of the same solvents. The first eluates contained the higher melting, more insoluble isomer while the later fractions contained the lower melting, more soluble form. Ultraviolet spectra maxima were determined for several of the fractions. No indication of the presence of more than two compounds was found. From the chromatographic separation 1.7 g. (59% of total material recovered) of low melting VB, m.p. 127–128°, λ_{max}, 2790 Å., and 0.95 g. (33% of total material recovered) of high melting VA, m.p. 141–142°, λ_{max}, 2840 Å., and 0.25 g. of a mixed fraction, m.p. 110–135°, resulted. The total recovery of material from the chromatographic separation was 2.9 g. (97%).

Anal. Calcd. for $C_{22}H_{25}NO$: C, 82.72; H, 7.89; N, 4.39. Found for (VB): C, 82.88; H, 7.62; N, 4.64.

Reaction of Ethylenimine Ketones with Phenylhydrazine.—A 1.90-g. (0.006 mole) sample of VA was dissolved in 25 ml. of 40–60 abs. alcohol–chloroform solution, cooled and treated with 0.75 g. (0.012 mole) of glacial acetic acid and 0.75 g. (0.006 mole) of phenylhydrazine. Almost immediately the solution began to show the characteristic blue fluorescence of the aminopyrazolines.[20] After standing at room temperature for 14 hours, isolation of the products produced 0.3 g. (16% yield) of 1-phenyl-3-(*p*-xenyl)-5-methylpyrazole (VII), m.p. 128–129.5°, as colorless plates, recrystallized from abs. alcohol; and 0.88 g. (40% yield) of 1-phenyl-3-(*p*-xenyl)-4-cyclohexylamino-5-methylpyrazoline (VI), m.p. 158.5–159.5°, as yellow-green hexagonal plates, recrystallized from benzene and petroleum ether (b.p. 60–68°). The product VI gave positive Knoor and Raiford pyrazoline tests.[7] The solid compound and solutions as dilute as 0.5×10^{-4} *M* showed a strong blue fluorescence when exposed to ultraviolet light.

Anal. Calcd. for $C_{28}H_{31}N_3$ (VI): C, 82.11; H, 7.63; N, 10.30. Found: C, 82.04; H, 7.63; N, 10.20. Calcd. for $C_{22}H_{18}N_2$ (VII): C, 85.13; H, 5.84; N, 9.03. Found: C, 84.87; H, 5.82; N, 9.19.

An identical experiment with the lower melting ethylenimine ketone VB produced an 88% yield of the pyrazole (VII), m.p. 128.5–129.5°. The solid compound but not dilute solutions of the pyrazole showed a blue fluorescence when exposed to ultraviolet light.

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LINCOLN, NEBRASKA

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF PARKE, DAVIS & CO.]

Anticonvulsants. IV. An Investigation of α-(Substituted phenyl)-succinimides

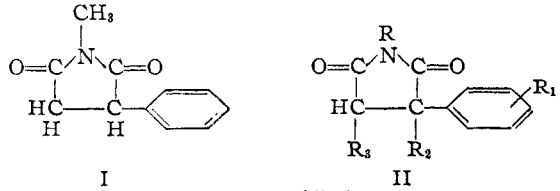
BY C. A. MILLER AND LOREN M. LONG

RECEIVED JULY 20, 1953

Thirty-three α-phenylsuccinimides containing a substituent on the phenyl group have been prepared and tested for anticonvulsant activity. Many compounds of this group effectively suppress metrazol and/or electrically-induced convulsions in laboratory animals. Clinical evaluation of a number of these products is in progress.

In the first paper[1] of this series a number of α-phenylsuccinimides were shown to possess a high degree of anticonvulsant activity.[2] Subsequently, a clinical study proved several of these to be effective anti-epileptic agents. N-Methyl-α-phenylsuccinimide (Milontin)[3] I is particularly efficacious in the treatment[4,5] of petit mal epilepsy and is relatively non-toxic.

Consequently, the study of this type of compound was extended by the synthesis of a group of α,β-substituted phenylsuccinimides[6] and alkylsuccinimides.[7] Many of these derivatives exhibited considerable activity[2] against metrazol-induced convulsions, and a few showed an appreciable activity against electrically-induced convulsions. None of the alkylsuccinimides was effective in the latter tests.



I II

R, R_2, R_3 = H, Alkyl
R_1 = Hal, CH_3, OH, CH_3O–

The present paper is concerned with the synthesis and anticonvulsant properties of a series of succinimides, illustrated by II, which contain a substituent on the phenyl group.

The method of synthesis which has been discussed previously[1,6,7] employs the condensation of the appropriate aldehyde[8] or ketone[9,10] with ethyl cyanoacetate. The α-cyanocinnamate thus formed is converted by means of potassium cyanide to the α,β-dicyanopropionate which is subsequently hydrolyzed to the succinic acid with concentrated hydrochloric acid or a mixture of hydrochloric and acetic acids. In one case the dicyano ester was methylated before hydrolysis. Conversion of succinic acid to the imide was effected by distillation of the amine salt. The pertinent data are given in Table I.

Anticonvulsant Activity.—The succinimides were tested for their anticonvulsant activity by a method[11] described earlier. As with the previously tested substituted succinimides, many of the compounds of the present series were effective in suppressing metrazol-induced convulsions. In a few cases the activity exhibited against electrically-induced convulsions was interesting; however, to date none of the compounds examined have approached the activity shown by 5,5-diphenylhydantoin (Dilantin).[12] A number of these com-

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(4) F. T. Zimmerman, *Arch. Neurol. Psychiat.*, **66**, 156 (1951).
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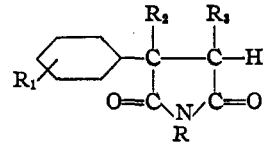
TABLE I



R	R_1	R_2	R_3	B.p. °C.	Mm.	M.p., °C.	Yield, %[a]	Formula	Nitrogen, %[b] Calcd.	Found	Anticonvulsant activity Metrazol[c]	PD_{50}[d]
H	*o*-Methyl	H	H	176–180	0.6	80–83	36	$C_{11}H_{11}NO_2$	7.40	7.41	4+/125	[f]
Methyl	*o*-Methyl	H	H	143	0.6		87	$C_{12}H_{13}NO_2$	6.89	6.74	3+/125	[f]
Ethyl	*o*-Methyl	H	H	106–161	2.9		67	$C_{13}H_{15}NO_2$	6.45	6.17	+/500	[f]
Allyl	*o*-Methyl	H	H	142	0.3		63	$C_{14}H_{15}NO_2$	6.11	5.82	+/125	[f]
Isopropyl	*o*-Methyl	H	H	157–158	2.6		63	$C_{14}H_{17}NO_2$	6.06	5.75	+/250	[f]
H	*o*-Hydroxy-	H	H			207–209	44	$C_{10}H_9NO_3$	7.33	7.06	4+/125	*ca.* 400
Methyl	*o*-Hydroxy-	H	H			136–138	57	$C_{11}H_{11}NO_3$	6.83	6.78	4+/125	[f]
H	*p*-Hydroxy-	H	H			204–205	61	$C_{10}H_9NO_3$	7.33	7.44	2+/500	[f]
Methyl	*p*-Hydroxy-	H	H			158–159	78	$C_{111}H_1NO_3$	6.83	6.73	+/500	[f]
Ethyl	*p*-Hydroxy-	H	H			167–168	60	$C_{12}H_{13}NO_3$	6.39	6.57	0/500	[f]
H	*p*-Methoxy-	H	H			135–137	73	$C_{11}H_{11}NO_3$	6.83	6.70	3+/500	[f]
Methyl	*p*-Methoxy-	H	H			125–126	75	$C_{12}H_{13}NO_3$	6.39	6.39	0/500	[f]
Ethyl	*p*-Methoxy-	H	H			53– 55	70	$C_{13}H_{15}NO_3$	6.00	6.00	2+/250	[f]
Isopropyl	β-Methoxy-	H	H			60– 62	72	$C_{14}H_{17}NO_3$	5.66	5.65	+/500	[f]
H	*o*-Chloro-	H	H			133–135	84	$C_{10}H_8NO_2Cl$	6.68	6.57	4+/125	*ca.* 100
Methyl[e]	*o*-Chloro-	H	H			127–129	82	$C_{11}H_{10}NO_2Cl$	6.26	6.16	2+/125	*ca.* 150
Ethyl	*o*-Chloro-	H	H	156	1.1	56– 58	70	$C_{12}H_{12}NO_2Cl$	5.89	5.69	2+/125	*ca.* 400
Allyl	*o*-Chloro-	H	H			57– 59	73	$C_{13}H_{12}NO_2Cl$	5.63	5.79	+/500	*ca.* 140
Isopropyl	*o*-Chloro-	H	H			74– 76	54	$C_{13}H_{14}NO_2Cl$	5.56	5.48	0/500	*ca.* 400
H	*p*-Chloro-	H	H			130–132	55	$C_{10}H_8NO_2Cl$	6.68	6.79	4+/125	<400>200
Methyl	*p*-Chloro-	H	H			107–109	51	$C_{11}H_{10}NO_2Cl$	6.26	6.25	2+/125	<400>200
Ethyl	*p*-Chloro-	H	H			50– 52	38	$C_{12}H_{12}NO_2Cl$	5.89	5.55	0/500	<200>100
Allyl	*p*-Chloro-	H	H			61– 63	46	$C_{13}H_{12}NO_2Cl$	5.63	5.61	0/500	*ca.* 200
Isopropyl	*p*-Chloro-	H	H			77– 79	48	$C_{13}H_{14}NO_2Cl$	5.56	5.72	0/500	<400>200
H	*o*-Chloro-	Methyl	H			152–155	79	$C_{11}H_{10}NO_2Cl$	6.26	6.03	4+/125	<100> 50
Methyl	*o*-Chloro-	Methyl	H			120–122	74	$C_{12}H_{12}NO_2Cl$	5.89	5.98	3+/125	*ca.* 100
Ethyl	*o*-Chloro-	Methyl	H			81– 82	70	$C_{13}H_{14}NO_2Cl$	5.56	5.42	+/125	<200>100
H	*p*-Chloro-	Methyl	H			146–148	33	$C_{11}H_{10}NO_2Cl$	6.26	5.98	3+/125	*ca.* 100
Methyl	*p*-Chloro-	Methyl	H			86– 87	52	$C_{12}H_{12}NO_2Cl$	5.89	5.84	+/500	*ca.* 100
Ethyl	*p*-Chloro-	Methyl	H	156–158	2		60	$C_{13}H_{14}NO_2Cl$	5.56	5.22	+/500	<400>200
Allyl	*p*-Chloro-	Methyl	H	163–164	1.1		63	$C_{14}H_{14}NO_2Cl$	5.31	5.00	0/500	*ca.* 200
H	*o*-Chloro-	H	Methyl			130–132	45	$C_{11}H_{10}NO_2Cl$	6.26	6.18	3+/125	<200>100
Methyl	*o*-Chloro-	H	Methyl			127–129	42	$C_{12}H_{12}NO_2Cl$	5.89	6.17	2+/250	<200>100

[a] Yields are based on the intermediate succinic acids. [b] Analytical data were determined by Mr. Charles E. Childs, Miss Virginia Pawlik and Mrs. Geraldine Koch of this Laboratory. [c] 4+/125 indicates that a group of five rats is completely protected against a convulsant dose of metrazol by 125 mg./kg. [d] PD_{50} indicates the dose in mg./kg. necessary to protect 50% of the animals (mice) against electrically-induced convulsions. See ref. 11 for a more complete discussion of test methods. [e] Prepared by M. Naps and I. B. Johns, THIS JOURNAL, 62, 2450 (1940). [f] Ineffective at 400 mg./kg.

pounds are being studied clinically in the treatment of epilepsy.

Acknowledgment.—The authors wish to thank Dr. Graham Chen, Mr. Charles Ensor, and Miss Ruth Portman of this Laboratory for permission to include the anticonvulsant data reported in this paper.

Experimental

α-(*p*-Chlorophenyl)-succinic Acid.—This procedure is typical for the preparation of the intermediate succinic acids when aldehydes were employed.

To a solution of 211 g. (1.5 moles) of *p*-chlorobenzaldehyde and 148 g. (1.5 moles) of methyl cyanoacetate in 200 ml. of 95% ethanol was added 3 ml. of piperidine. The mixture was allowed to stand until the temperature, which initially increased to about 65°, decreased to 30°. A solution of 108 g. (1.66 moles) of potassium cyanide in 200 ml. of water was added. The mixture was stirred until a clear solution was obtained and then heated on the steam-bath for about 10 minutes. After the addition of 200 ml. of water, 900 ml. of 12 *N* hydrochloric acid was added and the mixture refluxed 18 hours. The contents of the flask were cooled to 25° and filtered. The product was dissolved in 10% aqueous sodium hydroxide, charcoaled and reprecipitated by the addition of 12 *N* hydrochloric acid. It was filtered and recrystallized from hot 60% ethanol; m.p. 204–206°, yield 260 g. or 76%.

Anal. Calcd. for $C_{10}H_9O_4Cl$: C, 52.63; H, 3.96. Found: C, 52.94; H, 5.28.

α-(*o*-Chlorophenyl)-α-methylsuccinic Acid.—The α,α-disubstituted succinic acids were prepared in the following manner.

Ethyl α-cyano-β-(*o*-chlorophenyl)-β-methylacrylate was synthesized by condensing *o*-chlorophenyl methyl ketone and ethyl cyanoacetate according to the procedure of Cope, *et al.*[9]; b.p. 137° (0.9 mm.), yield 84%.

Anal. Calcd. for $C_{13}H_{12}NO_2Cl$: C, 62.52; H, 4.81. Found: C, 62.36; H, 4.92.

Sixty-five grams (1 mole) of potassium cyanide was added in one portion to 190 g. (0.76 mole) of ethyl α-cyano-β-(*o*-chlorophenyl)-β-methylacrylate and 300 ml. of 50% ethanol. The mixture was heated on the steam-bath with occasional shaking until a homogeneous solution formed. After cooling and diluting with 600 ml. of water, the solution was acidified to congo red with 12 *N* hydrochloric acid. The precipitated oil was separated.

The crude product, ethyl α,β-dicyano-β-(*o*-chlorophenyl)-butyrate, and 1 l. of 12 *N* hydrochloric acid were refluxed for 40 hours. After cooling, the water layer was decanted, 1 l. of fresh 12 *N* hydrochloric acid added and the mixture refluxed again for 40 hours. The contents of the flask were cooled and filtered. The residue was dissolved in 10% aqueous sodium hydroxide, extracted once with 200 ml. of ether, mixed with a moderate amount of charcoal and filtered. After adjusting the solution to *p*H 7, it was cooled and filtered. Acidification to congo red with 12 *N* hydrochloric acid yielded a product which was filtered and then recrystallized from hot 50% ethanol; m.p. 204–205°, yield 80 g.

Anal. Calcd. for $C_{11}H_{11}O_4Cl$: C, 54.44; H, 4.57. Found: C, 54.14; H, 4.89.

α-(*o*-Chlorophenyl)-succinimide.—The succinimides in Table I were prepared by the general procedure described below.

Two hundred and fourteen grams (0.93 mole) of *o*-chlorophenylsuccinic acid was added portionwise to a flask containing 150 g. of concentrated ammonium hydroxide and 50 ml. of water. The solution was heated until the internal temperature increased to 200°. After cooling somewhat, the residue was dissolved in 600 ml. of hot ethanol, charcoaled and filtered. The filtrate was cooled thoroughly and the white crystalline product filtered and dried; m.p 133–135°, yield 84%.

DETROIT, MICHIGAN

[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

Substituted 1-Phenyl-2-alkylaminoethanols and -propanols[1]

BY JOHN R. CORRIGAN,[2a] MARIE-JO SULLIVAN, HOWARD W. BISHOP AND A. WAYNE RUDDY[2b]

RECEIVED AUGUST 3, 1953

In order to establish better correlaton between molecular structure and bronchodilator or vasodepressor action 21 hydroxy and methoxyphenylalkylaminoethanols and -propanols were prepared and characterized. A brief summary of the correlation is presented. None of the compounds was found to be as active as 1-(3,4-dihydroxyphenyl)-2-isopropylaminoethanol.

Previous reports[3] from one of these laboratories have described the preparation of N-substituted 1-(4-hydroxyphenyl)- and 1-(3,4-dihydroxyphenyl)-2-aminoethanols as possible bronchodilators. In order to establish a better correlation between molecular structure and bronchodilator or vasodepressor action we have extended this series of compounds to include the 1-(3-hydroxyphenyl)-2-alkylaminoethanols, additional 1-(4-hydroxyphenyl)-2-alkylaminoethanols and 1-(hydroxyphenyl)-2-alkylamino-1-propanols as well as some of their methoxy analogs. Among these are a few cyclopentyl- and cyclohexylamino derivatives.

Most of the aminoalcohols were prepared by the catalytic hydrogenation of the corresponding aminoketone salts with palladium-on-charcoal catalyst. In order to avoid debenzylation the N-benzyl derivatives, 1-(4-methoxyphenyl)-2-benzylaminoethanol and 1-(4-methoxyphenyl)-2-benzylmethylaminoethanol, were prepared from their aminoketone salts by the Meerwein–Ponndorff–Verley reduction method employing aluminum isopropoxide as modified by Burger and Deinet.[4] This procedure was also used in preparing 1-(4-hydroxyphenyl)-2-diisopropylaminoethanol. Two of the tertiary amines, 1-(4-hydroxyphenyl)-2-methylisopropylaminoethanol and its 4-methoxy analog, were obtained from the available secondary aminoalcohols by reductive alkylation with formaldehyde as described by Woodruff, *et al.*[5]

The general method of Bockmühl, *et al.*,[6] was followed in the preparation of most of the aminopropanols from the corresponding benzyloxy-α-bromopropiophenones, but was modified by purifying and characterizing the intermediate α-alkylaminobenzyloxypropiophenone hydrochlorides. Hydrogenation in the presence of palladium catalyst produced a simultaneous reduction of the carbonyl group and hydrogenolysis of the benzyl ethers. After this series was completed Sprague, *et al.*,[7] reported the preparation of several of these aminopropanols by the reductive alkylation of the corresponding 2-amino-1-(hydroxyphenyl)-1-propanols.

The preliminary data furnished by Dr. A. M. Lands and his staff of our Pharmacology Department indicate that the bronchodilator and vasodepressor activity of these compounds is decreased when a phenolic group is blocked as the methyl ether, and the activity is insignificant when the secondary amines are converted to tertiary amines. The propanols are less active than the corresponding ethanols. None of the compounds was found to be as active as 1-(3,4-dihydroxyphenyl)-2-isopropylaminoethanol.[3]

Acknowledgment.—The authors are indebted to Mrs. Eleanor Kovach and Mr. David Jackman for technial assistance, and to Miss Elizabeth B. Macks, Mr. M. E. Auerbach and staff for the analytical data.

Experimental[8]

Bromoketones.—The bromoketones not commercially available were obtained by bromination of the appropriate ketones in chloroform or methylene chloride. Those prepared which have been reported previously are α-bromo-4-methoxyacetophenone,[9] α-bromo-4-benzyloxypropiophenone,[10] α-bromo-3,4-dimethoxypropiophenone[11] and α-bromo-3,4-dibenzyloxypropiophenone.[10]

(1) A portion of this work was carried out in the former Research Laboratories of Frederick Stearns and Company Division of Sterling Drug, Inc.

(2) (a) Sharp & Dohme Division, Merck & Co., West Point, Pa.; (b) Warner–Chilcott Research Laboratories, Morris Plains, N. J.

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