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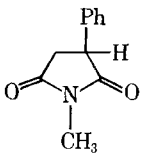
Synthesis and Anticonvulsant Properties of Some Derivatives of *N*-Methyl-2-phenylsuccinimide II

H. C. CLEMSON*, E. O. MAGARIAN†, and J. F. REINHARD*

Abstract □ Several substituted *N*-methyl-2-phenylsuccinimides have been prepared and evaluated for protective activity against convulsions induced by electroshock and pentylenetetrazole.

Keyphrases □ *N*-Methyl-2-phenylsuccinimide derivatives—synthesis □ Anticonvulsant activity—*N*-methyl-2-phenylsuccinimide derivatives □ IR spectrophotometry—structure □ NMR spectroscopy—structure

Phensuximide,[1] *N*-methyl-2-phenylsuccinimide (I), is a well-known anticonvulsant agent which has been employed in the treatment of petit mal epilepsy. The first paper of this series described the synthesis and biological evaluation of several *tert*-aminoalkyl derivatives of Structure I as potential anticonvulsants (1). As part of a continuing study, several additional derivatives of I have been prepared and screened for anticonvulsant properties.

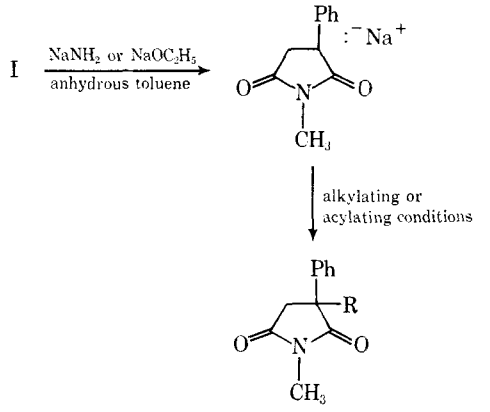


I

[1] Marketed as Milontin by Parke, Davis and Co., Detroit, MI 48232

DISCUSSION

Until recently, the methods used in the preparation of succinimide anticonvulsants have involved the cyclization of appropriate succinonitrile and succinic acid derivatives (2–6). However, the feasibility of direct substitution on the succinimide ring has been demonstrated as a useful synthetic tool (1, 7, 8).



IIa; R = $-CH_2Ph$
IIb; R = $-COCH_3$
IIc; R = $-COPh$

Scheme I

Table I—NMR Spectral Data

No.	Chemical Shift (δ)[a, b]
I	3.00 (2H,M), 3.02 (3H,S), 4.00 (1H,Q), 7.23 (5H,M)
II*a*	2.85 (3H,S), 3.06 (2H,S), 3.10 (1H,D),[c] 3.58 (1H,D),[c] 7.38 (10H,M)
II*b*	2.20 (3H,S), 2.69 (1H,D),[d] 3.03 (3H,S), 4.01 (1H,D),[d] 7.31 (5H,S)
II*c*	2.98 (1H,D),[d] 3.12 (3H,S), 4.07 (1H,D),[d] 7.42 (8H,M), 7.96 (2H,M)
III	3.07 (3H,S), 3.23 (1H,D),[d] 3.88 (1H,D),[d] 5.78 (1H,S), 7.18 (10H,M)
IV	2.60 (3H,S), 3.24 (1H,D),[d] 3.58 (1H,D),[d] 5.49 (1H,S), 7.43 (10H,M)
V	3.15 (3H,S), 3.71 (2H,S), 7.67 (5H,M)

[a] S = singlet, D = doublet, M = multiplet, Q = quartet. [b] All compounds were run as 10% solutions in deuterochloroform, excepting Compound IV whose concentration was 4% in deuterochloroform. [c] J = 13.5 c.p.s. [d] J = 18.0 c.p.s.

The proton in the 2-position of I is relatively acidic, because it is flanked by a benzene ring and a carbonyl group. Consequently, it was readily removed using either sodium amide or sodium ethoxide in anhydrous toluene. The resulting carbanion intermediate was subsequently utilized in alkylating and acylating reactions, as outlined in Scheme I.

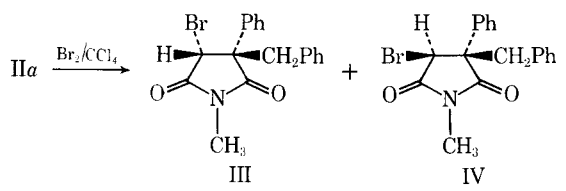
The bromination of II*a* in carbon tetrachloride yielded two compounds which are isomeric (Scheme II). The NMR spectra of the products indicate that they are geometric isomers having Formulas III and IV (Table I). The resonance peak for the methyl protons (2.60δ) in IV appears upfield to the corresponding peak in III (3.07δ).

It would appear from Dreiding stereomodels that Structure IV should possess a strong conformational bias, since the benzyl group is flanked on the one side by the large bromine atom and on the other side by the rather bulky phenyl group. As a result of this strong restriction to free rotation, the benzyl group is so oriented that the methyl group appears in the shielding portion of the induced currents of the aromatic ring. With less restriction to rotation, the benzyl group in III has a decreased influence on the methyl protons; consequently, their resonance peak occurs at a lower field position. The absorption peak for the methyl protons (2.84δ) in II*a*, the parent molecule, is intermediate in position to those in III and IV. Location of the methyl peak in III downfield to that in II*a* may be attributed to the influence of the bromine atom. Compound V, which was prepared by treating I with bromine in carbon tetrachloride (Scheme III), also displayed a similar deshielding effect by its bromine atom (Table I).[2]

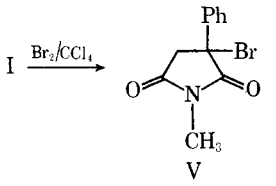
The substitution of the bromine atoms on the benzylic carbons to give diastereomers was also considered. However, the large difference in chemical shifts of the methyl protons cannot be rationalized in terms of these structures. Dreiding stereomodels indicate that the benzyl group should influence the methyl protons to about the same degree in either diastereomer, and that there should be little difference in their chemical shifts.

EXPERIMENTAL

All melting points have been determined on either a Fisher-Johns block or a Kofler micro hot stage and have been corrected.



Scheme II



Scheme III

Pertinent physical data for each of the products are listed in Table II.[3]

The IR spectra were determined on a Beckman IR-8 spectrophotometer using KBr pellets. All succinimide derivatives exhibited the two characteristic frequencies between 1690 and 1775 cm.$^{-1}$ (9–11).

NMR spectra were acquired using a Varian A-60 spectrometer and deuterochloroform solutions with tetramethylsilane as an internal standard. Appropriate data are given in Table I.

***N*-Methyl-2-phenylsuccinimide (I)**—This compound was prepared according to the procedure of Miller and Long (12).

2-Benzyl-*N*-methyl-2-phenylsuccinimide (II*a*)—To 0.10 mole of sodium amide in liquid ammonia (2.3 g. of sodium metal in 150 ml. of liquid ammonia), 18.9 g. (0.10 mole) of *N*-methyl-2-phenylsuccinimide (I) in 150 ml. of anhydrous toluene was added with stirring. After heating at reflux for 3 hr., the mixture was cooled to room temperature and a solution of freshly distilled benzyl chloride (12.7 g., 0.10 mole in 50 ml. of anhydrous toluene) was added with stirring over a period of 15 min. The reaction mixture was heated at reflux for 30 min. and then allowed to stir at room temperature for 12 hr. Finally, it was treated with 20 ml. of water, and the organic layer was separated and dried ($MgSO_4$). The toluene was removed *in vacuo*, yielding an oil which solidified upon standing. The product was recrystallized from 95% ethanol to give 20.2 g. of II*a*.

2-Acetyl-*N*-methyl-2-phenylsuccinimide (II*b*)—A solution of 18.9 g. (0.10 mole) of *N*-methyl-2-phenylsuccinimide (I) and 150 ml. of anhydrous toluene was added to 0.15 mole of sodium ethoxide in 200 ml. of absolute ethanol. The ethanol–toluene azeotropic mixture was distilled, and the volume of the reaction mixture was kept constant by the addition of anhydrous toluene. After the suspension had been cooled to 35°, 15.3 g. (0.15 mole) of acetic anhydride dissolved in 60 ml. of anhydrous toluene was added and the mixture was stirred for 8 hr. at 35°. The mixture was then treated with 100 ml. of a 10% sodium bicarbonate solution. The toluene layer was dried over anhydrous $MgSO_4$ and evaporated *in vacuo* to give a viscous, yellow liquid which solidified when triturated with 95% ethanol. Recrystallization from the same solvent gave 13.6 g. of II*b*.

2-Benzoyl-*N*-methyl-2-phenylsuccinimide (II*c*)—This derivative was prepared in a manner similar to the procedure for II*b* except that 15.5 g. (0.11 mole) of benzoyl chloride was used in place of the anhydride. The product was recrystallized from 95% ethanol, yielding 14.9 g. of II*c*.

Bromination of 2-Benzyl-*N*-methyl-2-phenylsuccinimide (III and IV)—To a mixture of 4.9 g. (0.018 mole) of 2-benzyl-*N*-methyl-2-phenylsuccinimide (II*a*) and 50 ml. of carbon tetrachloride at reflux was added dropwise 2.8 g. (0.018 mole) of bromine over a period of several hours. When the addition was complete, the mixture was heated at reflux for an additional 14 hr., followed by the addition of 50 ml. of water. The organic layer was separated and dried ($MgSO_4$). Evaporation of the carbon tetrachloride solution *in vacuo* gave an oil which solidified upon cooling. Recrystallization from *sec*-butyl alcohol resulted in two fractions. The less soluble fraction gave 1.7 g. of III, and the second fraction yielded 3.8 g. of IV.

2-Bromo-*N*-methyl-2-phenylsuccinimide (V)—A stirred solution of 2.5 g. (0.013 mole) of *N*-methyl-2-phenylsuccinimide (I) in 20 ml. of carbon tetrachloride was treated dropwise with 2.1 g. (0.013 mole) of bromine in 20 ml. of carbon tetrachloride. After the reaction mixture had been heated at reflux for 48 hr., the solvent was removed *in vacuo*. The residue was triturated with 95% ethanol; the solid, thus obtained, was recrystallized from this solvent, affording 2.1 g. of V.

[2] The preparation of V by a different method was previously reported by Izzo (13).

[3] Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn., and by Micro-Analysis, Inc., Wilmington, Del.

Table II—Derivatives of *N*-Methyl-2-phenylsuccinimide

No.	M.p.	Molecular Formula	Anal., % Calcd.	Found	Yield, %
II*a*	65–67°	$C_{18}H_{17}NO_2$	C, 77.43 H, 6.09 N, 5.02 O, 11.46	C, 77.27 H, 6.15 N, 5.05 O, 11.23	72
II*b*	92–94°	$C_{13}H_{13}NO_3$	C, 67.53 H, 5.63 N, 6.06 O, 20.78	C, 67.38 H, 5.52 N, 6.20 O, 20.64	58
II*c*	147–149°	$C_{18}H_{15}NO_3$	C, 73.72 H, 5.12 N, 4.78 O, 16.38	C, 73.73 H, 5.10 N, 4.78 O, 16.32	51
III	161–164°	$C_{18}H_{16}BrNO_2$	C, 60.37 H, 4.47 Br, 22.32 N, 3.90 O, 8.93	C, 60.21 H, 4.55 Br, 22.35 N, 3.74 O, 9.09	21[a]
IV	117–119°	$C_{18}H_{16}BrNO_2$	C, 60.37 H, 4.47 Br, 22.32 N, 3.90 O, 8.93	C, 60.14 H, 4.36 Br, 22.57 N, 3.76 O, 9.11	48[a]
V	113–115°[b]	$C_{11}H_{10}BrNO_2$	C, 49.29 H, 3.73 Br, 29.82 N, 5.22 O, 11.94	C, 49.50 H, 3.91 Br, 29.62 N, 5.31 O, 12.07	60

[a] Combined yield from the bromination of II*a* = 69%. [b] Lit. m.p. (13) = 110.5–112°.

PHARMACOLOGY

Methods and Materials—The succinimides were tested for anticonvulsant activity by modifications of two methods described by Swinyard *et al.* (14). In the first procedure (maximal electroshock seizures), the compounds were suspended in 10% (aqueous) acacia and administered orally to adult, male, albino mice in groups of 10 at a dosage of 200 mg./kg. At intervals of 0.5, 1, and 2 hr. thereafter, the animals of each group were challenged by delivering 60 ma. (a.c.) through the corneal electrodes for 0.2 sec. The end-point indicating anticonvulsant activity is the abolition of the hindlimb tonic extensor component of the maximal seizure pattern. The time of peak effect was determined by observing which time interval gave optimum protection. Whenever substantial effectiveness was demonstrated in this manner, a second investigation was undertaken to determine potency more precisely. The compound was administered at three or more dosage levels, generally 10 animals per dosage, and the animals were challenged at the predetermined time of peak effect. The dosage of compound required to produce the anticonvulsant end-point in 50% of the animals (ED_{50} with 95% fiducial limits) was computed by the method of Litchfield and Wilcoxon (15).

The second procedure (chemoshock) involved protection against a chemical convulsant, pentylenetetrazol.[4] Again, the compound was administered orally at a dosage of 200 mg./kg. to 10 adult, male, albino mice. At the time of peak effect, a 97% convulsant dosage of pentylenetetrazol (106 mg./kg.) was injected subcutaneously. Anticonvulsant activity was indicated by the failure of clonic convulsive seizures to appear within 1 hr. following pentylenetetrazol. Whenever indicated, ED_{50}'s were determined in the manner previously described.

The mice[5] employed in these investigations were housed 20 per cage and fed Charles River Rat and Mouse Food and tap water *ad libitum*.

[4] Marketed as Metrazol by Knoll Pharmaceutical Co., Orange, NJ 07051

[5] Obtained from the Charles River Breeding Laboratories, N. Wilmington, Mass.

Table III—Anticonvulsant Activity of Succinimide Derivatives in the Mouse

Compound	Fraction of Animals Protected following 200 mg./kg. of Compound: Electroshock	Chemoshock	Time of Peak Activity, hr.
I	9/10[a]	9/10[b]	0.5
II*a*	0/5	0/10	—
II*b*	9/10[c]	9/10[d]	0.5
II*c*	0/10	2/10[e]	—
III	0/10	0/10[f]	—
IV	0/10	0/10	—
V	1/10	2/10[g]	1

[a] ED_{50} = 115 (92–144) mg./kg. [b] ED_{50} = 134 (87–208) mg./kg. [c] ED_{50} = 96 (64–144) mg./kg. [d] ED_{50} = 86 (60–124) mg./kg. [e] ED_{50} = 610 mg./kg. (approx.). [f] 4/10 protected at 400, only 2/10 at 800 mg./kg. [g] 6/10 protected at 400, but only 2/10 at 600 mg./kg.

Results and Discussion—The data summarized in Table III reveal that, in general, anticonvulsant potency was inversely proportional to the size of the side chain in the 2-position. Where this chain contained a benzyl or benzoyl group, anticonvulsant activity was either absent or weak in the sense that total protection could not be achieved at any dosage, owing to the superimposition of the toxicity of the test compound. However, the 2-acetyl derivative (II*b*) was the most active member of the series, equalling the potency of the parent compound, phensuximide (I). A similar relationship between the size of alkyl substituents in some aryldialkylsuccinimides and anticonvulsant potency was reported by Hauck *et al.* (6).

In all of the studies conducted on these succinimides, anticonvulsant activity was in all cases associated with depression of the CNS; yet the hypnotic activity did not appear in response to high dosage, even in the toxic range. Therapeutically, this combination of effectiveness against seizures without risk of undue CNS depression is a distinctly desirable feature of any anticonvulsant, since it must be given daily for prolonged periods.

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Kinetic Salt Effect in Pharmaceutical Investigations

J. THURØ CARSTENSEN

Abstract □ The use of the kinetic salt effect in kinetic investigations has been widespread since its original derivation by Brønsted and Bjerrum in 1925. Its derivation is tied in with the Debye-Hückel theory, and it would be expected that the concentration range of applicability of the kinetic salt effect would be confined to that of the corresponding Debye-Hückel expression, *i.e.*, less than 0.01 *M*. A review of the pharmaceutical literature shows that applications may be extended to higher concentration ranges. Deviations from the Debye-Hückel expressions by the charged reactants and by the transition complex may be of the same magnitude and sign, and this may be the cause for the concentration range extension.

Keyphrases □ Kinetic salt effect—pharmaceutical solutions □ Ionic strength effect—high ionic concentrations □ Hydrolysis—kinetic salt effect □ Degradation, drug—kinetic salt effect

Properly conducted kinetic studies always, directly or indirectly, take into account the so-called kinetic salt effect. By varying the ionic strength by addition of an inert electrolyte (*e.g.*, NaCl) while keeping other concentrations constant, the rate constants for reacting species will either increase, remain constant, or decrease. Accordingly, the effect is denoted positive, absent, or negative. As shall be seen in the following discussion, the sign or the absence of the kinetic salt effect is a valuable aid in interpretation of mechanisms. Strictly quantitative relations between rate constants and ionic strength are only theoretically valid at exceedingly low concentrations. Since pharmaceutical investigations are most often conducted at ionic strength ranges higher than the theoretical limits, a review of findings from kinetics of pharmaceutical model systems might throw light on the actual range to which the kinetic salt effect can be extended.

THEORY

It can be shown (1) by means of transition-state theory that for a reaction in solution:

$$A + B \rightarrow [AB^{\dagger}] \rightarrow \text{products} \qquad \text{(Eq. 1)}$$

the rate constant, k, is related to the activity coefficients, γ, of the reactants (A and B) and the transition complex ($[AB^{\dagger}]$) by:

$$\log k = \alpha + \log [\gamma_A \gamma_B / \gamma_{[AB^{\dagger}]}] \qquad \text{(Eq. 2)}$$

The charges, z, of the three species are related to one another by $z_A + z_B = z_{[AB^{\dagger}]}$. Applying this and the Debye-Hückel limiting law:

$$\log \gamma = -Q \cdot z^2 \sqrt{\mu} \qquad \text{(Eq. 3)}$$

Table I—Values of $2Q = 3.65 \cdot 10^6 \cdot [\rho/\epsilon^3 T^3]^{0.5}$ at Various Temperatures

Temperature	$2Q^a$
20	1.008
25	1.018
30	1.026
35	1.036
40	1.046
45	1.057
50	1.068
55	1.079
60	1.092
70	1.117
80	1.145
90	1.174
100	1.198

[a] ϵ-values used in the computation are from *Reference 43*, and ρ-values are from *Reference 44*.

to Eq. 2 for a solution of overall ionic strength, μ, leads to the well-known Brønsted-Bjerrum equation (2–5):

$$\log k = \alpha + 2 \cdot Q \cdot z_A \cdot z_B \cdot \sqrt{\mu} \qquad \text{(Eq. 4)}$$

where $2Q = 1.018$ for aqueous solutions at 25°. Since $Q = 1.825 \cdot 10^6 \cdot [\rho/\epsilon^3 T^3]^{0.5}$, where ϵ is the dielectric constant, ρ is density, and T is the absolute temperature, the coefficient to $\sqrt{\mu}$ changes with temperature. A list of values of $2Q$ is given in Table I.

The Debye-Hückel equation is usually only obeyed in ionic strength ranges up to 0.01 (6). Figure 1 is an example of this showing the mean activity coefficients of hydrochloric acid in potassium chloride solutions of varying ionic strength (7). Equation 4 is, therefore, only strictly applicable up to this concentration.

The modified Debye-Hückel equation for higher concentrations is

$$\log \gamma_{\pm} = \frac{z^2 \cdot Q \cdot \sqrt{\mu}}{1 + \beta\sqrt{\mu}} \qquad \text{(Eq. 5)}$$

and holds up to an ionic strength of about $\mu = 0.1$ (8). Using this in the development outlined for Eq. 4 yields

$$\log k = \alpha + 2 \cdot Q \cdot z_A \cdot z_B \cdot \frac{\sqrt{\mu}}{1 + \beta\sqrt{\mu}} \qquad \text{(Eq. 6)}$$

It is recalled that μ is the overall ionic strength, but β depends on the ionic diameter of the reacting species, and this usually is unknown. Linearity and slopes, however, are not very sensitive to the magnitude of β, which is always close to unity; it is the practice of some authors (9) to test kinetic salt effects with this assumption, *i.e.*,

$$\log k = \alpha + 2 \cdot Q \cdot z_A \cdot z_B \cdot \frac{\sqrt{\mu}}{1 + \sqrt{\mu}} \qquad \text{(Eq. 7)}$$

The slope of such a plot should be close to the value of $2 \cdot Q \cdot z_A \cdot z_B$ (which is not necessarily an integer, all depending on tem-