(4) N. Brock and H.-J. Hohorst, *Arzneim.-Forsch.*, **13**, 1021 (1963).
(5) (a) D. L. Hill, M. C. Kirk, and R. F. Struck, *J. Amer. Chem. Soc.*, **92**, 3207 (1970); (b) R. F. Struck, M. C. Kirk, L. B. Mellett, S. ElDareer, and D. L. Hill, *Mol. Pharmacol.*, **7**, 519 (1971).
(6) K. Norpoth, E. Golovinsky, and H. M. Rauen, *Hoppe-Seyler's Z. Physiol. Chem.*, **351**, 377 (1970).
(7) H.-J. Hohorst, A. Ziemann, and N. Brock, *Arzneim.-Forsch.*, **21**, 1251 (1971).
(8) D. L. Hill, W. R. Laster, Jr., and R. F. Struck, *Cancer Res.*, **32**, 658 (1972).
(9) A. Takamizawa, S. Matsumoto, T. Iwata, K. Katagiri, Y. Tochino, and K. Yamaguchi, *J. Amer. Chem. Soc.*, **95**, 985 (1973).
(10) Y. Tochino, T. Iwata, A. Takamizawa, and Y. Hamashima, *Proc. Symp. Drug Metab. Action, 3rd*, 139 (1971).
(11) C. Djerassi, *Org. React.*, **5**, 207 (1951).
(12) K. E. Pfitzner and J. G. Moffatt, *J. Amer. Chem. Soc.*, **87**, 5670 (1965).
(13) H. Stephen, *J. Chem. Soc.*, 1874 (1925).
(14) O. G. Backeberg and B. Staskun, *J. Chem. Soc.*, 3961 (1962).
(15) H. Pobiner, *Anal. Chem.*, **33**, 1423 (1961).
(16) A. Camerman, private communication.
(17) H. Sternglanz, H. M. Einspahr, and C. E. Bugg, *J. Amer. Chem. Soc.*, **96**, 4014 (1974).
(18) A. Takamizawa, S. Matsumoto, T. Iwata, and I. Makino, unpublished results.
(19) G. Völker, U. Dräger, G. Peter, and H.-J. Hohorst, *Arzneim.-Forsch.*, **24**, 1172 (1974).
(20) A. Rieche, M. Schulz, and D. Becker, *Chem. Ber.*, **98**, 3627 (1965).
(21) R. Criegee and G. Wernner, *Justus Liebigs Ann. Chem.*, **564**, 9 (1946).
(22) A. Takamizawa, S. Matsumoto, and T. Iwata, *Tetrahedron Lett.*, 517 (1974).
(23) S. Fliszár, J. Renard, and D. Z. Simon, *J. Amer. Chem. Soc.*, **93**, 6953 (1971), and references cited therein.
(24) S. Fliszár and M. Granger, *J. Amer. Chem. Soc.*, **92**, 3361 (1970).
(25) S. Fliszár and M. Granger, *J. Amer. Chem. Soc.*, **91**, 3330 (1969).
(26) R. F. Struck and D. L. Hill, *Proc. Amer. Ass. Cancer Res.*, **13**, 50 (1972).
(27) N. E. Sladek, *Cancer Res.*, **33**, 651 (1973).
(28) A. Takamizawa, S. Matsumoto, and T. Iwata, unpublished results.
(29) R. F. Struck, private communication.
(30) E. G. E. Hawkins, *Angew. Chem.*, **85**, 850 (1973).
(31) J. van der Steen, E. C. Timmer, J. G. Westra, and C. Benckhuysen, *J. Amer. Chem. Soc.*, **95**, 7535 (1973).
(32) R. F. Struck, M. C. Thorpe, W. C. Coburn, Jr., and W. R. Laster, Jr., *J. Amer. Chem. Soc.*, **96**, 313 (1974).
(33) A. Takamizawa, S. Matsumoto, T. Iwata, S. Sakai, and I. Makino, *Heterocycles*, **2**, 255 (1974).
(34) R. A. Alarcon and J. Meienhofer, *Nature (London), New Biol.*, **233**, 250 (1971).
(35) M. Colvin, C. A. Padgett, and C. Fenselau, *Cancer Res.*, **33**, 915 (1973).
(36) M. Thomson and M. Colvin, *Cancer Res.*, **34**, 981 (1974).
(37) J. W. E. Glattfeld and F. V. Sander, *J. Amer. Chem. Soc.*, **43**, 2675 (1921).
(38) O. M. Friedman and A. M. Seligman, *J. Amer. Chem. Soc.*, **76**, 655 (1954).

Anticonvulsants. 5. Derivatives of 5-Ethyl-5-phenylhydantoin and 5,5-Diphenylhydantoin

Julius A. Vida,* Mary H. O'Dea, Carlos M. Samour,

Kendall Company, Lexington, Massachusetts 02173

and John F. Reinhard

Department of Medicinal Chemistry and Pharmacology, Graduate School of Pharmacy and Allied Health Professions, Northeastern University, Boston, Massachusetts 02115. *Received November 8, 1974*

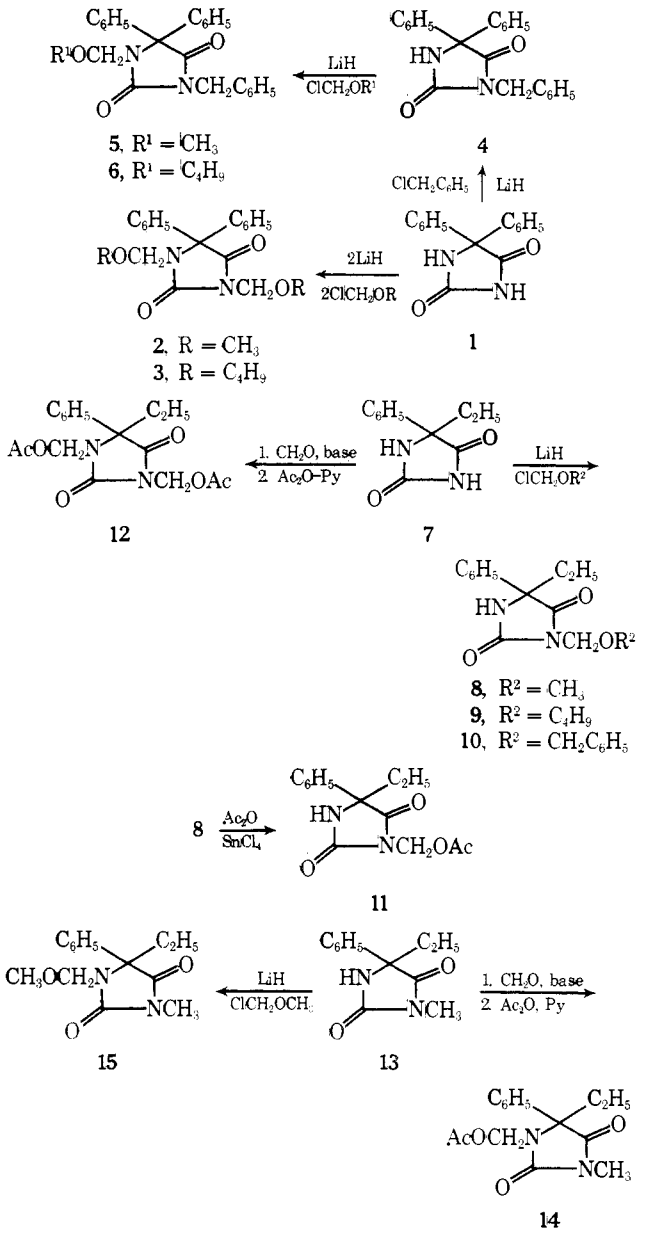
Alkoxymethyl, acyloxymethyl, and mixed alkylalkoxymethyl or alkylacyloxymethyl derivatives of 5-ethyl-5-phenylhydantoin exhibit anticonvulsant activity. Also effective are bis(alkoxymethyl) and mixed alkylalkoxymethyl derivatives of 5,5-diphenylhydantoin. Of particular interest are 1,3-bis(methoxymethyl)-5,5-diphenylhydantoin and 3-acetoxymethyl-5-ethyl-5-phenylhydantoin, which show good activity against maximal electroshock seizures, and 3-methoxymethyl-5-ethyl-5-phenylhydantoin, which is effective against both maximal electroshock and pentylenetetrazole. None of the above compounds show greater activity against maximal electroshock seizures than the parent compounds, however.

We reported earlier[1] that both 3-acetoxymethyl- and 1,3-bis(acetoxymethyl)-5,5-diphenylhydantoin showed good activity against maximal electroshock seizures. We also reported[2] that 3-alkoxymethyl derivatives of diphenylhydantoin possess activity against maximal electroshock seizures but, unlike diphenylhydantoin,[3] were effective against chemoshock as well. We were therefore interested in investigating the activities of the corresponding derivatives of 5-ethyl-5-phenylhydantoin, itself an effective compound against both electroshock and electroshock seizures.[3] It was also of interest to determine the effects induced by introduction of an additional alkoxymethyl group at the remaining nitrogen atom of the diphenylhydantoin ring and by mixed alkylation–alkoxymethylation of the ring nitrogen atoms of both 5,5-diphenyl- and 5-ethyl-5-phenylhydantoin.

The synthetic methods used for the preparation of compounds are outlined in Scheme I.

Chemistry. The synthesis of 1,3-bis(alkoxymethyl)-5,5-diphenylhydantoins (2 and 3) was accomplished from 5,5-diphenylhydantoin (1) with the appropriate chloromethyl alkyl ether in the presence of two equivalents of base. Mixed alkylalkoxymethyl derivatives (5 and 6) of 5,5-diphenylhydantoin were obtained by alkylation of 3-benzyl-5,5-diphenylhydantoin[4] (4) with chloromethyl alkyl ethers in the presence of base. From the base-catalyzed reaction of 5-ethyl-5-phenylhydantoin (7) with alkyl chloromethyl ethers, 3-alkoxymethyl-5-ethyl-5-phenylhydantoins (8–10) were obtained. Treatment of compound 7 with excess CH_2O in the presence of base, followed by Ac_2O and pyridine, provided 1,3-bis(acetoxymethyl)-5-ethyl-5-phenylhydantoin (12). 3-Methoxymethyl-5-ethyl-5-phenylhy-

Scheme I



dantoin (8) could be converted into 3-acetoxymethyl-5-ethyl-5-phenylhydantoin (11) with Ac_2O in the presence of $SnCl_4$.[1]

Mixed alkylalkoxymethyl and alkylacyloxymethyl derivatives of 5-ethyl-5-phenylhydantoin (14 and 15) were obtained from 3-methyl-5-ethyl-5-phenylhydantoin (13).

Pharmacology. Anticonvulsant Activity (MES). All of the compounds listed in Table I were tested for anticonvulsant activity against maximal electroshock seizures (MES), although only two of the derivatives were as effective as the parent compounds 1, 7, and 13. In the diphenylhydantoin series, the best activity against MES was shown by the 1,3-bis(methoxymethyl) derivative 2, which was approximately one-third as potent as compound 1. Compounds 3, 5, and 6 exhibited only weak activity at high doses. Of the 5-ethyl-5-phenylhydantoin derivatives, the most active compounds were 3-acetoxymethyl-5-ethyl-5-phenylhydantoin (11), which was equally effective as the known 5-ethyl-5-phenylhydantoin (7), and 3-methoxymethyl-5-ethyl-5-phenylhydantoin (8), which showed one-half the potency of compound 7. Compounds 9, 10, and 12 displayed one-eighth, one-fourth, and one-fifth the potency of compound 8, respectively. The derivatives of 3-methyl-5-ethyl-5-phenylhydantoin (14 and 15) were approximately equal in activity, exhibiting one-eighth the potency of the parent compound 13.

In addition to the newly synthesized compounds, the known compounds, for which no complete pharmacologic data are available, were also evaluated. These are 3-methyl-5,5-diphenylhydantoin[5] (16), 1-methyl-3-benzyl-5,5-diphenylhydantoin[4] (17), and 1,3-dimethyl-5,5-diphenylhydantoin[6] (18). Only compounds 16 and 18 were found to be effective against MES.

Met. Of the 5,5-diphenylhydantoin derivatives, only the known 1,3-dimethyl derivative 18 exhibited good activity against pentylenetetrazole-induced seizures (Met) in contrast to the parent compound which exhibited no activity. Weak activity was shown by compounds 2, 3, 5, 6, and 17. Compound 16, which was previously reported to have activity against pentylenetetrazole,[7] showed very little activity at the doses employed. In the 5-ethyl-5-phenylhydantoin series, compounds 8, 9, 11, and 12 had activity against pentylenetetrazole. Compound 8 was approximately one-half as active as the parent compound 7 while compounds 9, 11, and 12 had only weak activity. The 3-methyl-5-ethyl-5-phenylhydantoin derivatives 14 and 15 were both weakly active against pentylenetetrazole.

CNS Depression. These compounds, for the most part, did not exhibit CNS-depressant effects. Compounds 6, 9, 11, 14, and 16 displayed CNS depression only at high dosage. Neurological deficit was noted after administration of large doses of compounds 8 and 14.

Hypnotic Activity and Acute Toxicity. The compounds listed in Table I all exhibited little or no hypnotic activity. Acute toxicities were also extremely low. Only compounds 2 (>200 < 500) and 11 (~500) showed LD_{50} values less than 1000 mg/kg. The LD_{50}'s of compounds 2 and 11 were, however, significantly higher than that of 5,5-diphenylhydantoin (1, 150 mg/kg). The margins of safety of compounds 2 and 11 ($LD_{50}/ED_{50} \geq 10$) appear to be well within acceptable limits.

Experimental Section

Pharmacology. All compounds were administered orally suspended in 10% aqueous acacia. Adult male albino mice (18–30 g, Charles River) were used throughout this study. Protection against maximal electroshock (MES) and pentylenetetrazole (Met) were determined according to Swinyard, *et al.*[8]

Peak Time. Time of peak anticonvulsant activity (maximal electroshock seizures) was determined according to Swinyard, *et al.*,[8] except that different groups of five mice were tested at the approximate ED_{50} at intervals of 0.5, 1, 2, and 3 hr (or longer) following drug administration. In our experience different groups were necessary since repeated shocking of animals leads to false positive results. The peak time was taken to be the time at which maximum protection occurred.

Hypnotic Activity. Compounds were administered to groups of ten animals generally at five dosage levels. Hypnotic activity (sleep) was determined by loss of the righting reflex without regard to the duration of effect, *i.e.*, the interval between loss and return of the righting reflex. The number of mice sleeping was recorded for each dose, and the dose required to induce sleep in 50% of the animals (HD_{50}) was determined graphically according to Litchfield and Wilcoxon.[9] A compound was considered to have hypnotic activity only if the dose required to induce sleep in the animals differed significantly from the dosage required to cause death.

Acute Toxicity. The compounds were administered orally and the animals were observed for signs of toxicity over a period of several hours thereafter and again daily for a period of 1 week or until complete recovery had occurred. The number of deaths was recorded and the dosage required to cause death in 50% of the animals (LD_{50}) was computed according to Litchfield and Wilcoxon.[9]

CNS Depression. CNS depression was recorded if the animals (a) exhibited decreased spontaneous movements compared to untreated controls either by visual observation or by recording the

Table I. Pharmacologic Activity of Diphenylhydantoin and Ethylphenylhydantoin Derivatives

Compd no.	Peak time, hr	MES, ED_{50}, mg/kg	Met, ED_{50}, mg/kg
1	3	~7.5	Inactive
2	0.5	~25	~600
3	2	>200	>1000
4	2	>200	Inactive
5	1	>200	>200
6	2	~200	~200
7	1	~12.5	~16
8	0.5	~25	~38
9	1	~200	>200
10	2	~100	Inactive
11	1	~12.5	~100
12	2	~130	>200
13	1	~10	~30
14	0.5	~80	~200
15	0.5	50–80	~100
16	2	>3.125 < 6.25	>200
17	0.5	>200	~110
18	3	~50	~25

actual number of movements with the aid of a standard photoelectric cell apparatus; (b) were tame, *i.e.*, resisted handling less than untreated controls; and (c) showed decreased tonus of skeletal muscles on handling. In addition, neurological deficit was recorded if the animals showed ataxic movements of other signs as reported by Swinyard, *et al.*,[8] or failed to "log roll" for at least 1 min on a rod (Rotarod)[10] rotating at 6 rpm.

Analyses and Spectra. Microanalyses were within ±0.3% of the theoretical values as performed by Galbraith Laboratories, Knoxville, Tenn., or Atlantic Microlab, Inc., Atlanta, Ga. Melting points were obtained on a Fisher-Johns hot stage and are corrected. Ir spectra were recorded on a Perkin-Elmer 337 grating ir spectrophotometer. Nmr spectra were run on Varian A-60A and HA-100 spectrometers in $(CD_3)_2SO$ with Me_4Si as internal reference. Uv spectra were recorded on a Bausch & Lomb spectronic 505 spectrophotometer. Mass spectra were determined on a Hitachi RMU-6D double-focusing spectrometer at 70 eV. Type Q1F silica gel plates from Quantum Industries were used for tlc development with PhH–EtOAc mixtures. E. M. Merck 70–325 mesh silica gel (0.05–0.2 mm) pretreated with benzene 2:1 (weight of silica gel–volume of benzene) was used for chromatographic separations. Ir, nmr, uv, mass spectra, and tlc were all appropriate.

1,3-Bis(methoxymethyl)-5,5-diphenylhydantoin (2). Diphenylhydantoin 1 (25.3 g, 0.1 mol) was dissolved in dimethylacetamide (150 ml) and LiH (2.0 g, 0.25 mol) was added. The mixture was stirred 15 min at 50°. CH_3OCH_2Cl (20 g, 0.25 mol) was added dropwise over a 15-min interval. Stirring was continued at 50° for 1 hr. The solution was allowed to stand at 25° for 16 hr, after which ice–H_2O (300 ml) containing HCl (2 ml) was added. After extraction of the aqueous solution with EtOAc, the extract was evaporated and the remaining oil was chromatographed on silica gel (300 g). Elution with EtOAc–C_6H_6 (1:19) gave **2** (14.5 g, 42.5%): mp 98.5–100.5°. *Anal.* ($C_{19}H_{20}O_4N_2$) C, H, N.

1,3-Bis(butoxymethyl)-5,5-diphenylhydantoin (3). Compound **3** was prepared from 1 (25.3 g, 0.1 mol) and $C_4H_9OCH_2Cl$ (27.0 g, 0.22 mol) in the same way as described for the preparation of compound **2**. Elution of the column (300 g of silica gel) with C_6H_6–hexane (3:1) gave **3** (16.0 g, 38%), an oil. *Anal.* ($C_{25}H_{32}O_4N_2$) C, H, N.

1-Methoxymethyl-3-benzyl-5,5-diphenylhydantoin (5). To a solution of 4 (6.8 g, 0.02 mol) in DMF (50 ml) was added LiH (800 mg, 0.1 mol), and the solution was stirred at 25° for 30 min. CH_3OCH_2Cl (9.6 g, 0.12 mol) was added dropwise over a 15-min interval. The solution was stirred 16 hr at 100°, then cooled, and poured into ice–H_2O (200 ml). The oily precipitate was extracted into EtOAc and the extract was evaporated. The remaining oil solidified upon standing 24 hr and was crystallized from MeOH to give **5** (4.4 g, 57%): mp 107–108°. *Anal.* ($C_{24}H_{22}O_3N_2$) C, H, N.

1-Butoxymethyl-3-benzyl-5,5-diphenylhydantoin (6). Compound **6** was obtained from 4 (6.8 g, 0.02 mol) and $C_4H_9OCH_2Cl$ (14.7 g, 0.12 mol) in the same way as described for the preparation of compound **5**. The product was chromatographed on silica gel (200 g). Elution with C_6H_6–hexane (3:1) gave **6** (4.2 g, 49%), an oil. *Anal.* ($C_{27}H_{28}O_3N_2$) C, H, N.

3-Methoxymethyl-5-ethyl-5-phenylhydantoin (8). To a solution of LiH (600 mg, 0.075 mol) in DMF (50 ml) was added **7** (6.0 g, 0.03 mol). The solution was stirred at 25° for 1 hr. CH_3OCH_2Cl (20 g, 0.25 mol) was added dropwise over a 15-min interval, and stirring at 25° was continued for 16 hr. The solution was poured into ice–H_2O (300 ml) and the resulting oil was extracted with EtOAc. The extract was evaporated and the residue was chromatographed on silica gel (250 g). Elution with EtOAc–C_6H_6 (1:9) gave **8** (4.4 g, 59%), an oil. *Anal.* ($C_{13}H_{16}O_3N_2$) C, H, N.

3-Butoxymethyl-5-ethyl-5-phenylhydantoin (9). Compound **9** was prepared from **7** (6.0 g, 0.03 mol) and $C_4H_9OCH_2Cl$ (20 g, 0.16 mol) in the same way as described for the preparation of compound **8**. Obtained was **9** (6.9 g, 79%), an oil. *Anal.* ($C_{16}H_{22}O_3N_2$) C, H, N.

3-Benzyloxymethyl-5-ethyl-5-phenylhydantoin (10). Compound **10** was prepared from **7** (5.1 g, 0.025 mol) and $C_6H_5CH_2OCH_2Cl$ (8.0 g, 0.051 mol) in the same way as described for the preparation of compound **8**. Obtained was **10** (1.5 g, 18.5%), an oil. *Anal.* ($C_{19}H_{20}O_3N_2$) C, H, N.

3-Acetoxymethyl-5-ethyl-5-phenylhydantoin (11). To a solution of **8** (2.45 g, 0.01 mol) in Ac_2O (7.5 ml) was added $SnCl_4$ (3 drops). The mixture was stirred 16 hr, and the solid was filtered and chromatographed on silica gel (200 g). Elution with EtOAc–C_6H_6 (1:19) followed by crystallization from MeOH–H_2O (2:1) gave **11** (1.4 g, 51%): mp 97–98°. *Anal.* ($C_{14}H_{16}O_4N_2$) C, H, N.

1,3-Bis(acetoxymethyl)-5-ethyl-5-phenylhydantoin (12). To a solution of **7** (4.0 g, 0.02 mol) in AcOH (40 ml) was added 37% HCHO (10 ml, 0.12 mol). The solution was heated at reflux 16 hr, then cooled, and extracted with EtOAc. The extract was evaporated and the remaining oil was dissolved in pyridine (10 ml). Ac_2O (10 ml) was added and the solution was allowed to stand 16 hr and then poured into ice–H_2O (200 ml) containing 38% HCl (10 ml). The aqueous solution was extracted with EtOAc, the extract was evaporated, and the remaining oil was chromatographed on silica gel (200 g). Elution with EtOAc–C_6H_6 (1:9) gave **12** (1.6 g, 23%), an oil. *Anal.* ($C_{17}H_{20}O_6N_2$) C, H, N.

1-Acetoxymethyl-3-methyl-5-ethyl-5-phenylhydantoin (14). Compound **14** was prepared from **13** (4.4 g, 0.02 mol) in the same way as described for the preparation of compound **12**. Obtained was **14** (2.3 g, 40%), an oil. *Anal.* ($C_{15}H_{18}O_4N_2$) C, H, N.

1-Methoxymethyl-3-methyl-5-ethyl-5-phenylhydantoin (15). Compound **15** was prepared from **13** (4.4 g, 0.02 mol) and CH_3OCH_2Cl (2.0 g, 0.025 mol) in the same way as described for the preparation of compound **8**. Obtained was **15** (1.8 g, 35%): mp 68.5–70.5°. *Anal.* ($C_{14}H_{18}O_3N_2$) C, H, N.

References

(1) J. A. Vida, W. R. Wilber, and J. F. Reinhard, *J. Med. Chem.*, 14, 190 (1971).
(2) C. M. Samour, J. F. Reinhard, and J. A. Vida, *J. Med. Chem.*, 14, 187 (1971).
(3) E. A. Swinyard and J. E. P. Toman, *J. Pharmacol. Exp. Ther.*, **100**, 151 (1950).
(4) H. C. Carrington and W. S. Waring, *J. Chem. Soc.*, 354 (1950); *Chem. Abstr.*, **44**, 7778*f* (1950).
(5) F. Sandberg, *Acta Physiol. Scand.*, **24**, 149 (1951); *Chem. Abstr.*, **46**, 4122*e* (1952).
(6) R. G. Neville, *J. Org. Chem.*, **23**, 1588 (1958).
(7) J. E. P. Toman and L. S. Goodman, *Physiol. Rev.*, **28**, 409 (1948).
(8) E. A. Swinyard, W. C. Brown, and L. S. Goodman, *J. Pharmacol. Exp. Ther.*, **106**, 319 (1952).
(9) J. T. Litchfield and F. Wilcoxon, *J. Pharmacol. Exp. Ther.*, **96**, 99 (1949).
(10) A. W. Dunham and T. S. Miya, *J. Amer. Pharm. Ass.*, **46**, 208 (1957).