other sources. Oligo-1,6-glucosidase differs from R-enzyme (plants) in that the latter does not hydrolyze the terminal α-1,6-linked glucose residues of isomaltose or panose (except possibly when acting with α-amylase).[2] A limit dextrinase from *Aspergillus oryzae* culture filtrate has been described[17] which would seem to have an activity similar to oligo-1,6-glucosidase on "branched" oligosaccharides.

(17) L. A. Underkofler and D. K. Roy, *Cereal Chem.*, **28**, 18 (1951).

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THE SYNTHESIS OF (+)-α-LIPOIC ACID AND ITS OPTICAL ANTIPODE

Sir:

The racemic form of a compound active as a coenzyme in the oxidative decarboxylation of pyruvate has been synthesized.[1,2] This racemate has been designated DL-α-lipoic acid[1] and 6-thioctic acid.[2] The synthesis of the naturally occurring biologically active isomer, (+)-α-lipoic acid, has not been reported. We wish to report a new synthesis which has made possible the preparation of (+)-, (−)- and DL-α-lipoic acid.

The addition of thioacetic acid to 7-carboethoxy-2-heptenoic acid (I)[3] yielded 7-carboethoxy-3-acetylthioheptanoic acid (II) which was converted to 7-carboethoxy-3-acetylthioheptanoyl chloride (III). The reduction of III with sodium borohydride yielded a mixture of ethyl 6-acetylthio-8-hydroxyoctanoate (IV) and ethyl 6-thiol-8-hydroxyoctanoate (V). The mixture was converted by alkaline hydrolysis to 6-thiol-8-hydroxyoctanoic acid (VI), $n^{23.5}$D 1.4989. Iodine oxidation of VI produced bis-[3-(1-hydroxy-7-carboxyheptyl)] disulfide (VII). The introduction of the thiol group into the 8-position of both VI and VII was carried out by refluxing with thiourea in aqueous hydrobromic acid followed by alkaline hydrolysis. Following the introduction of sulfur into VII, the product was reduced with sodium borohydride and reoxidized to yield DL-α-lipoic acid (VIII), m.p. 59.5–61.0° (micro-block); $\lambda_{max}^{CH_3OH}$ 333 mμ (ϵ 150); *anal.* Calcd. for $C_8H_{14}O_2S_2$ (206.2): C, 46.60; H, 6.84; S, 31.05. Found: C, 46.90; H, 6.91; S, 31.34; mol. wt. (ebull.), 212 ± 7; neut. equiv., 206.

For the preparation of (+)- and (−)-α-lipoic acid, DL-7-carboethoxy-3-acetylthioheptanoic acid (II) was resolved. Treatment of II with *l*-ephedrine yielded the crystalline salt of the levorotatory form, m.p. 130.0–134.5°. The dextrorotatory isomer was isolated from the residue by precipitation in the form of its benzhydrylamine salt, m.p. 92–96°.

(+)-7-Carboethoxy-3-acetylthioheptanoic acid, $[\alpha]^{24}$D + 7.1° (*c*, 6.93; CH_3OH), when used in the above sequence yielded (+)-α-lipoic acid, m.p. 46.0–48.0° (micro-block); $[\alpha]^{23}$D +104° (*c*, 0.88; C_6H_6), $\lambda_{max}^{CH_3OH}$ 333 mμ (ϵ 150). *Anal.* Calcd. for $C_8H_{14}O_2S_2$ (206.2): C, 46.60; H, 6.84; S, 31.05. Found: C, 46.95; H, 6.85; S, 31.00; mol. wt. (ebull.), 194 ± 2; neut. equiv., 208. In a similar manner (−)-7-carboethoxy-3-acetylthioheptanoic acid, $[\alpha]^{24}$D −7.2 (*c*, 6.91; CH_3OH), yielded (−)-α-lipoic acid, m.p. 45.5–47.5° (micro-block); $[\alpha]^{23}$D −113° (*c*, 1.88; C_6H_6); $\lambda_{max}^{CH_3OH}$ 333 mμ (ϵ 140). Found: C, 46.65; H, 6.66; S, 31.32; mol. wt. (ebull.), 212 ± 3; neut. equiv. 208. When equal amounts of (+)- and (−)-α-lipoic acid were mixed and recrystallized from cyclohexane, the racemic compound, DL-α-lipoic acid, m.p. 60–61° (micro-block), was obtained.

In the enzymatic POF assay,[4] the activity of synthetic (+)-α-lipoic acid was double that of DL-α-lipoic acid. The activity of (−)-α-lipoic acid was essentially zero, *ca.* 1% that of DL-α-lipoic acid. The properties listed above substantiate the identity of our synthetic (+)-α-lipoic acid and the natural α-lipoic acid.[5,6,7] This lends additional support to the structural conclusions advanced[5,6] previously.

(1) C. S. Hornberger, Jr., R. F. Heitmiller, I. C. Gunsalus, G. H. F. Schnakenberg and L. J. Reed, THIS JOURNAL, **75**, 1273 (1953).

(2) M. W. Bullock, J. A. Brockman, Jr., E. L. Patterson, J. V. Pierce, M. H. von Saltza, F. Sanders and E. L. R. Stokstad, *ibid.*, **76**, 1828 (1954).

(3) G. B. Brown, M. D. Armstrong, A. W. Moyer, W. P. Anslow, Jr., B. R. Baker, M. V. Querry, S. Bernstein and S. R. Safir, *J. Org. Chem.*, **12**, 160 (1947).

(4) I. C. Gunsalus, M. I. Dolin and L. Struglia, *J. Biol. Chem.*, **194**, 849 (1952).

(5) 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).

(6) 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).

(7) M. Calvin and J. A. Barltrop, *ibid.*, **74**, 6153 (1952).

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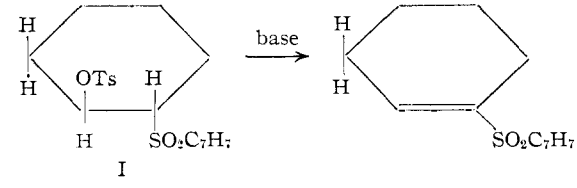
E2 ELIMINATION REACTIONS IN THE CYCLOHEXANE AND CYCLOPENTANE SERIES[1]

Sir:

A study of base-catalyzed E2 elimination reactions of *trans*-2-(*p*-tolylsulfonyl)-cyclohexyl *p*-toluenesulfonate (I), its *cis* isomer (II), the corresponding *trans* and *cis* isomers (III and IV) in the cyclopentane series, and an open-chain analog, 1-(*p*-tolylsulfonyl)-2-propyl *p*-toluenesulfonate, $C_7H_7SO_2CH_2CH(OTs)CH_3$ (V), with trimethylamine, triethylamine and hydroxide ion has revealed the information reported below.



I

(1) Each of these reactions gives an α,β-unsaturated sulfone. For I and III this corresponds to elimination of a hydrogen *cis* to the tosylate group in preference to a hydrogen *trans* to the tosylate

(1) This investigation was supported by the Office of Naval Research under Contract No. N7onr-45007.

group.[2] The product from the latter mode of action would have been a β,γ-unsaturated sulfone, which has been shown not to rearrange under the reaction conditions.

(2) All of these reactions are general base rather than specific hydroxide ion catalyzed. This result shows that if a carbanion intermediate is formed in either the *cis* or *trans* eliminations observed for I, II, III, IV or V it must have a very short life. From the measured rate of ionization and a calculated value for the acid–base equilibrium constant the life of such a carbanion intermediate would be less than 10^{-8} sec.[3]

(3) The reactions are first order in base and first order in tosylate; the relative rates measured in 50% dioxane at 25° are summarized in Table I.

TABLE I

Compound	Me_3N	Et_3N	^-OH	K_{Et_3N}/k_{Me_3N}	$k_{^-OH}/k_{Me_3N}$
I	0.98	0.14	0.19	0.062	272
II	21.7	15.7	81	.324	5220
III	98.5	17.4	11.9	.077	169
IV	118	114	235	.435	2780
V	1000[a]	1000	1000	.45	1400

[a] $k = 1.32 \times 10^{-1}$ m.$^{-1}$ sec.$^{-1}$.

The fact that reaction of IV is more rapid than II with all three bases (factors of 2.9 to 7.3) is significant since elimination from II can proceed readily by way of a planar transition state, whereas elimination from IV cannot without some strain.[4,5]

The consistently slower rates for the reactions of triethylamine with I–V as compared to trimethylamine must be due to a steric factor, since in water triethylamine is the stronger base. The effect is largest for I and III where the approach of the base to the hydrogen is more effectively blocked by the tosylate group.[6]

The rate with hydroxide ion is always much faster than with trimethylamine but again I and III show a relative retardation, which is best interpreted as an electrostatic repulsion between the negative ion and the tosylate group. The magnitude of this effect is well within the range calculated by Cristol[3] for the contribution of electrostatic effects to preferred *trans* elimination.

Our general conclusion from these results is that although a *trans* relationship of groups being eliminated and a planar transition state for elimination are important factors, they are not necessarily dominant, as might be assumed from the data on systems previously studied.[3,4] Other factors, such as the acidity of the hydrogen atom eliminated, structural relationships (*e.g.*, ring size), steric hindrance to the approaching base, and electrostatic effects may often play prominent and even decisive roles in determining the course and rate of E2 elimination reactions.

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(2) See F. G. Bordwell, R. J. Kern and M. L. Peterson, of Abstracts of the Milwaukee Meeting of the American Chemical Society, April, 1952, p. 84K.

(3) S. J. Cristol, *et al.*, THIS JOURNAL, **69**, 338 (1947); **73**, 674 (1951); **75**, 2647 (1953), have suggested that the *cis* elimination of hydrogen chloride from the β-isomer of benzene hexachloride proceeds by way of a carbanion intermediate.

(4) D. H. Barton and W. J. Rosenfelder, *J. Chem. Soc.*, 1048 (1951), and previous papers, have presented evidence that in certain cyclohexane systems elimination of *trans* axial (polar) groups is greatly favored over elimination of *trans* equatorial groups.

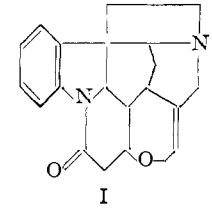
(5) This difference in rates appears to be indicative of the relative rates for *trans* eliminations in the cyclopentane and cyclohexane series, since we have found (unpublished results) that elimination of bromine from *trans*-1-2-dibromocyclopentane by reaction with iodide ion in 99% methanol at 75° is about 4.5 times as rapid as the corresponding elimination from *trans*-1-2-dibromocyclohexane; $k = 9.78 \times 10^{-2}$ m.$^{-1}$ hr.$^{-1}$ *vs.* 2.12×10^{-2} m.$^{-1}$ hr.$^{-1}$. S. Winstein, THIS JOURNAL, **64**, 2792 (1942), gives a value of 2.04×10^{-2} m.$^{-1}$ hr.$^{-1}$ for the latter at 75° in 99% methanol.

(6) H. C. Brown and I. Moritani, THIS JOURNAL, **75**, 4112 (1953), have recently demonstrated the importance of a similar steric effect in controlling the course of E2 eliminations.

THE TOTAL SYNTHESIS OF STRYCHNINE

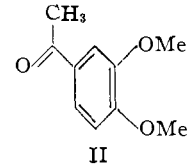
Sir:

Strychnine was one of the first of the alkaloids to be isolated in a pure state—in 1818 by Pelletier and Caventou. The tangled skein of atoms which constitutes its molecule provided a fascinating structural problem which was pursued intensively during the century just past, and was solved finally only within the last decade. We now wish to record the total synthesis of strychine (I).

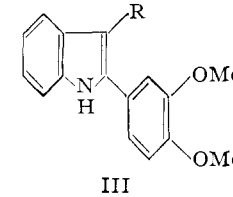


I

2-Veratrylindole (III, R = H) (m.p. 190–192°, calcd. for $C_{16}H_{15}O_2N$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.36; H, 6.03; N, 5.95), from acetoveratrone (II), phenylhydrazine and polyphosphoric acid, was converted by formaldehyde and dimethylamine to the gramine (III, R = CH_2NMe_2) (m.p.



II



III

123–125° dec.; *picrate*, m.p. 182–183°, calcd. for $C_{19}H_{22}O_2N_2.C_6H_3O_7N_3$: C, 55.65; H, 4.67; N, 12.98. Found: C, 55.27; H, 4.39; N, 12.83), and thence to the methiodide (III, R = CH_2NMe_3I), which with sodium cyanide in dimethylformamide furnished the nitrile (III, R = CH_2CN) (m.p. 237–238°, calcd. for $C_{18}H_{16}O_2N_2$: C, 73.95; H, 5.52; N, 9.58. Found: C, 74.11; H, 5.68; N, 9.34). Reduction of the nitrile with lithium aluminum hydride gave 2-veratryltryptamine (III, R = $CH_2CH_2NH_2$) (m.p. 146–148°). With ethyl glyoxylate in benzene, the amine gave the Schiff base (III, R = $CH_2CH_2N{=}CHCOOEt$), which was transformed directly by toluenesulfonyl chloride and pyridine into the indolenine (IV) (m.p. 145–146°, calcd. for $C_{29}H_{30}O_6N_2S$: C, 65.16; H, 5.66; N, 5.24; S,