fluxed with stirring for four hours. A white precipitate appeared during this reflux period. Hydrolysis was effected by the addition of 120 ml. of a saturated aqueous ammonium chloride solution.[12] The bulky magnesium salts were removed by filtration and washed well with xylene. After removal of the solvent, the product was isolated by distillation at reduced pressure.

Method B.—A mixture consisting of 0.15 mole of the ethyl or methyl ether of 2-bromo-1-phenylethanol and 0.30 mole of the amine was heated under reflux in an oil-bath until an exothermic reaction occurred (Method B-1). When the reaction had abated somewhat, the mixture was then refluxed from one-half to 23 hours. The length of the heating period depended upon the amount of visible decomposition. In some cases the two reactants were refluxed in 100 ml. of benzene or toluene for 16–40 hours (Method B-2). In the reaction with dimethylamine, the gaseous base was bubbled into the bromo ether over a three-hour period while the latter was heated at a bath temperature of 120° (Method B-3). After cooling, ether was added (in Methods B-1 and B-3) and the hydrobromide of the excess starting amine was separated by filtration and washed well with ether. The solvents were removed and the residue was distilled *in vacuo*. In several preparations where the amine hydrobromide separated as an oil or hygroscopic solid, the salt was dissolved in water and the product separated from the aqueous solution of the salt by extraction several times with ether. After drying over anhydrous potassium carbonate and removing the solvent, the product was obtained by distillation *in vacuo*.

Method C. Methyl Ether of 2-Amino-1-phenylethanol.[8]—A solution of 18.9 g. of the methyl ether of 2-benzylamino-1-phenylethanol in 200 ml. of absolute ethanol was hydrogenated at an initial pressure of 58 lb. in the presence of 3.2 g. of 10% palladium-on-charcoal catalyst.[16] The calculated amount of hydrogen was absorbed in 24 hours. The catalyst was removed by filtration, washed well with ethanol, and the solvent removed from the filtrate by distillation. The product, collected at 111–116° (20 mm.), weighed 8.7 g. (73%).

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(16) Purchased from Baker and Co., Inc., Newark, N. J.

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

Anticonvulsants. I. An Investigation of N-R-α-R₁-α-Phenylsuccinimides

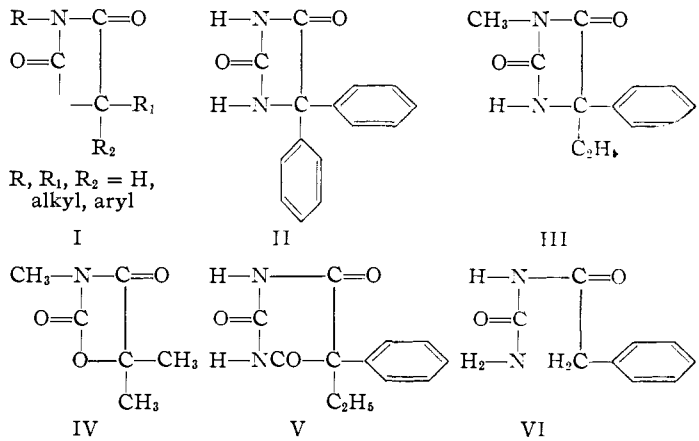
BY C. A. MILLER AND LOREN M. LONG[1]

A series of substituted succinimides has been prepared and tested for anticonvulsant properties. Many of the derivatives exhibit appreciable activity against metrazol and/or electrically-induced convulsions. Several of these have proved effective in clinical studies of petit mal epilepsy.

Since the discovery of the usefulness of 5,5-diphenylhydantoin[2] (Dilantin)[3] in the treatment of grand mal epilepsy, much effort has been expended in the search for new agents which might suppress convulsive seizures in man. The field of hydantoin derivatives has been examined rather thoroughly. Although many of these exhibit activity against electrically-induced convulsions,[4] none has shown any particular advantage over Dilantin in the treatment of grand mal epilepsy.[5]

Anticonvulsants which are effective against grand mal seizures usually do not show a similar activity against petit mal epilepsy. Indeed, until the introduction of 3,5,5-trimethyloxazolidinedione[6,7] (Tridione)[8] there was no drug known which could be employed with any appreciable success against the lesser convulsive seizures. However, because of certain side effects, the use of this drug demands unusual care.[9a,b,10] Therefore, a more effective agent devoid of toxic properties remains an important objective. This paper is a report on the results obtained in a study of a series of succinimide derivatives, including certain members which show promise of proving useful in the treatment of this type of epilepsy.

It has been observed that group I occurs in many of the effective anticonvulsants as well as sedatives and hypnotics.



Among these may be cited Dilantin (II), Mesantoin

(1) Address inquiries to L. M. L.

(2) H. H. Merritt and T. J. Putnam, *J. Am. Med. Assoc.*, **111**, 1068 (1938).

(3) Parke, Davis & Co. registered trademark for 5,5-diphenylhydantoin.

(4) H. H. Merritt and T. J. Putnam, *Epilepsia*, **3**, 51 (1945).

(5) J. A. Abbott and R. S. Schwab, *New Engl. J. Med.*, **242**, 943 (1950).

(6) M. A. Spielman, THIS JOURNAL, **66**, 1244 (1944).

(7) (a) G. M. Everett and R. K. Richards, *J. Pharmacol. Exp. Therap.*, **81**, 402 (1944); (b) W. G. Lennox, *J. Am. Med. Assoc.*, **129**, 1069 (1945).

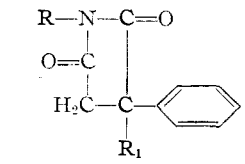
(8) Abbott Laboratories registered trademark for 3,5,5-trimethyloxazolidinedione.

(9) (a) J. N. Briggs and J. L. Emery, *Lancet*, **1**, 59 (1949); (b) H. S. Mustard, S. C. Anderson and S. Livingston, *J. Pediat.*, **35**, 540 (1949).

(10) S. E. Leard, W. E. R. Greer and I. C. Kaufman, *New Engl. J. Med.*, **240**, 962 (1949).

(III), Tridione (IV), phenobarbital (V) and Phenurone (VI). That the presence of a group similar to I is not a necessary condition for anticonvulsant activity is shown, for example, by the activity of various aldehydes and ketones,[4] isopropyl alcohol[11] and 2,2-diethyl-1,3-propanediol.[12,13] Nevertheless, derivatives containing I constitute a very important group of agents for controlling convulsive seizures.

The substituted succinimides which were prepared for this study may be represented by VII. Apparently, this ring system has not been examined

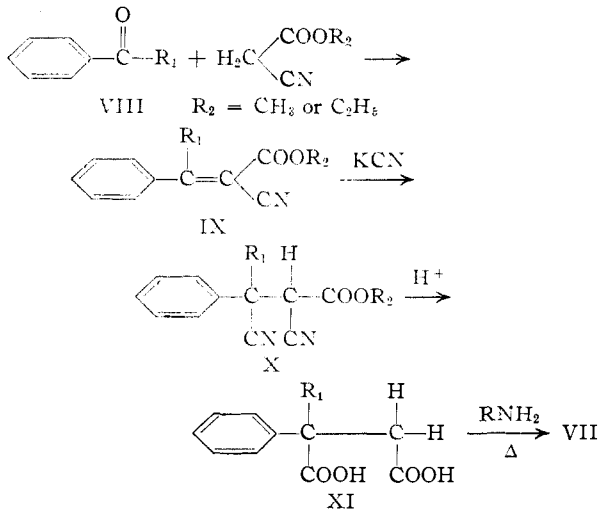


VII R = H, alkyl
R_1 = H, alkyl, aryl

previously for possible anticonvulsant activity. Structure VII differs from those represented by II–VI inclusive in that hydrolysis yields a substituted succinic acid. Since a number of the succinimides exhibited a surprising degree of activity against metrazol-induced convulsions, the series was investigated rather thoroughly.

Succinimides containing at least one phenyl group were chosen for initial study. As there is no generalization which enables one to predict accurately the effect of placing substituents on the nitrogen atoms of anticonvulsants, N-alkyl derivatives were prepared in each series. Similar to Dilantin (II),[4,14] N-methylation of α,α-diphenylsuccinimide decreased activity against electrically-induced convulsions.

The following reactions illustrate the method generally employed for the preparation of compounds summarized in Table I.



VIII R_2 = CH_3 or C_2H_5

IX

X

XI

The procedure for preparing intermediate succinic acids (XI) is essentially that of Lapworth and McRae,[15] who synthesized phenylsuccinic acid, except that IX (R_1 = H) was not isolated but was converted directly to X (R_1 = H) which was then hydrolyzed in excellent yields. Smith and Horwitz[16] in preparing XI avoided the isolation of IX; however, the method gave poor yields when R_1 was hydrogen or methyl.

The condensation of ketones with cyanoacetic esters has been investigated extensively by Cope, *et al.*[17] Further investigations indicating increased yields were reported by Cragoe, *et al.*[18] Addition of potassium cyanide to IX usually proceeds easily and hydrolysis of X (R_1 = hydrogen or methyl) was accomplished with hydrochloric acid alone; however, when R_1 contained two or more carbon atoms, it was desirable to add acetic acid to the hydrolysis mixture to obtain good yields. Neither of the procedures was satisfactory when R_1 was phenyl, therefore XI (R_1 = phenyl) was prepared by reaction of sodium diphenylacetonitrile with ethyl bromoacetate followed by hydrolysis. Salmon-Legagneur[19] reports a melting point of 197–199° with softening at 170°; whereas the product prepared by the authors melts at 173–175° in agreement with Cragoe, *et al.*[18]

The succinimides (VII) in Table I were prepared by distillation of the amine salts. The only exception was the α,α-diphenylenesuccinimides. Heating the α,α-diphenylenesuccinic acid amine salts resulted in decarboxylation and in several attempts β,β-diphenylenepropionic acid was obtained. The desired product was prepared by treating the α,α-diphenylenesuccinic anhydride with an amine and refluxing the resulting succinamic acid with acetyl chloride.

A number of N-substituted phenylsuccinamic acids[20] were prepared in order to compare the anticonvulsant activity of several amides with the corresponding imides. The amides were prepared, as mentioned above, from an anhydride and an amine. In several cases a mixture of α- and β-succinamic acids was obtained.[21] Separation of the isomers was easily effected because of the difference in water solubility of the amine salts.

Pharmacology.—The succinimides summarized in Table I have shown a surprising degree of activity against metrazol-induced convulsions in the rat, suppression[7] of such convulsions being employed as an indication of probable activity against petit mal epilepsy. A comprehensive pharmacological study has been made by Chen and associates of this Laboratory which will be reported elsewhere.

Although the main object of this investigation was the production of compounds likely to inhibit metrazol-induced convulsions, activity against electrically-induced convulsions was also examined. As indicated in Table I, several derivatives are ac-

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TABLE I

N-R-α-R₁-α-PHENYLSUCCINIMIDES

R	R₁	B.p., °C.	Mm.	M.p., °C.	Yield, %[a]	Formula	Nitrogen, % Calcd.	Nitrogen, % Found	Anticonvulsant activity Metrazol[c]	PD_{50}[d]
H[e]	H	223–225	11	88–90	86	$C_{10}H_9NO_2$	8.00	7.83	+/125	300
Methyl	H			71–73	83	$C_{11}H_{11}NO_2$	7.40	7.51	4+/125	255
Ethyl[f]	H	154–155	2.8		80	$C_{12}H_{13}NO_2$	6.88	6.74	+/125	400
Propyl	H			62–63	50	$C_{13}H_{15}NO_2$	6.44	6.21	+/250	
Isopropyl	H			60–61	88	$C_{13}H_{15}NO_2$	6.44	6.29	2+/125	800
Allyl	H			61–62	84	$C_{13}H_{13}NO_2$	6.50	6.46	4+/125	246
Butyl	H	157–158	1.2		80	$C_{14}H_{17}NO_2$	6.05	5.94	+/250	>400
Isobutyl	H			59–60	55	$C_{14}H_{17}NO_2$	6.05	5.91	+/250	>400
s-Butyl	H	142	0.7		80	$C_{14}H_{17}NO_2$	6.05	5.94	2+/125	>400
β-Hydroxyethyl	H	181	0.2		68	$C_{12}H_{13}NO_3$	6.39	6.56	+/250	500
β-Diethylaminoethyl	H	180–182	2		88	$C_{16}H_{22}N_2O_2$	10.14	10.19	0/500	>400
H	Methyl			83–84	88	$C_{11}H_{11}NO_2$	7.40	7.33	4+/125	120
Methyl	Methyl	166–167	13	52–54	90	$C_{12}H_{13}NO_2$	6.89	6.73	4+/125	120
Ethyl	Methyl	175–177	15.5		86	$C_{13}H_{15}NO_2$	6.44	6.35	4+/125	400
Propyl	Methyl	154–156	3.5		82	$C_{14}H_{17}NO_2$	6.06	6.14	4+/125	>400
Isopropyl	Methyl	129–130	1		73	$C_{14}H_{17}NO_2$	6.06	5.91	2+/250	400
Allyl	Methyl	149–150	2.5		77	$C_{14}H_{15}NO_2$	6.11	5.76	4+/125	300
Butyl	Methyl	155–156	2		81	$C_{15}H_{19}NO_2$	5.71	5.82	2+/250	>400
Isobutyl	Methyl	145–146	1.2		77	$C_{15}H_{19}NO_2$	5.71	5.74	+/250	>400
s-Butyl	Methyl	153–155	3		77	$C_{15}H_{19}NO_2$	5.71	5.64	2+/250	>400
H	Ethyl			99–100	70	$C_{12}H_{13}NO_2$	6.88	6.81	4+/125	60
Methyl	Ethyl	122–123	0.1		87	$C_{13}H_{15}NO_2$	6.44	6.36	4+/125	100
Ethyl	Ethyl	165–166	6.8		80	$C_{14}H_{17}NO_2$	6.05	5.79	+/250	300
Isopropyl	Ethyl	166–167	7		68	$C_{15}H_{19}NO_2$	5.71	5.73	0/250	
Allyl	Ethyl	168–170	6.4		61	$C_{15}H_{17}NO_2$	5.75	5.61	+/500	>400
H	Propyl	164	0.5		77	$C_{13}H_{15}NO_2$	6.44	6.23	2+/125	200
Methyl	Propyl	171–172	8		82	$C_{14}H_{17}NO_2$	6.06	5.76	+/500	300
Ethyl	Propyl	169–171	7		77	$C_{15}H_{19}NO_2$	5.71	5.58	0/500	>400
Isopropyl	Propyl	169–170	6.7		80	$C_{16}H_{21}NO_2$	5.40	5.28	0/500	>400
Allyl	Propyl	175–176	6.2		80	$C_{16}H_{19}NO_2$	5.43	5.42	0/500	>400
H	Phenyl[g]			140–142	77	$C_{16}H_{13}NO_2$	5.57	5.46	0/500	45
Methyl	Phenyl			89–91	84	$C_{17}H_{15}NO_2$	5.28	5.32	0/500	200
Ethyl	Phenyl			102–104	85	$C_{18}H_{17}NO_2$	5.02	5.05	0/500	500
Propyl	Phenyl			51–52	82	$C_{19}H_{19}NO_2$	4.55[h]	4.82	0/500	500
Isopropyl	Phenyl			92–94	85	$C_{19}H_{19}NO_2$	4.55[i]	4.77	2+/500	500
Allyl	Phenyl	178–179	1		50	$C_{19}H_{17}NO_2$	4.77[j]	4.62	0/500	500
Butyl	Phenyl	187–189	0.7			$C_{20}H_{21}NO_2$	4.36[k]	4.53	0/500	500
Isobutyl	Phenyl			65–67	64	$C_{20}H_{21}NO_2$	4.36[l]	4.53	0/500	500
s-Butyl	Phenyl	178–180	0.8		86	$C_{20}H_{21}NO_2$	4.36[m]	4.40	0/500	500
H	α,α-Diphenylene			241–243		$C_{16}H_{11}NO_2$	5.62	5.81	0/500	150
Methyl	α,α-Diphenylene			190–192		$C_{17}H_{13}NO_2$	5.32	5.29	0/500	>400

[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] An antimetrazol rating of 4+/125 indicates that a group of five rats is completely protected against a convulsant dose of metrazol by 125 mg./kg. of the drug. [d] PD_{50} indicates the dose in mg./kg. necessary to protect 50% of the animals (mice) against electrically-induced convulsions. For a more complete discussion of test methods see G. Chen and C. R. Ensor, *Arch. Neurol. Psychiat.*, **63**, 56 (1950). [e] Prepared by R. Wegscheider and J. Hecht, *Monatsh.*, **24**, 422 (1903). [f] N. J. Leonard, A. B. Simon and D. L. Felley, THIS JOURNAL, **73**, 857 (1951). [g] See ref. 19. [h] Calcd. for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53. Found: C, 77.93; H, 6.40. [i] Found: C, 77.85; H, 6.48. [j] Calcd. for $C_{19}H_{17}NO_2$: C, 78.33; H, 5.88. Found: C, 78.17; H, 6.11. [k] Calcd. for $C_{20}H_{21}NO_2$: C, 78.15; H, 6.88. Found: C, 78.30; H, 6.92. [l] Found: C, 78.36; H, 6.83. [m] Found: C, 77.88; H, 6.84.

TABLE II

N-R-PHENYLSUCCINAMIC ACIDS

R[a]	M.p., °C.	Yield, %[b]	Formula	Nitrogen, % Calcd.	Nitrogen, % Found
Methyl[c]	158–160	20	$C_{11}H_{13}O_3N$	6.75	6.87
Ethyl	107–109	88	$C_{12}H_{15}O_3N$	6.32	6.34
Propyl	97–99	50	$C_{13}H_{17}O_3N$	5.94	5.88
Isopropyl	117–119	50	$C_{13}H_{17}O_3N$	5.94	5.86
Allyl	94–96	82	$C_{13}H_{15}O_3N$	5.99	5.86
Butyl	108–110	95	$C_{14}H_{19}O_3N$	5.61	5.64
Isobutyl	154–156	62	$C_{14}H_{19}O_3N$	5.61	5.77
s-Butyl	130–132	60	$C_{14}H_{19}O_3N$	5.61	5.77

[a] These compounds did not exhibit any anticonvulsant activity. [b] Based on phenylsuccinic anhydride. [c] Prepared by Naps and Johns.[20] A compound melting at 140–143° was obtained in 64% yield. According to the yields and melting points obtained in several cases it is not clear whether the action of amine on phenylsuccinic anhydride gives predominantly the β-amide as stated by Anschütz.[21]

tive against both types of induced seizures while α,α-diphenylsuccinimide, resembling Dilantin (II) in structure is apparently active against only electrically-induced convulsions. The succinamic acids (Table II) were inactive.

Clinical studies, which are now in progress, with a number of the substituted succinimides have

shown this type of compound to be effective in the treatment of petit mal epilepsy. In a series of fifty cases N-methyl-α-phenylsuccinimide exhibited excellent control of the attacks in a majority of the patients while causing only minor side reactions in a few cases.[22]

Acknowledgment.—The authors are indebted to Dr. Graham Chen, Mr. Charles Ensor and Miss Ruth Portman for granting permission to include pharmacological data on the substituted succinimides reported herein.

Experimental

Phenylsuccinic Acid (XI, R_1 = H).—Most of the substituted succinic acids were prepared by the following method which is a modification of that of Lapworth and McRae.[15]

To a solution of 106 g. (1.0 mole) of benzaldehyde and 99 g. (1.0 mole) of methyl cyanoacetate in 275 ml. of 60% ethyl alcohol was added 3 ml. of piperidine. The temperature slowly increased to 60°. When the mixture had cooled to 25°, it was diluted with 100 ml. of water and 49 g. (1.0 mole) of sodium cyanide was added portionwise over a period of 20 minutes. Stirring was continued until a clear solution was obtained. After dilution with 800 ml. of water, the mixture was acidified to congo red with hydrochloric acid (sp. gr. 1.18). The oil which precipitated was stirred until solidification and then filtered.

The solid methyl α,β-dicyano-β-phenylpropionate (X, R_1 = H) was refluxed with 900 ml. of hydrochloric acid (sp. gr. 1.18) for six hours or until solution was complete. On cooling to 25° a solid precipitated which was filtered off and washed with 200 ml. of water and dried; m.p. 162–165°, yield 161 g. (83%).

α,α-Diphenylenesuccinic Acid.—This acid was prepared earlier[23] from the sodium salt of ethyl 9-fluoreneacetate and ethyl chloroacetate; however, the authors prefer to use fluorenone.

Ethyl α-cyano-β,β-diphenyleneacrylate was prepared from fluorenone and ethyl cyanoacetate with piperidine as a catalyst; m.p. 65–68°. Cragoe, *et al.*,[18] reported m.p. 58–60°.

Anal. Calcd. for $C_{18}H_{13}NO_2$: C, 78.54; H, 4.72. Found: C, 78.37; H, 4.72.

Thirty-five grams (0.54 mole) of potassium cyanide was added in small portions within 20 minutes to a mixture of 75 g. (0.27 mole) of ethyl α-cyano-β,β-diphenyleneacrylate and 150 ml. of 50% ethyl alcohol. The mixture was then heated on a steam-bath for 15 minutes. The solution was cooled, diluted with 450 ml. of water and made acid to congo red with 6 *N* hydrochloric acid. The cooled mixture was filtered.

The solid product, ethyl 9,α-dicyano-9-fluoreneacetate, was added to a solution of 400 ml. of hydrochloric acid (sp. gr. 1.18) and 200 ml. of glacial acetic acid. After refluxing for 48 hours, the solution was cooled and the product removed by filtration. It was dissolved in 5–10% aqueous sodium hydroxide and reprecipitated with 6 *N* hydrochloric acid. The material so obtained was recrystallized from ethyl alcohol; m.p. 192–194°, yield 60 g. (83%).

α,α-Diphenylsuccinic Acid (XI, R = phenyl).—Since Salmon-Legagneur[19] did not record details of this preparation and since the m.p. of the final product differed, the procedure will be given here.

Seventeen grams (0.75 mole) of sodium was dissolved in 400 ml. of absolute ethanol in a 1-l. flask equipped with a reflux condenser, a drying tube and a mechanical stirrer. Ninety-seven grams (0.5 mole) of diphenylacetonitrile was added in one portion. The resulting mixture was refluxed for one hour. After cooling to 50°, 125 g. (0.75 mole) of ethyl bromoacetate was added with stirring at such a rate as to cause moderate refluxing. The flask was heated to reflux for an additional three hours. Most of the ethanol was removed *in vacuo* and the residue was stirred with 300 ml. of water for one-half hour. After filtration the solid product was recrystallized from 150 ml. of 95% ethyl alcohol; m.p. 102–105, yield 103 g. (74%).

The ethyl β-cyano-β,β-diphenylpropionate was added to a solution of 60 g. of potassium hydroxide in 500 ml. of 95% ethyl alcohol and heated for 15 minutes on a steam-bath. The solid was removed by filtration and dissolved in 400 ml. of water. On acidifying the solution with 6 *N* hydrochloric acid, a solid precipitated which was filtered off and dried; m.p. 178–181°, yield 89 g. (quantitative). Hydrolysis of the product to form α,α-diphenylsuccinic acid was accomplished by refluxing in 600 ml. of hydrochloric acid (sp. gr. 1.18) for 64 hours. The succinic acid derivative was filtered off and purified by dissolving in 5–10% aqueous sodium hydroxide and reprecipitating with 6 *N* hydrochloric acid; m.p. 170–172°, yield 88 g. (90%). Recrystallization from ethyl alcohol increased the m.p. to 173–175°.

N-Methyl-α-phenylsuccinimide (VII, R = CH_3, R_1 = H).—The preparation of this derivative is typical of the procedure for preparing the imides from corresponding amine salts.

Ninety-seven grams (0.5 mole) of phenylsuccinic acid was added in small portions to 31 g. (1.0 mole) of methylamine in 100 ml. of water. The flask was heated in a Glas-Col mantle until the temperature of the contents reached 210°. The residue was cooled somewhat and dissolved in 250 ml. of hot 95% ethyl alcohol. After mixing with a moderate amount of Darco and filtering, the yellowish filtrate was cooled thoroughly in an ice-bath. The white product was filtered off and dried *in vacuo;* m.p. 71–73°, yield 78 g. (83%).

α,α-Diphenylenesuccinimide.—Thirty-two grams (0.12 mole) of α,α-diphenylenesuccinic acid and 100 ml. of acetyl chloride were refluxed together until the evolution of hydrogen chloride ceased. The mixture was filtered and the filtrate concentrated to remove excess acetyl chloride. The residue[23] was recrystallized from hot benzene; m.p. 154–160°, yield 20 g.

Six grams (0.024 mole) of the anhydride was dissolved in 100 ml. of dry ether and ammonia was passed through the solution until precipitation was complete. The solid was filtered off, dissolved in water and the α,α-diphenylenesuccinamic acid precipitated by the addition of 6 *N* hydrochloric acid. After removal by filtration the solid was dried; m.p. 155–160°, yield 4.5 g.

The succinamic acid was refluxed with 20 ml. of acetyl chloride for two hours. α,α-Diphenylenesuccinimide was filtered off, dried and recrystallized from hot absolute ethanol; m.p. 241–243°, yield 3 g.

DETROIT, MICHIGAN RECEIVED APRIL 12, 1951

(22) Reported by Dr. Frederic T. Zimmerman before the Annual Meeting of the American Branch of the International League Against Epilepsy, Virginia Beach, April, 1951.

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