TABLE I

THE HETEROYOHIMBINE ALKALOIDS

		Free bases			Methiodide salts[a]		
Groups and stereochemistry	Alkaloids	C/D quinolizidine fusion (from infrared at 3.4μ)	C-19 methyl chemical shift (and *J* in c.p.s.)	$^+$N-CH$_3$ chemical shift	C/D fusion	C-19 chemical shift (and *J* in c.p.s.)	Δ p.p.m. C-19 methyl base − salt
A (*allo*) C-19 CH$_3$: α and e	Tetrahydroalstonine (I)	*trans*	1.38 (6.1)	3.42	*trans*	1.46 (5.8)	−0.08
	Aricine		1.37 (6.3)	3.43		1.47 (5.4)	−0.10
	Reserpinine		1.38 (6.1)	3.39		1.48 (5.4)	−0.10
	Isoreserpiline		1.39 (6.2)	3.41		...	...
B (*epiallo*) C-19 CH$_3$: α and e	Akuammigine (II)	*cis*	...	...	...	...	...
	Isoreserpinine		1.32 (6.5)	3.32	*trans*	1.39 (6.2)	−0.07
	Reserpiline		1.32 (6.3)	3.35		1.39 (5.7)	−0.07
C (*allo*) C-19 CH$_3$: β and a	Rauniticine (III)	*trans*	1.42 (6.7)	3.50	*cis*	1.40 (6.5)	+0.02
	Raunitidine		1.42 (7.1)	3.49		1.41 (6.1)	+0.01
D (*epiallo*) C-19 CH$_3$: β and e	Mayumbine (IV)	*trans*	1.35 (6.3)	...	...	...	...
	Isoraunitidine		1.35 (6.8)	3.31	*trans*	1.43 (6.0)	−0.08
E (*normal*) C-19 CH$_3$: α and a	Ajmalicine[b]	*trans*	1.16 (6.7)	3.35	*trans*	1.26 (6.2)	−0.10
	Tetraphylline		1.16 (6.5)	3.36		1.26 (6.2)	−0 10
F (*normal*) C-19 CH$_3$: β and e	Raumitorine[c]	*trans*	...	...	...	...	...

[a] The n.m.r. spectra of the methiodide salts were obtained in formamide solution with TMS as an internal solvent. All spaces left blank signify that insufficient samples were available for the spectral measurements. [b] An early suggestion that the stereochemical proposals of Wenkert for the heteroyohimbine alkaloids needed to be modified was made by Professor E. E. van Tamelen at the 139th meeting of the American Chemical Society held in St. Louis, Missouri. [c] The C-3 hydrogen in raumitorine is *alpha* and axial as indicated originally by J. Poisson in his Docteur-ès-Sciences thesis, "Recherches sur les Alkaloides des Racines du *Rauwolfia vomitaria*," Department of Pharmacy, University of Paris, p. 46 (1959).

To settle whether the above isomerization was of the *allo* to *epiallo* type or *vice versa*, we had resort to a new criterion based on the n.m.r. chemical shifts of the $^+$N-CH$_3$ protons of the corresponding methiodide salts. We found that, in analogy with Katritzky's original findings in a series of N-methylquinolizidinium cations,[8] the $^+$N-CH$_3$ protons absorb at lower fields in salts with *cis*-fused C/D rings than in the *trans*-fused analogs. Hence raunitidine must be as in III, and must undergo a conformational change before methylation to yield ultimately IIIa which has a *cis*-fused C/D system. In other words, *it is the conformer with the less hindered nitrogen atom that undergoes methylation.* On the other hand, isoraunitidine must be represented by IV which methylates directly to the quaternary salt IVa. The conversion of raunitidine to isoraunitidine therefore involves an *allo* to *epiallo* isomerization.

To determine the stereochemistry of the C-19 methyl group, two lines of reasoning were used. First, it can be seen that the alkaloids of groups B and D although belonging to the *epiallo* series exist in different conformations, namely, II and IV, so that they can in each case accommodate the C-19 methyl group in the preferred equatorial configuration.

The second criterion is based on the chemical shifts of the C-19 methyl doublets in the n.m.r. spectra after treatment of the free bases with methyl iodide. As can be seen from Table I, the C-19 methyl groups of the methiodide salts experienced a downfield shift in relation to the corresponding free bases, due to the deshielding of the C-methyl protons by the net positive charge on the nitrogen. However, in group C a small upfield shift (~0.015 p.p.m.) was recorded. This apparent anomaly can be explained in terms of the immediate proximity of the C-19 methyl protons in III to Nb which leads to some hydrogen bonding and a consequent diamagnetic shift for the protons in question.

We have now defined the complete stereochemistry of two groups of *allo* and two of *epiallo* heteroyohimbines. The remaining two stereochemical groups are E and F. The alkaloids of group E are now known to be of the *normal* configuration with the C-19 methyl group *alpha* and axial.[1] Hence by a simple process of elimination raumitorine[9] in group F must also be *normal* but with the methyl group *beta* and equatorial.

Acknowledgments.—The authors wish to thank S. B. Penick and Co. for a most generous gift of rauniticine, raunitidine, and isoraunitidine, and Dr. R. Goutarel for providing samples of the rare mayumbine and raumitorine. We are grateful to the National Science Foundation for financial support (Grant No. NSF-G19876).

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(8) A. R. Katritzky, private communication. This work on the stereochemistry of the quinolizidines will appear in the *Journal of the Chemical Society*.

(9) There was insufficient sample of raumitorine for an n.m.r. spectrum, but the infrared spectrum in carbon disulfide solution near 8.4μ clearly indicated this alkaloid to be different from any other heteroyohimbine here discussed.

(10) Recipient of pre-doctoral fellowship No. GF-17,292 from the Division of General Medical Sciences of the National Institutes of Health.

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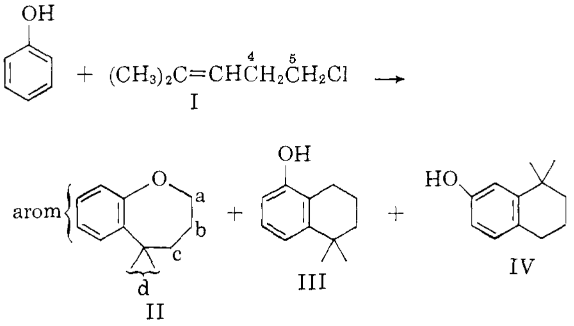
ALKYLATION OF PHENOL WITH A HOMOALLYLIC CHLORIDE

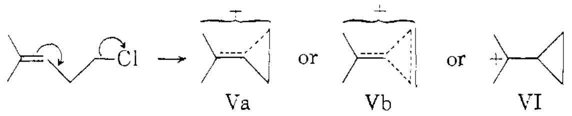
Sir:

We wish to report on the uncatalyzed alkylation of phenol with 5-chloro-2-methyl-2-pentene (I). This reaction has uncommon features among which are the facile formation of a seven-membered cyclic ether and nucleophilic attack only at the primary carbon of a tertiary homoallylic (or cyclopropylcarbinyl) cation.[1]

When I was heated at 150° for several hours with excess (1:4) phenol, hydrogen chloride was evolved.[2] The three 1:1 alkylation products[3] were characterized by infrared, ultraviolet and n.m.r. spectra and by unequivocal independent syntheses.[4] They are 5,5-dimethylhomochroman (II),[5] 1,1-dimethyl-5-tetralol (III) and 1,1-dimethyl-7-tetralol (IV).[10] Neither of the two remaining phenolic isomers of III and IV, nor the anticipated product, *p*-dimethylcyclopropylcarbinylphenol[11] was present.



The orientation in III and IV, with tertiary carbons *meta* rather than *para* to the hydroxyls was at first surprising and suggested that I might ionize in phenol to a homoallylic (V) or dimethylcyclopropylcarbinyl (VI) cation. Nucleophilic attack by the oxygen or *ortho* or *para* carbon of phenol *at the primary* carbon of any of these intermediates would lead ultimately to the only observed products.



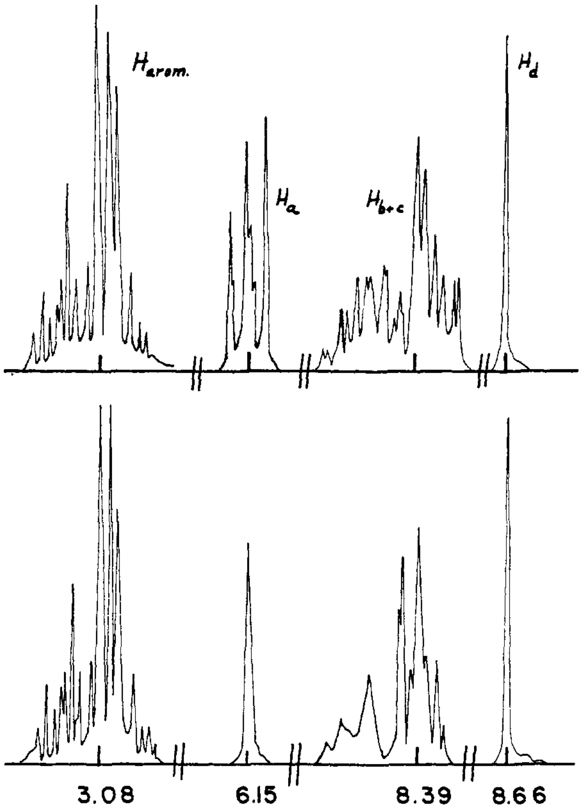


Fig. 1.—N.m.r. spectra of unlabelled II (above) and of II obtained from I-5-d_2 (below), in carbon tetrachloride, scale in τ. The peak at 8.66 τ is at one-tenth the amplitude of the remainder of the spectrum.

To test whether an unsymmetrical (Va) or symmetrical (Vb or VI) intermediate was involved, 5-chloro-2-methyl-2-pentene-5-d_2 was synthesized and subjected to the reaction. The n.m.r. spectra of unlabelled II and of II obtained from labelled I are shown in Fig. 1. Not only is there a change in the relative areas of H_a:H_{b+c}:H_d:H_{arom} from 2:4:6:4 to 1:3:6:4, but H_a which is a triplet in the spectrum of unlabelled II is a singlet in the labelled product (implying that whenever H_a is a CH_2 in labelled II, its neighbor must be CD_2). There can be no doubt that the two methylenes (C_4 and C_5) in I become equivalent during the reaction.[12] The n.m.r. spectra of III and IV from labelled II show similar scrambling.

Additional mechanistic details of this reaction and its general significance in the reaction of nucleophiles with homoallylic systems and in cyclialkylations[13] will be investigated.

Acknowledgments.—We are grateful to the Petroleum Research Fund of the American Chemi-

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[1] For leading references concerning charge distribution in homoallylic and cyclopropylcarbinyl cations, see S. Winstein and E. Kosower, *J. Am. Chem. Soc.*, **81**, 4399 (1959); G. H. Whitham, *Proc. Chem. Soc.*, 422 (1961); R. A. Sneen, K. M. Lewandowski, I. A. I. Taha and B. R. Smith, *J. Am. Chem. Soc.*, **83**, 4843 (1961); M. S. Silver, M. C. Caserio, H. E. Rice and J. D. Roberts, *J. Am. Chem. Soc.*, **83**, 3671 (1961).

[2] No reaction occurred with a saturated analog under similar conditions.

[3] At least 82% yield, formed in comparable quantities. Two very minor products, with 2× and 3× the retention times of the phenols III and IV, probably represent 2:1 alkylation; they were not investigated.

[4] Reaction of I with phenol in acetone containing suspended potassium carbonate gave 5-phenoxy-2-methyl-2-pentene, b.p. 85–90° at 1 mm., $n^{20}\mathrm{D}$ 1.5112 which, with a drop of sulfuric acid gave II, m.p. 47–48°, in nearly quantitative yield. III, m.p. 112.5–113.5°, was obtained from 1,1-dimethyl-5-methoxy-2-tetralone[6] by Wolff–Kishner reduction and hydriodic acid-acetic acid cleavage. IV, m.p. 105–106°, was synthesized by dimethylation of 7-methoxy-2-tetralone[7] with sodium isopropoxide and methyl iodide, Wolff–Kishner reduction and acid cleavage. All compounds gave satisfactory analyses.

[5] The remarkable ultraviolet absorption spectrum[8] and basicity[9] of II prepared in this way has been described.

[6] J. W. Cornforth, R. H. Cornforth and R. Robinson, *J. Chem. Soc.*, 689 (1942).

[7] B. W. Horrom and H. E. Zaugg, *J. Am. Chem. Soc.*, **72**, 721 (1950).

[8] H. Hart and C. R. Wagner, *Proc. Chem. Soc.*, 284 (1958).

[9] E. M. Arnett and C. Y. Wu, *J. Am. Chem. Soc.*, **82**, 5660 (1960).

[10] Identical products are obtained when hydrogen chloride is passed through a heated solution of 2,2-dimethyltetrahydrofuran in phenol.

[11] Expected, because I is converted readily in high yield by aqueous potassium carbonate to dimethylcyclopropylcarbinol; T. A. Favorskaya and Sh. A. Fridman, *Zhur. Obshchei Khim.*, **15**, 421 (1945).

[12] Whether recovered I in an interrupted alkylation shows C_4–C_5 scrambling will be determined.

[13] H. A. Bruson and J. W. Kroeger, *J. Am. Chem. Soc.*, **62**, 36 (1940); H. A. Bruson, F. W. Grant and E. Bobko, *ibid.*, **80**, 3633 (1958); L. R. C. Barclay, J. W. Hilchie, A. H. Gray and N. D. Hall, *Can. J. Chem.*, **38**, 94 (1960).

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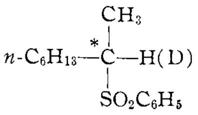
CONFIGURATIONAL STABILITY OF CARBANIONS STABILIZED BY *d*-ORBITALS[1]

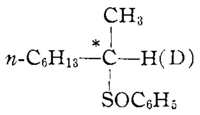
Sir:

In an earlier investigation, the stereochemical course of base-catalyzed hydrogen–deuterium exchange of sulfone I was studied through determination of k_e/k_α, in which k_e was the rate constant for exchange and k_α for racemization. Values of this ratio varied between a high of about 2000 with *tert*-butyl alcohol as solvent to a low of 10 with dimethyl sulfoxide.[2]



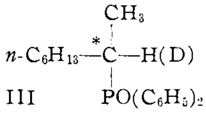
$$\begin{array}{rcl} & CH_3 & \\ & | & \\ n\text{-}C_6H_{13}\text{—} & \overset{*}{C} & \text{—}H(D) \\ & | & \\ & SO_2C_6H_5 & \end{array}$$

I



$$\begin{array}{rcl} & CH_3 & \\ & | & \\ n\text{-}C_6H_{13}\text{—} & \overset{*}{C} & \text{—}H(D) \\ & | & \\ & SOC_6H_5 & \end{array}$$

II



$$\begin{array}{rcl} & CH_3 & \\ & | & \\ n\text{-}C_6H_{13}\text{—} & \overset{*}{C} & \text{—}H(D) \\ & | & \\ & PO(C_6H_5)_2 & \end{array}$$

III

We have now prepared by conventional reactions both diastereomers of sulfoxide II[3] and phosphine oxide III[3] in optically pure states, and have determined approximate values of the ratio of k_e/k_α for the three substances in a number of different solvents (see Table I). Since the configuration at sulfur of IIa and IIb was unaltered during the exchange at carbon, k_α for these compounds actually is associated with the rate at which the systems approached epimeric equilibrium. This was measured by oxidizing each sample to sulfone I, whose rotation and deuterium content were measured by methods previously reported.[2b] With phosphine oxide, the polarimetric rates were measured in a conventional manner, and the deuterium content measured through use of the infrared bands at 10.98 and 14.29 μ present in the deuterated and absent in the undeuterated compounds.

TABLE I

STERIC COURSE OF HYDROGEN-DEUTERIUM EXCHANGE

Compound		Solvent	Base		T, °C.	k_e/k_α
Nat.	Concn. N		Nature	Concn. N		
IIa-h	0.17	$(CH_3)_3COD$[a]	$(CH_3)_3COK$	0.78	60	2
IIa-d	0.17	$(CH_3)_3COH$	$(CH_3)_3COK$	0.79	60	3
IIb-h	0.17	$(CH_3)_3COD$[a]	$(CH_3)_3COK$	0.78	60	3
III-h	0.20	$(CH_3)_3COD$[a]	$(CH_3)_3COK$	0.34	100	3
III-d	0.20	$(CH_3)_3COH$	$(CH_3)_3COK$	0.34	100	3
IIa-d	0.17	$(CH_3)_2SO$[b]	CH_3OK	0.23	60	1
III-d	0.20	$(CH_3)_2SO$[b]	CH_3OK	0.21	75	1
III-h	0.20	$DOCH_2CH_2OD$[a]	$DOCH_2CH_2OK$	0.28	175	1
III-d	0.21	$HOCH_2CH_2OH$	$HOCH_2CH_2OK$	0.29	175	1
III-d	0.21	CH_3OH	CH_3OK	0.30	175	1

[a] 99% deuterated (ref. 1b). [b] 1.2 M in methanol.

Comparison of the steric courses of the exchange reactions of sulfoxides II and phosphine oxide III with that of 2-phenylbutane indicates that the d-orbital containing functional groups exercise even less stereochemical control over the course of the exchange reaction than does a phenyl group.[4] Indeed, the data suggest that what stereospecificity is observed with the sulfoxide and phosphine oxide systems is associated with asymmetric solvation rather than with carbanion asymmetry. This conclusion is in striking contrast to that drawn for sulfone system I, which provided high though differing retention for exchange in all solvents.

Two different hypotheses could account for the difference in behavior of carbanions derived from sulfone I and oxides II and III. (1) Non-stabilized carbanions probably have sp^3 hybridization similar to amines. Carbanions stabilized by d-orbitals might have a tendency to rehybridize to sp^2-p since p-d overlap might be more favorable than sp^3-d overlap. However, many investigators have concluded that d-orbital stabilization of carbanions does not have rigid geometric requirements, although different geometries provide different stabilities.[5] Superimposed on overlap effects are electrostatic effects. In the most favorable conformations, repulsion between the negative charge on carbon and the partial charges on oxygen attached to sulfur or phosphorus would be less for sp^3 than for sp^2-p hybridization at carbon. Thus the overlap and electrostatic effects might oppose one another and a continuous spectrum of configurations at carbon ranging from trigonal to tetrahedral can be envisioned. Possibly no configurational stability is associated with trigonal carbon, whereas

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[1] We are pleased to acknowledge financial support of the research reported here by the National Science Foundation.

[2] (a) D. J. Cram, W. D. Nielsen and B. Rickborn, *J. Am. Chem. Soc.*, **82**, 6415 (1960); (b) D. J. Cram, D. A. Scott and W. D. Nielsen, *ibid.*, **83**, 3696 (1961).

[3] Carbon, hydrogen, sulfur and phosphorus analyses deviated from theory by a maximum of 0.28%. Deuterated IIa, IIb and III contained 97–98% deuterium in the position indicated (combustion analysis and falling drop method by J. Nemeth). Isomer IIa had m.p. 20.5–21.5°, $[\alpha]^{25}_{546}$ −192 ± 3° (*c* 2, 95% ethanol), and isomer IIb was an oil which was separated from IIa by chromatography on silica gel, $[\alpha]^{25}_{546}$ +166 ± 3° (*c* 2, 95% ethanol). These isomers possessed the same configuration at carbon, but differed at sulfur. Compound III possessed m.p. 94–96°, $[\alpha]^{25}_{546}$ −14.7° (*c* 6, carbon tetrachloride). All three compounds were prepared from optically pure 2-octyl tosylate.

[4] In *tert*-butyl alcohol, $k_e/k_\alpha > 10$ for the exchange of 2-phenylbutane-2-*d* [ref. 1a and D. J. Cram, C. A. Kingsbury and B. Rickborn, *J. Am. Chem. Soc.*, **83**, 3688 (1961)].

[5] (a) W. E. Doering and L. K. Levy, *ibid.*, **77**, 511 (1955); (b) H. E. Zimmerman and B. S. Thyagarajan, *ibid.*, **82**, 2505 (1960); (c) R. Breslow and E. Mohacsi, *ibid.*, **83**, 4100 (1961); (d) S. Oae, W. Tagaki and A. Ohno, *ibid.*, **83**, 5037 (1961).