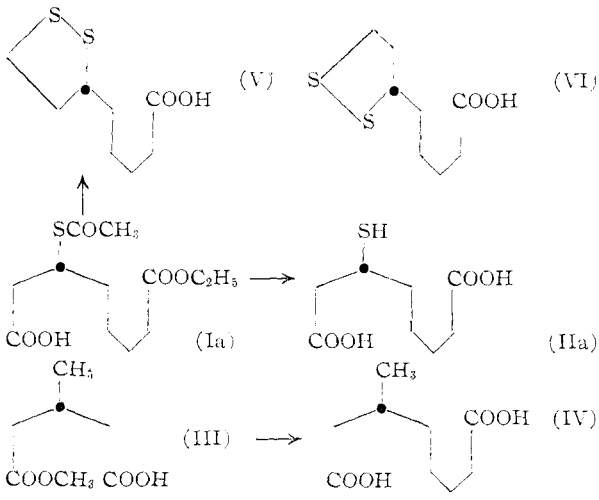


glutarate (III)[4] yielded benzyl 6-methyl-7-carbomethoxyheptanoate, b.p. 156–157° (0.23 mm.), $n^{25}D$ 1.4886, d^{25}_4 1.046, $[\alpha]^{26}D$ +4.6° (*c* 6.7, pyridine); calcd. for $C_{17}H_{24}O_4$: C, 69.6; H, 8.2; MD, 80.2; found: C, 69.0; H, 7.9; MD 80.4. Catalytic hydrogenolysis over 5% Pd/C gave 6-methyl-7-carbomethoxyheptanoic acid, b.p. 141–143° (0.2 mm.), $n^{25}D$ 1.4444, d^{25}_4 1.045, $[\alpha]^{27}D$ +5.5° (*c* 6.4, pyridine); calcd. for $C_{10}H_{18}O_4$: C, 59.4; H, 9.0; MD 51.6; found: C, 59.9; H, 8.6; MD 51.5. Saponification yielded 3-methyloctanedioic acid (IV), m.p. 97–98°, $[\alpha]^{22}D$ + 6.9° (*c* 5.1, pyridine); calcd. for $C_9H_{16}O_4$: C, 57.4; H, 8.6; found: C, 57.9; H, 8.3. The configuration of III has been elucidated[5]; consequently that of IV is now established.

It was found (Fig. 1) that IV and IIa form a continuous series of solid solutions, while IV and IIb are immiscible in the solid state. These results permit the conclusion[6] that IV and IIa, and therefore Ia, have the same configuration. The configuration of (+)-α-lipoic acid, which is prepared[7] from Ia, is hence correctly represented by V, and that of (−)-α-lipoic acid by VI.

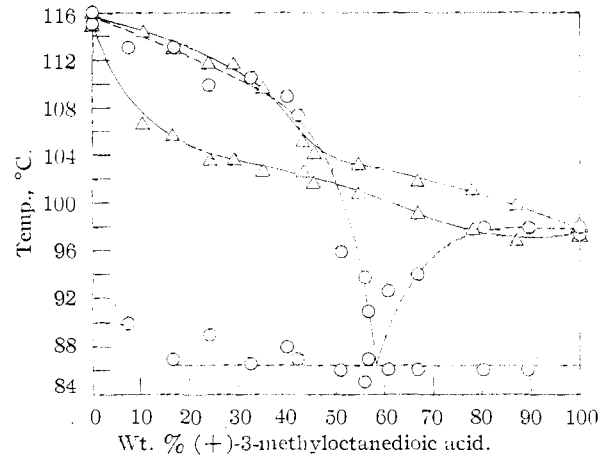


Fig. 1.—Melting point–composition diagrams for the systems (+)-3-methyloctanedioic acid–(+)-3-thioloctanedioic acid (circles, dashed line), and (+)-3-methyloctanedioic acid–(−)-3-thioloctanedioic acid (triangles, solid line).

It is interesting to note that aleprestic acid ((+)-5-(2-cyclopenten-1-yl)-pentanoic acid), a chaulmoogra oil acid which differs from α-lipoic acid in having an ethylene function in place of the disulfide linkage, has the same configuration as V.[7]

(4) R. P. Linstead, J. C. Lunt and B. C. L. Weedon, *J. Chem. Soc.*, 3338 (1950).

(5) S. Ställberg-Stenhagen, *Arkiv Kemi, Mineral. Geol.*, **25A**, No. 10 (1948).

(6) A. Fredga in "The Svedberg," Almqvist and Wiksells, Uppsala, 1944, p. 261 ff.; *Arkiv Kemi Mineral. Geol.*, **15B**, No. 23 (1942); M. Matell, *Arkiv Kemi*, **5**, 17 (1952); J. Timmermans, *J. chim. phys.*, **49**, 162 (1952); K. Mislow and M. Hellier, THIS JOURNAL, **74**, 3668 (1952).

(7) K. Mislow and I. V. Steinberg, *ibid.*, **77**, 3807 (1955), and unpublished results.

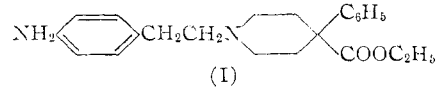
WM. H. NICHOLS CHEMICAL LABORATORY
NEW YORK UNIVERSITY KURT MISLOW
NEW YORK 53, N. Y. WILLIAM C. MELUCH

RECEIVED APRIL 3, 1956

A NEW SYNTHETIC ANALGESIC

Sir:

Efforts begun here some years ago had as their most stimulating result the recognition of phenethyl as a potentiating group when substituted for methyl on the nitrogen atom of certain analgesic compounds. Thus N-phenethylnormorphine[1] is eight times as potent as morphine though also much more toxic.[2] This is a somewhat surprising finding since heretofore all the evidence has supported the belief that the methyl radical is optimal for the production of significant analgesic action.[3] In fact diminished activity or even antagonism to analgesia have been by far the more frequent results of modification of the methyl group on the tertiary nitrogen of analgesic substances.[1,4] However, while N-substituents which on normorphine produce antagonism frequently fail to produce similar results when substituted for the N-methyl of other types of analgesic agent, our studies and those of Perrine and Eddy[5] suggest that the beneficial effect of phenethyl is more generally obtained. We have found also that further substitution, now on the aromatic ring of the phenethyl radical, produces still further benefits. An extensive program based on these findings has led to selection of ethyl 1-(4-aminophenethyl)-4-phenylisonipecotate (I) as a most promising candidate for further study.



(I)

When *p*-aminophenethyl chloride hydrochloride[6] was allowed to react with ethyl 4-phenylisonipecotate "carbonate"[7] in alcohol with added sodium bicarbonate there was formed a base which could be precipitated from ether solution as a dihydrochlo-

(1) R. L. Clark, *et al.*, THIS JOURNAL, **75**, 4963 (1953).

(2) We are indebted to Dr. C. A. Winter for this observation.

(3) O. J. Braenden, N. B. Eddy and H. Halbach, *Bull. World Health Org.*, **13**, 937 (1955); A. Burger, *Medicinal Chemistry*, Vol. I, p. 173 (1951); O. Schaumann, *Arch. exp. Pathol. Pharmakol.*, **196**, 109 (1940). See, however, R. A. Millar and R. P. Stephenson, *Brit. J. Pharmacol. Chemotherapy*, **11**, 27 (1956) which appeared after submission of this communication.

(4) K. Unna, *J. Pharmacol. Exp. Therap.*, **79**, 27 (1943); A. F. Green, G. K. Ruffell and E. Walton, *J. Pharmacy and Pharmacol.*, **6**, 390 (1954).

(5) T. D. Perrine and N. B. Eddy, *J. Org. Chem.*, **21**, 125 (1956).

(6) H. Sobotka, *Ber.*, **62**, 2191 (1929).

(7) R. H. Thorpe and E. Walton, *J. Chem. Soc.*, 559 (1948). Their analyses, confirmed in these laboratories, indicate that the material is actually the carbamate derived from two molecules of secondary amine.

ride. Purification by crystallization from methanol-ether and then methanol gave material of m.p. 280–287° dec. *Anal.* Calcd. for $C_{22}H_{28}O_2N_2 \cdot 2HCl$: C, 62.12; H, 7.11; N, 6.59. Found: C, 61.97; H, 6.97; N, 6.71. Determination of *p*Ka values in aqueous ethanol gave values of 3.7 and 7.5. Absorption measurements in the ultraviolet at *p*H 7 gave $\lambda_{max}^{CH_3OH}$ 2350Å., *E*% 293; 2890Å., *E*% 34.5. Treatment of the free base (I, m.p. 83°) with acetic anhydride-acetic acid at 90–100° and conversion to the salt gave the N-acetyl monohydrochloride, m.p. 264–265°; *Anal.* Calcd. for $C_{24}H_{30}O_3N_2 \cdot HCl$: C, 66.88; H, 7.25; N, 6.50. Found: C, 67.18; H, 7.57; N, 6.39.

Ethyl 1-(4-aminophenethyl)-4-phenylisonipecotate is a potent analgesic with high oral activity and relatively mild side reactions. Mild anti-acetylcholine and antihistaminic activity has been observed in both isolated organs and in intact animals. In animals, the compound approaches morphine in analgesic potency and is several times more active than meperidine (ethyl 1-methyl-4-phenylisonipecotate). Unlike meperidine, it is a good antitussive agent against experimental cough in guinea pigs and dogs.

The side reactions in animals such as general depression and sedation, depression of respiration and lowering of blood pressure, are considerably milder than those produced by morphine, and somewhat milder than those of meperidine. The new compound does not produce nausea, vomiting or constipation in animals.

The acute oral and subcutaneous toxicity of the compound, as measured in mice, is of the same order as meperidine, but it is somewhat more toxic on intravenous administration.

After subcutaneous injection into rats, a bound form, probably the N-acetyl derivative, was found in the tissues. The synthetic N-acetyl derivative has analgesic activity of the same order as the parent compound when tested in rats.

Ethyl 1-(4-aminophenethyl)-4-phenylisonipecotate has been given the generic name anileridine. Preliminary results in man by oral and parenteral administration indicate an analgesic potency at least twice that of meperidine.

JOHN WEIJLARD
PETER D. ORAHOVATS
ALAN P. SULLIVAN, JR.
GEORGE PURDUE
FREDERICK K. HEATH
KARL PFISTER, 3RD

CONTRIBUTION FROM THE
MERCK SHARP AND DOHME
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RAHWAY, N. J.

RECEIVED APRIL 5, 1956

BOOK REVIEWS

An Introduction to Paper Electrophoresis and Related Methods. By MICHAEL LEDERER, Institut du Radium Paris. Elsevier Publishing Company, 2330 Holcombe Boulevard, Houston, Texas. 1955. xii + 206 pp. 16 × 23.5 cm. Price, $7.75.

For those investigators who are not familiar with the field of electrophoresis and who are interested in applying the new and simple procedures on filter paper to a specialized problem, this is a very welcome book. There are certainly many people in such a category because of the widespread applications ranging from the separation of isotopes to the classification of blood proteins in human disease. This broad range of subjects is well covered in Doctor Lederer's book and it is apparent that he has had a long and diversified experience in this field. The book is written in a clear and simple manner supplemented by many illustrations and is easily read by the novice. In addition, there is sufficient theoretical background along with a very complete and extensive bibliography to make it a useful volume to experienced workers. One might wish that the author had been more critical of the various procedures for carrying out paper electrophoresis, particularly in view of his own experience, so that the reader could better evaluate the method that he should apply. This is a most difficult problem because all the techniques of paper electrophoresis work fairly well and no one unbiased observer has had sufficient experience with the whole group to really classify them.

A relatively small portion of the book is devoted to electrophoresis in other supporting media besides filter paper. The section on gels is quite complete but this whole subject is developing so rapidly at the present time that any attempt at a review is almost immediately outdated.

Despite these natural limitations, this work should be a valuable addition to any laboratory applying or interested in applying electrophoretic methods.

THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH
66TH STREET AND YORK AVENUE
NEW YORK 21, NEW YORK
HENRY G. KUNKEL

Basic Processes of Gaseous Electronics. By LEONARD B. LOEB. University of California Press, Berkeley 4, California. 1955. xvii + 1012 pp. 16 × 24.5 cm. Price, $13.50

In the first edition of his classic "Conduction of Electricity through Gases" (1903), J. J. Thomson wrote:

> With the discovery and study of Cathode rays, Röntgen rays and Radio-activity a new era has begun in Physics, in which the electrical properties of gases have played and will play a most important part...

Nearly a half-century later, however, H. D. Smyth (writing in the *American Scientist* in 1947), after affirming the origin of many great discoveries of the modern period of physics in studies of discharges in gases, remarks that:

> the innumerable series [of experiments] on the discharge of electricity through gases...has been going on now for nearly a hundred years, has given us the fluorescent lamp and other devices, but has still not told us what happens in an electrical discharge in gases.

The truth of this melancholy observation is amply attested in L. B. Loeb's most recent book, a dishearteningly massive tome which may quickly give mental indigestion to any but the most expert and tenacious reader. Although great progress has certainly been achieved—thus, contemporary techniques in electronics have, just in the past decade, virtually revolutionized the experimental approach, and greatly enhanced the accessibility of many long-studied phenomena—the analysis of numerous important aspects of gaseous conduction still ends in a bewildering morass of complexity.

"Gaseous electronics," incidentally, is the apt designation used to replace "electrical discharges in gases" in this triumphant modern era. The plan of the book is separately to treat various basic phenomena which are important in gaseous conduction, such as drift velocity, diffusion and recombination of charge carriers, and only then to deal with the properties of discharges themselves. The division of