Ethylation and Ethanolysis of an Alkyl Diazotate. The Stereochemistry of Alkyl Diazo Ether Collapse[1,2]

Sir:

Diazo ethers have been implicated in the alkylation of diazotates and/or the alcoholysis of diazoalkanes.[3] Stereochemical studies of these reactions have not yet appeared, though this aspect of diazo *ester* decomposition has received much attention.[4] Here, we report stereochemical studies of the direct formation and collapse of an alkyl diazo ether and of a related ethanolysis reaction. The results contribute importantly to mechanistic understanding of deamination reactions.

Reaction of triethyloxonium tetrafluoroborate with 1-phenylethane-1-diazotate (I) in CH_2Cl_2 (−20°) gave nitrogen (39%), styrene(7.3%), α-phenylethyl ethyl ether (II) (15.3%), and the azoxyalkane III (46%), eq 1.[2]

$$\underset{\text{I}}{C_6H_5(CH_3)CH{-}N{=}N{-}O^-K^+} + (C_2H_5)_3O^+BF_4^- \xrightarrow{CH_2Cl_2} N_2 + KBF_4 + (C_2H_5)_2O + C_2H_5OH + \underset{\text{II}}{C_6H_5(CH_3)CHOC_2H_5} + \underset{\text{III}}{C_6H_5(CH_3)CH{-}\overset{O}{\overset{\uparrow}{N}}{=}N{-}C_2H_5} + C_6H_5CH{=}CH_2 \quad (1)$$

Diazotate I, from optically active *l*-α-phenylethylamine,[5,6] was decomposed as in eq 1. Gc isolation of II (Carbowax) permitted polarimetric analysis. Isolated II was pure (gc, ir) and optically stable to experimental procedures. Table I gives the results.

Table I. Stereochemistry of α-Phenylethyl Ethyl Ether as per Equation 1[a]

Reaction	Temp, °C	α_D, deg (temp, °C)	% net retention[b]
1	−40 to −20	−48.43 (22.5)	56.90
2	−55 to −34	−13.88 (22)[c]	65.57
3	−60 to −40	−60.04 (29)	70.56
4	+3 to +18	−45.14 (25)	53.05

[a] $\alpha^{22}D$ of starting α-phenylethylamine was −37.43°, 97.7% optically pure.[5] [b] Optically pure II has $\alpha^{28}D$ −87.09°: K. Mislow, *J. Amer. Chem. Soc.*, **73**, 4043 (1951). Results are corrected for optical purity of amine. In the α-phenylethyl system, amine, alcohol, and ethoxy derivatives of analogous configuration exhibit similar rotational sign (see J. A. Mills and W. Klyne, *Progr. Stereochem.*, **1**, 194 (1954)). [c] Sample diluted from 30.5 to 122.6 mg with racemic II; *i.e.*, dilution factor, 1226/305.

Addition of excess ethanol to I gave nitrogen (85–90%), styrene (17.1%), II (43.5%), and α-phenylethanol (17.6%); isolated by gc (Carbowax, 115–168°). Some phenylmethyldiazomethane (ir 2060 cm^{-1}) also formed and was thermalized over molecular sieves before gc. Yields are typical, though II/α-phenylethanol was variable, 2.89 ± 0.45 (3 runs). Use of C_2H_5OD gave essentially unlabeled II;[7] ethanolysis of diazoalkane was not a significant route to II.

Ethanolysis (5–7°) of I, derived from optically active *d*-α-phenylethylamine, afforded active II and α-phenylethanol. Three procedures were used for the ethanolysis: (1) 30 ml of (anhydrous) ethanol was added to 112.6 mmol of dry I; (2) 112.6 mmol of colloidal I in 4.7 g of ethanol and 70 ml of CH_2Cl_2 was slowly added to 300 ml of stirred ethanol; (3) a clear dark red-brown "solution" of 112.6 mmol of I in 50 ml of hexamethylphosphoric triamide containing 9 g (242 mmol) of purified dicyclohexyl-18-crown-6[8] was slowly added to 300 ml of stirred ethanol. Pure products (gc, ir) were polarimetrically analyzed as neat liquids (diluted with racemic material, if required); Table II.

Table II. Product Stereochemistry, Ethanolysis of I[a]

Reaction	II: α_D, deg (temp, °C)	II: % net inv[b]	α-Phenylethanol: α_D, deg (temp, °C)	α-Phenylethanol: % net retention[b,c]
1[d]	−15.51 (22)[e]	29.61	+8.43 (22)[f]	77.29
2[d]	−24.06 (23)	28.78	+11.35 (23)[g]	68.16
3[h]	−22.58 (23)	27.01	+10.63 (23)[i]	76.77
4[j]	−26.35 (21)	31.52	+8.04 (21)[k]	72.32

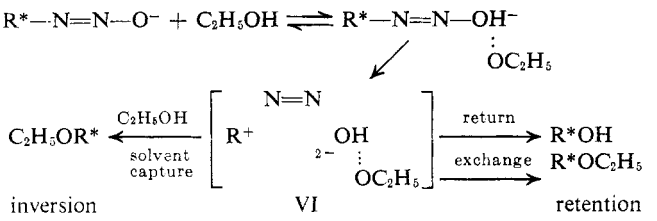
[a] Initial amine had $\alpha^{24}D$ +36.76°, 95.98% optically pure.[5] Results are corrected. [b] See footnote *b*, Table I. [c] Optically pure α-phenylethanol has $\alpha^{25}D$ +43.7°: R. L. Burwell, Jr., A. D. Shields, and H. Hart, *J. Amer. Chem. Soc.*, **76**, 908 (1954). [d] Procedure 1. [e] Dilution factor: 1216/762. [f] Dilution factor: 1569/408. [g] Dilution factor: 1801/715. [h] Procedure 2; II/α-phenylethanol was 2.84. [i] Dilution factor: 1875/619. [j] Procedure 3. [k] Sample contained 43.7 mg of product alcohol, 14.6 mg of hexamethylphosphoric triamide, and 106.5 mg of racemic alcohol (gc). A prepared, *identical* dilution of α-phenylethanol ($\alpha^{20}D$ +10.60°) had $\alpha^{20}D$ +2.81°. Diluted reaction alcohol therefore corresponded to pure reaction alcohol with $\alpha^{21}D$ +30.34°.

In alkylation reaction 1, II forms with substantial retention; in ethanolysis it forms with inversion, while α-phenylethanol is formed with retention. Reaction 1, we suggest, involves direct O alkylation of I, giving the diazoether, $C_6H_5(CH_3)CHN{=}NOC_2H_5$ (IV) which collapses to the ion pair, $[C_6H_5(CH_3)CH^+{-}OC_2H_5]$ (V). In CH_2Cl_2, and in the absence of strong, competing nucleophiles, V collapses to II with substantial retention. This diazo ether reaction is then stereochemically analogous to diazo ester decompositions in which retention is generally observed.[4] In eq 1, R^+ may also lose H^+, giving styrene. α-Phenylethyl chloride, product of R^+ and solvent, was not detected. The racemization may reflect R^+ which escapes from V and/or reacts with ethanol liberated in the styrene formation.

Ethanolysis of I is rationalized *via* Scheme I. Ionic assembly VI is subject to ethanolysis yielding inverted II. Alternatively, collapse affords (returned) alcohol with retention. Some retained II presumably forms by

(1) Alkyl Diazotates. VIII.
(2) Part VII: R. A. Moss and M. J. Landon, *Tetrahedron Lett.*, 3897 (1969).
(3) Examples include: H. v. Pechmann and L. Frobenius, *Chem. Ber.*, **27**, 672 (1894); E. Bamberger, *ibid.*, **28**, 225 (1895); A. Hantzsch, *ibid.*, **36**, 3097 (1903); F. W. Bollinger, F. N. Hayes, and S. Siegel, *J. Amer. Chem. Soc.*, **72**, 5592 (1950); R. Huisgen and J. Reinertshofer, *Justus Liebigs Ann. Chem.*, **575**, 174 (1952); C. D. Gutsche and H. E. Johnson, *J. Amer. Chem. Soc.*, **77**, 109 (1955); K. Heyns and A. Heins, *Justus Liebigs Ann. Chem.*, **604**, 133 (1957); D. E. Applequist and D. E. McGreer, *J. Amer. Chem. Soc.*, **82**, 1965 (1960); W. M. Jones and D. L. Muck, *ibid.*, **88**, 3798 (1966); R. A. Moss, *J. Org. Chem.*, **31**, 1082 (1966); W. Kirmse and G. Wächterhäuser, *Justus Liebigs Ann. Chem.*, **707**, 44 (1967); W. Kirmse and H. A. Rinkler, *ibid.*, **707**, 57 (1967).
(4) E. H. White and D. J. Woodcock in "The Chemistry of the Amino Group," S. Patai, Ed., Interscience, New York, N. Y., 1968, pp 440 ff.
(5) W. Theilaker and H.-G. Winkler, *Chem. Ber.*, **87**, 690 (1954).
(6) Preparative steps resemble those in R. A. Moss and S. M. Lane, *J. Amer. Chem. Soc.*, **89**, 5655 (1967). *All rotations* below refer to neat liquids, 1-dm path length.
(7) Analysis by mass spectroscopy.
(8) C. J. Pedersen, *J. Amer. Chem. Soc.*, **89**, 7017 (1967).

Scheme I



a front-side exchange process. The results parallel $H_2{}^{18}O$ hydrolysis of optically active octane-2-diazotate, in which 2-octanol from OH return showed retention, whereas 2-octanol from solvent capture showed inversion.[9] There are also analogies to diazo ester collapse in carboxylic acids.[4,10] In polar solvents, such esters collapse with return and retention.[4] The esters formed by solvent capture, however, may form with retention or inversion.[4,10] In ethanolysis of I, the high nucleophilicity of the solvent (as compared to a carboxylic acid) ensures that its capture by VI will occur mainly with inversion.

The present results support the generality of ion pair intermediates in deaminative reactions and extend the "counterion hypothesis"[4] to diazo ethers. The persistence of the return with retention, solvolysis with inversion dichotomy[4,9] in the diazotate ethanolysis reaction, is especially noteworthy.

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(9) R. A. Moss, D. W. Reger, and E. M. Emery, *J. Amer. Chem. Soc.*, **92**, 1366 (1970).
(10) E. H. White and F. W. Bachelor, *Tetrahedron Lett.*, 77 (1965); E. H. White and C. A. Aufdermarsh, Jr., *J. Amer. Chem. Soc.*, **83**, 1179 (1961); E. H. White, *ibid.*, 77, 6014 (1955).
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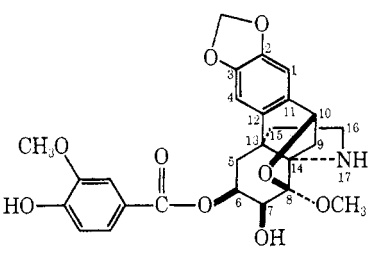
The Structure of Stephavanine, a Novel Hasubanan Ester Alkaloid

Sir:

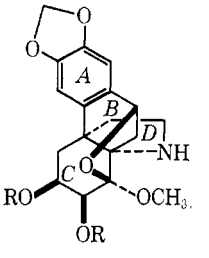
We wish to report the structure of a new alkaloid isolated from the rhizomes of *Stephania abyssinica* Walp., a creeping plant indigenous to Eastern and Southern Africa which is reputed to possess a variety of medicinal uses.[1,2] The principal alkaloid, stephavanine (**1**), is the most highly oxygenated hasubanan alkaloid reported to date, and the first recognized to contain ester or ketal functions.

Crystallization of the "weak base" fraction[2] from chloroform yielded stephavanine hydrochloride, $C_{26}H_{28}ClNO_9$[3]: mp 217–218° dec; $[\alpha]^{32}D$ +16° (*c* 0.73, MeOH). Treatment with ammonia gave stephavanine (**1**), $C_{26}H_{27}NO_9$ (mp 229–230° dec; $[\alpha]^{32}D$ +30° (*c* 0.90, pyr); *m/e* 497 (M^+)); 7-trimethysilyl ether (**2**), $C_{29}H_{35}NO_9Si$ (mp 201–202° dec); *O,O,N*-triacetyl derivative **3**, $C_{32}H_{33}NO_{12}$ (mp 189–190°); and hydrobromide $C_{26}H_{28}NO_9Br$ (mp 191–192° dec). The mass spectrum of **1** showed one major fragmentation, characteristic of a hasubanan-type alkaloid,[4] to an ion at *m/e* 214. Alkaline hydrolysis of **1** gave vanillic acid; stephine (**4**), $C_{18}H_{21}NO_6$ (mp 224–226° dec); and 6,7-bistrimethylsilyl ether (**5**), $C_{24}H_{37}NO_6Si_2$ (mp 197–199° dec). The nmr spectrum of **5** (Table I) showed singlets for the two aromatic protons, indicative that the methylenedioxy group was attached at C(2) and C(3).

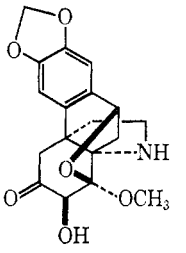
Oxidation of stephine (**4**) with Jones reagent in acetone–HOAc gave 6-dehydrostephine (**6**, $C_{18}H_{19}NO_6$, mp 191–192° dec) after $NaHCO_3$ work-up. After NaOH work-up, or by brief treatment of **6** with NaOH, iso-6-dehydrostephine (**7**, $C_{18}H_{19}NO_6$, mp 128–130°) was obtained. Whereas **6** showed its base peak at *m/e* 214, corresponding to loss of the C ring to give **8**, **7** showed its base peak at *m/e* 301, corresponding to loss of the D ring to give ion **9**. We have also observed loss of the D ring to be the preferred fragmentation in other C-ring enone hasubanan alkaloids.[5] Reduction



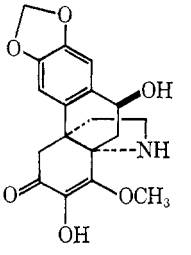
1



4, R = H
5, R = $Si(CH_3)_3$

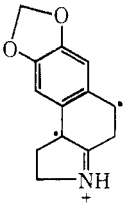


6



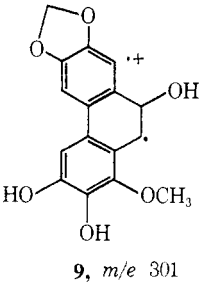
7

-ring C



8, *m/e* 214

-ring D



9, *m/e* 301

of **6** with $NaBH_4$ led to stereospecific conversion to stephine (**4**).

(1) J. M. Watt and M. G. Breyer-Brandwijk, "The Medicinal and Poisonous Plants of Southern and Eastern Africa," E. and S. Livingstone Ltd., London, 1962, p 458.
(2) S. M. Kupchan, M. I. Suffness, and E. M. Gordon, *J. Org. Chem.*, 35, 1682 (1970).
(3) All crystalline compounds have been characterized by concordant elemental analyses.
(4) M. Tomita, A. Kato, and T. Ibuka, *Tetrahedron Lett.*, 1019 (1965).
(5) S. M. Kupchan, M. I. Suffness, D. N. J. White, A. T. McPhail, and G. A. Sim, *J. Org. Chem.*, 33, 4529 (1968).