Over temperature ranges of 0° to reflux conditions the results were the same. With sodium hydrosulfite again denitroguanylation was the main effect observed. However, with the acid reducing agents, a different reaction appeared to take place. Thus, 16 g. of stannous chloride was dissolved in 14 ml. of concentrated hydrochloric acid and 3.66 g. of 3,5-dimethyl-1-nitroguanylpyrazole was added. On heating, the pyrazole went into solution and a yellow color developed. After standing for 3 days without the deposition of any material the solution was adjusted to the correct *p*H, and the tin present removed as sulfide. The filtrate, after evaporation deposited a white solid, which after separation from some further inorganic contaminant by solution in absolute ethanol, formed a picrate of m.p. 202–204°. The yield was small (*ca.* 20%). After recrystallization from water, the picrate was obtained as fine yellow needles of m.p. 209°. It was found to be 3,5-dimethyl-1-guanylpyrazole picrate. *Anal.* Calcd. for $C_{12}H_{13}N_7O_7$: C, 39.2; H, 3.7; N, 26.7. Found: C, 39.6; H, 3.7; N, 26.2.

The reaction product between crotonaldehyde and nitroaminoguanidine was shown to be a hydrazone by acid (dil. HCl) hydrolysis. Cyclization attempts using the Nisbet,[17,18] technique, of acetic acid–water mixtures effected a characteristic color development (deep brown) with the crotonylnitroguanylhydrazone, which did not take place with crotonaldehyde, nitroaminoguanidine, acetonenitroguanylhydrazone, benzylidenenitroaminoguanidine, cinnamylidine or crotonylaminoguanidine nitrates, but no pyrazoline was isolated from the colored solution.

Hydrazinolyses and Ammonolyses of 3,5-Dimethyl-1-nitroguanylpyrazole.—Ammonia or hydrazine hydrate afford 90% yields of nitro- or nitroaminoguanidines, respectively, when heated in ethanolic solution in 1-molar quantities with 1-molar quantities of the nitroguanylpyrazole. The remaining experiments are summarized in Table II. The following two examples illustrate the general methods employed.

(a) **Reaction with Phenylhydrazine.**—To a solution of 3 g. of 3,5-dimethyl-1-nitroguanylpyrazole in 90 ml. of absolute ethanol was added 1.7 ml. of phenylhydrazine. The solution was then refluxed for 1.5 hours, during which time it became orange colored. During the heating, a white solid gradually separated out, which after recrystallization from aqueous ethanol melted at 164° and proved to be 1-phenylamino-3-nitroguanidine[16] (yield 1.73 g.). On dilution of the filtrate with water, an orange-colored solid separated which on recrystallization from aqueous ethanol melted at 143°[16] (yield was *ca.* 0.15 g.). The nature of this substance is unknown. 3,5-Dimethylpyrazole was identified when the aqueous diluted filtrate was extracted with ether and the ethereal extracts evaporated. It was characterized by its picrate and silver salt.

When 2,4-dinitrophenylhydrazine in acetic acid solution was refluxed with an equimolar quantity of 3,5-dimethyl-1-nitroguanylpyrazole for 90 minutes and the solution then diluted, 2,4-dinitrophenylhydrazine acetate of m.p. 193° separated. *Anal.* Calcd. for $C_8H_{10}N_4O_6$: C, 37.2; H, 3.8; N, 21.6. Found: C, 37.3; H, 3.5; N, 21.6. No hydrazinolysis was observed in this case.

(b) **Reaction with Thiosemicarbazide.**—To 2 g. of 3,5-dimethyl-1-nitroguanylpyrazole dissolved in 30 ml. of absolute ethanol was added 1.0 g. of thiosemicarbazide dissolved in 25 ml. of water. The solution was refluxed for 90 minutes and on allowing to cool overnight some unchanged pyrazole (0.70 g.) was deposited. From the filtrate, after evaporation in a current of air, 1.30 g. of solid of m.p.'s *ca.* 120° and (major portion) *ca.* 166° separated. On extraction with absolute ether 0.30 g. of 3,5-dimethylpyrazole was obtained in the extracts. The residual 0.90 g. of solid was recrystallized repeatedly from water and obtained as a fine, white powder of m.p. 182–183° (with violent explosion). It proved to be 1-thioureido-3-nitroguanidine[16]; yield 70%.

3,5-Dimethyl-1-nitroguanylpyrazole was recovered unchanged from 1 hour refluxing with either 5-aminotetrazole or *p*-toluenesulfonhydrazide. With benzalaminoguanidine an anomalous reaction resulted.

Acknowledgment.—The authors wish to acknowledge the assistance of Mr. A. C. Coleman, M.Sc., in the preliminary part of the work.

CORK, IRELAND

(17) H. J. Nisbet, *J. Chem. Soc.*, 1237 (1938).

(18) H. J. Nisbet and C. G. Gray, *ibid.*, 839 (1933).

[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

The Structure of Camphenamine[1]

BY EUGENE E. VAN TAMELEN, WILLIAM F. TOUSIGNANT AND PAUL E. PECKHAM

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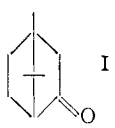
On the basis of previously known as well as newly acquired evidence, the structure 7-aminocamphene (VIII) is proposed for the liquid base camphenamine; the latter is ordinarily obtained by dehydrohalogenating chlorocamphanamine (IV), the reaction product of phosphorus pentachloride and α-aminoborneol (III) (hydrochloride). The stereochemical relationships of α-aminoborneol, the diastereoisomeric β-aminoborneol, and camphenamine have been deduced by means of: (i) acyl migration studies on the aminoalcohols; (ii) the transformation of β-aminoborneol to camphenamine; and (iii) the inertness of N-*p*-nitrobenzoyl-β-aminobornyl tosylate toward strong base. N-*p*-Nitrobenzoyl-α-aminoborneol has been shown to afford N-*p*-nitrobenzoylcamphenamine on treatment with thionyl chloride; the corresponding derivative of β-aminoborneol interacts with this same reagent to yield the cyclic imide derived from N-*p*-nitrobenzoyl-β-bornylsulfurous acid.

In an effort to elaborate a synthetic route to epicamphor (I), Duden and his collaborators[2] carried out, at the turn of the present century, a reaction sequence starting with the reduction of α-aminocamphor (II). The action of sodium and ethanol

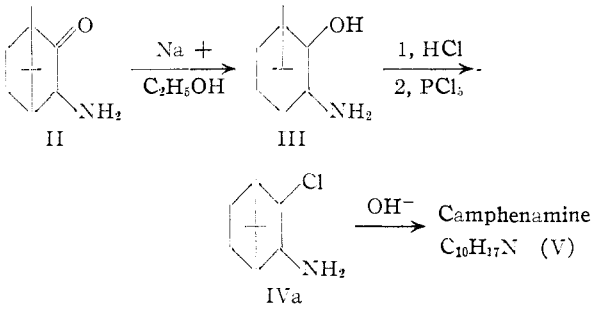


I

led to an aminoalcohol, which was designated as "α-aminoborneol" (III) to distinguish it from a diastereoisomer, "β-amino borneol" (IIIa), formed when the reduction was carried out by means of sodium and wet ether. Oxidation of each aminoborneol regenerated α-aminocamphor, thereby confirming the assigned structure III. Phosphorus pentachloride converted the hydrochloride of α-aminoborneol to "chlorocamphanamine" (IV), which was regarded as the 2,3-chloroamine (IVa). Finally, this chloroamine, on treatment with an equivalent of aqueous sodium hydroxide or simply on heating in aqueous solution, was transformed into a halogen-free base (b.p. 205–207° at 748 mm.)

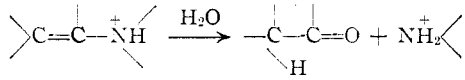
(1) Abstracted in part from research reports submitted by W. F. Tousignant and P. E. Peckham in partial fulfillment of the requirements for the Master of Science degree, University of Wisconsin.

(2) P. Duden and A. E. Macintyre, *Ann.*, **313**, 59 (1900).



which possessed the molecular formula $C_{10}H_{17}N$ and for which Duden proposed the name "camphenamine" (V). The base exhibited unsaturation in that it absorbed two moles of hydrogen bromide and was oxidized by dilute permanganate. Evaporation of camphenamine with excess concentrated hydrochloric acid regenerated chlorocamphanamine (IV); the *solid* hydrochloride, on the other hand, could be distilled without decomposition. Two structural possibilities for camphenamine were entertained,[2,3,4] mainly on the basis of the above findings: bornylene imine (VI) and 3-aminobornylene (VII). The former was soon effectively excluded[5] by the demonstration that camphenamine exhibited the characteristic reactions of a primary amine. Thus structure VII for camphenamine was accepted by Duden, in spite of the fact that it could not be transformed on treatment with ni-

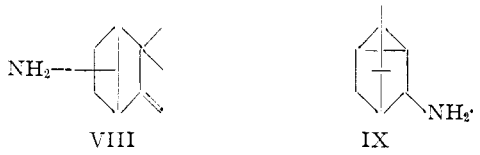
trous acid to epicamphor, as he had anticipated. In view of the facile hydrolysis of eneamine hydrohalides to the parent carbonyl compounds,[6] a hydrochloride of structure VII would, as a matter of



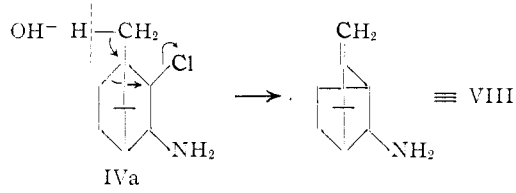
fact, be expected *not* to add hydrogen chloride, but to undergo hydrolysis with the formation of epicamphor. Actually, the Curtius or Lossen degradation of bornylene-3-carboxylic acid[7] affords epicamphor directly and almost certainly by the intermediate formation and hydrolysis of 3-aminobornylene (VII); this observation satisfactorily confirms an instability for VII which excludes it as a possible structure for camphenamine.

In order to obtain camphenamine for the purposes of a closer investigation, we have attempted to repeat Duden's work and find all the steps readily reproducible, save one. Numerous attempts to reduce α-aminocamphor to α-aminoborneol according to Duden's directions were unavailing—only colored oils were obtained. Extensive modification, involving change of reaction time and inverse addition of aminocamphor, finally led to the desired crystalline product in fair yield. The identity of each of these bases as well as that of β-aminoborneol was confirmed by the preparation of suitable, known derivatives.

We have considered two alternate structures for camphenamine: (i) 7-aminocamphene (VIII), formed from IV by a Wagner–Meerwein rearrangement; and (ii) 3-aminotricyclene (IX), a distinct[8] but perhaps less likely possibility. Structure IX can be excluded because it does not exhibit absorp-



tion at 12.4–12.5 μ in the infrared; as Roberts has shown,[9] authentic tricyclenes absorb strongly in this region. Furthermore, we have corroborated the unsuitability of VI by means of the infrared spectrum of N-*p*-nitrobenzoylcamphenamine (X); the presence of N–H stretching bands at 2.87 μ constitutes unmistakable evidence for the primary nature of the original amino group. Insofar as 7-aminocamphene (VIII) is concerned, we feel that the previously recorded and the presently uncovered pieces of evidence establish it as a unique vehicle for the chemistry of camphenamine. Thus, the ready conversion of chlorocamphanamine to VIII is paralleled by the action of aqueous base or even boiling water[10] on isobornyl chloride, a process



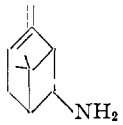
which produces camphene. Structure VIII accommodates the presence of camphenamine's double bond, which was confirmed by the absorption of bromine as well as the reduction of permanganate by its N-*p*-nitrobenzoyl derivative. The stability of camphenamine hydrochloride under conditions which promote pyrolysis of many basic terpenes[11] to an olefin and ammonium chloride, is understandable on the basis of VIII; a double bond cannot form without violation of Bredt's rule, and no obvious course for pyrolysis with rearrangement to a stable diene is available. Moreover, the regeneration of chlorocamphanamine from camphenamine appears to exclude all reasonable struc-

(3) P. Duden and A. E. Macintyre, *Ber.*, **33**, 477 (1900).
(4) W. Marckwald, *ibid.*, **33**, 765 (1900).
(5) P. Duden and A. E. Macintyre, *ibid.*, **33**, 481 (1900).
(6) M. E. Herr and F. W. Heyl, THIS JOURNAL, **74**, 3627 (1952).
(7) J. Bredt and W. H. Perkin, Jr., *J. Chem. Soc.*, **103**, 2182 (1913).
(8) H. Meerwein and R. Wortman, *Ann.*, **435**, 190 (1924).
(9) J. D. Roberts, E. R. Trumbull, Jr., W. Bennett and R. Armstrong, THIS JOURNAL, **72**, 3116 (1950).
(10) J. Kachler, *Ann.*, **197**, 104 (1879).
(11) Some of the terpene bases which exhibit this type of behavior are: 2-amino-α-fenchane and 2-amino-β-fenchane, N. J. Toivonen, V. Alfthan, L. H. Böök, M. I. Erich and E. K. Heino, *J. prakt. Chem.*, [2], **159**, 70 (1941); 6-aminocamphene, S. Nametkin and A. Zabrodin, *Ber.*, **61**, 1491 (1928); dihydrocarvylamine, O. Wallach, H. Kruse and F. Kerkhoff, *Ann.*, **275**, 125 (1893). On the other hand, those hydrohalides which, for steric reasons, cannot form a double bond without rearrangement, distil undecomposed: *cf.* carylamine, A. Baeyer, *Ber.*, **27**, 3488 (1894); fenchylamine, O. Wallach, *Ann.*, **272**, 106 (1893).

tures[12] but VIII; addition of hydrogen chloride to camphene, yielding isobornyl chloride *via* rearrangement of camphene hydrochloride, provides a reliable precedent. The infrared spectrum of camphenamine clearly reveals the RR'C=CH_2 portion of structure VIII in that distinct absorption bands appear at 6.02 and 11.35 μ.[13] Analogous bands are exhibited by camphene itself; in fact, the high degree of similarity between the entire spectra of camphene and camphenamine constitutes good confirmation for the structure of the latter. N-*p*-Nitrobenzoylcamphenamine (X), like camphene,[14] was only slowly attacked by N-bromosuccinimide and then only in the presence of benzoyl peroxide and ultraviolet light. This result is consistent with the absence of a non-bridgehead allylic hydrogen, a structural feature demanded by VIII. Finally, alternate partial syntheses of camphenamine support the proposed structure. The *p*-bromobenzenesulfonate of N-*p*-nitrobenzoyl-α-aminoborneol (XI), on short warming with alcoholic sodium hydroxide, furnished N-*p*-nitrobenzoylcamphenamine (X). Since *both* IV and XI (the structure of which is beyond question) lead to the amide X, IV is probably a correct representation of the chloroamine; and therefore the reaction of phosphorus pentachloride with III cannot involve any deep-seated, unexpected change.[15] N-*p*-Nitrobenzoyl-α-aminoborneol itself, on treatment with thionyl chloride, was converted to X, a result which brings to mind the well-known dehydration of borneol or isoborneol to camphene. Thus, taken altogether, the parallelism between the reactions and properties of camphenamine on the one hand and authenticated transformations of known terpenes on the other, leaves little doubt that VIII represents the correct structure of this base.

After the evidence described had been satisfactorily accommodated, we turned our attention to the more challenging question of the stereochemical nature of camphenamine and related bases. Because no inversions on C-3 should be involved in converting an aminoborneol to camphenamine, the former was selected as a starting point for investigations which, if successful, would automatically define the stereochemistry of the latter base.

(12) A base such as 6-amino-α-pinene would no doubt also afford a

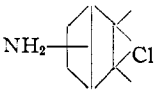


chlorocamphanamine (IV) on treatment with hydrogen chloride (*cf.* the transformation of α-pinene to bornyl chloride). However, the *formation* of such a structure or any other strained ring system from IV, appears highly unlikely.

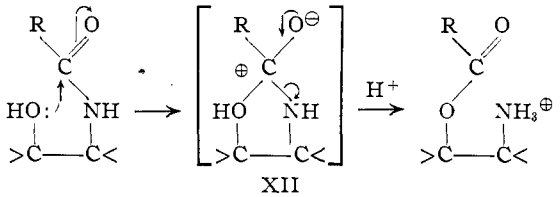
(13) H. W. Thompson and D. H. Whiffen, *J. Chem. Soc.*, 1412 (1948).

(14) J. D. Roberts and E. R. Trumbull, THIS JOURNAL **71**, 1630 (1949). In contrast to camphene, the amide X yielded no pure product on treatment with N-bromosuccinamide.

(15) The less likely (*cf.* the instability of camphene hydrochloride; H. Meerwein and K. van Emster, *Ber.*, **55**, 2500 (1922)) "camphenamine hydrochloride" structure has not been excluded; however, the realization of this possibility would not alter the essential arguments presented in this paper.



The first problem attacked was the steric relationship of the hydroxyl and amino substituents in both α- and β-aminoborneols. From the several methods available for such determinations[16a,b] we selected that involving N → O acyl migration



XII

In this technique, the particular 1,2-amidoalcohol (of an epimeric pair) which leads to the more strained cyclic intermediate XII, undergoes acyl exchange at the slower rate. Thus an amide derived from a *trans*-2-aminocycloalkanol will ordinarily rearrange more slowly than that from the *cis* isomer.[16b] In point of fact, the *p*-nitrobenzamide of α-aminoborneol (XIII) was almost quantitatively recovered after 24 hours contact with dry hydrogen chloride in refluxing dioxane. Therefore the α-isomer is assigned the *trans* configuration. The same derivative (XIV) of β-aminoborneol, on mere saturation in dioxane solution with hydrogen chloride, afforded the migration product, β-aminobornyl *p*-nitrobenzoate hydrochloride (XV), in 91% yield. The structure of the salt was proved by its reversion, on addition of aqueous base, to the parent amide by means of an O → N migration. The *cis* configuration can be confidently assigned, then, to β-aminoborneol.

None of the results described so far in this account sheds any clear light on the relationship of the hydroxyl or amino group to the remainder of the bicyclic system. Because of the element of uncertainty regarding the skeletal structure of chlorocamphanamine (ref. 15), deductions based on its chemistry, although possible, would not be entirely convincing and therefore will not be considered at this stage. Although there can be no doubt about the structures of N-*p*-nitrobenzoyl-α-aminoborneol (XIII) and its *p*-bromobenzenesulfonate (XI), the stereochemistry of the conversion of either substance to N-*p*-nitrobenzoylcamphenamine is beset with ambiguity. It is tempting to conclude that, because each, like isobornyl chloride (*exo*),[17] undergoes the Wagner–Meerwein shift with relative ease, the hydroxyl or brosyloxy group must have the *exo* configuration. However, the displacement of either anion may well be assisted by the *p*-nitrobenzamido group, which is properly oriented (*trans*) for neighboring group participation; a molecular model shows that the *p*-nitrobenzamido system is sufficiently flexible to allow an optimum backside approach by the oxygen of the carbonyl.[18,19] The increase in reaction rate due to the latter effect might be of such magnitude in this instance that, even though the incipient anion is not

(16) (a) G. E. McCasland and E. C. Horswill, THIS JOURNAL, **73**, 3744 (1951); (b) E. E. van Tamelen, *ibid.*, **73**, 5773 (1951).

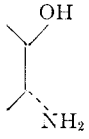
(17) Bornyl chloride, which as the *endo* configuration, is considerably more stable. See A. Riban, *Ann. chim.*, [5] **6**, 6 (1875), and also ref. 21.

(18) S. Winstein, E. Grunwald, R. E. Buckles and L. Hanson, THIS JOURNAL, **70**, 816 (1948).

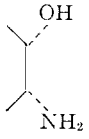
(19) S. Winstein and R. Boschan, *ibid.*, **72**, 4669 (1950).

favorably oriented for the Wagner–Meerwein shift, the reactivity would approximate that of an isobornyl arylsulfonate[20]; and an erroneous assignment of configuration would therefore be made. Because of these difficulties we have sought more reliable evidence from independent systems.

Clarification of the stereochemical relationships was forthcoming in a study of compounds in the β-aminoborneol series. The hydrochloride of this *cis* base afforded a significant yield of camphenamine on treatment with phosphorus pentachloride followed by dehydrohalogenation. As emphasized before, epimerization of the amino group would not be expected to take place during these steps, and therefore this group must have the same configuration relative to the endomethylene bridge in *both* α-aminoborneol (XVIa) and β-aminoborneol (XVIb).[21] Valid evidence for the exact nature of

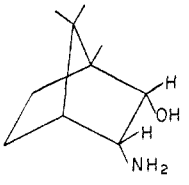


XVIa

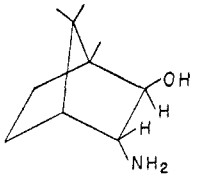


XVIb

the hydroxyl group was gained in observing the behavior of N-*p*-nitrobenzoyl-β-aminobornyl *p*-toluenesulfonate (XVII) toward base. After being refluxed for one hour in alcoholic sodium hydroxide, XVII was recovered unchanged. Because the tosyloxy and *p*-nitrobenzamido groups are *cis*, no participation of the latter can occur in the transition state (or intermediate state) of a tosyloxy displacement reaction. Therefore the marked inertness of XVII must reflect the character of the tosyloxy group *per se;* the latter (and therefore the hydroxyl group in β-aminoborneol) must then be *endo*, as it is in the relatively unreactive bornyl tosylate.[20] With this evidence at hand, the complete stereochemical structures of the two aminoborneols are elucidated: β-aminoborneol can be described as 3-*endo*-aminoborneol (XVIII), and α-aminoborneol is therefore 3-*endo*-aminoisoborneol (XIX). The amino group of camphenamine must bear, then, the

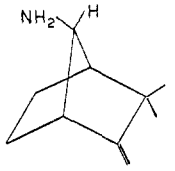


XVIII



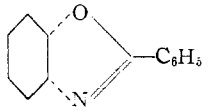
XIX

endo relationship to the substituted ethylene bridge, as represented in XX.[22]

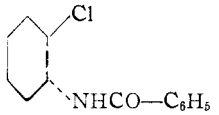


XX

It is appropriate at this point to discuss in some detail the course of the reaction of thionyl chloride with α- and β-N-*p*-nitrobenzoylaminoborneols. The nature of this reagent's action on *cis*- and *trans*-2-benzamidocyclohexanols has been previously reported.[23] The *trans* isomer cyclizes with inversion at the carbinol carbon to the *cis*-oxazoline (XXI), whereas the *cis* isomer merely suffers displacement of hydroxyl by halogen, affording *trans*-2-benzamidocyclohexyl chloride (XXII). In the case of the *cis*- and *trans*-aminoborneols, *neither* of these paths is followed. Earlier in the present account, it was



XXI



XXII

reported that N-*p*-nitrobenzoyl-α-aminoborneol (the *trans* isomer) led to N-*p*-nitrobenzoylcamphenamine on treatment with thionyl chloride; none of the oxazoline to be expected on the basis of the *trans* formulation was isolated. Apparently in the competition between the two neighboring groups—the No. 6 carbon atom and *p*-nitrobenzamido—the former ultimately wins out, although the latter may well assist in the expulsion of the hydroxyl group.

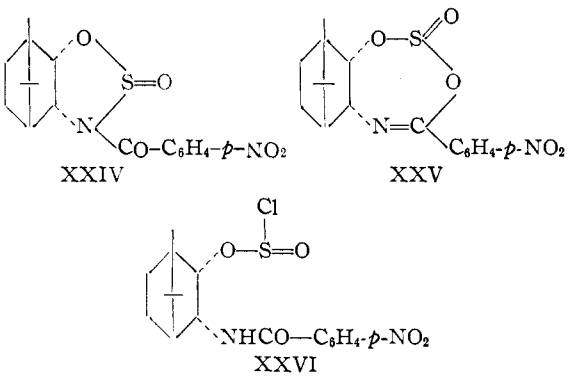
Turning to N-*p*-nitrobenzoyl-β-aminoborneol, we find that thionyl chloride converts it in fair yield to a sulfur-containing solid (XXIII), m.p. 169.5–170.5°, whose analysis corresponds to the formula $C_{17}H_{20}N_2O_5S$. Two possible structures, XXIV and XXV, for this substance come to mind, each presumably formed by the intramolecular elimination of hydrogen chloride from the intermediate N-*p*-nitrobenzoyl-β-aminobornyl chlorosulfinate (XXVI). Similar heterocyclic systems fused to the isocamphane rather than the camphane skeleton we consider unlikely, because the configuration of the amino group prevents the formation of any such structure. Moreover, initiation of the rearrangement route would be expected to terminate with the formation of N-*p*-nitrobenzoylcamphen-

(20) S. Winstein, *et al.*, THIS JOURNAL, **74**, 1127 (1952).

(21) This relationship would not necessarily follow from the fact that the aminoborneol isomers are obtained from a common parent (α-aminocamphor); the decided inhomogeneity of the latter[2] as well as the possibility of enolization of C-3 weaken the validity of such a conclusion.

(22) It may be well to point out in passing that if the structure IVa be accepted for chlorocamphanamine (IV), then the halogen in that molecule is better considered as *exo*. The free amino group—whether it be *cis* or *trans*—cannot readily assist in the release of halogen by means of neighboring group participation. The *cis* relationship is obviously unfavorable.[18] In the *trans* form, the four atomic centers (N–C–C–Cl) do not lie in a single plane; therefore the halogen cannot undergo effective rearward displacement by nitrogen. Thus the activity of the halogen in IV, if *endo*, should approximate that of cyclohexyl chloride[20]; this does not accord with the facts. Since inversion at C-3 is improbable, the structure IVa can be defined more completely as 3-*endo*aminoisobornyl chloride. Assignment of the *exo* configuration to the halogen means then that III (hydrochloride) must have undergone displacement by phosphorus pentachloride *with retention of configuration;* on the other hand, *cis*- and *trans*-2-aminocycloalkanol hydrochlorides undergo reaction *with inversion*,[27] yielding epimeric 2-aminocycloalkyl chlorides. However, the behavior of III in this respect is not unprecedented, because isoborneol (*exo*) yields—without inversion—isobornyl chloride on treatment with this same reagent[19] (see E. Jünger and A. Klages, *Ber.*, **29**, 544 (1896)). Such a course is clearly explicable by C-6 displacement of, for example, a tetrachlorophosphate ester, followed by addition *cum* rearrangement of chloride ion to camphene or an equivalent. The latter addition, as is well-known, affords isobornyl chloride rather than bornyl chloride.[15]

(23) W. S. Johnson and E. N. Schubert, THIS JOURNAL, **72**, 2187 (1950).



amine (X), as in the α-aminoborneol case. The hydrolysis of XXIII by warm alcoholic sodium hydroxide regenerated N-*p*-nitrobenzoyl-β-aminoborneol. To distinguish between possibilities XXIV and XXV, we attempted a similar hydrolysis under much milder conditions, *viz.*, standing in aqueous acetone solution for 12 hours. XXIII was then recovered quantitatively. This result favors XXIV, since XXV should exhibit (assuming the system R-O-SO-O-R to exhibit halide reactivity, as does aryl sulfonate) the reactivity of aromatic iminohalides (R—N=C(X)—Ar), which are instantly hydrolyzed by cold water to the parent amide and hydrochloric acid.[24] Furthermore, the infrared spectrum of XXIII (Fig. 1a), in addition to having no N-H stretching bands, exhibits carbonyl absorption which is very similar to that of authentic *p*-nitrobenzamides (*e.g.*, Fig. 1b); a substance possessing structure XXV might be expected to show a single, sharper peak at a somewhat higher wave length, as does an oxazoline (Fig. 1c), to which XXVII is similar. The unexpected behavior of XIV in this reaction is undoubtedly a consequence of, at least in part, the *endo* nature of the hydroxyl group; cyclization to XXIV becomes operative since rearrangement to X is not sterically favorable.

Experimental[25]

α-Aminoborneol (III).—The following procedure represents a modification of that described by Duden.[2]

Sixteen grams (0.7 mole) of sodium was converted to shot by stirring vigorously with 50 cc. of dry toluene or xylene contained in a one-liter three-necked flask equipped with a mechanical stirrer, dropping funnel and efficient reflux condenser (calcium chloride drying tube attached). To the vigorously stirred mixture brought initially to 60° was added a solution of 21 g. (0.125 mole) of freshly distilled α-aminocamphor[26] dissolved in 100 cc. of absolute ethanol. The addition was carried out as rapidly as possible (two to three minutes), since too slow an addition results in a considerably decreased yield; cooling by ice-water is imperative. Immediately thereafter, a second portion of 100 cc. of absolute ethanol was run in. After the initial, vigorous reaction had subsided, the mixture was heated on the steam-bath to dissolve the remaining sodium. The mixture was then steam distilled until the turbidity disappeared and the distillate came over clear. The distillation residue was extracted with three 75-cc. portions of ether, and the extracts were dried over anhydrous potassium carbonate. After reduction of the volume to about 40 cc., the solution was placed in the refrigerator to allow crystallization of the α-aminoborneol. The colorless needles which formed were recrystallized from 60–70° petroleum ether and then melted at 187–188°. The yield was 7.0–10.5 g. (33–48%). α-Aminoborneol and its hydrochloride are reported to melt, respectively, at 187° and 285° (obsd. m.p. for hydrochloride, 284–285°).

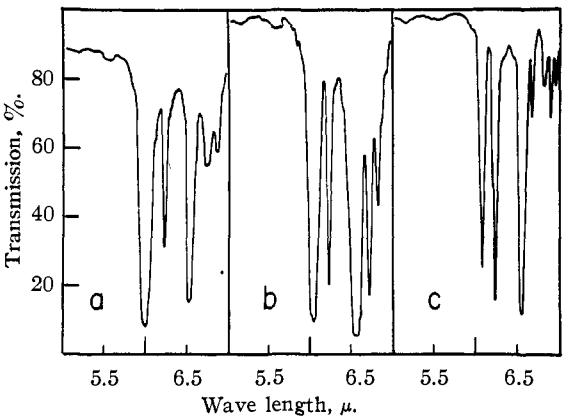


Fig. 1.—Infrared absorption spectra of: a, imide of N-*p*-nitrobenzoyl-β-aminobornylsulfurous acid, 0.40 *M*; b, N-*p*-nitrobenzoylcamphenamine, 0.31 *M*; c, *cis*-2-*p*-nitrobenzoyl-4,5-trimethylene oxazoline, 0.35 *M*. All spectra were taken in chloroform solution using 0.1 mm. matched sodium chloride prisms.

The N-*p*-nitrobenzoyl derivative of α-aminoborneol (XIII) melted at 224–225° after recrystallization from 95% ethanol.

Anal. Calcd. for $C_{17}H_{22}N_2O_4$: C, 64.13; H, 6.97. Found: C, 63.78; H, 7.08.

β-Aminoborneol (IIIa).—The directions of Duden[2] for the preparation of this aminoalcohol were followed, except that, after the initial reduction reaction abated, additional water was added to the suspension of sodium in ether so as to efficiently complete the reduction. A single recrystallization from 60–70° petroleum ether afforded β-aminoborneol melting at 167–168° (reported[2] 167–168°). Material of the highest degree of purity (m.p. 169–170°) was obtained after several more recrystallizations from ether–petroleum ether. The reported and observed melting points of the urea derivative are, respectively, 211°[2] and 210–211°.

β-Aminoborneol formed a *p*-nitrobenzamide (XIV) which melted at 228–229° after recrystallization from 95% ethanol.

Anal. Calcd. for $C_{17}H_{22}N_2O_4$: C, 64.13; H, 6.97. Found: C, 63.96; H, 6.82.

Camphenamine (V).—Repetition of the directions of Duden[2] readily furnished the free base ($n^{20}D$ 1.4937, reported $n^{20}D$ 1.4935). The melting points observed for the picrate, hydrochloride, nitrate and sulfate agreed well with those reported for these salts. The infrared spectrum of this base shows, among others, maxima at 6.02 and 11.35 μ, and is strikingly similar to that of camphene.

N-*p*-Nitrobenzoylcamphenamine (X) was recrystallized from 95% ethanol and then melted at 179.5–180.0°: $[\alpha]^{30}D$ +58° (*c* 0.69, in chloroform).

Anal. Calcd. for $C_{17}H_{20}N_2O_3$: C, 67.98; H, 6.71. Found: C, 68.05; H, 6.47.

The amide, dissolved in acetic acid, readily decolorized a solution of bromine in carbon tetrachloride and was oxidized by dilute, aqueous permanganate. In addition to the characteristic bands in the infrared reproduced in Fig. 1b, a sharp, well-defined peak indicative of N-H stretching appeared at 2.87 μ. In a projected bromination with N-bromosuccinimide, 130 mg. of X was refluxed in dry carbon tetrachloride solution with an equivalent amount of the reagent and 5 mg. of benzoyl peroxide. The mixture was irradiated at a distance of six inches with a G.E. 275 w. ultraviolet lamp. After four hours, there was no evidence of reaction; but within ten hours, some succinimide (10–15 mg.) had appeared, and the solution had turned deep

(24) Merck, German Patent 168,728; *Chem. Zentr.*, **77 I**, 1469 (1906).

(25) All melting points are corrected. The infrared spectra were recorded on a Baird automatic recording infrared spectrophotometer.

(26) Alternately, freshly prepared α-aminocamphor can be taken up without distillation in a minimum amount of toluene; the solution, after drying by removal of part of the solvent *in vacuo*, is diluted with the proper amount of absolute ethanol and used for the reduction.

yellow. Evaporation of solvent from the cooled solution afforded a solid mixture which could not be separated into pure components by fractional crystallization.

Preparation of N-*p*-Nitrobenzoylcamphenamine (X) from N-*p*-Nitrobenzoyl-α-aminoborneol (XIII).—The amide XIII (1.06 g., 3.30 mmoles) was dissolved in 5 cc. of thionyl chloride, and the resulting solution was allowed to stand for five hours. After evaporation of most of the excess solvent *in vacuo*, the addition of 30 cc. of dry ether induced crystallization of the rearrangement product X. After one recrystallization from 95% ethanol, the material melted at 174.5–176.5°. Concentration of the mother liquors afforded 60 additional mg. of slightly less pure material, making a total of 420 mg. (42%). The undepressed mixed m.p. with authentic N-*p*-nitrobenzoylcamphenamine served to identify the product.

Alternately, X could be obtained from XIII *via* the *p*-bromobenzenesulfonate (XI). Four hundred and ninety milligrams (1.54 moles) of XIII and 450 mg. of *p*-bromobenzenesulfonyl chloride were dissolved in 4 cc. of pyridine. After standing at room temperature for 40 hours, the clear solution was poured, with stirring, into a slurry of 4.5 cc. of concentrated hydrochloric acid in ice. The tan solid was filtered off, washed well with water and dried at room temperature. Because of the rather pronounced instability of *trans*-2-N-aroylcycloalkyl arylsulfonates,[19] XI was not recrystallized but was used as such for the following reaction. The entire lot of XI was suspended in 5 cc. of 95% ethanol; after the addition of 15.5 cc. of 0.1 *N* alcoholic sodium hydroxide, the suspension was brought into solution by refluxing for five minutes. The addition of 50 cc. of cold water to the cooled reaction mixture resulted in the separation of impure N-*p*-nitrobenzoylcamphenamine, which, after drying at 100°, melted at 153–165°. Successive recrystallizations from benzene and 95% ethanol raised the m.p. to 180.5–181.5°, $[\alpha]^{30}D$ +60° (*c* 0.67, in chloroform). The m.p. was undepressed on admixture with authentic X. Two hundred and thirty milligrams of product was obtained (50% on the basis of starting amide).

β-Aminobornyl *p*-Nitrobenzoate Hydrochloride (XV).—A solution of 1.27 g. of N-*p*-nitrobenzoyl-β-aminoborneol in 50 cc. of dry dioxane was rapidly saturated with dry hydrogen chloride gas. On cooling to room temperature, the solution deposited a precipitate of the migration product, which was removed by filtration. The filtrate was concentrated *in vacuo* to a small volume, and addition of water caused the precipitation of 780 mg. of starting material. The crude β-aminobornyl *p*-nitrobenzoate hydrochloride was recrystallized from absolute ethanol. It melted at 211.0–211.5° and weighed 490 mg. (91% on the basis of starting material consumed).

Anal. Calcd. for $C_{17}H_{23}ClN_2O_4$: C, 57.55; H, 6.53. Found: C, 57.11; H, 6.48.

On addition of aqueous sodium hydroxide to an aqueous solution of XV, N-*p*-nitrobenzoyl-β-aminoborneol precipitated. Its m.p. (227–228°) did not depress that of an authentic sample.

An attempted acyl migration using similar quantities of dioxane and the N-*p*-nitrobenzoyl derivative of α-aminoborneol (XIII), failed altogether. The saturation with hydrogen chloride was carried out, and then a reflux condenser equipped with a drying tube was attached to the flask. After refluxing the solution for an hour, the top of the condenser was stoppered to prevent escape of hydrogen chloride. The solution was refluxed for a total of 24 hours and then was concentrated *in vacuo* to a volume of about 10 cc. On cooling to about 10°, 1.11 g. (88%) of starting material precipitated (m.p. and mixed m.p. 223–224°).

Preparation of Camphenamine from β-Aminoborneol (IIIa).—The most nearly pure β-aminoborneol (m.p. 169–170°) available was subjected to a slight modification of the reaction conditions outlined by Duden[2] for the conversion of α-aminoborneol to camphenamine.

The aminoalcohol was first dissolved in a slight excess of 5% hydrochloric acid, and the resulting solution was evaporated to dryness on the steam-bath. After drying at 80° for two hours, the hydrochloride was treated with the appropriate amounts of phosphorus pentachloride and phosphorus oxychloride.[2] The reaction was exothermic. After standing for one-half hour, the semi-solid mass was taken to near dryness by evaporation *in vacuo* at 100°. The residue was dissolved in 10 cc. of water, and non-basic impurities were then extracted with ether. After removal of the ether dissolved in the aqueous solution with a jet of air, the solution was saturated with solid potassium hydroxide (external cooling). The supernatant oil which had formed was taken up in 5 cc. of benzene and converted to the N-*p*-nitrobenzoyl derivative. The total yield of material melting at 177–179° was 350 mg. (23%), after concentration of the mother liquors from the initial crystallization. There was no depression of melting point when authentic X was mixed with the product obtained by this sequence.

The yield of camphenamine reported by Duden[2] is 49%. In utilizing α-aminoborneol in the procedure described above, the yield of amide X of a comparable degree of purity (m.p. 180–181°, after one recrystallization from benzene) fell to 27–31%. This difference between α- and β-isomers is consistent with that previously observed between *cis*- and *trans*-2-aminocycloalkanols in the reaction with phosphorus pentachloride.[27]

N-*p*-Nitrobenzoyl-β-aminobornyl *p*-Toluenesulfonate (XVII).—Two hundred and forty-five milligrams (0.77 mmole) of N-*p*-nitrobenzoyl-β-aminoborneol and 200 mg. of *p*-toluenesulfonyl chloride were dissolved in 2 cc. of dry pyridine. After standing for 12 hours at room temperature, the solution was heated on the steam-bath for four hours. On cooling and subsequent addition of the reaction product to a mixture of 2 cc. of concentrated hydrochloric acid and ice, an oil precipitated which solidified on scratching. Recrystallization from the minimum amount of boiling 95% ethanol afforded 165 mg. (45%) of the *p*-toluenesulfonate, m.p. 170.0–171.5° (dec.). For analysis, the derivative was recrystallized once more from 95% ethanol and then melted at 175.0–175.5°.

Anal. Calcd. for $C_{24}H_{28}N_2O_6S$: C, 61.00; H, 5.97. Found: C, 61.15; H, 6.01.

Sixty milligrams (0.13 mmole) of the tosylate was dissolved in 5 cc. of boiling 90% ethanol containing an equivalent amount of sodium hydroxide. Refluxing was continued for one hour. On cooling the solution, crystals formed (50 mg.) which proved to be starting material (m.p. 175.0–175.5°). On dilution of the alcoholic solution with water, an additional small amount of tosylate precipitated.

Reaction of N-*p*-Nitrobenzoyl-β-aminoborneol (XIV) with Thionyl Chloride.—Seven hundred milligrams (2.20 mmoles) of XIV was dissolved in 4 cc. of thionyl chloride. After standing for five hours, the reaction mixture was diluted with 25 cc. of dry ether. Complete removal of the solvent pair *in vacuo* on the steam-bath left a gum which crystallized readily on addition of 10 cc. of absolute ethanol. After being triturated thoroughly, the solid was filtered and dried. Two hundred and fifty-five milligrams (32%) of product (m.p. 165–168°) was obtained. The use of solvents which were not completely dry appeared to result in a decided decrease in yield. The substance, which gave a qualitative test for sulfur, may be described as the imide of N-*p*-nitrobenzoyl-β-aminobornylsulfurous acid (XXIV). One recrystallization from ethanol furnished an analytically pure sample, m.p. 169.5–170.5°.

Anal. Calcd. for $C_{17}H_{20}N_2O_5S$: C, 56.03; H, 5.53. Found: C, 56.13; H, 5.51.

The imide exhibited no absorption in the 2–3 μ region of the infrared, thereby indicating the absence of N–H bonds in the system.

A portion of the material was dissolved in aqueous acetone, and the solution was allowed to stand for 12 hours. Water was then added to effect precipitation of a solid, which was shown to be starting material by a mixed melting point determination. Hydrolysis of the imide was readily effected, however, by strong base. To a solution of 60 mg. (0.165 mmole) of XXIV in 5 cc. of warm ethanol was added an aliquot consisting of 13.2 mg. (0.33 mmole) of sodium hydroxide dissolved in 1 cc. of 80% ethanol. Refluxing of the clear solution on the steam-bath for ten minutes was followed by cooling and filtration of the solid (Na_2SO_3) which subsequently precipitated. Twenty-five cc. of water was added to the filtrate. The solid which formed was shown to be N-*p*-nitrobenzoyl-β-aminoborneol by its melting point (226–227°) and by the mixed melting point with authentic material.

MADISON, WISCONSIN

(27) E. E. van Tamelen and R. S. Wilson, THIS JOURNAL, **74**, 6299 (1952).