THE REMAINING STEREOISOMERS OF THE SPARTEINE GROUP

Sir:

We have found that the alkaloid *l*-spartalupine, $C_{15}H_{26}N_2$, which we have isolated for the first time from specimens of *Lupinus sericeus* Pursh collected in Utah, is one of the enantiomorphs of the third and remaining racemic pair stereoisomeric with *dl*-sparteine and *dl*-α-isosparteine. Our structure proof consists of epimerization to *d*-sparteine and to *d*-α-isosparteine and the direct comparison of the natural base with *dl*-spartalupine, which we have synthesized along with its diastereoisomers. The only other naturally occurring alkaloid thus far isolated having the same stereochemical configuration as spartalupine is lupanoline, $C_{15}H_{24}N_2O_2$, a hydroxy-lactam.[1]

Isolation.—Alcoholic extraction of the dried plant yielded 1–2% of total alkaloid, which gave directly upon distillation mostly *l-spartalupine base*, b.p. 110° (0.03 mm.), m.p. 32.2–32.4° (calcd. for $C_{15}H_{26}N_2$: C, 76.86; H, 11.18; N, 11.96. Found: C, 76.99; H, 11.18; N, 12.02; $[\alpha]^{25}D$ −15.4° (abs. alc.)) *Monoperchlorate*, m.p. 211.5–212° (calcd. for $C_{15}H_{26}N_2 \cdot HClO_4$: C, 53.80; H, 8.13; N, 8.37; Cl, 10.59. Found: C, 53.82; H, 8.20; N, 8.06; Cl, 10.53). *Dipicrate*, m.p. 133–133.5° (calcd. for $C_{15}H_{26}N_2 \cdot 2C_6H_2(NO_2)_3OH$: C, 46.82; H, 4.66; N, 16.18. Found: C, 47.03; H, 4.43; N, 16.40). The infrared spectrum of the base was very similar to that of the base obtained from lupanoline with $LiAlH_4$.[2]

Structure Proof.—*l*-Spartalupine was treated with mercuric acetate by the method of Winterfeld and Rauch.[3] Under mild conditions, a dehydro base was formed which was hydrogenated over platinum to *d*-sparteine, $[\alpha]^{28}D$ +19.5° (ethanol). Under more drastic conditions, a didehydro base was obtained which was rehydrogenated to *d*-α-isosparteine monohydrate, m.p. 110–115°, $[\alpha]^{28}D$ +48.4° (methanol). The infrared spectra of the products were identical with those of their respective authentic *l*-isomers.

Synthesis.—The synthesis of Šorm and Keil[4] was repeated, except for reduction of the dioxo compound with $LiAlH_4$. Three dioxo compounds were isolated: A, m.p. 173–173.5° (calcd. for $C_{15}H_{22}N_2O_2$: C, 68.67; H, 8.45; N, 10.68. Found: C, 68.83; H, 8.59; N, 10.63). Reduction of A yielded *dl*-spartalupine (and not *dl*-α-isosparteine[4]). The infrared spectra of the natural *l*- and synthetic *dl* bases were superimposable. *dl*-Spartalupine dipicrate, m.p. 220.5–221° dec. (calcd. for $C_{15}H_{26}N_2 \cdot 2C_6H_2(NO_2)_3OH$: C, 46.82; H, 4.66; N, 16.18. Found: C, 46.64; H, 4.64; N, 16.19). The dioxo compound B, m.p. 132–133.5°, reduced to *dl*-sparteine, and a third dioxo compound C, isolated as a monohydrate, m.p. 159–160°, reduced to *dl*-α-isosparteine monohydrate. The two latter bases were identified by direct comparison of the bases with their optically active forms and with the picrates of authentic synthetic *dl*-bases,[5] using infrared spectra and melting points where applicable.

(1) L. Marion, N. J. Leonard, and B. P. Moore, *Can. J. Chem.*, **31**, 181 (1953); *cf.* J. F. Couch, THIS JOURNAL, **62**, 554 (1940).

(2) B. P. Moore and L. Marion, *Can. J. Chem.*, **31**, 187 (1953).

(3) K. Winterfeld and C. Rauch, *Arch. Pharm.*, **272**, 273 (1934).

(4) F. Šorm and B. Keil, *Coll. Czech. Chem. Comm.*, **13**, 544 (1948).

(5) Kindly supplied by Professor N. J. Leonard; *cf.* N. J. Leonard and R. E. Beyler, THIS JOURNAL, **72**, 1316 (1950).

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MERCAPTAN CATALYSIS IN THERMONEUTRAL FREE RADICAL EXCHANGE: $R\cdot + R^*H \leftrightharpoons RH + R^*\cdot$

Sir:

It has been proposed that when a free radical is generated in a solvent from which it may be thought of as being derived by removal of one atom, the radical will be continually regenerated in type by exchange with the solvent.[1] However, the formation of acetate radical $CH_3COO\cdot$ in solvent $C^{14}H_3COOH$ by decomposition of acetyl peroxide led to CH_4 containing about 1% of the radioactivity of the solvent,[2] indicating that the postulated exchange reaction

$$CH_3COO\cdot + C^{14}H_3COOH \rightleftharpoons CH_3COOH + C^{14}H_3COO\cdot$$

was slow compared to loss of CO_2 by the unstable acetate radical.

We have formed a more stable radical, $(C_6H_5)_2CH\cdot$[3] (I), in $(C_6H_5)_2C^{14}H_2$ (II) by decomposition of $(C_6H_5)_2CH—N{=}N—CH(C_6H_5)_2$[3] in 0.017 *m* solution in 3:1 $(C_6H_5)C^{14}H_2$:C_6H_6 at 64° under CO_2. 1,1,2,2-Tetraphenylethane (III) was obtained in 95% yield, and its radioactivity was only 1.1% of that of the solvent. The exchange was far

$$(C_6H_5)_2CH\cdot + (C_6H_5)C^{14}H_2 \rightleftharpoons (C_6H_5)CH_2 + (C_6H_5)C^{14}H\cdot \quad (1)$$

slower than the dimerization reaction

$$2(C_6H_5)_2CH\cdot \longrightarrow (C_6H_5)_2CHCH(C_6H_5)_2 \quad (2)$$

However, in the presence of 0.035 *m* C_6H_5SH (IV) the yield of nitrogen remained nearly quantitative, and the yield of III fell to 59%, but its radioactivity was 17% of that of the solvent, the exchange reaction (1) having effectively occurred to this extent in the presence of the mercaptan.

This may be accounted for by a sequence of two reactions[4,5] of lower activation energy than re action (1) which tend to equilibrate diphenylmethyl, diphenylmethane, thiophenol and phenylthio radical.

$$(C_6H_5)_2CH\cdot + C_6H_5SH \rightleftharpoons (C_6H_5)_2CH_2 + C_6H_5S\cdot \quad (3a)$$

$$C_6H_5S\cdot + (C_6H_5)_2C^{14}H_2 \rightleftharpoons C_6H_5SH + (C_6H_5)_2C^{14}H\cdot \quad (3b)$$

Reaction (3a) leads to diminished yield of III since

(1) W. A. Waters, "The Chemistry of Free Radicals," Oxford University Press, New York, N. Y., second edition, 1948, p. 19, 139, 231.

(2) A. J. Fry, B. M. Tolbert and M. Calvin, *Trans. Faraday Soc.*, **49**, 1444 (1953).

(3) S. G. Cohen and C. H. Wang, THIS JOURNAL, **77**, 2457 (1955).

(4) A. F. Bickel and E. C. Kooyman, *Nature*, **170**, 211 (1952).

(5) K. E. J. Barrett and W. A. Waters, *Disc. Faraday Soc.*, **14**, 221 (1953).

in addition to undergoing reactions (3b), $C_6H_5S\cdot$ enters into two termination processes:

$$C_6H_5S\cdot + (C_6H_5)_2CH\cdot \longrightarrow (C_6H_5)_2CHSC_6H_5 \text{ (V)} \quad (4a)$$
$$2\ C_6H_5S\cdot \longrightarrow C_6H_5SSC_6H_5 \text{ (VI)} \quad (4b)$$

The infrared spectrum of residues after isolation of III was identical with that of a solution prepared from an authentic sample of V[6] and VI.[7] Evidence for the occurrence of reaction (3b) was found in the formation of tetraphenylethane III in 72% yield by exposure of a dilute solution of diphenyl disulfide VI in diphenylmethane to a sun lamp. Studies with S^{35} have shown that disulfides dissociate into mercaptyl radicals on irradiation.[8] Blank experiments indicated that compounds IV, V and VI did not cause formation of III from II, nor did they adversely affect the isolation of III from II.[9]

(6) C. Fingi and V. Bellavita, *Gazz. chim. ital.*, **62**, 699 (1932).
(7) T. Zinke and W. Frohneberg, *Ber.*, **43**, 840 (1910).
(8) E. N. Guryanova and V. N. Vasileva, *Zhur. Fiz. Khim.*, **28**, 60 (1954).
(9) This work was supported by a grant from the National Science Foundation.

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CONCERNING THE STEREOSPECIFICITY OF THE FUMARASE REACTION AND THE DEMONSTRATION OF A NEW INTERMEDIATE[1]

Sir:

When fumarase catalyzes the addition of water to fumarate only the L-isomer of malate is produced.[2] While the hydroxyl group is added stereospecifically, the question still arises as to the stereospecificity of the addition of the hydrogen atom. We have been able to demonstrate that this process is absolutely stereospecific.[3] Dipotassium fumarate was added to a reaction mixture containing crystalline fumarase,[4] 0.038 *M* K_2HPO_4, and 0.015 *M* KH_2PO_4 in a medium of 99.5% D_2O at 25°. After equilibration it was found that the resulting L-malate, isolated as diphenacyl-L-malate, containing 0.97 excess atom of deuterium per molecule after exhaustive washing with water. The fumaric acid isolated had incorporated less than 1×10^{-4} atom of non-exchangeable deuterium per molecule. This shows that the entering hydrogen atom is added in only one of the two possible positions and that a hydrogen atom from the identical position is removed in the dehydration reaction.

The stereospecificity with regard to the hydrogen atom having been established, the question as to whether the hydrogen and hydroxyl groups are added to fumarate in a *cis* or *trans* manner is currently being investigated in this laboratory.

The availability of the particular diamer of monodeutero-L-malate which is produced enzymatically made it possible to determine whether the breaking of the methylene carbon–hydrogen bond is the rate determining step in the enzymatic reaction. The breaking of the methylene carbon–deuterium bond in deutero-L-malate must proceed at approximately one-sixth the rate of that for the corresponding carbon–hydrogen bond.[5] If the breaking of a carbon–hydrogen bond were rate limiting, the over-all rate of reaction would be decreased by a factor of six in the dehydration of deutero-L-malate.

When monodeutero-L-malate was dehydrated enzymatically at *p*H 8.0 in 0.005 *M* tris-(hydroxymethyl)-aminomethane perchlorate buffer it was found that both the maximum initial velocity and Michaelis constant were unchanged after a correction for a small amount of fumarate in the malate preparation. Thus the breaking of the carbon–hydrogen bond is not involved in the rate-determining step. It seems likely from kinetic arguments[6,7] that the dissociation of fumarate from the enzyme is not the rate-determining step for the dehydration reaction at high L-malate concentrations.

The fact that the deuterium of monodeutero-L-malate was removed in a step which is not rate limiting suggested that there should be a sterically specific exchange of this hydrogen atom proceeding at a rate faster than the dehydration reaction. Such a rapid exchange was indeed found to occur in an experiment in which L-malate was dehydrated enzymatically in 99.5% D_2O to the extent of 0.04%. The amount of deutero-L-malate which could have been formed by the reverse reaction from the fumarate so produced and initially present in the sample would be immeasurably small. However, the dipotassium malate recovered had incorporated about 0.003 atom of deuterium per molecule. This relatively rapid exchange demonstrates the existence of an intermediate in which the hydrogen atom has been removed from the methylene carbon of L-malate and which may be converted either into the enzyme–fumarate or enzyme–L-malate complex.

(5) F. H. Westheimer and N. Nicolaides, *ibid.*, **71**, 25 (1949).
(6) C. Frieden and R. A. Alberty, *J. Biol. Chem.*, **212**, 859 (1955).
(7) R. A. Alberty, *J. Cellular Comp. Physiol.*, in press.

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THE ADRENAL HORMONES AND RELATED COMPOUNDS. I. A "DIRECT" SYNTHESIS OF HYDROCORTISONE ACETATE AND CORTISONE ACETATE FROM 11α-HYDROXYPROGESTERONE

Sir:

The microbiological oxidation of progesterone described by Peterson, Murray, *et al.*,[1] provides an elegant method for the synthesis of 11α-hydroxyprogesterone (I) in high yield. The synthesis of

(1) This work was supported by research grants from the Research Committee of the University of Wisconsin (Rockefeller Grant) and from the National Science Foundation.
(2) H. D. Dakin, *J. Biol. Chem.*, **52**, 183 (1922).
(3) S. Englard and S. P. Colowick (personal communication) have arrived at this same conclusion from indirect evidence using a particulate preparation from heart muscle.
(4) C. Frieden, R. M. Bock and R. A. Alberty, THIS JOURNAL, **76**, 2482 (1954).

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