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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RECEIVED JUNE 10, 1954

(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.

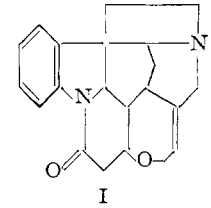
(5) This difference in rates appears to be indicative of the relative rates for *trans* eliminations in the cyclopentane and cyclohexane series, since we have found (unpublished results) that elimination of bromine from *trans*-1-2-dibromocyclopentane by reaction with iodide ion in 99% methanol at 75° 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

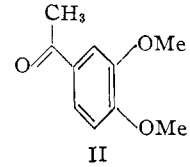
Sir:

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).

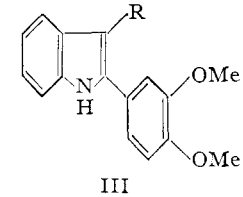


I

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.

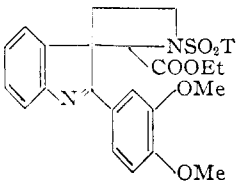


II

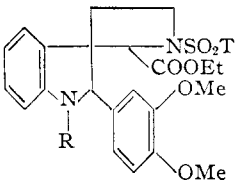


III

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,

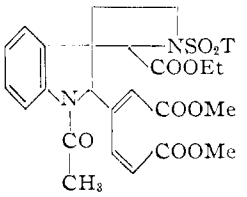


IV

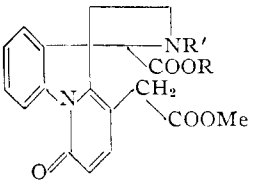


V

5.99. Found: C, 64.25; H, 5.82; N, 5.24; S, 6.00). Reduction of (IV) with sodium borohydride gave the indoline (V, R = H) (m.p. 180–181°, calcd. for $C_{29}H_{32}O_6N_2S$: C, 64.91; H, 6.01; N, 5.22; S, 5.98. Found: C, 64.59; H, 6.06; N, 5.47; S, 5.57), which was converted to its N-acetyl derivative (V, R = CH_3CO) (m.p. 206°, calcd. for $C_{31}H_{34}O_7N_2S$: C, 64.35; H, 5.92; N, 4.84; S, 5.54. Found: C, 64.46; H, 5.75; N, 5.05; S, 5.42) and ozonized to give the muconic ester (VI) (m.p. 165°, calcd. for $C_{31}H_{34}O_9N_2S$: C, 60.97; H, 5.61; N, 4.59; S, 5.24. Found: C, 60.67; H, 5.56; N, 4.83; S, 5.45). The latter with methanolic hydrogen chloride furnished the pyridone (VII, R = Et,

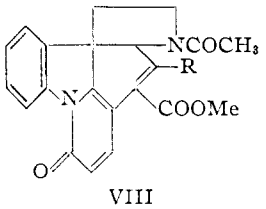


VI

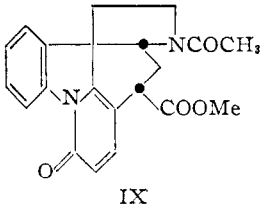


VII

R′ = SO_2T) (m.p. 187–188°, calcd. for $C_{28}H_{28}O_7N_2S$: C, 62.68; H, 5.26; N, 5.22; S, 5.97. Found: C, 62.46; H, 5.29; N, 5.50; S, 5.92), which was subjected to vigorous hydrolysis with hydrogen iodide and red phosphorus, re-esterification with methanolic hydrogen chloride, and acetylation, to give (VII, R = Me; R′ = CH_3CO) (m.p. 175–176°, calcd. for $C_{22}H_{22}N_2O_6$: C, 64.38; H, 5.40; N, 6.83. Found: C, 63.88; H, 5.32; N, 6.19). The latter was converted by methanolic sodium methoxide to the enol-ester (VIII, R = OH) (m.p. dec. from 200°, calcd. for $C_{21}H_{18}O_5N_2$: C, 66.66; H, 4.80; N, 7.40. Found: C, 66.43; H, 4.86; N, 7.56) whose tosylate (VIII, R =

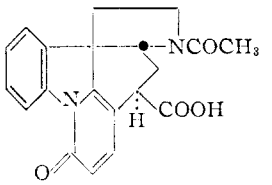


VIII

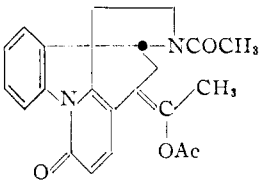


IX

$OSO_2C_7H_7$) (m.p. 217°, calcd. for $C_{28}H_{24}O_7N_2S$: C, 63.15; H, 4.54; N, 5.26; S, 6.01. Found: C, 63.15; H, 4.66; N, 4.70; S, 6.17) gave, with sodium benzylmercaptide, the thiobenzyl ether (VIII, R = $SCH_2C_6H_5$) (m.p. 249–251°, calcd. for $C_{28}H_{24}O_4N_2S$: C, 69.41; H, 4.99; N, 5.78; S, 6.63. Found: C, 68.81; H, 4.93; N, 5.51; S, 6.48). Desulfurization by Raney nickel led to the unsaturated ester (VIII, R = H) (m.p. 234°, calcd. for $C_{21}H_{18}O_4N_2$: C, 69.60; H, 5.00; N, 7.73. Found: C, 69.71; H, 5.12; N, 7.45), which was reduced by hydrogen in the presence of palladium–charcoal to the *cis* ester (IX) (m.p. 186°, calcd. for $C_{21}H_{20}O_4N_2$: C, 69.21; H, 5.53; N, 7.69. Found: C, 69.12; H, 5.55; N, 7.10). Hydrolysis of the ester with aqueous methanolic potash gave the *racemic trans* acid (X) (m.p. 284°, calcd. for $C_{20}H_{18}O_4N_2$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.36; H, 5.50; N 7.53—*methyl ester*, m.p. 212°, calcd. for $C_{21}H_{20}O_4N_2$: C, 69.21; H, 5.53; N, 7.69. Found: C, 69.32; H, 5.46; N, 8.25), which with quinidine gave a nicely crystalline *salt* (m.p. 160–172°), from which on decomposition with carbonate the *levorotatory* acid (X) (m.p. 295–300°—

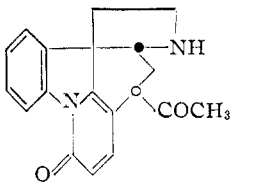


X

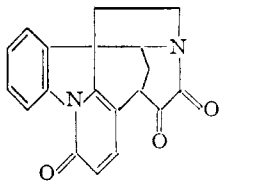


XI

methyl ester, m.p. 196°, $[\alpha]^{23}D$ −285 ± 8° [*c* = 1.25 ($CHCl_3$)]) was obtained. This acid was identical in all respects with a substance of the same structure (X) (m.p. 295–300°, —*quinidine salt*, m.p. 160–172°,—, *methyl ester*, m.p. 196°, $[\alpha]^{21}D$ −292 ± 5° [*c* = 1.14 ($CHCl_3$)], calcd. for $C_{21}H_{20}O_4N_2$: C, 69.21; H, 5.53; N, 7.69. Found: C, 68.85; H, 5.65; N, 8.34) which could be obtained, *inter alia*, by hydrogen peroxide–barium hydroxide oxidation of dehydrostrychninone (XIII)[1], followed by acetylation, and served as a first relay. When the acid (X) was heated with acetic anhydride–pyridine, it was converted to the enol acetate (XI) (m.p. 254–255°, calcd. for $C_{23}H_{22}O_4N_2$: C, 70.75; H, 5.68; N, 7.18. Found: C, 70.24; H, 5.38; N, 7.73), which gave on vigorous acid hydrolysis an oily mixture of stereoisomeric methyl ketones (XII).



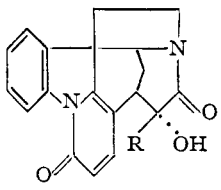
XII



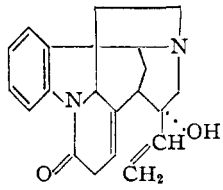
XIII

The latter was oxidized by selenium dioxide in ethanol to dehydrostrychninone (XIII) (*methanolate*, m.p. 172–174°, resolidifying and remelting at 254–258°, $[\alpha]^{24}D$ −521 ± 4° [*c* = 1.05 ($CHCl_3$)]), identical in all respects with an authentic sample[1] (*methanolate*, m.p. 172–174°, resolidifying and remelting at 254–258°, $[\alpha]^{21}D$ −512 ± 4° [*c* = 1.17 ($CHCl_3$)]) which was used as a second relay. Addition of sodium acetylide to dehydrostrychninone gave the tertiary carbinol (XIV, R = —C≡CH) (m.p. 302–305°, calcd. for $C_{21}H_{16}O_3N_2$: C, 73.24; H, 4.68; N, 8.14. Found: C, 73.06; H, 4.58; N, 8.47) which was hydrogenated over the Lindlar catalyst to the vinyl carbinol (XIV,R = —CH=CH_2) (m.p. 244–245°, calcd. for $C_{21}H_{18}O_3N_2$: C, 72.82; H, 5.24; N, 8.09. Found: C, 72.58; H, 5.75; N, 8.24). Reduction of (XIV, R = —CH=CH_2) by lithium aluminum hydride gave the car-

(1) V. Prelog, M. Kocór and W. I. Taylor, *Helv. Chim. Acta*, **32**, 1052 (1949).

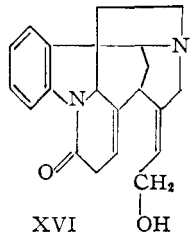


XIV



XV

binol (XV) (*hydrochloride*, m.p. 195–205° dec., calcd. for $C_{21}H_{22}O_2N_2Cl\cdot 2H_2O$: C, 61.97; H, 6.69; N, 6.89. Found: C, 61.87; H, 6.97; N, 6.97), which was rearranged by hydrogen bromide in acetic acid, followed by boiling aqueous sulfuric acid, to isostrychnine I (XVI)[2] (m.p. [evacuated tube] 229–230°, $[\alpha]^{22}D$ +23 ± 4° (c = 2.54 [EtOH])), identical in all respects with an authen-



XVI

tic sample (m.p. [evacuated tube] 228–230°, $[\alpha]^{25}D$ +25 ± 4° (c = 2.44 [EtOH])), and further characterized through isomerization by ethanolic potash[3] to strychnine (I), identical in infrared spectrum, melting point, and chromatographic behavior with the natural alkaloid.

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RECEIVED AUGUST 23, 1954

(2) H. Leuchs and H. Schulte, *Ber.*, **75**, 1522 (1942).

(3) V. Prelog, J. Battegay and W. I. Taylor, *Helv. Chim. Acta*, **31**, 2244 (1948).

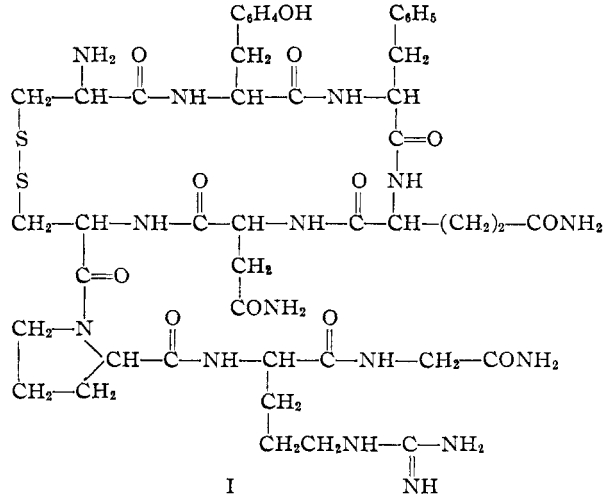
(4) On leave of absence from the University, Bristol, England.

A SYNTHETIC PREPARATION POSSESSING BIOLOGICAL PROPERTIES ASSOCIATED WITH ARGININE-VASOPRESSIN

Sir:

In a recent Communication[1] on the structures of arginine-vasopressin and lysine-vasopressin it was recorded in a footnote that a synthesis by du Vigneaud, Popenoe and Roeske of the octapeptide structure proposed for lysine-vasopressin had led to biologically active material. As this work continued, the synthesis of arginine-vasopressin was undertaken.

The present Communication is concerned with the preparation and partial purification of a product synthesized according to the structure (I) proposed for arginine-vasopressin.[1,2] The synthesis was approached through the preparation of the appropriate benzylated cysteine-containing nonapeptide, N-carbobenzoxy-S-benzyl-L-cysteinyl-L-tyrosyl-L-phenylalanyl-L-glutaminyl-L-asparaginyl-S-benzyl-L-cysteinyl-L-prolyl-L-arginylglycinamide (II), debenzylation of this compound with sodium in liquid ammonia and cyclization of the resulting sulfhydryl nonapeptide to the disulfide. Synthesis of II was accomplished by coupling N-carbobenzoxy-S-benzyl-L-cysteinyl-L-tyrosyl-L-phenylalanyl-L-glutaminyl-L-asparagine (III) with S-benzyl-L-cysteinyl-L-prolyl-L-arginylglycinamide monohydrobromide (IV).



I

L-Phenylalanyl-L-glutaminyl-L-asparagine[3] was coupled with N-carbobenzoxy-S-benzyl-L-cysteinyl-L-tyrosine[4] by the isobutyl chlorocarbonate mixed anhydride procedure[5] to give III, m.p. 208–209°, $[\alpha]^{22}D$ −26° (c 1, dimethylformamide) (calcd. for $C_{45}H_{51}O_{11}N_7S$: C, 60.2; H, 5.72; N, 10.9; S, 3.57. Found: C, 59.9; H, 5.77; N, 10.4; S, 3.57).

N^{α}-*p*-Nitrobenzyloxycarbonyl-L-arginylglycinamide was prepared by the procedure of Gish and Carpenter[6] and isolated as the picrate (V), m.p. 168–171°, $[\alpha]^{22}D$ −3.8° (c 1, acetone–water (4:1)) (calcd. for $C_{16}H_{23}O_6N_7\cdot C_6H_3O_7N_3$: C, 41.4; H, 4.10; N, 21.9. Found: C, 41.4; H, 4.17; N, 21.8). V was treated with HBr–acetic acid and the reaction product isolated as the monohydrobromide (VI).

S-Benzyl-N-*p*-nitrobenzyloxycarbonyl-L-cysteine, m.p. 132.5–133°, $[\alpha]^{22}D$ −47.0° (c 1, 95% ethanol) (calcd. for $C_{18}H_{18}O_6N_2S$: N, 7.18; S, 8.21. Found: N, 7.05; S, 8.03), as its acid chloride was condensed with proline benzyl ester. Saponification of the peptide ester gave S-benzyl-N-*p*-nitrobenzyloxycarbonyl-L-cysteinyl-L-proline (VII) as an oil (neut. equiv., calcd., 487.5. Found, 487).

VI was condensed with VII by the pyrophosphite method[7] to give S-benzyl-N-*p*-nitrobenzyloxycarbonyl-L-cysteinyl-L-prolyl-L-arginylglycinamide hydrobromide (VIII) characterized as the picrate, m.p. 182–185°, $[\alpha]^{22}D$ −47.7° (c 1, acetone–water (4:1)) (calcd. for $C_{31}H_{41}O_8N_9S\cdot C_6H_3O_7N_3$: C, 47.8;

(1) V. du Vigneaud, H. C. Lawler and E. A. Popenoe, THIS JOURNAL, **75**, 4880 (1953).

(2) R. Archer and J. Chauvet, *Biochim. et Biophys. Acta*, **12**, 487 (1953).

(3) E. A. Popenoe and V. du Vigneaud, THIS JOURNAL, in press.

(4) C. R. Harington and R. V. Pitt Rivers, *Biochem. J.*, **38**, 417 (1944).

(5) J. R. Vaughan, Jr., and J. A. Eichler, THIS JOURNAL, **75**, 5556 (1953).

(6) D. T. Gish and F. H. Carpenter, *ibid.*, **75**, 5872 (1953).

(7) G. W. Anderson, J. Blodinger and A. D. Welcher, *ibid.*, **74**, 5309 (1952).