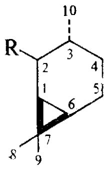
The Chemistry of Terpenes. Part IX. Deamination of the Caranamines.[1]†

By **W. Cocker,*** **D. P. Hanna,** and **P. V. R. Shannon,** Trinity College, Dublin 2, Ireland

The products of deamination of (−)-*trans*-caran-*cis*-2-amine, (−)-*cis*-caran-*trans*-2-amine, (−)-*cis*-caran-*trans*-4-amine, (+)-*cis*-caran-*cis*-4-amine, (−)-*cis*-caran-*trans*-5-amine, and (+)-*cis*-caran-*cis*-5-amine have been isolated, and characterised by using chromatographic, chemical, and spectroscopic techniques. The 2- and the 5-amines yielded products expected from the appropriate cyclopropyl-stabilised carbonium ion, whilst the 4-amines afforded a more complex range of products, including the new compounds, *R*(−)-*trans*-3-(1-hydroxyethyl)-6,6-dimethylbicyclo[3,1,0]hexane and (+)-3β,7,7-trimethyl-*anti*-*cis*-*anti*-tricyclo[4,1,0,0^{2,4}]heptane.

In 1927, K. N. Menon and J. L. Simonsen [2] reported that the deamination of a (+)-caran-2-amine, probably (+)-*trans*-caran-*cis*-2-amine, the enantiomorph of (I; R = β-NH_2),[3] gave a caran-2-ol. Our own interest in carane chemistry, which has led to the synthesis of a number of stereoisomeric caranamines,[3] and the current interest in these amines by other workers,[4,5] prompted us to re-investigate the deamination reaction described above and carry out analogous deaminations of the caranamines mentioned in the summary. The only other deamination in the caranamine series so far described reports [4] uncharacterised products. More rigorous investigations have been carried out [6] in the menthylamine series.



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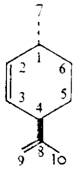

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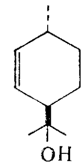

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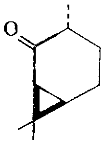

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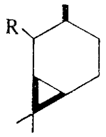

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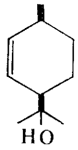

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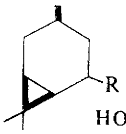

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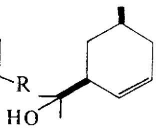

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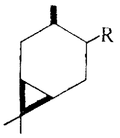

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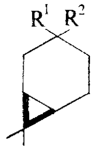

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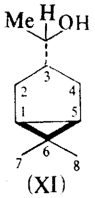

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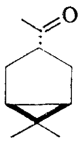

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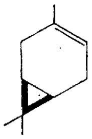

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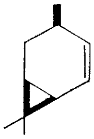

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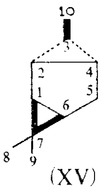

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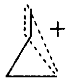

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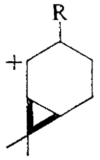

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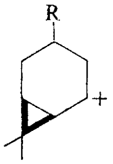

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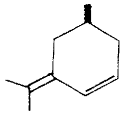

(XIX)

Our deamination reactions were performed under standard conditions, with aqueous solutions of nitrous acid generated from sodium nitrite and sulphuric acid. The products of deamination were estimated qualitatively and quantitatively by analytical g.l.c. with authentic compounds as standards where possible. In most cases, the products were isolated preparatively. Care was taken to avoid dehydration of the alcoholic products on the g.l.c. columns. As a further check, measured amounts of authentic deamination products, both alone and as mixtures, were subjected to g.l.c. under standard conditions. Peak response was as expected and no new products were formed on the column. The yields of products, shown in the Table, are the averages of several experiments.

Products of deamination of caranamines

Amine	Product (%)
(I; R = β-NH_2)	(I; R = α-OH) (14), (I; R = β-OH) (19), (II) (41), (III) (24), and other hydrocarbons (2)
(V; R = α-NH_2)	(V; R = α-OH) (26), (V; β-OH) (21), (VI) (49), and hydrocarbons (4)
(VII; R = α-NH_2)	(VII; R = α-OH) (7), (VII; R = β-OH) (7), (VIII) (81), and hydrocarbons (5)
(VII; R = β-NH_2)	(VII; R = α-OH) (7), (VII; R = β-OH) (7), (VIII) (81), and (+)-car-3- and (−)-*cis*-car-4-ene (5)
(IX; R = α-NH_2)	(IX; R = α-OH) (18), (IX; R = β-OH) (15), (X; R^1 = α-Me; R^2 = β-OH) (7), (X; R^1 = β-Me, R^2 = α-OH) (2), (XI) (12), (XIII) (21), (XIV) (13), and (XV) (8)
(IX; R = β-NH_2)	(IX; R = α-OH) (12), (IX; R = β-OH) (12), (X; R^1 = α-Me, R^2 = β-OH) (14), (X; R^1 = β-Me, R^2 = α-OH) (4), (XI) (14), (XIII) (29), (XIV) (8·5), (XV) (1), and uncharacterised substances (5·5%)

RESULTS

Deamination of (−)-*trans*-caran-*cis*-2-amine (I; R = β-NH_2) [3] gave a product which contained four components (*cf.* ref. 2) of which the major one was (+)-*trans*-*p*-mentha-2,8-diene (II). This was isolated by preparative g.l.c. and proved to be identical in all respects with an authentic specimen.[7] The tertiary alcohol, (+)-*trans*-*p*-menth-2-en-8-ol (III) [7] was also isolated and similarly characterised. The remaining two products were

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† For a brief account see *Tetrahedron Letters*, 1968, 4217.

[1] Part VIII, W. D. P. Burns, M. S. Carson, W. Cocker, and P. V. R. Shannon, *J. Chem. Soc.* (*C*), 1968, 3037.

[2] K. N. Menon and J. L. Simonsen, *J. Indian Inst. Sci.*, 1927, **10**, *A*, 1.

[3] W. Cocker, A. C. Pratt, and P. V. R. Shannon, *J. Chem. Soc.* (*C*), 1968, 484.

[4] A. Hendrich and H. Kuczyński, *Roczniki Chem.*, 1967, **41**, 2107.

[5] H. Kuczyński, K. Piatkowski, A. Hendrich, and A. Kubic, *Tetrahedron Letters*, 1967, 2371.

[6] H. Feltkamp, F. Koch, and T. N. Thank, *Annalen*, 1967, **707**, 95.

[7] W. Cocker, D. P. Hanna, and P. V. R. Shannon, *J. Chem. Soc.* (*C*), 1968, 489.

(+)-*trans*-caran-*trans*-2-ol (I; R = α-OH) and (−)-*trans*-caran-*cis*-2-ol (I; R = β-OH). The former (I; R = α-OH) was, at first, given [8] the β-hydroxyl-configuration, but this was later corrected [9] when its epimer (I; R = β-OH) was prepared and conclusively identified. We subsequently confirmed [7] the configuration of (I; R = β-OH). The earlier workers [8] stated that (+)-*trans*-caran-*trans*-2-ol (I; R = α-OH) was obtained by the aluminium isopropoxide reduction of (+)-*trans*-caran-2-one [(+)-carone], whilst we obtained this dextrorotatory alcohol from (−)-caran-*trans*-2-one (IV). We now confirm that reduction of this ketone (IV) with aluminium isopropoxide gives a mixture of the caran-2-ols, (I; R = α-OH) and (I; R = β-OH) (*cf.* ref. 9), and we have now, for the first time, isolated the former (I; R = α-OH) from the mixture. We have also confirmed the distinction [9] between the hydroxyl-configurations of these alcohols by measurement of the respective α-carbinol-proton band-widths in their n.m.r. spectra. These are 7 c./sec. for (I; R = α-OH) and 12 c./sec. for (I; R = β-OH). Both alcohols on re-oxidation gave (−)-*trans*-caran-2-one (IV).

The deamination of the di-epimeric caranamine, (−)-*cis*-caran-*trans*-2-amine (V; R = α-NH_2), gave a similar range of products, each having the 3β-methyl configuration. The absence of any menthadiene is remarkable, but there is an enhanced yield of the corresponding tertiary alcohol, (−)-*cis*-*p*-menth-2-en-8-ol (VI), which was isolated in 90% purity by preparative g.l.c. Its n.m.r. spectrum showed a 2H singlet at τ 4·33 (2- and 3-olefinic hydrogens), two 3H singlets at τ 8·85 and 8·89 (oxisopropyl group), a 3H doublet at τ 9·03 (*J* 6 c./sec.; 7-methyl group), and a singlet at τ 6·42, removed by D_2O (hydroxy-group). The 2,3-position of the double bond was confirmed by a band at 728 cm.$^{-1}$ (*cis*-CH=CH) in its i.r. spectrum.

Dehydration of the alcohol (VI) gave (g.l.c.) a single hydrocarbon, catalytic hydrogenation of which afforded a mixture of *p*-cymene and *cis*- and *trans*-*p*-menthanes, which were identified by g.l.c. comparisons with authentic specimens.[10] No *m*-menthanes were present. The only remaining structural uncertainty in (VI) was at C-1, but the anticipated *cis*-β-methyl configuration was confirmed by the fact that it was resolved on a capillary g.l.c. column from its C-1 epimer (III).[7]

The remaining two significant products, namely (−)-*cis*-caran-*trans*-2-ol (V; R = α-OH) and (−)-*cis*-caran-*cis*-2-ol (V; β-OH) were isolated by preparative g.l.c. and identified by spectroscopic and g.l.c. comparisons with authentic compounds.[11,12] The very small amounts of hydrocarbons found amongst the deamination products were not further investigated.

Deaminations of (−)-*cis*-caran-*trans*-5-amine (VII; R = α-NH_2) and (+)-*cis*-caran-*cis*-5-amine (VII; R = β-NH_2) each gave products analogous to those obtained from the 2-amines. Thus the major products were (−)-*cis*-*m*-menth-4-en-8-ol (VIII), (−)-*cis*-caran-*trans*-5-ol (VII; R = α-OH) and (+)-*cis*-caran-*cis*-5-ol (VII; R = β-OH). They were all isolated by preparative g.l.c. and their identities confirmed by spectroscopic and g.l.c. comparisons with authentic compounds.[11,13]

Deaminations of (−)-*cis*-caran-*trans*-4-amine (IX; R = α-NH_2) and (+)-*cis*-caran-*cis*-4-amine (IX; R = β-NH_2) afforded eight significant deamination products. Appreciable amounts of (−)-*cis*-caran-*trans*-4-ol (IX; R = α-OH) and (+)-*cis*-caran-*cis*-4-ol (IX; R = β-OH) were formed. These compounds were separately isolated from the mixture by chromatography on alumina followed by preparative g.l.c., and were identified by spectroscopic and g.l.c. comparisons with authentic specimens.[11] It is appropriate to mention that the *cis*-4-ol (IX; R = β-OH), with the greater intramolecular hydroxy-group protection [12] is the less strongly bound on the alumina. The tertiary alcohols (+)-*trans*-caran-*cis*-3-ol (X; R^1 = α-Me; R^2 = β-OH), and (+)-*cis*-caran-*trans*-3-ol (X; R^1 = β-Me; R^2 = α-OH) were also isolated and found to be identical in all respects with authentic specimens kindly provided by Dr. P. J. Kropp.[14] We also obtained (+)-*trans*-caran-*cis*-3-ol (X; R^1 = α-Me; R^2 = β-OH) (*endo*-OH) as the sole product (g.l.c.) of the oxymercuration of (+)-car-3-ene followed by reduction of the mercurial, by the method of Brown *et al.*[15] These workers hydrated a number of bicyclic olefins by the oxymercuration method and obtained alcohols having an *exo*-hydroxy-group. However, the reaction is not always so highly specific.[16] We envisage the oxymercuration of car-3-ene as involving attack of mercuric acetate on the less hindered α-side of the double bond and attack of water on the opposite side (*cf.* ref. 17).

The other alcohol isolated from the deamination products of the caran-4-amines was the previously undescribed *R*(−)-*trans*-3-(1-hydroxyethyl)-6,6-dimethylbicyclo[3,1,0]hexane (XI). It was obtained pure from (IX; R = α-NH_2) after careful chromatography on alumina followed by preparative g.l.c.; starting, however, from (IX; R = β-NH_2) the alcohol was contaminated with (X; R^1 = α-Me; R^2 = β-OH) and could not be obtained in greater than 89% purity. Its n.m.r. spectrum which suggested a symmetrical structure, showed the expected *gem*-dimethyl singlet at τ 9·05, a doublet (*J* 6 c./sec.) at τ 8·95 (side-chain methyl), and an obscured multiplet at 8·9—9·28 (cyclopropyl protons). In addition there was a broad signal at

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[8] A. Hendrich and H. Kuczyński, *Roczniki Chem.*, 1965, **39**, 7.

[9] S. P. Acharya and H. C. Brown, *J. Amer. Chem. Soc.*, 1967, **89**, 1925.

[10] W. Cocker, P. V. R. Shannon, and P. A. Staniland, *J. Chem. Soc. (C)*, 1966, 946.

[11] W. Cocker, P. V. R. Shannon, and P. A. Staniland, *J. Chem. Soc. (C)*, 1967, 485.

[12] M. S. Carson, W. Cocker, D. H. Grayson, A. C. Pratt, and P. V. R. Shannon, *J. Chem. Soc. (B)*, 1968, 1136.

[13] W. Cocker, P. V. R. Shannon, and P. A. Staniland, *J. Chem. Soc. (C)*, 1967, 915.

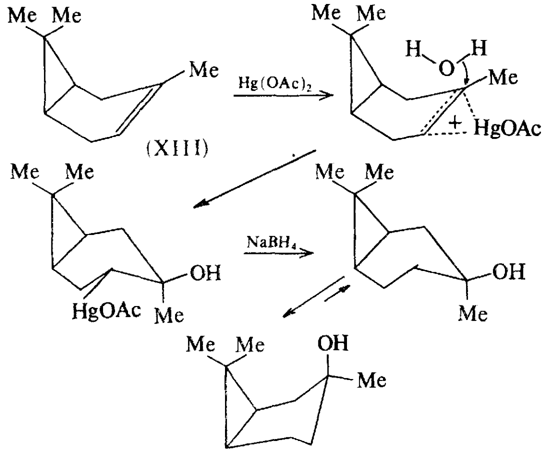
[14] P. J. Kropp, *J. Amer. Chem. Soc.*, 1966, **88**, 4926.

[15] H. C. Brown and P. Geoghegen, *J. Amer. Chem. Soc.*, 1967, **89**, 1522; H. C. Brown, J. H. Kawakami, and S. Ikegami, *J. Amer. Chem. Soc.*, 1967, **89**, 1524.

[16] M. Johnson and B. Rickborn, *Chem. Comm.*, 1968, **18**, 1073.

[17] H. B. Henbest and B. Nicholls, *J. Chem. Soc.*, 1959, 227.

τ 8·2—8·36 derived from the four equivalent methylene hydrogens and one hydroxyl-proton, which was exchanged with deuterium oxide; the α-carbinol-proton gave a quintet at τ 6·6 (J 6 c./sec.) resulting from effectively equal coupling with four adjacent protons. This grouping was confirmed by oxidation of the alcohol (XI) to the optically inactive ketone (XII), which showed a maximum at 1704 cm.$^{-1}$ in its i.r. spectrum, a signal at τ 9·02 (*gem*-dimethyl groups) and a new 3H singlet at τ 7·96 (MeCO) in its n.m.r. spectrum. No skeletal rearrangement took place during the oxidation for the original alcohol (though presumably optically inactive) was regenerated quantitatively (g.l.c.) on reduction with lithium aluminium hydride.



(X; R¹=α—Me, R²=β—OH)

The mass spectrum of the alcohol (XI) was in accord with its structure. It showed m/e 154 (M^+), 136 ($M^+ - H_2O$) (54%), 121 ($M^+ - [H_2O + Me]$) (96%) and a base peak at 93 corresponding to loss of the *gem*-dimethylcyclopropyl (Me_2CH)-ring system and water. Our experience with other members of the carane series has been that cleavage of this cyclopropyl system characteristically involves loss of 43 units.

The hydroxyethyl side-chain is assigned the *trans*-configuration to the cyclopropyl ring since there is only a very small n.m.r. deshielding (*ca.* 1 c./sec.) in pyridine of the two *gem*-dimethyl signals which coincide in carbon tetrachloride. Models indicate that the less stable *cis*-arrangement should give a large (*ca.* 16 c./sec.) deshielding for the nearest of the *gem*-dimethyl groups to the carbinol grouping as, for example, in borneol and isoborneol [18a] and related systems.[18b]

The symmetrical ketone (XII) displayed ions at m/e 152 (M^+) (15%), a base peak at 109 ($M^+ - MeCO$ and/or $M^+ - Me_2CH$), and an intense peak at 43 ($MeCO^+$ and/or Me_2CH^+).

A racemic form of the alcohol (XI), with unspecified configuration at C-3, has been obtained [19] by treatment of car-3-ene dibromide with silver oxide in water giving the ketone [(XII), configuration at C-3 unspecified], followed by reduction of this with lithium aluminium hydride.

The hydrocarbon products of the caran-4-amine deaminations contained (+)-car-3-ene (XIII) and (—)-*cis*-car-4-ene (XIV).[11] However a third, highly volatile, dextrorotatory hydrocarbon was also, with difficulty, isolated by preparative g.l.c. It showed only end-absorption (ε 252 at 2300 Å) in the u.v. region, whilst its n.m.r. spectrum, measured at 100 Mc./sec., showed no olefinic hydrogen or vinylic methyl group resonances. It was thus probably tricyclic. Its n.m.r. spectrum (100 Mc./sec.) displayed a methyl doublet at τ 9·05, two methyl singlets at τ 8·97 and 9·11, a saturated methylene signal (2H) at τ 8·21, and cyclopropyl resonances (5H) between τ 8·91 and 9·65. This spectrum strongly suggested the skeleton of the hydrocarbon (XV) which was confirmed by its mass spectrum. This displayed ions at m/e 136 (M^+), 107 ($M^+ - MeCH_2$), and 93 ($M^+ - Me_2CH$) (base peak). The loss of $MeCH_2$ (29 units) from the methylcyclopropane ring is evidently an analogous process to the cleavage of the *gem*-dimethylcyclopropane ring which leads to the loss of Me_2CH (43 units).

Dreiding models indicate that a *cis*-arrangement of the two cyclopropyl rings is prohibited. The original β-configuration of the 3-methyl group is retained since C-3 is unlikely to participate in the formation of the new hydrocarbon. In any case the β-methyl configuration has fewer steric interactions than its epimer. All available evidence suggests that the new hydrocarbon is (+)-3β,7,7-trimethyl-*anti*-*cis*-*anti*-tricyclo[4,1,0,0^{2,4}]heptane (XV).

DISCUSSION

Caran-2-and 5-amines.—Earlier work [20] on the cyclopropylcarbinyl cation has shown that when formed by deamination, partial equivalence of the methylene groups takes place involving a non-classical ion (XVI), or a rapidly equilibrating series of classical carbonium ions. The carbonium ions (XVII) and (XVIII), derived from the caran-2- and 5-amines respectively, may analogously exist, and these might be expected to be precursors of general rearrangements of the carane skeleton. Nonetheless it has been shown [21] that ring-opening of the cyclopropyl carbinyl cation, derived by protonation of the corresponding carbinol, occurs specifically towards the carbon atom which, by nature of its substituents, can best delocalise a positive charge. Indeed our own experiments [7] involving the acid-catalysed rearrangements of the analogous caranols, (—)-*trans*-caran-*cis*-2-ol (I; R = β-OH) and (+)-*cis*-caran-*cis*-5-ol (VII;

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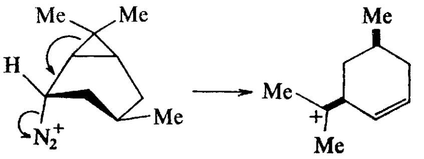
[18] (*a*) C. R. Narayanan, N. R. Bhandane, and M. R. Sarma, *Tetrahedron Letters*, 1968, 1561; (*b*) P. V. Demarco, E. Farkas, D. Doddrell, B. L. Mylari and E. Wenkert, *J. Amer. Chem. Soc.*, 1968, **90**, 5480.

[19] H. Kuczyński and M. Walkowicz, *Roczniki Chem.*, 1964, **38**, 1625; *Chem. Abs.*, 1965, **62**, 9176.

[20] R. H. Mazur, W. N. White, D. A. Semenov, C. C. Lee, M. S. Silver, and J. D. Roberts, *J. Amer. Chem. Soc.*, 1959, **81**, 4390.

[21] H. M. Walborski and L. Plonsker, *J. Amer. Chem. Soc.*, 1961, **83**, 2138.

R = β-OH) have confirmed that the major pathway in the rearrangement of the cyclopropyl carbinyl cations thus formed, involves the breakage of the 1,7- or 6,7-bonds respectively.



However, the properties of carbonium ions produced by deamination are frequently significantly different from those formed by other methods.[22] It was therefore imperative to show that the *trans-p*-menthadiene (II) and its accompanying alcohol (III), the *cis-p*-menthenol (VI), and the *m*-menthenol (VIII), formed in the deamination of the 2- and 5-amines, were not artifacts of the accompanying respective caranols (I; R = α-, β-OH), V; R = α- and β-OH), and (VII; R = α-, β-OH) (*cf.* ref. 7). Although the pH of the deamination mixture is initially sufficiently low to promote this rearrangement, after all the nitrite is added to the amine salt, the pH (3·5) is such that the rearrangement does not then occur.[7] This was readily demonstrated by the recovery, unchanged, of the caranols (V; R = α-OH) and (VII; R = α-OH) after treatment with the deaminating solution at pH 3·5. The primary origin of the menthadiene and menthenols was confirmed by the fact that when the amines (I; R = β-NH$_2$) and (VII; R = β-NH$_2$) were added to a preformed mixture of sodium nitrite and sulphuric acid, the proportion of menthadiene and menthenol was comparable to that obtained when the nitrite was added last.

There is also no evidence of the formation of caranol from menthadiene under deamination conditions. Both (+)-*trans-p*-mentha-2,8-diene (II) and (+)-*m*-mentha-3(8),4-diene (XIX)[7] were recovered unchanged after treatment with nitrite and sulphuric acid.

Deamination of the 5-amines leads predominantly to rearranged products, whilst (—)-*trans*-caran-*cis*-2-amine (I; R = β-NH$_2$) and (—)-*cis*-caran-*trans*-2-amine (V; R = α-NH$_2$) afford over 60% and *ca.* 50% rearranged products respectively.

Both electronic and steric factors may be involved in these rearrangements. The latter would be expected to favour the rearrangement of a trigonal cyclic carbonium ion, for release of strain would ensue from migration of the carbonium ion to the side-chain. This factor would probably have a similar effect on both the 2- and the 5-carbonium ions. However, the electronic factors operating on these differ. Thus, the inductive effect of the adjacent 10-methyl group is likely to depress the rearrangement of a 2-carbonium ion by opposing the drift of electrons to it from the cyclopropane ring. A similar effect on a 5-carbonium ion will be considerably reduced and thus there will be larger amounts of unrearranged products from the 2- than the 5-amines. The formation of equal amounts of the epimeric caran-5-ols may stem from the equal facility of approach of water molecules along quasi-axial and quasi-equatorial paths (*cf.* ref. 12) to a common carbonium ion at C-5. Similar remarks may be made about the formation of the 2-ols. There is, however, a slight preference in the case of the 2-amines for the formation of the caranols having the *trans*-arrangement of 2-hydroxy- and 3-methyl groups but the differences may be within experimental error. It should be noted that whilst the preferred alcohol has the more stable configuration, in which the hydroxy-group is quasi-equatorial,[12] there is no evidence of equilibration about C-2 in the caranols of either type (I) or type (V) under deamination conditions. In any case, product-development control would lead to considerably greater preference for the more stable epimer.

A further point to be considered, is that the diazonium ions derived from the caran-*trans*-2- and *trans*-5-amines may undergo concerted ring-rearrangement, with loss of nitrogen. In these ions the C–N$_2^+$ bond is approximately *trans-anti*-parallel to the 1,7- and 6·7-bonds respectively, assuming that the diazonium ions have the conformations of their amines.[3] There is, however, no compelling evidence (see Table) to suggest that this is a major operative factor.

Caran-4-amines.—On deamination, these amines (IX; R = α-, β-NH$_2$) form carbonium ions which must be less affected by the cyclopropane ring than the carbonium ions derived from the 2- and the 5-amines. It was therefore expected that on deamination, they would give a more complex range of products than the 2- and 5-amines. Assuming similar conformations for the epimeric 4-amines and their respective diazonium ions, the latter would in each case be equatorial, though in the case of (IX; R = β-NH$_2$) the ring system would be in the boat form.[3]

The formation of approximately equal amounts of the caran-4-ols (IX; R = α, β-OH) from both *cis*- and *trans*-amines suggests a common carbonium ion and equal facility of attack on it by solvent molecules. As expected, the initially formed 4-carbonium ion rearranges to the more highly substituted 3-carbonium ion, from which the caran-3-ols (X; R^1 = α, β-Me; R^2 = β, α-OH) are derived. It is significant that the yields of 3β-ol are *ca.* three times those of its epimer. This suggests product-development control, since, unless the hydroxy-group is solvated, this has a smaller conformational energy than the methyl group.[23] However, attempts to equilibrate either one or other of the 3-ols under deamination conditions or with 2N-sulphuric acid were unsuccessful, though some dehydration took place with sulphuric acid.

(+)-Car-3-ene (XIII) is derivable from the 3-carbonium ion and the 4-carbonium ion or its diazonium ion. (—)-*cis*-Car-4-ene (XIV) is derivable from both of the last two ions.

The formation of the tricyclic hydrocarbon (XV) may be portrayed as a 1,3-migration of electrons from

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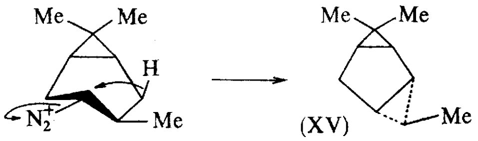
[22] A. Streitwieser, *J. Org. Chem.*, 1957, **22**, 861.

[23] E. L. Eliel, *Angew. Chem. Internat. Edn.*, 1965, **4**, 761.

C-2 to C-4 in either the 4-carbonium ion or diazonium ion. The geometry is more favourable for this in the 4-*trans*-diazonium ion, derived from (IX; R = α-NH_2), than in the ion derived from (IX; R = β-NH_2). The experimental results suggest that this geometrical factor may have some significance. The skeletal rearrangement is unlikely to involve C-3, and thus its configuration remains unchanged.

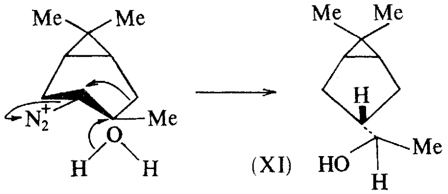


(XV)

It was expected[24] that a Demjanov rearrangement would play some part in the course of the deamination to give the skeleton of the cyclopentyl carbinol (XI). Both caran-4-amines afford an appreciable quantity of this compound. There is no certainty that the carbinol is optically pure, but at least we know that one configuration predominates for (XI) to have optical activity. We are reasonably certain that (XI) is configurationally pure at C-3; its n.m.r. spectrum (see above) indicates this, and, furthermore the specimen of (XI), derived from (IX; R = α-NH_2), gives only a single peak on several (including capillary) g.l.c. columns.

Loss of nitrogen from the diazonium salt of the 4α-amine can take place by a concerted reaction to give (XI) with the *trans*-arrangement of side-chain and cyclopropane ring, since the geometry of the molecule is favourable for this reaction.

Such a concerted reaction is, however, very unlikely to take place with the epimeric diazonium salt in which (in both extreme conformations) the geometry is unfavourable. It seems therefore that, at least in the case of the deamination of (IX; R = β-NH_2), a carbonium ion formed at C-4 in the carane molecule is attacked by electrons of the C(2)–C(3) bond so as to give the more thermodynamically stable *trans*-arrangement of side-chain with respect to the cyclopropane ring.



(XI)

Rearward attack of water at C-3 of the carane molecule, synchronous with the breaking of the C(2)–C(3) bond and formation of the five-membered ring, must on deamination of both caran-4-amines afford the *R*-configuration at the chiral carbinol centre. This is confirmed by the application of Horeau's[25] reaction to (XI).

EXPERIMENTAL

I.r. spectra were measured on a Perkin-Elmer 137 Infracord spectrophotometer with liquid films unless otherwise stated. U.v. spectra were measured in ethanol on a Unicam SP 800 spectrophotometer. N.m.r. spectra were recorded on a Perkin-Elmer R10 instrument at 60 Mc./sec. with carbon tetrachloride as solvent; optical rotations were measured on a Perkin-Elmer automatic polarimeter 147, with chloroform as solvent. Analytical g.l.c. was carried out at 140—150° on 10 ft. Carbowax 20M, and 10 ft. Castorwax columns with an Aerograph 600 apparatus. Preparative g.l.c. was carried out with an Aerograph Autoprep A700 apparatus. The silica-gel used was Merck's Kieselgel, 0·05—0·2 mm., and the alumina was Merck's neutral, activity 1 brand.

Deamination Conditions.—The amines were, in each case, purified by preparation of an appropriate salt,[3] from which the amine was liberated immediately before use.

The following were the general deamination conditions employed. Amine (1 mol.) was added dropwise to stirred, ice-cold 2N-sulphuric acid (3 mol.) to give a solution of pH *ca.* 0·4. A solution of sodium nitrite (6 mol.) in water (10 c.c. for 2·71 g. nitrite) at 0° was then added dropwise during 0·5—1 hr. (pH then 3·5), and stirring was continued for a further 9 hr. at 0°. The mixture (pH then 4·9) was extracted with ether (2 × 20 c.c.) and the extract was washed with water and dried; it gave a pale yellow oil which was examined by g.l.c. The aqueous solution, basified and extracted with ether afforded unchanged amine (up to 10%).

(−)-*trans*-Caran-*cis*-2-amine (I; R = β-NH_2) (5 g.; $[\alpha]_D^{20}$ −56·5°, *c* 1·4)[3] treated with 2N-sulphuric acid (49·05 c.c.) and sodium nitrite (13·55 g.) in water (50 c.c.) afforded a deamination product (4 g.) consisting (g.l.c. on Castorwax at 145°) of (+)-*trans-p*-mentha-2,8-diene (II), (+)-*trans-p*-menth-2-en-8-ol (III), (−)-*trans*-caran-*cis*-2-ol (I; R = β-OH), and (+)-*trans*-caran-*trans*-2-ol (I; R = α-OH) eluted in this order. Separated by preparative g.l.c. (20 ft. by $\frac{3}{8}$ in. Carbowax at 160°), the diene (II) had $[\alpha]_D^{21}$ +192·1° (*c* 0·33), n_D^{21} 1·4676, identical on g.l.c. and in its i.r. and n.m.r. spectra with an authentic specimen.[7] The tertiary alcohol (III) had $[\alpha]_D^{20}$ +95·3° (*c* 1·2), n_D^{20} 1·4750 and was also identical in other respects with an authentic specimen.[7]

(−)-*trans*-Caran-*cis*-2-ol (I; R = β-OH) had $[\alpha]_D^{22}$ −55·4° (*c* 0·7), n_D^{22} 1·4828, identical on g.l.c., and its i.r. and n.m.r. spectra with a sample prepared by the published method.[9] Its epimer, (+)-*trans*-caran-*trans*-2-ol (I; R = α-OH) had $[\alpha]_D^{22}$ +14·5° (*c* 0·47), τ 6·39 (C*H*OH), 8·1 (OH, removed by D_2O), 8·96 and 9·04 (gem-dimethyl groups and methyl doublet) and 9·15 and 9·4 (cyclopropyl protons) (see below). It was identical on g.l.c. and in its i.r. spectrum, and similar in its $[\alpha]_D$ and n.m.r. spectrum with the synthetic specimen described below.

Reduction of (−)-trans-*Caran-2-one* (IV) *with Aluminium isopropoxide* (cf. *ref.* 8, 9).—A solution of freshly distilled aluminium isopropoxide (4 g.), in anhydrous propan-2-ol (100 c.c.), was warmed to 50° and the ketone [IV; $(\alpha)_D^{20}$ −137° (*c* 2·6)][2,3] (3 g.) was slowly added with stirring. The temperature was slowly raised until propan-2-ol distilled through a 3 ft. air-condenser at 6 c.c. per hr., and then maintained at this for 7 hr. Propan-2-ol was periodically added to replenish loss. The solution was poured into water (600 c.c.) and extracted with ether (3 × 100 c.c.); the extract was washed with water (3 × 50 c.c.) and dried

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[24] C. K. Ingold, 'Structure and Mechanism in Organic Chemistry,' Bell, London, 1953, 486.

[25] A. Horeau, *Tetrahedron Letters*, 1961, 506; 1962, 965; A. Horeau and H. B. Kagan, *Tetrahedron*, 1964, **20**, 2431; A. Marquet and A. Horeau, *Bull. Soc. chim. France*, 1967, 124.

to give a pale yellow oil (2 g.). Analytical g.l.c. (Castorwax at 150°) revealed the presence of (−)-*trans*-caran-*cis*-2-ol (I; R = β-OH) (36%) and its epimer (I; R = α-OH) (44%) eluted in this order, with unchanged ketone (IV) (19%), and another ketone. The caranols (I; R = β- and α-OH) were isolated by preparative g.l.c. (20 ft. by $\frac{3}{8}$ in. Carbowax at (150°). (−)-*trans*-Caran-*cis*-2-ol had $[\alpha]_D^{20}$ −57·5° (*c* 0·4) and was identical in its i.r. and n.m.r. spectra with an authentic specimen.[9] Its 3,5-*dinitrobenzoate* consisted of silvery plates (MeOH), m.p. 125° (lit.,[8] 115—116° for its enantiomer), $[\alpha]_D^{22}$ −55·7° (*c* 1·4 in $CHCl_3$) (lit.,[8] +56·6° for its enantiomer), $\nu_{max.}$ (Nujol) 1718, 1608, 1546, 1458, 1342, 1294, 1271, 1174, 1094, 1073, 1018, 978, 952, 925, 913, 889, 774, 730, and 719 cm.$^{-1}$, τ ($CDCl_3$) 0·86 (ArH), 4·80 (CHOCOR), 7·84 (CH_2), 8·97 (d, *J* 6 c./sec., Me), 8·77 and 9·02 (s, Me_2C), and 9·07 (cyclopropyl H) (Found: C, 58·3; H, 6·25; N, 8·0. $C_{17}H_{20}N_2O_6$ requires C, 58·6; H, 5·8; N, 8·0%). (+)-trans-*Caran*-trans-2-*ol* (I; R = α-OH) had $[\alpha]_D^{20}$ +12·1° (*c* 0·6), $\nu_{max.}$ 3333, 2924, 2857, 1453, 1441, 1399, 1368, 1339, 1309, 1256, 1129, 1107, 1058, 1046, 1024, 978, 938, 896, 844, 804, 772, 753, and 718 cm.,$^{-1}$ τ 6·4 (C*H*OH), 7·05 (O*H*, removed by D_2O), 8·96 and 9·04 (*gem*-dimethyl groups and methyl doublet), and 9·15 and 9·4 (cyclopropyl protons). It was pure by analytical g.l.c. Its 3,5-*dinitrobenzoate* consisted of silvery flakes (MeOH), m.p. 92°, $[\alpha]_D^{24}$ +9·2° (*c* 1·27), $\nu_{max.}$ (Nujol) 1724, 1629, 1543, 1449, 1340, 1277, 1174, 1099, 1089, 1071, 1013, 988, 923, 914, 884, 769, 730, and 719 cm.$^{-1}$ (Found: C, 58·5; H, 5·8; N, 8·0. $C_{17}H_{20}N_2O_6$ requires C, 58·6; H, 5·8; N, 8·0%). This ester (20 mg.) was stirred with aqueous 20% sodium hydroxide (1 c.c.) at room temperature overnight. Ether (10 c.c.) was added and the extract was washed with water (2 × 2 c.c.) and dried. Removal of solvent gave a single alcohol (*ca.* 5 mg.), $[\alpha]_D^{20}$ +12·5° (*c* 0·15) unresolved by analytical g.l.c. on Carbowax at 150° from (+)-*trans*-caran-*trans*-2-ol obtained by the deamination route.

Oxidation of (+)-trans-*Caran*-trans-2-*ol* (I; R = αOH).—This alcohol (30 mg.) in ether (1 c.c.) was stirred with sodium dichromate (40 mg.), sulphuric acid (30 mg.), and water (1 c.c.). After 2 hr. the ether layer was collected, washed, and dried and gave the ketone (IV) (22 mg.), $[\alpha]_D^{22}$ −143° (*c* 0·7) as a single product identical with authentic ketone on g.l.c. and in i.r. spectrum.

(−)-*cis*-Caran-*trans*-2-amine (V; R = α-NH_2) was deaminated (*a*) on a micro-scale with pure material[3] and the product was analysed by g.l.c., and (*b*) with 1·5 g. (70% pure by g.l.c.) when a pale yellow oil (1 g.) was isolated. In (*a*) three main peaks were revealed on Castorwax at 134°, consisting of (−)-*cis*-*p*-menth-2-en-8-ol (VI), (−)-*cis*-caran-*cis*-2-ol (V; R = β-OH),[12] and (−)-*cis*-caran-*trans*-2-ol (V; R = α-OH),[11] eluted in this order. The product from (*b*) was submitted to preparative g.l.c. (20 ft. by $\frac{3}{8}$ in. Carbowax at 140°). There was some overlapping of peaks but, by taking cuts over a small range, (−)-cis-p-*menth*-2-*en*-8-*ol* (VI) was isolated having $[\alpha]_D^{20}$ −47·3° (*c* 0·54 in PhH), $\nu_{max.}$ 3254, 2950, 1965, 1645, 1453, 1362, 1304, 1272, 1209, 1139, 1114, 1089, 1022, 987, 965, 939, 918, 900, 849, 805, 791, 770, 727, and 692 cm.$^{-1}$. This alcohol was not resolved from (+)-*trans*-*p*-menth-2-en-8-ol (III) on ordinary g.l.c. columns, but resolution was affected at 72° on a 170 ft. capillary column coated with diethyleneglycol succinate. The ratio of retention times, *trans*/*cis* = 0·98. Also isolated from (*b*) by preparative g.l.c. was (−)-*cis*-caran-*cis*-2-ol (V; R = β-OH) identical in g.l.c. and in its i.r. spectrum with an authentic specimen,[9] and (−)-*cis*-caran-*trans*-2-ol (V; R = α-OH), $[\alpha]_D^{22}$ −31·7° (*c* 0·8) (lit.,[11] gives −34°), identical in other respects with an authentic specimen.[11]

Dehydration of (−)-cis-p-*Menth*-2-*en*-8-*ol* (VI).—This alcohol (7·1 mg.) in benzene (1·3 c.c.) was heated under reflux for 1 hr. with toluene-*p*-sulphonic acid (4 mg.) to give a single hydrocarbon product (g.l.c. on Castorwax). It was hydrogenated over 5% palladised charcoal (20 mg.) to give a mixture (g.l.c. on Carbowax at 130°) containing *cis*-(15%)[10] and *trans*-*p*-menthane (35%),[10] and *p*-cymene, identical with authentic specimens.

(−)-*cis*-Caran-*trans*-5-amine (VII; R = α-NH_2) (0·5 g., $[\alpha]_D^{20}$ −29·7°, *c* 0·85)[3] gave a pale yellow deamination product (0·35 g.). G.l.c. on Castorwax at 150° revealed four peaks corresponding to (−)-*cis*-*m*-menth-4-en-8-ol (VIII), (+)-*cis*-caran-*cis*-5-ol (VII; R = β-OH), and (−)-*cis*-caran-*trans*-5-ol (VII; R = α-OH), eluted in this order. All were unresolved from authentic specimens (refs, 7, 11, 13 and see below).

(+)-*cis*-Caran-*cis*-5-amine (VII; R = β-Me) (7 g., $[\alpha]_D^{20}$ +51·7°. *c* 0·9),[3] on deamination gave a pale yellow oil (4·5 g.), b.p. 23—55°/0·4 mm. Unchanged amine (0·6 g.) was recovered. Analytical g.l.c. on Castorwax at 155° revealed five components (see Table). These were separated by preparative g.l.c. (20 ft. by $\frac{3}{8}$ in. Carbowax at 145°), eluted in the following order: (+)-car-3- (XIII) and (−)-*cis*-car-4-ene (XIV), identified by analytical g.l.c. and spectroscopy, with authentic specimens, (−)-*cis*-*m*-menth-4-en-8-ol (VIII), m.p. 51°, $[\alpha]_D^{22}$ −10·5° (*c* 0·4),[13] (+)-*cis*-caran-*cis*-5-ol (VII; R = β-OH), $[\alpha]_D^{22}$ +45·1° (*c* 0·4)[11,13] of 91% purity (g.l.c. on Castorwax at 150°), (−)-*cis*-caran-*trans*-5-ol (VII; R = α-OH), $[\alpha]_D^{22}$ −20·4° (*c* 0·38)[11,13] as an oil of 85% purity (g.l.c.).[11,13]

Effect of Deamination Conditions on (−)-cis-*Caran*-trans-5-*ol* (VII; R = α-OH) *and on* (−)-cis-*Caran*-trans-2-ol (V; R = α-OH).—Sodium nitrite (2·71 g.) in water (10 c.c.) was slowly added to stirred 2N-sulphuric acid (9·8 c.c.) kept at 0°. (−)-*cis*-Caran-*trans*-5-ol[11,13] (1 g.) was then slowly added and the mixture was stirred overnight at 0°. The product (0·7 g.), collected in ether, consisted only of the starting alcohol (g.l.c.). Similarly, (−)-*cis*-caran-*trans*-2-ol was unaffected by the deaminating reagents.

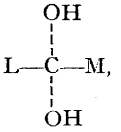
(−)-*cis*-Caran-*trans*-4-amine (IX; R = α-NH_2) (20 g., b.p. 35°/0·5 mm., $[\alpha]_D^{20}$ −75·3°, *c* 0·85),[3] on deamination gave a neutral product (15 g.) which on analytical g.l.c. (Castorwax at 150°) showed eight major peaks corresponding to (+)-3β,7,7-trimethyl-*anti*-*cis*-*anti*-tricyclo(4,1,0,0,^{2,4}]-heptane (XV), (−)-*cis*-car-4-ene (XIV), (+)-car-3-ene (XIII), (+)-*cis*-caran-*trans*-3-ol (X; R^1 = β-Me, R^2 = α-OH), (+)-*trans*-caran-*cis*-3-ol (X; R^1 = α-Me, R^2 = β-OH), R(−)-*trans*-3-(1-hydroxyethyl)-6,6-dimethylbicyclo-[3,1,0]hexane (XI), (+)-*cis*-caran-*cis*-4-ol (IX; R = β-OH), and (−)-*cis*-caran-*trans*-4-ol (IX; R = α-OH), eluted in this order. Unchanged amine (IX: R = α-NH_2) (1·5 g.) was recovered. The most minor component (X; R^1 = β-Me, R^2 = α-OH) was identified by g.l.c. comparison with an authentic sample.[14]

Distillation of the crude, neutral deamination product gave a colourless hydrocarbon fraction (5·6 g.), b.p. 25—35°/0·5 mm. and an alcoholic fraction (6·2 g.), b.p. 30—70°. A residue (3·2 g.) was left. On analytical g.l.c. (Castorwax at 150°), the hydrocarbon fraction showed three major peaks corresponding to (XV), (XIV), and (XIII) eluted in this order. Preparative g.l.c. (20 ft. by $\frac{3}{8}$ in.

Carbowax at 90°) afforded (+)-3β,7,7,-trimethyl-*anti*-*cis*-*anti*-tricyclo[4,1,0,0,^{2,4}]heptane (XV), $[\alpha]_D^{20}$ +73·65° (*c* 0·26), n_D^{22} 1·4563, $\nu_{max.}$ 3003, 2924, 2857, 1447, 1368, 1318, 1292, 1259, 1205, 1190, 1176, 1120, 1079, 1055, 1046, 979, 952, 943, 884, 862, 815, 776, and 706 cm.$^{-1}$ It gave a single peak on g.l.c. (Carbowax at 140°). (−)-*cis*-Car-4-ene (XIV), $[\alpha]_D^{20}$ −143° (*c* 0·5), n_D^{20} 1·4650,[11] unresolved from authentic material on g.l.c., and identical with it in i.r. and n.m.r. spectra, and (+)-car-3-ene (XIII), $[\alpha]_D^{20}$ +14·3° (*c* 0·75) were also isolated.

The alcohol fraction (5 g.) was chromatographed on neutral alumina (200 g., Merck, activity 1) with light petroleum (b.p. 40—60°) with increasing amounts of ether as solvent. (+)-*cis*-Caran-*cis*-4-ol (IX; R = β-OH) and minor products were first eluted by solvent containing up to 70% ether. This alcohol, purified by preparative g.l.c. had $[\alpha]_D^{20}$ +47·4°, n_D^{20} 1·4838,[11] and was identical in g.l.c. and in its i.r. and n.m.r. spectra with authentic material. After this a mixture of (+)-*trans*-caran-*cis*-3-ol (X; R^1 = α-Me, R^2 = β-OH) [14] and (*R*) (−)-*trans*-3-(1-hydroxyethyl)-6,6-dimethylbicyclo[3,1,0]hexane (XI) and (−)-*cis*-caran-*trans*-4-ol (IX; R = α-OH) [11] was eluted. These were separated by preparative g.l.c. (20 ft. by $\frac{3}{8}$ in. Carbowax at 140°) with 200 μl. injections. The 3-ol (X; R^1 = α-Me, R^2 = β-OH), m.p. 68°, $[\alpha]_D^{22}$ +13·4° (*c* 0·35) was identical in g.l.c., and in its i.r., and n.m.r. spectra with those of an authentic specimen.[14] (*R*)-(−)-trans-3-(1-*Hydroxyethyl*)-6,6-*dimethylbicyclo*[3,1,0]*hexane* (XI) was obtained as colourless needles, m.p. 48° (lit.,[19] 44—46° for a racemic specimen), $[\alpha]_D^{22}$ −14·83° (*c* 0·3), $\nu_{max.}$ 3333, 2924, 2882, 1445, 1368, 1299, 1290, 1263, 1209, 1185, 1121, 1099, 1067, 998, 964, 885, 846, and 795 cm.$^{-1}$, (*cf.* ref. 19).

Configuration of the Carbinol Group in (XI).—*Horeau's method* (*with* M. S. CARSON). The method described in ref. 12 was used. Only one determination of configuration was possible because of shortage of material, but the method was checked with (−)-*cis*-caran-*trans*-4-ol (IX; R = α-OH). The alcohol (XI) (11·6 mg.) was treated in pyridine (0·5 c.c.) with (±)-α-phenylbutyric anhydride (60 mg.) and the product was worked up as in ref. 12. The sign of the unchanged acid was (+), the esterification yield was 68%, and optical yield was 21%. These data indicate that the absolute configuration at the asymmetric centre is



$$\mathrm{L{-}\overset{\displaystyle OH}{\underset{\displaystyle OH}{C}}{-}M}$$

i.e. (*R*)-configuration.

trans-3-*Acetyl*-6,6-*dimethylbicyclo*[3,1,0]*hexane* (XII).—A stirred solution of the above alcohol (38 mg., 97% purity) in ether (1 c.c.) was slowly treated with a solution of sodium dichromate (45 mg.), water (1 c.c.), and sulphuric acid (35 μl.). Stirring was continued for 12 hr. when 97% conversion (g.l.c.) to ketone had taken place. Ether (5 c.c.) was added, the mixture was stirred, and the ether layer was separated. After washing with 5% sodium hydrogen carbonate (2 × 1 c.c.), and water (1 c.c.), the required ketone was obtained as an oil (96% purity; g.l.c. on Carbowax at 150°), $[\alpha]_D$ 0°, n_D^{22} 1·4631 (*cf.* ref. 19), $\nu_{max.}$ 3021, 2941, 2874, 1704, 1543, 1449, 1420, 1368, 1351, 1284, 1248, 1212, 1179, 1163, 1124, 1089, 1038, 1020, 980, 943, 842, and 795 cm.$^{-1}$, (*cf.* ref. 19) τ 7·4 (m, C*H*COCH$_3$), 7·96 (s, COC*H*$_3$), 8·27 (m, 4H, methylene protons), 8·7—9·13 (m, cyclopropyl protons), and 9·02 (s, *gem*-dimethyls) (Found: C, 78·4, 78·6; H, 10·7, 10·9. Calc. for $C_{10}H_{16}O$: C, 78·9; H, 10·6%). This ketone (4·7 mg.) in ether (0·5 c.c.), carefully treated with lithium aluminium hydride (15 mg.) was then stirred for 1 hr. The product was unresolved on g.l.c. (Carbowax at 140°) from the alcohol (XI).

(+)-*cis*-Caran-*cis*-4-amine (IX; R = β-NH$_2$) (19 g.) on deamination afforded a product (5 g.), b.p. 60°/0·5 mm. which was chromatographed as described for the products of (IX; R = α-NH$_2$). The alcohol (XI) was isolated in 89% purity (g.l.c.), $[\alpha]_D^{22}$ −17·0° (*c* 0·2 in CCl$_4$), τ (CCl$_4$) 8·95 (d, *J* 6 c./sec.) and 9·05 (s, *gem*-dimethyls). On addition of pyridine the *gem*-dimethyl groups gave signals at 9·04 and 9·06.

Oxymercuration of (+)-*Car*-3-*ene* (XIII) (*cf.* ref. 15).—(+)-trans-*Caran*-cis-3-*ol* (X; R^1 = α-Me, R^2 = β-OH). (+)-Car-3-ene (5 g.) was added to a mixture of mercuric acetate (12·76 g.), water (40 c.c.), and tetrahydrofuran (40 c.c.), and the mixture was stirred for 7 hr. when it had become colourless. Sodium hydroxide (3N; 40 c.c.) was slowly added, followed by sodium borohydride (0·76 g.) in sodium hydroxide (3N, 40 c.c.). Mercury was very quickly deposited, the aqueous layer was separated, it was saturated with sodium chloride, and extracted with ether (2 × 150 c.c.). The ether layer, washed several times with water and dried, gave a red oil (3·5 g.) consisting of (+)-*trans*-caran-*cis*-3-*ol* (40%) and (+)-car-3-ene (60%) (g.l.c. on Castorwax at 160°). The former (X; R^1 = α-Me, R^2 = β-OH), isolated by preparative g.l.c. (Carbowax at 180°) had m.p. 69°, $[\alpha]_D^{20}$ +13·2° (*c* 0·41), (*cf.* ref. 14) identical in g.l.c. (Carbowax at 160°), and in its i.r. spectrum with an authentic specimen, τ 7·98 (s, O*H* removed by D$_2$O), 8·28 (m, CH$_2$), 8·81 (obscured m, CH$_2$), 8·86 (s, 10 Me), 8·95 (s, *gem*-dimethyls) and 9·51 (m, cyclopropyl protons). This was identical with the n.m.r. spectrum of a specimen supplied by Dr. Kropp.[14]

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