension in nujol mull in the range of 600-4000 cm^{-1}. The presence of the characteristic bands of C=O (~ 1750 cm^{-1}) in the infrared spectrum provided support for the structure of **7-9** and **10-24**, respectively.

Ethyl- β-Aryl- or β-diphenylmethylhydracrylate (**1-3**).

Zinc wool (0.6 mole), suspended in 200 ml. of dry benzene, was gradually added to a 60 ml. mixture consisting of 3,4-dimethoxybenzaldehyde, 3,4,5-trimethoxybenzaldehyde or diphenylacetaldehyde (0.55 mole), ethylbromoacetate (0.6 mole), and dry benzene. The mixture was heated on a water bath until the reaction set in and the contents were then refluxed for 2 hours until all the metal disappeared. After refluxing, the mixture was acidified with dilute sulfuric acid. The benzene layer was separated in a separating funnel and was washed with water, sodium carbonate, and again with water. The benzene layer was dried over magnesium sulfate. The excess of benzene was removed by distillation under reduced pressure at a temperature not exceeding 50°. used for preparation of the subsequent substituted hydrazide without further purification.

β-Aryl- or β-diphenylmethylhydracrylyl Hydrazides (**4-6**).

To a solution of appropriate β-aryl- or β-diphenylmethylhydracrylate (0.8 mole) in 60 ml. of ethanol was added 80 g. of 50% hydrazine hydrate (0.8 mole). The exothermic reaction, resulting in the production of a white mass, was completed by refluxing at 50° for 1 hour (4). The crude products, recorded in Table I, were filtered, washed with ethanol, and finally recrystallized from ethanol.

Table I

β-Aryl- or β-diphenylmethylhydracrylyl Hydrazides

Compound No.	Aryl	M.p. °C	Yield %	Molecular Formula	Analysis % Calcd. C	H	N	Found C	H	N
4	3,4-$(CH_3O)_2C_6H_3$	170	75	$C_{11}H_{16}N_2O_4$	55.00	6.66	11.66	55.26	6.41	11.78
5	3,4,5-$(OCH_3)_3C_6H_2$	165	70	$C_{12}H_{18}N_2O_5$	53.33	6.66	10.37	53.55	6.86	10.17
6	$(C_6H_5)_2CH$	176	75	$C_{16}H_{18}N_2O_2$	71.11	6.66	10.37	70.96	6.59	10.64

Table II

5-Aryl- or 5-diphenylmethyl-2-oxazolidones

Compound No.	Aryl	M.p. °C	Yield %	Molecular Formula	Analysis % Calcd. C	H	N	Found C	H	N
7	3,4-$(CH_3O)_2C_6H_3$	115	60	$C_{11}H_{13}NO_4$	59.19	5.82	6.27	58.88	6.03	6.21
8	3,4,5-$(CH_3O)_3C_6H_2$	126	65	$C_{12}H_{15}NO_5$	56.91	5.92	5.53	57.18	6.16	5.62
9	$(C_6H_5)_2CH$	150	55	$C_{16}H_{15}NO_2$	75.88	5.92	5.53	75.62	6.29	5.51

Table III

5-Aryl- or 5-diphenylmethyl-3-alkyl-2-oxazolidone

Compound No.	Aryl	Alkyl	M.p. °C	Yield %	Molecular Formula	Analysis % Calcd. C	H	N	Found C	H	N
10	3,4-$(CH_3O)_2C_6H_3$	CH_3	56	40	$C_{12}H_{15}NO_4$	60.75	6.32	5.90	60.57	6.16	6.13
11	3,4-$(CH_3O)_2C_6H_3$	C_2H_5	89- 90	45	$C_{13}H_{17}NO_4$	62.15	6.77	5.57	61.95	6.81	6.52
12	3,4-$(CH_3O)_2C_6H_3$	$CH_2CH_2CH_3$	52	45	$C_{14}H_{19}NO_4$	63.39	7.16	5.28	63.48	6.85	5.58
13	3,4-$(CH_3O)_2C_6H_3$	$CH_2CH{=}CH_2$	62	50	$C_{14}H_{17}NO_4$	63.87	6.46	5.32	64.02	6.63	5.14
14	3,4-$(CH_3O)_2C_6H_3$	$CH_2CH_2CH_2CH_3$	48- 49	50	$C_{15}H_{21}NO_4$	64.58	7.52	5.01	64.22	7.76	5.11
15	3,4,5-$(CH_3O)_3C_6H_2$	CH_3	51	52	$C_{13}H_{17}NO_5$	58.42	6.36	5.24	58.76	6.18	5.64
16	3,4,5-$(CH_3O)_3C_6H_2$	C_2H_5	101	45	$C_{14}H_{19}NO_5$	59.78	6.76	4.98	59.59	6.96	5.21
17	3,4,5-$(CH_3O)_3C_6H_2$	$CH_2CH_2CH_3$	55	50	$C_{15}H_{21}NO_5$	61.01	7.11	4.74	61.36	6.96	5.02
18	3,4,5-$(CH_3O)_3C_6H_2$	$CH_2CH{=}CH_2$	105	54	$C_{15}H_{19}NO_5$	61.43	6.48	4.77	61.52	6.69	4.67
19	3,4,5-$(CH_3O)_3C_6H_2$	$CH_2CH_2CH_2CH_3$	41- 42	48	$C_{16}H_{23}NO_5$	62.13	7.44	4.53	61.89	7.44	4.76
20	$(C_6H_5)_2CH$	CH_3	92	60	$C_{17}H_{17}NO_2$	76.40	6.36	5.24	76.75	6.66	6.36
21	$(C_6H_5)_2CH$	C_2H_5	122	57	$C_{18}H_{19}NO_2$	76.86	6.76	4.98	77.15	6.48	5.21
22	$(C_6H_5)_2CH$	$CH_2CH_2CH_3$	96- 97	55	$C_{19}H_{21}NO_2$	77.28	7.11	4.74	77.36	6.92	4.63
23	$(C_6H_5)_2CH$	$CH_2CH{=}CH_2$	141-142	65	$C_{19}H_{29}NO_2$	77.81	6.48	4.77	78.06	6.76	5.03
24	$(C_6H_5)_2CH$	$CH_2CH_2CH_2CH_3$	99-100	60	$C_{20}N_{23}NO_2$	77.66	7.44	4.53	77.32	7.15	4.46

5-Aryl- or 5-diphenylmethyl-2-oxazolidones (**7-9**).

With continuous stirring, while maintaining the temperature of the reaction at 15°, a solution of 2.1 g. of sodium nitrite (0.03 mole) in water was added gradually to a mixture of the appropriate β-aryl- or β-diphenylmethyl hydrazide (0.03 mole) in 40 ml. of 0.1 *N* hydrochloric acid. The stirring was continued for 15 minutes, and the mixture was extracted with three 50 ml. portions of benzene. The combined benzene layer was dried quickly over magnesium sulfate, filtered, and heated over a water bath at 50-60°, resulting in an exothermic reaction with a vigorous evolution of nitrogen. After the reaction had subsided, the mixture was refluxed on a water bath for 15 minutes. The excess of benzene was then removed by distillation. The crude oxazolidones which separated out were filtered and recrystallized from a benzene-hexane (1:1) mixture (Table II).

5-Aryl- or 5-diphenylmethyl-3-alkyl-2-oxazolidones (**10-24**).

A solution of **7-9** (0.01 mole) in 20 ml. of dry DMF was added to a stirred suspension of hexane-washed sodium hydride (0.3 g.) in 50 ml. of DMF. The mixture was stirred until the evolution of hydrogen ceased and then was treated with the appropriate alkyl bromide (0.015 mole) or alkyl iodide (0.015 mole) in 10 ml. of dry DMF. The mixture was further stirred for 1 hour and then refluxed gently for another 1 hour. The excess of DMF was removed by distillation under reduced pressure, and the residue was dissolved in 100 ml. of benzene. The benzene layer was washed twice with water and dried over magnesium sulfate. The crude product which separated after distilling off the benzene was filtered, washed with benzene, and recrystallized from the benzene-hexane mixture. The various 5-aryl- or 5-diphenylmethyl-3-alkyl-2-oxazolidones (**10-24**) are recorded in Table III.

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