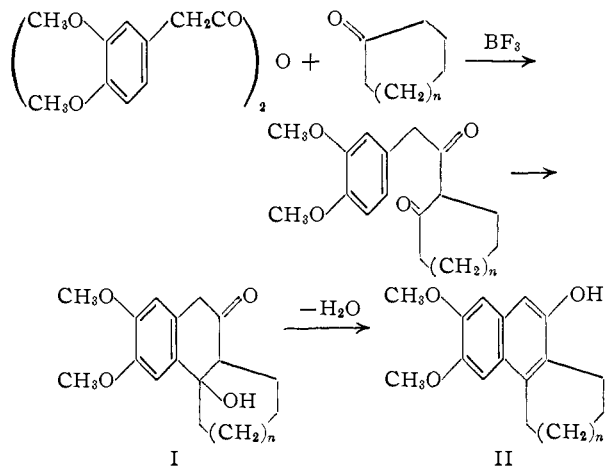
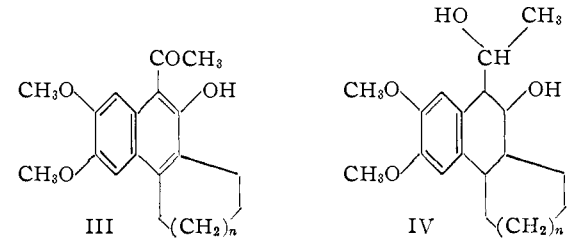
clization are accomplished together in one step and substituted β-naphthols or 4-hydroxy-2-tetralones are isolated.



I II

A mixture of homoveratric anhydride,[6] cyclohexanone and boron trifluoride etherate was allowed to stand for three days, and the boron complex was decomposed with sodium acetate solution. Compound I (n = 1), m.p. 140–141° (*Anal.* Calcd. for $C_{16}H_{20}O_4$: C, 69.54; H, 7.30. Found: C, 69.55; H, 7.34), showing infrared absorption at 2.8–2.9 and 5.79–5.85 μ, was isolated in 68% yield. Dehydration by brief treatment with polyphosphoric acid gave II (n = 1), m.p. 219–221° (*Anal.* Calcd. for $C_{16}H_{18}O_3$: C, 74.40; H, 7.02. Found: C, 74.50; H, 7.09). Similar condensation of homoveratric anhydride with cycloheptanone gave II (n = 2) directly (29%), m.p. 207–208° (*Anal.* Calcd. for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40. Found: C, 74.93; H, 7.45). The infrared spectra of compounds II each showed a band at 2.76 μ. The ultraviolet spectra of II (n = 1) (λ_{max}^{EtOH} 237, 272, 282, 293, 322 and 336 mμ; log ε 4.86, 3.60, 3.59, 3.46, 3.59 and 3.72, respectively) and of II (n = 2) (λ_{max}^{EtOH} 237, 274, 285, 296, 324 and 337 mμ; log ε 4.91, 3.61, 3.61, 3.49, 3.58, and 3.72, respectively) were typical of naphthalene derivatives. O-Acetates of II (n = 1), m.p. 170–171° (*Anal.* Calcd. for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 72.03; H, 6.69) and of II (n = 2), m.p. 139–141° (*Anal.* Calcd. for $C_{19}H_{22}O_4$: C, 72.59; H, 7.06. Found: C, 72.84; H, 7.06) had similar ultraviolet spectra and absorbed light at 5.70 μ in the infrared region.

When boron trifluoride in acetic acid was used in condensation of homoveratric anhydride with cyclohexanone and cycloheptanone, acetylation of the phenolic ring also occurred, probably through Fries rearrangement of O-acetates, giving III (n = 1), m.p. 167–168° (*Anal.* Found: C, 72.01; H, 6.75) and III (n = 2), m.p. 157–158° (*Anal.* Found: C, 72.64; H, 7.06) in yields of 38% and 11%, respectively. These yellow compounds gave characteristic ferric chloride tests and had infrared spectra similar to that of 1-hydroxy-2-acetonaphthone, with no hydroxyl or normal carbonyl peaks. The ultraviolet spectra of III (n = 1) (λ_{max}^{EtOH} 234, 294 and 340, mμ; log ε 4.80, 3.57 and 4.00, respectively) and of III (n = 2) (λ_{max}^{EtOH} 235, 291 and 345 mμ; log ε 4.84, 3.56 and 4.02, respectively) again were typical of naphthalene derivatives. Trihydrogenation of hydroxy ketones III (n = 1 and 2) in the presence of palladium-charcoal in ethyl acetate at 80° gave diols IV (n = 1), m.p. 171–173° (*Anal.* Calcd. for $C_{18}H_{26}O_4$: C, 70.56; H, 8.55. Found: C, 70.50; H, 8.23) and IV (n = 2), m.p. 142–144° (*Anal.* Calcd. for $C_{19}H_{28}O_4$: C, 71.22; H, 8.81. Found: C, 71.44; H, 8.75), respectively. The infrared spectra of compounds IV (n = 1 and 2) each had a doublet at 2.76–2.98 μ, and their ultraviolet spectra had λ_{max}^{EtOH} 288 mμ (log ε 3.34) and λ_{max}^{EtOH} 291 mμ (log ε 3.43), respectively.



III IV

The synthesis permits variation of the size of ring C and thus will be useful in getting compounds related to colchicine[7] as well as new phenanthrenes.

(6) Prepared by refluxing homoveratric acid with acetic anhydride in the presence of pyridine; m.p. 83–84°.

(7) H. Rapoport, *et al.*, THIS JOURNAL, **73**, 1414 (1951); **77**, 670 (1955).

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RECEIVED APRIL 2, 1956

THE CONFIGURATION OF (+)-α-LIPOIC ACID

Sir:

The synthesis of naturally occurring (+)-α-lipoic acid[1] has recently been described.[2] We wish to report on the elucidation of its stereochemistry.

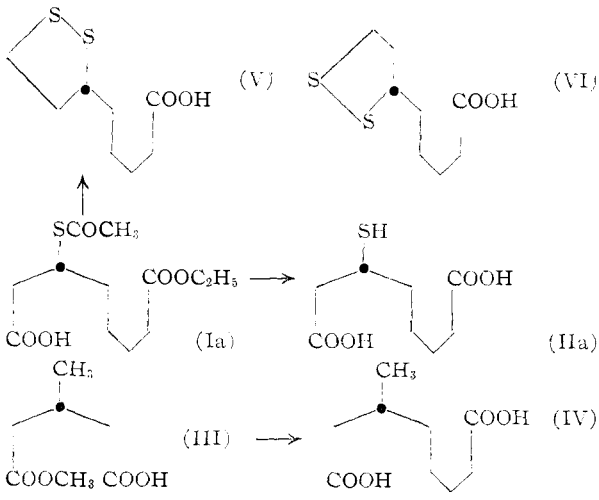
(+)-3-Acetylthio-7-carbethoxyheptanoic acid (Ia)[2,3] was treated with cold 10% sodium hydroxide to give 3-thioloctanedioic acid (IIa), m.p. 114.5–115.5°, $[\alpha]^{27}D$ −7.9° (*c* 3.4, pyridine); calcd. for $C_8H_{14}O_4S$: C, 46.6; H, 6.8; S, 15.6; found: C, 46.6; H, 6.6; S, 15.4. Similarly (−)-3-acetylthio-7-carbethoxyheptanoic acid (Ib)[2,3] gave 3-thioloctanedioic acid (IIb), m.p. 115–116°, $[\alpha]^{27}D$ +7.9° (*c* 2.5, pyridine), calcd. for $C_8H_{14}O_4S$: C, 46.6; H, 6.8; S, 15.6; found, C, 46.8; H, 6.8; S, 15.4.

Benzyl hydrogen glutarate was prepared from glutaric anhydride, benzyl alcohol and pyridine, b.p. 153–155° (0.05 mm.), $n^{25}D$ 1.5108; calcd. for $C_{12}H_{14}O_4$: C, 64.8; H, 6.4; neut. eq., 222; found: C, 65.0; H, 6.1; neut. eq., 221. Anodic cross-coupling with (+)-methyl hydrogen β-methyl-

(1) L. J. Reed, I. C. Gunsalus, G. H. F. Schnakenberg, Q. F. Soper, H. E. Boaz, S. F. Kern and T. V. Parke, THIS JOURNAL, **75**, 1267 (1953); E. L. Patterson, J. V. Pierce, E. L. R. Stokstad, C. E. Hoffmann, J. A. Brockman, Jr., F. P. Day, M. E. Macchi and T. H. Jukes, *ibid.*, **76**, 1823 (1954).

(2) E. Walton, A. F. Wagner, F. W. Bachelor, L. H. Peterson, F. W. Holly and K. Folkers, *ibid.*, **77**, 5144 (1955).

(3) A sample was kindly supplied by Dr. F. M. Robinson, Merck and Co.



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; M_D, 80.2; found: C, 69.0; H, 7.9; M_D 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; M_D 51.6; found: C, 59.9; H, 8.6; M_D 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[2] from Ia, is hence correctly represented by V, and that of (−)-α-lipoic acid by VI.

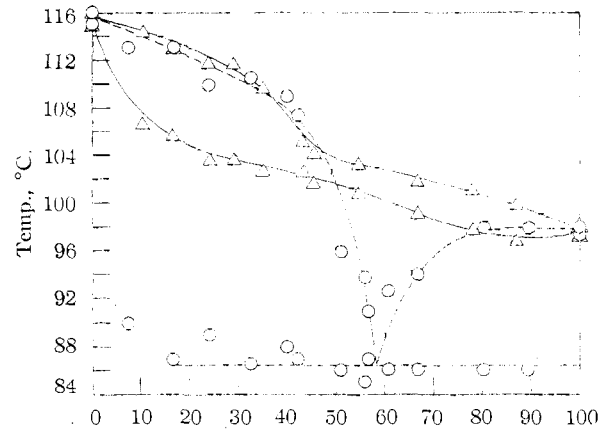


Fig. 1.—Melting point-composition diagrams for the systems (+)-3-methyloctanedioic acid–(+)-3-thioloctanedioic acid (circles, dashed line), and (+)-3-methyloctanedioic acid–(−)-3-thioloctanedioic acid (triangles, solid line).

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.*, 3333 (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. Heffler, THIS JOURNAL, **74**, 3668 (1952).

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

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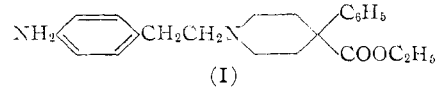
RECEIVED APRIL 3, 1956

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**, 4063 (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. 1, 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.