in the presence of high concentrations of trypsin, chymotrypsin, and carboxypeptidase inhibitors (Table II). Explanation (a) a new proteinase, remains.

TABLE II

INFLUENCE OF INHIBITORS ON PROTEOLYTIC ACTIVITIES

Inhibitor	Trypsin Activity[a]	Trypsin Inhibition, %	α-Chymotrypsin Activity[a]	α-Chymotrypsin Inhibition, %	Pankrin Activity[a]	Pankrin Inhibition, %
None	11.94		5.70		35.80	
Soybean trypsin inhibitor[b]	1.58	87	3.67	36	28.20	21
Pancreatic trypsin inhibitor[b]	2.41	80	4.63	19	24.50	32
β-Phenylpropionate[c] 0.09 *M*			1.60	72	16.49	54

[a] Denatured hemoglobin substrate. [b] 100 γ inhibitor per hemoglobin activity unit for each enzyme. This amounts to inhibitor to enzyme weight ratio of 4 (pankrin), 1.2 (trypsin), and 0.6 (α-chymotrypsin). [c] Specific inhibitor for both chymotrypsin and carboxypeptidase: Kaufman and Neurath, *Arch. Biochem.*, 21, 245 (1949).

Other characteristics of pankrin are these: It is inhibited by DFP and serum. It clots milk. It is unable to clot citrated plasma on any basis of comparison with trypsin—equal weights, proteolytic units, or TSAME units—indicating the probable lack of a trypsin contaminant. Its ATEE splitting activity appears to be less sensitive to β-phenyl propionate than the esterase activity of α-chymotrypsin. Its *p*H optimum (D hemoglobin) is approximately 8.5. Details of purification and substrate specificity will be reported later.

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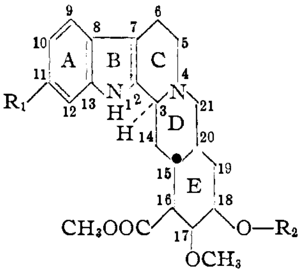
THE STEREOCHEMISTRY OF RESERPINE

Sir:

Recently deserpidine, an alkaloid closely related to reserpine[1] (I), has been isolated from various Rauwolfia species.[2] It was shown to possess structure II and to be stereochemically related to 3-epi-α-yohimbine (which defines the hydrogen atoms at C_{15} and C_{20} to be *trans* to the hydrogen at C_3).

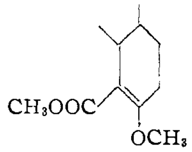
It was furthermore suggested that the same relationship holds for reserpine. We now wish to present chemical evidence for the relative and absolute configurations of four centers (C_{15}, C_{16}, C_{18} and C_{20}) in reserpine.

In the course of our investigation, we had occasion to study the collidine detosylation of methyl reserpate tosylate (III), first reported by Dorfman, *et al.*[1a] By chromatography of the reaction product

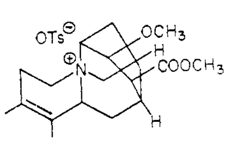


I, $R_1 = —OCH_3$;
$R_2 = —COC_6H_2(OCH_3)_3$
II, $R_1 = —H$;
$R_2 = —COC_6H_2(OCH_3)_3$
III, $R_1 = —OCH_3$;
$R_2 = —O_2SC_7H_7$

on acid-washed alumina we obtained a 10% yield of methyl anhydroreserpate (IV), previously described,[1a] but the major product (30% yield) was a more polar compound which could be eluted with



IV



V

acetone-methanol (20:1). This substance, m.p. 290–291°, $[\alpha]^{23}\mathrm{D}$ +88.5° (*c* 0.75, HOAc), was found to be isomeric with methyl reserpate tosylate (III). *Anal.* Calcd. for $C_{30}H_{36}O_7N_2S$: C, 63.36; H, 6.38; N, 4.93; S, 5.63; 3 MeO–, 16.36. Found: C, 63.27; H, 6.23; N, 4.93; S, 5.54; MeO–, 16.16.

That this new tosylate was a quaternary salt was proved by the following observations: It could not be titrated as a base with perchloric acid in acetic acid nor as an acid with sodium hydroxide in 67% dimethylformamide as could the *p*-toluenesulfonic acid salt of methyl reserpate (*pK'*a 7.10). When treated with sodium iodide in acetonitrile it gave an instantaneous precipitate of sodium *p*-toluenesulfonate to form an iodide, m.p. 238–240°, $[\alpha]^{23}\mathrm{D}$ +93° (*c* 0.71, MeOH), which was also a neutral salt. *Anal.* Calcd. for $C_{23}H_{29}O_4N_2I \cdot 2H_2O$: C, 49.29; H, 5.94; N, 5.00; I, 22.64. Found: C, 49.99; H, 5.90; N, 4.96; I, 22.31. The infrared spectrum of the isomeric tosylate confirmed its quaternary character since it showed four bands at 8.56, 8.95, 9.71 and 9.94 μ characteristic of the *p*-toluenesulfonate ion[3] but lacked absorption in the 3.8–4.0 μ region indicative of a $\gtrless NH^+$ group. From these results structure V was derived for the tosylate salt. Later, it was found that this quaternary compound could also be obtained from methyl reserpate tosylate (III) by refluxing in dimethylformamide. A similar intramolecular displacement reaction has been observed with isorubijervine[3] and other compounds.[4,5]

The formation of an N_4–C_{18} bond requires a *cis* D/E ring juncture, and since reserpine has been shown[2] to have the unstable configuration at C_3, its skeleton must correspond configurationally to that of epi-α-yohimbane. Further, since the quaternary salt (V) is most likely formed by a concerted displacement of tosylate ion by the tertiary nitrogen (N_4) resulting in inversion at C-18, the 18-acyloxy group of reserpine must also be

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(1) (a) L. Dorfman, A. Furlenmeier, C. F. Huebner, R. Lucas, H. B. MacPhillamy, J. M. Mueller, E. Schlittler, R. Schwyzer and A. F. St. Andre, *Helv. Chim. Acta*, **37**, 59 (1954); (b) C. F. Huebner, H. B. MacPhillamy, A. F. St. Andre and E. Schlittler, THIS JOURNAL, **77**, 472 (1955).

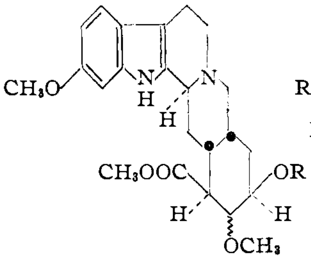
(2) H. B. MacPhillamy, L. Dorfman, C. F. Huebner, E. Schlittler and A. F. St. Andre, *ibid.*, **77**, 1071 (1955).

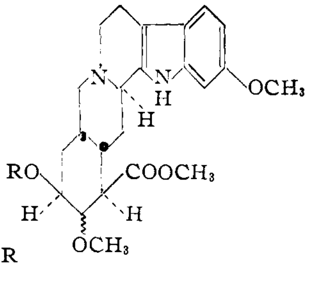
(3) F. L. Weisenborn and D. Burn, *ibid.*, **75**, 259 (1953).

(4) V. M. Clark, A. R. Todd and J. Zussman, *J. Chem. Soc.*, 2952 (1951).

(5) B. R. Baker and J. P. Joseph, THIS JOURNAL, **77**, 15 (1955).

cis to the hydrogens at C-15 and C-20. In addition, the carbomethoxy group at C-16 is *cis* to the C-18 function since reserpic acid readily forms a γ-lactone without inversion.[1] Thus the known stereochemical relationships of reserpine can be expressed by structure VI.


VI


VII

We have no conclusive evidence at present concerning the stereochemistry of the C-17 methoxyl group although, assuming a *trans* elimination in the formation of methyl anhydroreserpate, the 17-methoxyl would appear to be *cis* oriented.

It now seems possible to assign absolute configurations to the above mentioned asymmetric centers since Klyne has shown[6] that Hudson's lactone rule may also be applied to molecular rotations of polycyclic compounds. The change in molecular rotation from reserpic acid, $[M]_D$ $-692°$ (pyridine) to reserpic acid lactone, $[M]_D$ $+300°$ (pyridine), is $+992°$, therefore the hydroxyl at C-18 is related to D-glyceraldehyde and the absolute configuration of reserpine should be represented by structure VI and not VII.

[6] W. Klyne, *Chemistry and Industry*, 1198 (1954).

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THE TETRAMMINESODIUM ION

Sir:

Compounds of alkali halides and ammonia have been known for some time[1,2] but little information has been available as to the nature of the bonding involved or of their structures. We wish to present a preliminary report of studies made on liquid tetramminesodium iodide, $Na(NH_3)_4I$, which verify the existence of a tetramminesodium ion, $Na(NH_3)_4^+$, of remarkable stability.

The sample was prepared by reaction of anhydrous ammonia with anhydrous NaI and was a thermally stable liquid at 25° with a melting point of 3° and p_{NH_3} = 420 mm. at 25°. The ultraviolet spectrum has $\lambda_{min.}$ 309 and $\lambda_{max.}$ 330 and isd istinct from both NaI and ammonia. Infrared and Raman spectra of $Na(NH_3)_4I$ were obtained by standard methods.[3] The absence of characteristic NH_3 deformation frequencies and the observation of a new set of frequencies indicates that this compound has a distinct set of bond properties. The NH_3 deformation frequencies at 950 and 1627 cm.$^{-1}$ have shifted in $Na(NH_3)_4I$ to 1105 and 1525 cm.$^{-1}$ and are surprisingly close to the corresponding CH_3 deformation frequencies of tetramethyl compounds which occur near 1148 and 1448 cm.$^{-1}$ in $Pb(CH_3)_4$. In the Raman spectrum the Na–NH_3 skeletal stretching and deformation frequencies are readily assigned to 435 and 103 cm.$^{-1}$ bands. These frequencies are close to the corresponding frequencies of $Zn(NH_3)_4^{++}$ and $Pb(CH_3)_4$ indicating the existence of rather strong Na–NH_3 bonds.[3,4]

The calculated value of the Na–NH_3 stretching force constant compares favorably with those calculated for $Zn(NH_3)_4^{++}$ and $Pb(CH_3)_4$: ($k_{Na(NH_3^{++})_4}$ $= 1.9 \times 10^5$ dynes/cm., $k_{Zn(NH_3^{++})_4} = 1.85 \times 10^5$ dynes/cm. and $k_{Pb(CH_3)_4} = 1.87 \times 10^5$ dynes/cm.).

An assignment[3] of frequencies may be made on the basis of a $Na(NH_3)_4^+$ ion and in a manner analogous to that for $Pb(CH_3)_4$, if one assumes that in the Raman spectrum the close doublets have not been resolved and that the weakest bands present in $Pb(CH_3)_4$ have not been observed in $Na(NH_3)_4^+$. The NH_3 rocking frequency which is not present in the infrared spectrum of ammonia and observed at 765 cm.$^{-1}$ in $Pb(CH_3)_4$ appears near 500 cm.$^{-1}$ in $Na(NH_3)_4^+$. The distribution of the NH frequencies in $Zn(NH_3)_4^{++}$ and $Na(NH_3)_4^+$ ions is nearly the same.

The Raman lines observed for the $Na(NH_3)_4^+$ ion were much broader than the corresponding lines observed for $Zn(NH_3)_4^{++}$ and $Cd(NH_3)_4^{++}$ ions,[4] and the presence of other ionic species such as $Na(NH_3)_3^+$ and $Na(NH_3)_2^+$ cannot be completely eliminated.

The observation of a distinct ultraviolet spectrum along with the evidence for a distinct set of bond properties from the vibrational spectrum indicates that the stability of this compound is due to the presence of charge transfer forces involving resonance best illustrated in terms of no-bond and bonded structures such as $[Na–NH_3]$ and $\left[\overset{-}{Na}–\overset{+}{N}H_3\right]$.[5] However the presence of broad bands in the Raman spectrum and the observation of a low NH_3 rocking frequency suggests that ion-dipole forces are more important in $Na(NH_3)_4^+$ than in ammonia complexes of the transition metals.

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RECEIVED FEBRUARY 18, 1955

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[1] W. Biltz and W. Hansen, *Z. anorg. allgem. Chem.*, **127**, 1–33 (1922).

[2] M. Picon, *Compt. rend.*, **168**, 825 (1919).

[3] E. R. Lippincott and M. C. Tobin, THIS JOURNAL, **75**, 4141 (1953).

[4] J. L. Silver, Ph.D. Thesis, University of Connecticut, 1953.

[5] R. S. Mulliken, THIS JOURNAL, **64**, 811 (1952); *J. Phys. Chem.*, **56**, 801 (1952).

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