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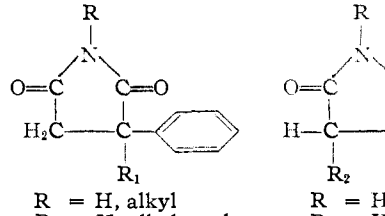
Anticonvulsants.[1] II. A Study of N-R-α,β-Substituted Succinimides

BY C. A. MILLER, HELEN I. SCHOLL AND LOREN M. LONG

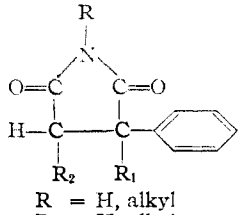
A second series of substituted succinimides has been prepared and examined for anticonvulsant properties. In addition to N,α-substituents these derivatives contain an alkyl or an aryl in the β-position. Many of the compounds have proved to be effective in preventing metrazol-induced and/or electrically-induced convulsions in animals. Several are being used in clinical studies of epilepsy.

In the first article[2] of this series the synthesis of a number of derivatives of α-phenylsuccinimide was reported. Many of these derivatives, represented by structure I, were found to be very active in suppressing metrazol-induced convulsions and, to a lesser degree, electrically-induced convulsions[3] in laboratory animals. When employed in clinical studies, several, *e.g.*, N-methyl-α-phenylsuccinimide,[4] proved to be surprisingly useful in the treatment of petit mal epilepsy while producing only minor toxic symptoms in a few patients. Although a number of the α-phenylsuccinimide derivatives, especially α,α-diphenylsuccinimide, exhibited activity against electrically-induced convulsions, none was comparable to 5,5-diphenylhydantoin (Dilantin)[5] illustrated by structure III.



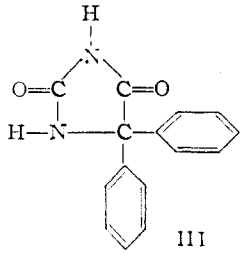
R = H, alkyl
R_1 = H, alkyl, aryl

I



R = H, alkyl
R_1 = H, alkyl
R_2 = alkyl, aryl

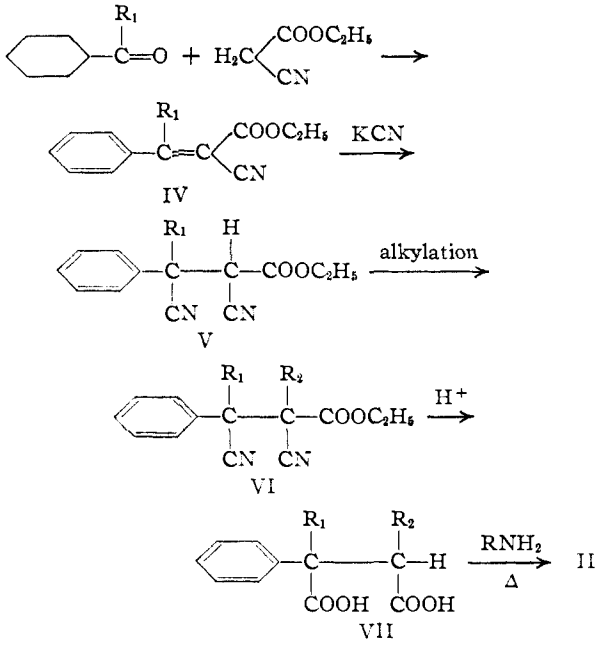
II



III

In view of the high degree of antimetrazol activity shown by the initial series of α-phenylsuccinimide derivatives, it seemed of interest to examine this type heterocyclic compound in greater detail. Therefore, the group of compounds reported herein was prepared and tested for anticonvulsant activity. This group may be represented by structure II, differing from the original series in possessing substituents on both the α- and β-positions.

The general method employed for the synthesis of the α,β-substituted succinimides, excepting α,β-diphenylsuccinimide, may be illustrated by the series of reactions, IV → V → VI → VII → II.



The condensation of aldehydes[6] and ketones[7,8] with ethyl cyanoacetate to produce compounds of type IV and the addition of potassium cyanide to α,β-unsaturated esters have been reported.[2] In adapting these methods to the synthesis of considerable quantities of succinic acids, the conversion of V to VI was effected by alkylation in the presence of sodium hydroxide, methyl sulfate being preferred for methylation while ethyl bromide was more effective for ethylation. The entire sequence of reactions was carried out without purification of intermediates. Hydrolysis and decarboxylation were effected with concentrated hydrochloric acid or a mixture of hydrochloric and acetic acids. The over-all yield for VII (R_1 = H, R_2 = methyl) was 70% while that for VII (R_1 = R_2 = methyl) was 35%. The lower yield is best explained by the difference in activity of benzaldehyde and acetophenone in condensing with ethyl cyanoacetate.

This procedure was superior with respect to availability of starting materials and over-all yield to that[9] used in the preparation of VII (R_1 = H, R_2 = methyl) from acetaldehyde and benzyl cyanide (yield 15%), as described below for the preparation of α,β-diphenylsuccinic acid,[10] or to the

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

(2) C. A. Miller and L. M. Long, THIS JOURNAL, **73**, 4895 (1951).

(3) G. Chen and co-workers, unpublished data.

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

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

(6) A. Lapworth and J. A. McRae, *J. Chem. Soc.*, **121**, 2741 (1922).

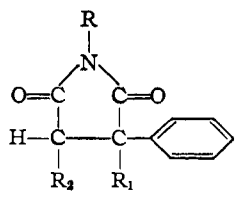
(7) A. C. Cope, C. M. Hoffman, C. Wyckoff and E. Hardenbergh, THIS JOURNAL, **63**, 3452 (1941).

(8) E. J. Cragoe, C. M. Robb and J. M. Sprague, *J. Org. Chem.*, **15**, 381 (1950).

(9) J. A. McRae and N. A. McGinnis, *Can. J. Research*, **18**, B, 90 (1940).

(10) A. Lapworth and J. A. McRae, *J. Chem. Soc.*, **121**, 1699 (1922).

TABLE I



R	R_1	R_2	B.p., °C.	Mm.	M.p., °C.[a]	Yield, %[b]	Formula	Nitrogen, % Calcd.	Found	Activity Metrazol	Electro-shock
H[c]	H	Methyl	173–177	1.4	91–95	76	$C_{11}H_{11}NO_2$	7.40	7.43	4+/125	*ca.* 400
Methyl	H	Methyl	132–133	0.5		66	$C_{12}H_{13}NO_2$	6.89	7.15	4+/125	<400 >200
Ethyl	H	Methyl	137–138	0.9		80	$C_{13}H_{15}NO_2$	6.45	6.70	+/125	>400
Isopropyl	H	Methyl	138–139	1.2		65	$C_{14}H_{17}NO_2$	6.06	5.80	3+/125	>400
Allyl	H	Methyl	136–138	0.2		65	$C_{14}H_{15}NO_2$	6.11	5.88	4+/125	*ca.* 200
H[d]	Methyl	Methyl	160	0.4	109–112	48	$C_{12}H_{13}NO_2$	6.89	6.78	4+/125	*ca.* 100
Methyl	Methyl	Methyl	137–138	1.3		87	$C_{13}H_{15}NO_2$	6.45	6.16	4+/125	*ca.* 150
Ethyl	Methyl	Methyl	148–149	3.3		84	$C_{14}H_{17}NO_2$	6.06	5.83	2+/125	<400 >200
Allyl	Methyl	Methyl	158	4.0		80	$C_{15}H_{17}NO_2$	5.76	5.40	+/125	>400
H	Ethyl	Methyl	172–173	1.6		50	$C_{13}H_{15}NO_2$	6.45	6.43	4+/125	<100 >50
Methyl	Ethyl	Methyl	139–141	1.6		50	$C_{14}H_{17}NO_2$	6.06	6.14	4+/125	*ca.* 200
Ethyl	Ethyl	Methyl	129–131	0.5		57	$C_{15}H_{19}NO_2$	5.71	5.60	2+/250	[g]
Allyl	Ethyl	Methyl	139–141	0.8		58	$C_{16}H_{19}NO_2$	5.40	5.17	3+/500	[g]
H	H	Ethyl	160–170	0.8		58	$C_{12}H_{13}NO_2$	6.89	6.60	4+/125	<200 >100
Methyl	H	Ethyl	133–134	0.5		60	$C_{13}H_{15}NO_2$	6.45	6.32	4+/125	<200 >100
Ethyl	H	Ethyl	127–129	0.3		64	$C_{14}H_{17}NO_2$	6.06	6.11	2+/125	<400 >200
Allyl	H	Ethyl	147–149	1.0		53	$C_{15}H_{17}NO_2$	5.71	5.56	3+/125	>400
H[e]	H	Phenyl			198–200	55	$C_{16}H_{13}NO_2$	5.58	5.39	+/500	*ca.* 100
Methyl[f]	H	Phenyl			103–105	66	$C_{17}H_{15}NO_2$	5.28	5.35	3+ 100	<400 >200
Ethyl	H	Phenyl			65–67	92	$C_{18}H_{17}NO_2$	5.02	4.95	0/500	[g]
Propyl	H	Phenyl			97–99	35	$C_{19}H_{19}NO_2$	4.77[h]	4.53	0/500	[g]
Isopropyl	H	Phenyl			152–154	91	$C_{19}H_{19}NO_2$	4.77[i]	4.53	0/500	[g]
Allyl	H	Phenyl			75–77	32	$C_{19}H_{17}NO_2$	4.81[j]	4.92	0/500	[g]
Butyl	H	Phenyl			54–56	57	$C_{20}H_{21}NO_2$	4.56[k]	4.30	0/500	[g]
s-Butyl	H	Phenyl			129–131	58	$C_{20}H_{21}NO_2$	4.56[l]	4.42	0/500	[g]

[a] In many cases the product obtained by distillation is a mixture of *cis*- and *trans*-isomers which may be separated by recrystallization. When the isomers were isolated and purified, it was found that there was no apparent difference in anticonvulsant activity. [b] Yields are based on the intermediate succinic acid. [c] See Ref. 9. The melting point may be increased to 109° by recrystallization from ether. [d] By repeated recrystallization from ethanol the melting point may be increased to 124–126°. [e] See ref. 10. [f] R. Lukeš and V. Sperling, *Collection Czechoslov. Chem. Commun.*, 8, 461 (1936); *C.A.*, 31, 2210 (1937). [g] Ineffective at 400 mg./kg. [h] Calcd. for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53. Found: C, 77.51; H, 6.56. [i] Found: C, 77.48; H, 6.47. [j] Calcd. for $C_{19}H_{17}NO_2$: C, 78.33; H, 5.88, Found: C, 78.66; H, 6.01. [k] Calcd. for $C_{20}H_{21}NO_2$: C, 78.15; H, 6.88. Found: C, 78.51; H, 6.90. [l] Found: C, 78.15, H, 6.81.

method of condensing[11] ethyl α-bromophenylacetate with ethyl α-cyanopropionate followed by hydrolysis (low yield[9]).

α,β-Diphenylsuccinic acid (VII, R_1 = H, R_2 = phenyl) was prepared by essentially the same procedure as that of Lapworth and McRae.[10] Benzaldehyde and benzyl cyanide were condensed, treated with potassium cyanide and then hydrolyzed with a mixture of sulfuric and acetic acids. The preparation of VII (R_1 = R_2 = methyl) from the sodium salt of α-methylbenzyl cyanide and ethyl α-bromopropionate gave a yield of about 14%.[12]

The succinimides (II) were prepared by distillation of the appropriate amine salts of the succinic acids. In some instances the yields were quite good; however, no attempt was made to obtain maximum yields. Pertinent data are summarized in Table I.

Pharmacology.—As indicated in Table I, the anticonvulsant properties of these derivatives have been determined. Many exhibit appreciable activity against metrazol-induced convulsions, maximum effectiveness being attained when the substituents (R, R_1, R_2) are hydrogen or short chain alkyl groups. α,β-Diphenylsuccinimide is practically inactive against metrazol and less effective than α,α-diphenylsuccinimide[2] in preventing electrically-induced convulsions. Several of the compounds are undergoing clinical studies in epilepsy.

Activities are reported by a previously described system,[13] *e.g.*, 4+/125 indicates that a group of five rats is completely protected against a convulsant dose of metrazol by a dose of 125 mg./kg. of the compound and PD_{50} indicates the dose in mg./kg. necessary to protect 50% of the animals (mice) against electrically-induced convulsions.

Acknowledgment.—The authors wish to thank Dr, Graham Chen, Mr. Charles Ensor and Miss Ruth Portman for making available the pharmacological data included in Table I. Analytical data were determined by Mr. Charles E. Childs, Miss Virginia Pawlik and Mrs. Geraldine Koch of this Laboratory.

(11) N. Zelinsky and L. Buchstab, *Ber.*, **24**, 1876 (1891).
(12) H. M. Crawford, THIS JOURNAL, **56**, 139 (1934).
(13) G. Chen and C. R. Ensor, *Arch. Neurol. Psychiat.*, **63**, 56 (1950).

Experimental

α-Methyl-β-phenylsuccinic Acid (VII, R_1 = H, R_2 = Methyl).—To a solution of 106 g. (1.0 mole) of benzaldehyde and 113 g. (1.0 mole) of ethyl cyanoacetate in 300 ml. of 60% ethanol was added 3 ml. of piperidine. The temperature slowly increased to 60° and then, on standing, decreased to 25°. The mixture 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. After stirring until a clear solution was obtained, 800 ml. of water was added. On acidification to congo red with 12 *N* hydrochloric acid, an orange-colored oil precipitated which solidified as the mixture was stirred.

The aqueous layer was decanted and the solid ethyl α,β-dicyano-β-phenylpropionate dissolved in a solution of 40 g. of sodium hydroxide in 200 ml. of water. While the solution was stirred 126 g. (1.0 mole) of methyl sulfate was added in 50-ml. portions over a period of one hour, basic conditions being maintained by the addition of alkali if necessary. When the temperature had decreased to 30°, 6 *N* hydrochloric acid was added until the mixture was acid to congo red.

The oily product was removed and refluxed with 1 l. of 12 *N* hydrochloric acid for 20 hours. The water layer was decanted from the cooled mixture and the residue dissolved in a solution of 60 g. of sodium hydroxide in 800 ml. of water. After adding a moderate amount of charcoal and filtering, the filtrate was made acid to congo red and 12 *N* hydrochloric acid. The mixture was cooled thoroughly, filtered and the solid washed with 200 ml. of water before being air-dried; yield 130 g. or 70%; m.p. 169–172°

α-Ethyl-β-phenylsuccinic Acid (VII, R_1 = H, R_2 = Ethyl).—A solution of 106 g. (1.0 mole) of benzaldehyde and 113 g. (1.0 mole) of ethyl cyanoacetate in 400 ml. of 95% ethanol was treated with 3 ml. of piperidine. When the solution had cooled to 30°, 54 g. (1.1 moles) of sodium cyanide was added. The solution obtained by stirring was heated on a steam-bath for 5 minutes and then cooled to 40°. After adding 109 g. (1.0 mole) of ethyl bromide in one portion, the mixture was refluxed for 10 hours, cooled and filtered to remove sodium bromide. The filtrate was concentrated on a steam-bath and the residue refluxed with 1.2 l. of 12 *N* hydrochloric acid for 20 hours. After cooling and decanting the aqueous layer, the oily material was dissolved in an excess of 10% aqueous sodium hydroxide and extracted with ether. The basic solution was mixed with a moderate amount of charcoal, filtered and the filtrate acidified with 6 *N* hydrochloric acid. Since the product remained an oil, it was refluxed with a mixture of 400 ml. of 12 *N* hydrochloric acid and 200 ml. of glacial acetic acid for 24 hours. On diluting with 400 ml. of water and cooling, a solid product was obtained which was filtered off and purified by precipitation from 10% aqueous sodium hydroxide with 6 *N* hydrochloric acid; yield 64 g. or 28%; m.p.[14] 160–166°.

Anal. Calcd. for $C_{12}H_{14}O_4$: C, 64.86; H, 6.30. Found: C, 64.93; H, 6.54.

α-Methyl-β-phenylsuccinimide (II, R = R_1 = H, R_2 = Methyl).—This procedure is typical for the preparation of the succinimides listed in Table I. Occasionally the product was recrystallized from a suitable solvent.

Five hundred grams (2.4 moles) of α-methyl-β-phenylsuccinic acid was added portionwise to a flask containing 500 g. of concentrated ammonium hydroxide. The mixture was heated on a Glas-Col mantle until the temperature of the product reached 225°. A solution of the residue in absolute ethanol was filtered and concentrated on a steam bath. The product obtained by distillation of the residue *in vacuo* solidified on standing.

(14) F. W. Upson and T. J. Thompson, THIS JOURNAL, **44**, 181 (1922). These authors reported that the substituted succinic acid obtained from the sodium salt of benzyl cyanide and ethyl α-bromobutyrate melted at 196°.

DETROIT, MICHIGAN RECEIVED MAY 25, 1951

[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

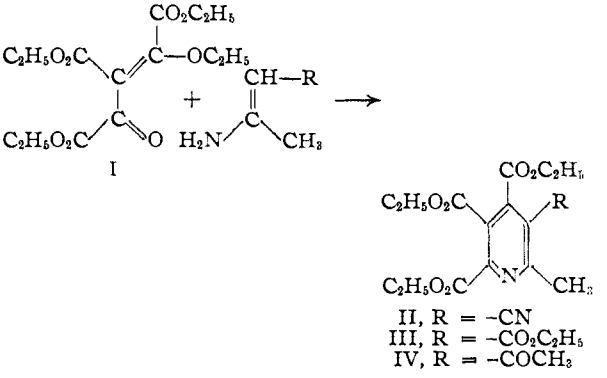
Pyridine Syntheses. III. Preparation and Reactions of Some Penta-substituted Pyridines

BY REUBEN G. JONES

Condensation of triethyl α-ethoxy-γ-ketoaconitate with β-aminocrotononitrile, ethyl β-aminocrotonate and iminoacetylacetone gave triethyl 5-cyano-6-methyl-2,3,4-pyridinetricarboxylate, tetraethyl 6-methyl-2,3,4,5-pyridinetetracarboxylate and triethyl 5-acetyl-6-methyl-2,3,4-pyridinetricarboxylate, respectively. Diethyl β-acetyl-α-ethoxy-γ-ketoglutaconate underwent condensation with iminoacetylacetone to yield diethyl 3,5-diacetyl-6-methyl-2,4-pyridinedicarboxylate. Hydrolysis of triethyl 5-acetyl-6-methyl-2,3,4-pyridinetricarboxylate followed by decarboxylation gave 5-acetyl-6-methyl-3,4-pyridinedicarboxylic acid. Triethyl 5-cyano-6-methyl-2,3,4-pyridinetricarboxylate has been converted to 5-amino-6-methyl-2,3,4-pyridinetricarboxylic acid, 5-hydroxy-6-methyl-2,3,4-pyridinetricarbroxylic acid, 5-hydroxy-6-methyl-3,4-pyridinedicarboxylic acid, 5-amino-6-methyl-2,4-pyridinedicarboxylic acid, 4-amino-6-methyl-2,5-pyridinedicarboxylic acid and related derivatives.

Preceding communications[1,2] from this Laboratory have been concerned with new methods of preparing 2,3,4,5-tetra-substituted pyridines suitable for conversion to vitamin B_6. One approach to the synthesis of these compounds appeared to be the elimination of a substituent such as carboxyl from the 6 position of appropriate penta-substituted pyridines. The purpose of this paper is to describe a new synthesis of such pentasubstituted pyridine compounds and their transformations into vitamin B_6 and related derivatives.

Triethyl α-ethoxy-γ-ketoaconitate (I)[3] has been found to undergo reaction readily with β-aminocrotononitrile, ethyl β-aminocrotonate, and iminoacetylacetone to form the pyridine compounds II,



II, R = –CN
III, R = –$CO_2C_2H_5$
IV, R = –$COCH_3$

III and IV, respectively, in yields of 65 to 70%. One additional example of this reaction was the condensation of diethyl β-acetyl-α-ethoxy-γ-ketoglutaconate[3] with iminoacetylacetone to yield

(1) E. M. Bottorff, R. G. Jones, E. C. Kornfeld and M. J. Mann, THIS JOURNAL, **73**, 4380 (1951)

(2) R. G. Jones, *ibid.*, **73**, 5168 (1951).

(3) R. G. Jones, *ibid.*, **73**, 5244 (1951).