obtained by distillation of the reaction mixture are given with their physical constants under the heading of the parent amine. 1-Methylcyclohexylamine, b.p. 144° at 10 mm., $n^{25}D$ 1.5429. *Anal.* Calcd. for $C_{14}H_{19}N$: N, 6.96. Found: N, 7.10. 1,2-Dimethylcyclohexylamine, b.p. 118° at 1.5 mm., $n^{25}D$ 1.5384. *Anal.* Calcd. for $C_{15}H_{21}N$: N, 6.51. Found: N, 6.52. 1,3-Dimethylcyclohexylamine, b.p. 100° at 1 mm., $n^{25}D$ 1.5324. *Anal.* Calcd. for $C_{15}H_{21}N$: N, 6.51. Found: N, 6.64. 1,4-Dimethylcyclohexylamine, b.p. 101–103° at 1 mm., $n^{25}D$ 1.5310. *Anal.* Calcd. for $C_{15}H_{21}N$: N, 6.51. Found: N, 6.60. 1-Methylcyclopentylamine, b.p. 148° at 18 mm., $n^{25}D$ 1.5432. *Anal.* Calcd. for $C_{13}H_{17}N$: N, 7.48. Found: N, 7.32. 3-Isopropyl-1-methylcyclopentylamine, b.p. 122–123° at 1 mm., $n^{25}D$ 1.5263. *Anal.* Calcd. for $C_{16}H_{23}N$: N, 6.11. Found: N, 6.14. 1,1-Dimethyl-*n*-hexylamine, b.p. 159–160° at 18 mm., $n^{25}D$ 1.5088. *Anal.* Calcd. for $C_8H_{19}N$: N, 6.45. Found: N, 6.52.

Method C. N-1-Dimethylcyclohexylamine.—With a few modifications, the method of Decker[3] was used for monomethylation of most of the primary amines given in Table I.

A mixture of 38 g. (0.19 mole) of benzylidene-1-methylcyclohexylamine and 27 g. (0.19 mole) of methyl iodide was heated at 125° for six hours in an autoclave. The red viscous material thus obtained was dissolved in 100 cc. of 85% methanol and the mixture was boiled for one hour. After the addition of 150 cc. of water, the liberated benzaldehyde was steam distilled. The residual mixture was evaporated to dryness *in vacuo* and then was made alkaline with 20% sodium hydroxide solution. The resulting base was extracted with ether, the ether extracts were dried and the solution was distilled. The physical data for this base and its salt are included in Table I.

Method D. 1-*n*-Butyl-N-methylcyclohexylamine.—A mixture of 1.5 g. (0.01 mole) of 1-*n*-butylcyclohexylamine and 2 cc. of 98% formic acid was heated at 180–190° for two hours and then cooled. This material was dissolved in ether and the ether solution was extracted with diluted hydrochloric acid and water. After the ether solution was dried over anhydrous magnesium sulfate, it was added dropwise to a solution of 1.52 g. (0.04 mole) of lithium aluminum hydride in ether. After the addition of the amide, the mixture was refluxed an additional six hours. Water was added until the complex and excess lithium aluminum hydride were decomposed. After filtration, the inorganic material was washed with ether and this filtrate was extracted well with ether. The ether extracts were combined, dried and then treated with a solution of anhydrous oxalic acid in ether. In this manner, 2.2 g. (83% yield) of the sesquioxalate of 1-*n*-butyl-N-methylcyclohexylamine was prepared; m.p. from ethyl acetate, 112–113°. This compound is further described in Table I. For additional confirmation of the structure of this amine, the picrate was formed in water. The yellow crystalline material was recrystallized from benzene, m.p. 122–123°. *Anal.* Calcd. for $C_{17}H_{26}N_4O_7$: N, 14.06. Found: N, 14.06.

Method E. N,N,1-Trimethylcyclohexylamine.—A mixture of 11.3 g. (0.1 mole) of 1-methylcyclohexylamine, 70 cc. of 90% formic acid and 13 cc. of formalin was boiled for four hours. After the mixture was evaporated to dryness *in vacuo*, the residue was made alkaline with 20% sodium hydroxide solution. The base which was formed in this manner was extracted with ether and the ether extracts were dried. After distillation, the desired N,N,1-trimethylcyclohexylamine was obtained in 85% yield (12 g.). Physical constants for this base and its salt are found in Table I.

Method F. N-Benzyl-1-methylcyclohexylamine.—A mixture of 25 g. (0.115 mole) of benzylidene-1-methylcyclohexylamine, 3 g. of Raney nickel catalyst and 75 cc. of methanol was subjected to a hydrogen pressure of 25 p.s.i. After the mixture was shaken for 12 hours, the catalyst was filtered and the filtrate was distilled. In this manner, 20.5 g. of N-benzyl-1-methylcyclohexylamine was obtained (80% yield). See Table I for physical data for this base and its salt.

N,1,2-Trimethylcyclohexylamine.—A mixture of 15 g. (0.065 mole) of N-benzyl-N,1,2-trimethylcyclohexylamine, 1.5 g. of 10% palladium–charcoal catalyst and 60 cc. of glacial acetic acid was subjected to a hydrogen pressure of 30 p.s.i. After the mixture was shaken for 12 hours, the catalyst was filtered and the filtrate was taken to dryness *in vacuo*. The residue was made strongly alkaline with 20% sodium hydroxide solution and the liberated base was extracted with ether. The ether extracts were dried and distilled. In this way, N,1,2-trimethylcyclohexylamine was obtained in an 87% yield (8 g.). Physical data for this amine and its salt are included in Table I.

Acknowledgment.—The authors wish to thank Doctor A. W. Weston for his advice and suggestions which prompted this investigation, Mr. F. E. Fischer for his technical assistance with the preparation of certain intermediates and Mr. E. F. Shelberg and the members of the Microanalytical Department for the microanalyses. The Department of Pharmacology of the Abbott Laboratories kindly provided a pharmacological survey of these compounds.

NORTH CHICAGO, ILLINOIS

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

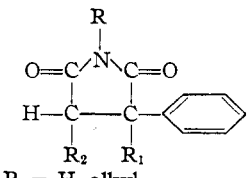
Anticonvulsants. III. A Study of N,α,β-Alkylsuccinimides

BY C. A. MILLER AND LOREN M. LONG

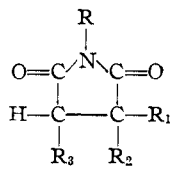
RECEIVED JULY 18, 1952

A third series of substituted succinimides has been synthesized and examined for anticonvulsant properties. Many of these alkyl derivatives exhibit a considerable degree of activity in preventing metrazol-induced convulsions in laboratory animals. However, at the dosage employed they are ineffective against electrically-induced convulsions.

The preparation and anticonvulsant properties of a number of substituted succinimides have been reported.[1,2] Each of these derivatives contained at least one phenyl group and may be represented by structure I. Certain members of this series are useful in the treatment of petit mal epilepsy. Indeed, N-methyl-α-phenylsuccinimide (Milontin)[3] is quite potent[4] against this type of convulsive disorder and is relatively non-toxic.



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



R, R_1, R_2, R_3 = H, alkyl
II

Since an appreciable number of the compounds I proved to be particularly effective in preventing metrazol-induced convulsions,[5] it is important

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

(2) C. A. Miller, H. I. Scholl and L. M. Long, *ibid.*, **73**, 5608 (1951).

(3) Parke, Davis and Co. trademark for N-methyl-α-phenylsuccinimide.

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

(5) G. Chen, R. Portman, C. R. Ensor and A. C. Bratton, *J. Pharmacol. Exp. Therap.*, **103**, 54 (1951).

TABLE I

N,α,β-ALKYLSUCCINIMIDES (II)

R[a]	R_1	R_2	R_3	B.p. °C.	B.p. Mm.	M.p., °C.	Yield,[b] %	Formula	Nitrogen, % Calcd.	Nitrogen, % Found	Anti-metrazol activity
H[c]	Ethyl	H	H			74–76	34	$C_6H_9NO_2$	11.02	10.83	0/500
H[d]	Methyl	Methyl	H			104–106	87			...	+/250
H[e]	Methyl	H	Methyl			107–109	39	$C_6H_9NO_2$	11.02	10.78	+/500
Methyl[f]	Methyl	H	H	115–117	17.5		58	$C_6H_9NO_2$	11.02	10.82	+/250
Methyl	Methyl	Methyl	H	98	13.5		67	$C_7H_{11}NO_2$	9.92	9.83	+/250
Methyl	Methyl	H	Methyl	115–117	20.5		59	$C_7H_{11}NO_2$	9.92	10.21	+/251
Ethyl[f]	Methyl	H	H	115–117	20.5		63	$C_7H_{11}NO_2$	9.92	9.46	+/125
Methyl	Methyl	Ethyl	H	111	15		77	$C_8H_{13}NO_2$	9.03	8.95	4+/125
Ethyl	Methyl	Methyl	H	76–77	5		76	$C_8H_{13}NO_2$	9.03	8.63	3+/125
Ethyl	Methyl	H	Methyl	109–111	18		76	$C_8H_{13}NO_2$	9.03	8.92	3+/250
Propyl[f]	Methyl	H	H	129–131	27		66	$C_8H_{13}NO_2$	9.03	8.77	3+/250
H	Methyl	Butyl	H	179–181	23		74	$C_9H_{15}NO_2$	8.28	7.98	4+/125
H	Ethyl	Ethyl	Methyl			73–74	39	$C_9H_{15}NO_2$	8.28	8.34	4+/125
Methyl	Ethyl	Ethyl	H	105–106	7.2		83	$C_9H_{15}NO_2$	8.28	7.98	4+/125
Ethyl	Methyl	Ethyl	H	112	14.8		57	$C_9H_{15}NO_2$	8.28	8.23	2+/125
Propyl	Methyl	H	Methyl	124–125	22.5		60	$C_9H_{15}NO_2$	8.28	8.05	3+/125
Isopropyl	Methyl	Methyl	H	87	7.4		78	$C_9H_{15}NO_2$	8.28	8.26	0/500
H	Ethyl	Butyl	H			62–64	33	$C_{10}H_{17}NO_2$	7.65	7.68	4+/125
Methyl	Methyl	Butyl	H	131–134	16.5		68	$C_{10}H_{17}NO_2$	7.65	7.52	4+/125
Methyl	Ethyl	Ethyl	Methyl	134–135	22.5		58	$C_{10}H_{17}NO_2$	7.65	7.91	4+/125
Ethyl	Ethyl	Ethyl	H	132	24.5		83	$C_{10}H_{17}NO_2$	7.65	7.88	0/500
Propyl	Methyl	Ethyl	H	128–129	19		70	$C_{10}H_{17}NO_2$	7.65	8.05	3+/125
Ethyl	Methyl	Butyl	H	132–135	11		70	$C_{11}H_{19}NO_2$	7.10	6.97	+/125
Ethyl	Ethyl	Ethyl	Methyl	135–136	21		75	$C_{11}H_{19}NO_2$	7.10	7.34	+/500
Ethyl	Ethyl	Butyl	H	169–171	47.6		73	$C_{12}H_{21}NO_2$	6.63	6.46	−/500

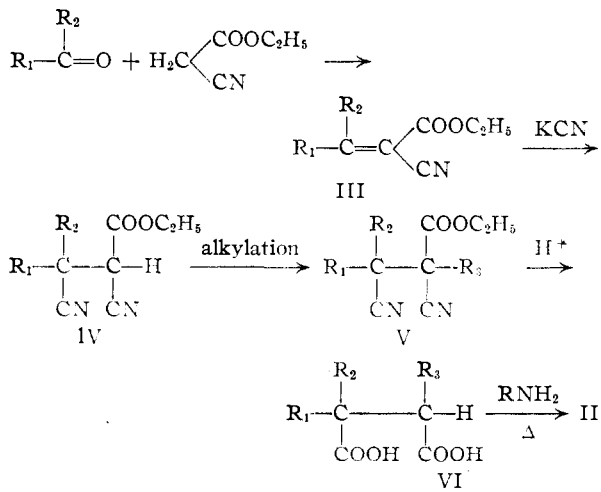
[a] Succinimide and N-methyl, N-ethyl, N-butyl and N-cyclohexylsuccinimide were tested. The N-butyl derivative was moderately active; the others did not show appreciable activity. [b] Yields are based on the intermediate succinic acids. [c] S. S. G. Sircar, *J. Chem. Soc.*, 1252 (1927). [d] A. Pinner, *Ber.*, **14**, 1070 (1881). [e] C. Bischoff and E. Voit, *ibid.*, **23**, 642 (1890). [f] M. Kling, *ibid.*, **30**, 3039 (1897).

from the viewpoint of structure *versus* anticonvulsant activity to investigate this ring system thoroughly. Therefore, of derivatives containing alkyl substituents only II have been prepared and this work as well as the results of pharmacological testing is reported herein.

As may be noted in structure II, all of the alkylsuccinimides contained in this study possess at least one α-hydrogen. The preparation of α,β-tetraalkylsuccinimides was considered, but Dox has indicated[6] that representatives of this type of compound tend to produce convulsions.

The compounds summarized in Table I were prepared by the series of reactions, III → IV → V → VI → II.

Usually compound III was produced by condensation of the aldehyde[7] or ketone[8] with ethyl cyanoacetate and the unsaturated derivative converted to IV by reaction with potassium cyanide. However, with dimethyl and methyl ethyl ketone higher yields could be obtained by employing the modifications of Smith and Horwitz.[9] The synthesis of IV (R_1 = methyl, R_2 = H) was accomplished by the method of Higson and Thorpe[10] in which lactonitrile is condensed with sodium ethyl cyanoacetate. Alkylation of compound IV to form V proceeded without difficulty. Hydrolysis and decarboxylation of IV and V were effected with concentrated hydrochloric acid or a mixture of either hydrochloric or sulfuric acid with acetic acid.



The substituted succinimides II were prepared as described previously[1,2] by distillation of the appropriate amine salts of the succinic acids. Pertinent data are summarized in Table I.

Anticonvulsant Activity.—All of the alkylsuccinimides reported here were tested against metrazol-induced as well as electrically-induced convulsions by previously described methods.[11] Since very little activity was shown against electrically-induced convulsions, the pharmacological data in

(6) A. W. Dox, THIS JOURNAL, **47**, 1471 (1925).

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

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

(9) P. A. S. Smith and J. P. Horwitz, *ibid.*, **71**, 3418 (1949).

(10) A. Higson and J. F. Thorpe, *J. Chem. Soc.*, **89**, 1455 (1906).

(11) G. Chen and C. R. Ensor, *Arch. Neurol. Psychiat.*, **63**, 56 (1950).

Table I refer only to metrazol-induced convulsions. The compounds are arranged in the order of increasing molecular weights. The maximum dosage employed was 500 mg./kg. At this level very few derivatives were entirely without activity. An appreciable number of the compounds gave complete protection against convulsive doses of metrazol to laboratory animals at a dosage of 125 mg./kg. of the drug, five rats being used at each dose level. It may be noted that in general the more active compounds are those containing either a hydrogen or a methyl as the nitrogen substituent. The α- or β-substituent may vary at least from methyl through butyl. Alkyls higher than butyl were not included in this study.

Acknowledgment.—Pharmacological studies were made by Dr. Graham Chen, Mr. Charles Ensor and Miss Ruth Portman. Analytical data were determined by Mr. C. E. Childs, Miss Virginia Pawlik and Mrs. Geraldine Koch of this Laboratory.

Experimental

α-Butyl-α-methylsuccinic Acid (VI, R_1 = methyl, R_2 = butyl, R_3 = H).—Several of the substituted succinic acids were prepared by the following method. To 121 g. (0.62 mole) of ethyl α-cyano-β-butyl-α-methylacrylate, prepared by the method of Cope, *et al.*,[8] from butyl methyl ketone and ethyl cyanoacetate, and 200 ml. of 50% ethanol was added 65 g. (1.0 mole) of potassium cyanide. The mixture was heated on a steam-bath until a clear solution was formed. After cooling, the solution was diluted with 500 ml. of water and made acid to congo red with 12 *N* hydrochloric acid. An oil precipitated which was removed before extraction of the aqueous layer with 250 ml. of ether. The organic fractions were combined and washed with 100 ml. of water, two 100-ml. portions of saturated sodium bicarbonate solution and finally 100 ml. of water. After the ether solution was dried over anhydrous magnesium sulfate and concentrated on a steam-bath, the residue was distilled *in vacuo*, b.p. 141–145° (2.3 mm.), yield 80 g. (58%).

Anal. Calcd. for $C_{12}H_{18}N_2O_2$: N, 12.61. Found: N, 12.46.

Eighty grams (0.36 mole) of the ethyl α,β-dicyano-β-methylheptanoate and 400 ml. of 12 *N* hydrochloric acid were refluxed together for 20 hours. After cooling, the oily layer was removed, dissolved in an excess of 10% aqueous sodium hydroxide, charcoaled and filtered. On acidification of the filtrate an oil was obtained which solidified after standing several days. The product was recrystallized from ether; m.p. 91–93°, yield 40 g. (59%).

Anal. Calcd. for $C_9H_{16}O_4$: C, 57.44; H, 8.51. Found: C, 57.40; H, 8.66.

α,α-Diethyl-β-methylsuccinic Acid (VI, R_1 = R_2 = ethyl, R_3 = methyl).—This acid has been prepared[12] previously, but the yield is improved substantially by the procedure described below.

To a solution of 91 g. (0.5 mole) of ethyl α-cyano-β,β-diethylacrylate[8] in 200 ml. of 95% ethanol was added 32.5 g. (0.5 mole) of potassium cyanide. The mixture was heated on a steam-bath until a clear solution was formed and then cooled to 25°. Seventy-one grams (0.5 mole) of methyl iodide was added. After refluxing for 4 hours the mixture was stirred with 400 ml. of water. The oil was separated and the aqueous layer extracted twice with 100-ml. portions of ether. The combined organic fractions were dried over anhydrous magnesium sulfate, concentrated on a steam-bath then distilled *in vacuo;* b.p. 178–179° (22 mm.), yield 75 g. (67%).

Sixty-seven grams (0.3 mole) of the α,β-dicyano-α-methyl-β,β-diethyl propionate was mixed with 150 ml. of concentrated sulfuric acid, 75 ml. of glacial acetic acid and 75 ml. of water and refluxed for 16 hours. The solution was cooled and mixed with 600 g. of chipped ice. The oil which formed was removed and the aqueous layer extracted twice with 200-ml. portions of ether. Concentration of the combined organic fraction gave a residue which was dissolved in an excess of 10% aqueous sodium hydroxide. After extracting with 100 ml. of ether, charcoaling and filtering the aqueous filtrate was acidified to congo red with 12 *N* hydrochloric acid. The oily product solidified on standing and was recrystallized from ethyl acetate by the addition of petroleum ether. The white crystalline product melted at 99–102°, yield 35 g. (62%).

α-Butyl-α-ethylsuccinimide (II, R = R_3 = H, R_1 = butyl, R_2 = ethyl).—The following procedure is typical for the preparation of the succinimides listed in Table I.

Ten grams of α-butyl-α-ethylsuccinic acid was added portionwise to a flask containing 15 ml. of concentrated ammonium hydroxide. The contents of the flask were heated until the internal temperature was 200°. The cooled residue was dissolved in ether, charcoaled and filtered. Dilution of the filtrate with petroleum ether produced the imide in the form of a white, crystalline solid.

(12) J. Colonge and D. Joly, *Ann. chim.*, **18**, 286 (1943).

DETROIT, MICHIGAN

[CONTRIBUTION FROM THE RICHARDSON CHEMICAL LABORATORY OF TULANE UNIVERSITY]

Metalation of Indole, N-Methylindole and N-Phenylindole with *n*-Butyllithium[1a]

BY DAVID A. SHIRLEY[1c] AND PHILIP A. ROUSSEL[1b]

RECEIVED AUGUST 25, 1952

Action of excess *n*-butyllithium on indole followed by carbonation with solid carbon dioxide gave only N-indolecarboxylic acid in 61% yield. There was no evidence of C-metalation under a variety of experimental conditions. N-Methylindole was metalated in the 2-position in 78% yield. N-Phenylindole with excess butyllithium showed evidence of dimetalation through the isolation of a dicarboxylic acid, probably 1-(2′-carboxyphenyl)-2-indolecarboxylic acid, and a cyclic ketone probably derived from the same dilithio compound. Both of the products represented a yield of dimetalation of about 55%. Reaction products of some of the lithioindole derivatives with a variety of reagents are reported.

The metalation of indole and certain of its derivatives with *n*-butyllithium was undertaken to provide information concerning the position of attack by this organometallic compound. As has been shown in the past, principally by Gilman and co-workers, introduction of a lithium atom into heterocyclic nuclei usually involves a position not attacked in ordinary electrophilic substitution processes. This has provided a useful technique in heterocyclic chemistry.

The reaction of indole with Grignard reagents gives an >N–MgX type which has been studied extensively by Oddo and co-workers[2a] and Majima and co-workers.[2b] Carbonation of this substance

(1) (a) Presented before the Seventh Southwest Regional Meeting of the American Chemical Society, Austin, Texas, Dec. 7, 1951. (b) Eli Lilly and Co. Research Fellow, 1951–1952. Now at E. I. du Pont de Nemours and Co. Jackson Laboratory, Deepwater, N. J. (c) Department of Chemistry, University of Tennessee, Knoxville, Tenn.

(2) For example see (a) B. Oddo and G. Sanna, *Gazz. chim. ital.*, **51**, II, 337–342 (1921) (*C. A.*, **16**, 1423 (1922)); (b) R. Majima and M. Kotake, *Ber.*, **55B**, 3865 (1922).