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Seven newer 1,3-disubstituted hydantoins (**17-23**) were synthesized from 4-alkoxyanilines. The anticonvulsant activity of these substituted hydantoins and their precursor carbamides (**10-16**) was reflected by their ability to provide 28-80% and 30-70% protection, respectively, against pentylenetetrazol-induced convulsions in mice. In general, substituted hydantoins possessed greater anticonvulsant activity than their corresponding precursor carbamides.

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Amongst a large number of hydantoin derivatives, 5,5-diphenyl hydantoin is a potent anticonvulsant which possesses minumum sedative and hypnotic side effects (1). Reecently some 1,3-bis(alkoxymethyl)-5,5-diphenyl hydantoins have been reported to be effective against both maximal electric shock and pentylenetetrazol-induced seizures (2). Attempts have been made earlier to obtain more active and less toxic hydantoin derivatives by introducing different substituents either at 1, 3 or 5 position in the hydantoin ring (3,4). These observations prompted the synthesis of some 1,3-disubstituted hydantoins according to the steps outlined in Scheme I.

The 4-alkoxyanilines **2-5**, obtained from 4-hydroxyacetanilide (**1**) by the reaction of alkylbromides in the presence of potassium carbonate followed by the hydrolysis with hydrochloric acid, were reacted with ethyl chloroacetate and sodium acetate to yield *N*-(4-alkoxyphenyl)glycine ethyl esters **6-9**. The reaction of **6-9** with aryl isocyanates gave 1-ethylacetate-1-(4-alkoxyphenyl)-3-aryl carbamides **10-16**, which on heating with ethanol under reflux were cyclized to 1,3-disubstituted hydantoins **17-23**.

All newly synthesized 1,3-disubstituted hydantoins **17-23** and their precursor carbamides **10-16** were evaluated for their anticonvulsant activity in albino mice against pentylenetetrazol-induced seizures. The anticonvulsant activity of these hydantoins **17-23** and carbamides **10-16** were found to be in the range of 28-80% and 30-70%, respectively, except compound **17** which was completely devoid of anticonvulsant activity. The maximum anticonvulsant activity of 80% was exhibited by compound **20**. The toxicity studies have revealed that these compounds possessed low toxicity since the approximate LD_{50} values were found to be in the range of 500- > 1000 mg./kg.

EXPERIMENTAL

All compounds were analyzed for their carbon, hydrogen and nitrogen contents. Melting points were taken in open capillary tubes with a partial immersion thermometer and are corrected. Infrared spectra were recorded on a Perkin-Elmer spectrophotometer.

4-Alkoxyanilines (**2-5**).

A mixture of 4-hydroxyacetamide (**1**) (0.1 mole), a suitable alkylbromide (0.11 mole), and potassium carbonate (0.25 mole) was refluxed in dry acetone for 25 hours. The solvent was removed and the solid thus obtained was hydrolyzed with concentrated hydrochloric acid and extracted with ether. The organic layer was washed with water and dried. The removal of ether gave an oily residue which was further purified by vaccum distillation (6-8).

N-(4-Alkoxyphenyl)glycine Ethyl Esters (**6-9**).

To a well stirred mixture of anhydrous sodium acetate (0.35 mole) and the appropriate **2-5** (0.2 mole) in 40 ml. of ethanol, was added ethyl chloroacetate (0.25 mole). After refluxing for 30 to 40 hours, the reaction mixture was cooled, poured into 500 ml. of ice cold water and extracted with ether. The organic layer was washed with water and dried. The removal of ether yielded an oily residue which was distilled under vacuum.

N-(4-Ethoxyphenyl)glycine Ethyl Ester (**6**).

This compound had b.p. 174°/16 mm, reported b.p. 170°/16 mm (9).

N-(4-*n*-Propoxyphenyl)glycine Ethyl Ester (**7**).

This compound had m.p. 42°, yield 36%.

Anal. Calcd. for $C_{13}H_{19}NO_3$: C, 65.83; H, 8.01; N, 5.91. Found: C, 65.85; H, 8.43; N, 5.49.

N-(4-*n*-Butoxyphenyl)glycine Ethyl Ester (**8**).

This compound had b.p. 245°/0.1 mm, yield 30%.

Anal. Calcd. for $C_{14}H_{21}NO_3$: C, 66.92; H, 8.30; N, 5.57. Found: C, 66.74; H, 8.29; N, 5.49.

N-(4-Allyloxyphenyl)glycine Ethyl Ester (**9**).

This compound had b.p. 189°/0.1 mm, yield 35%.

Anal. Calcd. for $C_{13}H_{17}NO_3$: C, 66.40; H, 7.23; N, 5.72. Found: C, 66.37; H, 7.04; N, 5.68.

1-Ethylacetate-(4-alkoxyphenyl)-3-substituted Carbamides (**10-16**).

Equimolar quantities of the suitable arylisocyanate and **6-9** were refluxed for 10 hours in dry benzene. After removing the excess solvent under reduced pressure, the solid mass which separated was filtered, dried and recrystallized from carbon tetrachloride. These carbamides were characterized by their sharp melting points, elemental analyses and ir spectral data (Table I).

1,3-Disubstituted Hydantoins (**17-23**).

The appropriate carbamide **10-16** in 12 ml. of ethanol was heated under reflux for 3-4 hours. The reaction mixture was diluted with ethanol while hot until the solution became clear. On cooling, the solid mass that separated out was collected by filtration and recrystallized from ethanol. The various hydantoins **17-23** were finally characterized by their sharp melting points, elemental analyses and ir spectral data (Table I).

Pharmacological Studies.

The anticonvulsant activities of **10-23** were determined in mice after

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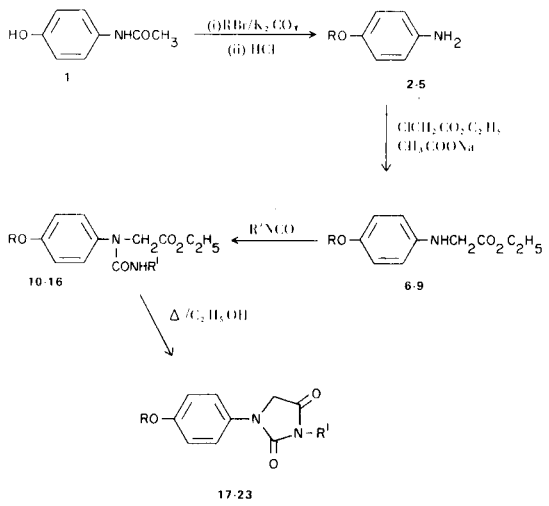
Table I

Physical Constants and Ir Spectral Data of 1-Ethylacetate-1-(*p*-alkoxyphenyl)-3-aryl Carbamides (**10-16**) and 1,3-Disubstituted Hydantoins (**17-23**)

Compound No.	R	R′	M. p. °C	Yield %	Molecular Formula	Analysis % Calculated C	H	N	Found C	H	N	Ir Spectral Data (a) cm^{-1}	(b) cm^{-1}
10	C_2H_5	C_6H_5	207	93	$C_{19}H_{22}N_2O_4$	66.66	6.43	8.18	66.61	6.35	8.00	1665	1730
11	C_2H_5	*m*-ClC_6H_4	75-76	91	$C_{19}H_{21}ClN_2O_4$	60.55	5.57	7.43	60.45	5.57	7.13	1660	1725
12	*n*-C_3H_7	C_6H_5	215	86	$C_{20}H_{24}N_2O_4$	67.41	6.74	7.86	67.62	6.48	7.80	1680	1739
13	*n*-C_4H_9	C_6H_5	195	80	$C_{21}H_{26}N_2O_4$	68.11	7.02	7.56	68.09	7.34	7.67	1665	1730
14	*n*-C_4H_9	*m*-ClC_6H_4	187	86	$C_{21}H_{25}ClN_2O_4$	62.30	6.18	6.92	62.35	6.09	6.77	1670	1740
15	$CH_2=CH-CH_2$	C_6H_5	185	90	$C_{20}H_{22}N_2O_4$	67.79	6.21	7.90	67.52	6.37	7.89	1660	1735
16	$CH_2=CH-CH_2$	*m*-ClC_6H_4	80	91	$C_{20}H_{21}ClN_2O_4$	61.77	5.40	7.20	61.63	5.14	7.19	1678	1720
17	C_2H_5	C_6H_5	210	76	$C_{17}H_{16}N_2O_3$	68.92	5.41	9.46	68.90	5.45	9.39	1725	1770
18	C_2H_5	*m*-ClC_6H_4	145	84	$C_{17}H_{15}ClN_2O_3$	61.72	4.54	9.47	61.57	4.44	9.41	1710	1765
19	*n*-C_3H_7	C_6H_5	220	65	$C_{18}H_{18}N_2O_3$	69.68	5.81	9.03	69.60	5.62	9.01	1712	1755
20	*n*-C_4H_9	C_6H_5	200	60	$C_{19}H_{20}N_2O_3$	67.30	6.17	6.64	67.28	6.17	6.23	1720	1750
21	*n*-C_4H_9	*m*-ClC_6H_4	123	80	$C_{19}H_{19}ClN_2O_3$	63.57	5.29	7.89	63.37	5.28	7.84	1712	1754
22	$CH_2=CH-CH_2$	C_6H_5	203-4	73	$C_{18}H_{16}N_2O_3$	70.13	5.19	9.09	70.41	5.43	9.22	1715	1765
23	$CH_2=CH-CH_2$	*m*-ClC_6H_4	117	75	$C_{18}H_{16}ClN_2O_3$	63.14	4.28	8.18	63.35	4.62	8.01	1720	1765

(a) Peak observed for -C-NH in **10-16** and -C- at position 2 of **17-23**. (b) Peak observed for -C-O in **10-16** and -C- at position 4 of **17-23**.

Scheme I



intraperitoneal administration in a dose of 100 mg./kg. against convulsions in albino mice induced by subcutaneous administration of 90 mg./kg. of pentylenetetrazol (5). The toxicities of **10-23** were reflected by their approximate LD_{50} values determined by intraperitoneal administration in albino mice by following the method reported earlier (10).

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