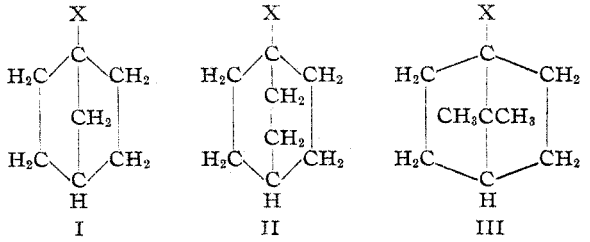
[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

Bicyclic Structures Prohibiting the Walden Inversion. Replacement Reactions in 1-Substituted 1-Apocamphanes[1]

BY PAUL D. BARTLETT AND LAWRENCE H. KNOX

Many replacement reactions at a saturated carbon atom are known to proceed with Walden inversion, many with racemization, and a few with retention of configuration. Recent research has resulted in great emphasis on the first of these groups. Indeed, some workers in this field[2] have proposed that one negative substituent cannot replace another at a saturated carbon atom without a Walden inversion, and that retention of configuration in such a reaction necessarily means that two successive steps each involving inversion have occurred. The present work was undertaken to test this hypothesis of the universality of the Walden inversion with respect to the replacement of the amino group by hydroxyl and by halogen, and to the interchange of hydroxyl groups and halogen atoms in a saturated compound.

A derivative of bicyclo-[2,2,1]-heptane (I) or bicyclo-[2,2,2]-octane (II) with a substituent on the bridge-head is incapable of reacting by the currently favored mechanism of negative substitution with Walden inversion. In the first place, no negative ion or other nucleophilic reagent can approach carbon atom 1 from the side opposite to the substituent and get within bond-forming distance, because carbon atoms 3, 4, 5, and 7 or 8 form a cage around it. In the second place, the three carbon atoms directly bound to the bridge-head (carbons 2, 6, and 7) are not free to alter their positions as required for an inversion of configuration. Both these restrictions apply whether there is optical activity present in the system or not. Hence we may work with an optically inactive series of compounds and still be sure that the mechanism of reaction which, in optically active compounds, underlies the Walden inversion, is excluded.



I II III

Compounds of this type containing the readily replaceable amino or hydroxyl group or halogen on the bridge-head are exceedingly rare. As the most available starting material we have chosen 1-apocamphanecarboxylic acid (III, X = COOH), which can be prepared by the reduction of ketopinic acid by the Wolff–Kishner or, better, by the Clemmensen method as modified by Martin.[3] The yields by these two methods are 62 and 50%, respectively, of purified acid melting at 217–218°. The greater convenience of the Clemmensen procedure for large quantities offsets its slightly lower yield.

In conformity with the experience of Houben and Pfankuch[4] with dihydrocamphene-4-carboxylic acid, we found that the amide of 1-apocamphanecarboxylic acid, treated with methyl alcoholic alkaline solution of bromine, readily gave the Hofmann reaction to methyl 1-apocamphylcarbamate, obtained in 60% yield. This urethan melted, after recrystallization from petroleum ether, at 93–94°. Though quite resistant to hydrolysis, it could be converted in 82% yield into 1-apocamphylamine, m. p. 175°, by refluxing for forty-three hours with concentrated potassium hydroxide in methanol–water solution. The amine yielded an acetyl derivative, m. p. 132°, which could not be hydrolyzed by twenty-four hours of boiling with 8 *N* potassium hydroxide in 80% ethyl alcohol. Since N-*t*-butylacetamide proved similarly resistant, this property is not to be attributed to the special character of the apocamphane ring system.

Treatment of 1-apocamphylamine with four equivalents of sulfuric acid and two equivalents of sodium nitrite in concentrated aqueous solution resulted in a quantitative evolution of nitrogen and a 66% yield of an alcohol melting at 161–162° which we believe to be apocamphanol-1 on the basis of the following evidence. The analysis

(1) Presented before the Organic Division of the American Chemical Society at Boston, September 12, 1939.

(2) See, for example, Olson, *J. Chem. Phys.*, **1**, 418 (1933); Olson and Voge, THIS JOURNAL, **56**, 1690 (1934); Ogg, *ibid.*, **61**, 1946 (1939).

(3) Martin, *ibid.*, **58**, 1440 (1936).

(4) Houben and Pfankuch, *Ann.*, **489**, 193 (1931).

for carbon and hydrogen is that of an apocamphanol. After standing for twenty-four hours at 25–30° with chromic anhydride in glacial acetic acid, it had produced no color change and the alcohol was recovered in 51% yield. The loss seems likely to have been manipulative, since a sample of only 0.115 g. was used in this experiment. This resistance to oxidation indicates a tertiary alcohol. In agreement with this, its esterification was very slow; the *p*-toluenesulfonate (m. p. 93°) being obtained in only 34% yield from the reaction of the alcohol with the acid chloride in anhydrous pyridine for twenty hours on the steam-bath.

In spite of being a tertiary alcohol, this compound dissolves reversibly and with no evidence of polymerization in concentrated sulfuric acid. A pale yellow color, which turns to red on standing, is produced in the solution but is discharged by the addition of water, which precipitates the original alcohol. This suggests that dehydration, and molecular rearrangements leading to it, are prohibited in this compound. This is what we should expect from Bredt's rule[5] and the considerations concerning rearrangements discussed later in this paper, if our alcohol is in fact apocamphanol-1 (III, X = OH). We have not succeeded in establishing this structure in any more direct way.

We attempted to replace the hydroxyl group of this tertiary alcohol with halogen by a number of standard methods, all with negative results. As was expected, 1-apocamphyl *p*-toluenesulfonate was recovered (in 91% yield) from refluxing with a saturated acetone solution of lithium iodide for twenty-three hours. This type of replacement reaction, when it occurs, always involves Walden inversion, and we tried this experiment merely for the sake of completeness. More surprising is the failure of thionyl chloride, which has been credited by Hughes, Ingold, and their co-workers[6] with the ability to replace certain hydroxyl groups by chlorine without the occurrence of any configurative inversion. On the addition of apocamphanol-1 to excess thionyl chloride, a vigorous reaction occurred, after which the mixture was refluxed on the steam-bath for fifteen hours. From the product, after pouring on ice, a white solid could be obtained, melting at 95–98°, which contained no halogen and which was slowly hydrolyzed to apocamphanol by dilute sodium hydroxide in 50% ethyl alcohol in the cold. This product was clearly a sulfite.

From the reaction of apocamphanol-1 with phosphorus pentachloride a white solid was obtained having the properties and composition of a loose molecular compound between two molecules of the alcohol and one of hydrogen chloride. Its melting point was not reproducible, ranging between 157 and 168°. It depressed the melting point of apocamphanol-1 slightly, but did not depress the melting point of camphor in an attempted molecular weight determination. This is consistent with the structure of an oxonium salt, insoluble in camphor. The proposed composition recalls the "dipinacol hydrobromide" of Ayers.[7]

The passage of gaseous hydrogen bromide into a petroleum ether solution of apocamphanol-1 deposited an oil which crystallized and yielded a product of melting point 83–84° which appeared to be the bromine counterpart of the hydrochloride just described. Water decomposed it immediately into hydrogen bromide and apocamphanol-1, as did mere standing in a desiccator over calcium chloride for several weeks. Its bromine content corresponded approximately to a diapocamphanol hydrobromide.

The treatment of N-apocamphylbenzamide with phosphorus pentachloride, a method successfully used by von Braun[8] for the conversion of an amine into a chloride, yielded only starting material and tars.

These experiments with apocamphanol-1 indicate clearly that this tertiary alcohol lacks a necessary structural feature for the direct replacement of its hydroxyl group by halogen. The obvious method remaining to be tried for the preparation of the chloride was the reaction between 1-apocamphylamine and nitrosyl chloride. The addition, in ether at −10°, of pure nitrosyl chloride to the amine resulted in a smooth evolution of nitrogen and a solid product which proved to be a mixture of the desired chloride with the alcohol, apocamphanol-1. This mixture could be separated completely by extraction of the petroleum ether solution with 95% sulfuric acid, which removed the alcohol. The resulting chloride was a white, very volatile, solid melting at 154–156°. Allowance being made for recovered amine, the yield of the chloride was 45%.

(5) Bredt, *ibid.*, **437**, 1 (1924).

(6) Cowdrey, Hughes, Ingold, Masterman and Scott, *J. Chem. Soc.*, 1267 (1937).

(7) Ayers, THIS JOURNAL, **60**, 2959 (1938).

(8) Von Braun, *Ber.*, **65B**, 880 (1932).

All attempts to replace the chlorine of 1-chloroapocamphane failed. After refluxing for twenty-one hours with 30% potassium hydroxide in 80% ethanol, 70% of the chloride was recovered unchanged and no apocamphanol could be obtained by a sulfuric acid extraction. The attack of the alkali upon the glass made the detection of small amounts of chloride ion impracticable. To escape this limitation an experiment was tried in which the chloride was refluxed with silver nitrate in aqueous ethanol solution for forty-eight hours. At the end of this time the solution was perfectly clear, with no opalescence, and 60% of the original 0.1-g. sample of chloride was recovered unchanged. All recovered products were identified by mixed melting points in these experiments. Taking the solubility product of silver chloride in this alcoholic medium to be the same as in water, a concentration of silver chloride as small as 2.4×10^{-10} should have been detectable by opalescence. If the concentration was less than this, then the bimolecular velocity constant (time in hours) for the reaction of silver nitrate with 1-chloroapocamphane is less than 1.7×10^{-10} at about 85°.

We were unable, by the use of ordinary dry ether and the usual methods and precautions, to prepare 1-apocamphylmagnesium chloride, but we are not ready to make this the basis of any theoretical conclusions.

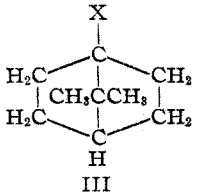
We then considered the possibility that some structural feature of the apocamphane derivatives other than location of the functional group on the bridgehead of a caged ring system might be responsible for the remarkable inertness of these compounds toward replacement reactions. One obvious suggestion is that the substituent X in Formula III, though on a tertiary carbon atom, has "neopentyl" character, that is, it is situated on a carbon atom which is adjacent to a quaternary carbon atom. Neopentyl alcohol is inert to ordinary methods of replacing the hydroxyl group, and the possibility is not to be ignored that apocamphanol-1 might owe some of its inertness to the same cause as neopentyl alcohol, whatever that cause may be. Accordingly we prepared *t*-butyldiethylcarbinol and its chloride (IV, X = OH and Cl) identical with III except for the replacement of two ring-closures remote from the functional group by four hydrogen atoms. This carbinol is converted into the chloride instantly by gaseous hydrogen chloride, and the resulting chloride reacts in ethyl alcohol–water much faster than *t*-butyl chloride. In 80% ethanol at 25° in eight hours, 98% of the possible hydrogen chloride has been liberated. We tried to estimate the amount of olefin formed in this reaction as was done by Hughes and his co-workers.[9] Unfortunately, in the present case variations in the time of the bromine titration produced continuous changes in the apparent fraction of olefin, up to well over 100% of the calculated. Evidently this nonene cannot be reliably titrated with bromine. There is, of course, a possibility that all the appearance of hydrogen chloride was due to elimination and none to direct replacement of halogen. However, this seems unlikely in view of the figures in Table I, where it appears that the actual rate of replacement is much greater in *t*-amyl than in *t*-butyl chloride despite the greater molecular size of the former. The experimental figures on these two chlorides are those of Hughes and his co-workers.

TABLE I

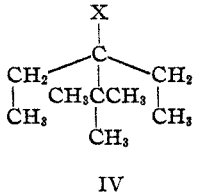
UNIMOLECULAR VELOCITY CONSTANTS AT 25° IN 80% ALCOHOL FOR THE FORMATION OF HYDROCHLORIC ACID (k_{HCl}) AND FOR SOLVOLYSIS (k_s) BY TERTIARY ALKYL CHLORIDES

Chloride	k_{HCl}	% Olefin in product	k_s
t-Butyl	0.0329	15	0.028
t-Amyl	.324	42	.19
α,α-Diethylneopentyl	.42	..	...

Another possibility to be reckoned with is that a rearrangement may have occurred in the reaction of nitrosyl chloride with 1-apocamphylamine. Past experience, and current theories, would not lead us to expect such rearrangements, and the behavior of our apocamphanol toward oxidizing and dehydrating agents seems to exclude them in its case. Nevertheless, it seemed well to make a comparison of the behavior of our chloroapocamphane with that of a similarly constituted and rather inert secondary chloride, bornyl chloride (V), which incidentally also contains a neopentyl system.

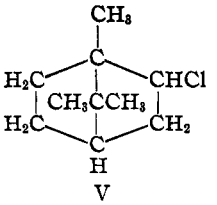


III



IV

(9) Hughes, Ingold and Shapiro, *J. Chem. Soc.*, 225 (1936).



V

At room temperature, in 75% (by volume) ethanol–water solution, neither bornyl chloride nor chloroapocamphane gave any hydrochloric acid. However, with silver nitrate, under the identical conditions of the negative experiment with chloroapocamphane, bornyl chloride lost 22% of its chlorine in five minutes and 84% in an hour. The latter figure corresponds to a bimolecular velocity constant (time in hours) for the reaction between silver nitrate and bornyl chloride of 11.25, thus certainly at least ten powers of ten greater than the corresponding constant for 1-chloroapocamphane. From all these experiments it appears that apocamphanol-1 and 1-chloroapocamphane are unique among known alcohols and saturated chlorides in their resistance to replacement of their functional groups, and that this uniqueness can be associated only with the location of these groups on the bridge-head of a bicyclic ring system.

Interpretation of Results

The reasoning out of which this work arose—that the Walden inversion is prohibited in replacement reactions among compounds of the type III—allows only positive results to be interpreted with certainty. We can now say quite definitely that no inversion, or series of inversions, need be involved in the Hofmann rearrangement of an amide or in the reaction of an amine with nitrous acid or nitrosyl chloride. All three of these reactions proceed as smoothly and rapidly when the Walden inversion is prohibited as when it is possible. It is still a question whether these reactions proceed by concerted intramolecular processes or through the intermediate formation of a practically free ion with its charge on carbon. In the case of the Hofmann rearrangement, such an ion, if formed, would carry a negative charge,[10] while the intermediate ions, if any, in the reaction of amines with nitrous acid and nitrosyl chloride would be positively charged. There are difficulties in both types of mechanism which are not resolved by the present work. In view of the considerations brought forward below, the purely intramolecular mechanism now seems the more probable for those cases of this reaction which proceed without inversion. This does not exclude the existence of a competing negative replacement reaction with inversion in compounds capable of inversion.

In the case of the reactions which fail to occur—reciprocal replacement of the hydroxyl group and halogen atom—the interpretation runs into complications. To be sure, the lack of any dehydration or elimination of hydrogen chloride is readily explained if we consider the large amount of strain which the formation of the resulting cycloolefin would necessarily entail. The impossibility of a double bond at the bridge-head of a bicyclo-[2,2,1]-heptane often has been discussed theoretically and supported experimentally.[11] Likewise, the failure of the system to rearrange into one capable of olefin formation can be correlated with the observation that the rearrangement of certain cyclic alcohols and chlorides is attended by inversion at the carbon atom originally holding the functional group.[12] The back side of carbon atom 1 in 1-apocamphanol can no more be attacked by a migrating radical or hydrogen atom than it can by an extraneous reagent, and hence the Wagner–Meerwein rearrangement is among the processes of which this compound is incapable.

With regard to the failure of replacement reactions in this alcohol and halide, the first explanation to present itself is that these reactions cannot proceed without Walden inversion, and that any racemization observed in them is ordinarily due to mobile inversions in the solvated cation (conjugate acid of the alcohol) reacting with the solvent. This may indeed be the correct explanation, but if it is it means the discarding of some very satisfactory features of the theory of the dual mechanism of solvolytic reactions of halides. Hughes and his co-workers have shown[13] that halides can be broadly divided into those in which the rate of replacement of the halogen atom by hydroxyl or alkoxyl is influenced by the concentration of the hydroxyl or alkoxyl ion, and which therefore react by a bimolecular mechanism, and those in which this rate of replacement is independent of the hydroxyl or alkoxyl ion concentra-

(10) See the discussion by Whitmore, THIS JOURNAL, **54**, 3281 (1932).

(11) For historical references, see ref. 5.

(12) Bartlett and Pöckel, THIS JOURNAL, **59**, 820 (1937); Bartlett and Bavley, *ibid.*, **60**, 2416 (1938).

(13) For a review of this field see Watson in "Annual Reports of the Chemical Society for 1938," Vol. XXXV, pp. 208–226.

tion, and which therefore may be said to react by a unimolecular or pseudo-unimolecular mechanism. Both these mechanisms are presumably possible in all halides, and in certain cases the presence of both has been demonstrated. Now, any theory which makes the attack of a nucleophilic reagent on the back side of the halogenated carbon atom necessary to the occurrence of replacement thereby postulates that the bimolecular and pseudo-unimolecular mechanisms are exactly alike except that in the former case a strongly basic ion, and in the latter case a weakly basic solvent molecule, does the attacking. It seems out of all reason that the hydroxyl ion should be the most powerful reagent for a primary chloride, but the water molecule the most powerful reagent for a tertiary chloride, as is actually observed, if the fundamental mechanism is exactly the same in both cases. The insertion of other solvent molecules in the activated complex, some of which may have an acceptor, rather than a donor, function, does nothing to resolve this difficulty since it would seem that with any halide an activated complex involving a powerful donor in the position where a donor is needed should have a lower activation energy for reaction than an otherwise identical one involving a weaker donor in the donor position.

This difficulty is avoided completely if we may assume, with Hughes and Ingold, that in the unimolecular mechanism there is no donor molecule contributing at all to the energy of the transition state, but that the rate-determining step is entirely a "pull" which removes the halogen leaving a carbonium ion.[14] Such an assumption is consistent, though not uniquely so, with observations of the catalytic effect of acceptor ions and molecules on the solvolysis of halides.[15] To make this assumption compatible with the facts about 1-chloroapocamphane, what we need is some reason why the 1-apocamphyl positive ion cannot be formed while the *t*-butyldiethylcarbonium ion can be. In this direction we have one suggestion to make.

Evidence has long been accumulating that carbonium ions either have a permanently planar arrangement of the three bonds attached to the unsaturated carbon atom, or oscillate rapidly between what may be called the *d*- and *l*-tetrahedral configurations. Recent evidence from electron diffraction[16] has shown that in the molecule of trimethylborane the boron and carbon atoms all lie in the same plane. The boron atom in this compound is the nearest analog in a stable compound to the carbon atom with an open sextet, and the situation here suggests that a permanently planar arrangement is the only possible one for any carbonium ion. If this is so, then it is to be expected that the formation of the 1-apocamphyl positive ion will be attended by considerable strain. In order to bring carbon atoms 2, 6, and 7 of the bicyclo-[2,2,2]-octane ring system into the same plane with carbon atom 1 a total strain of at least 58°24′ would be distributed among three valence angles, and for the apocamphane ring system the strain would be considerably greater. A strain of 19°28′ per CH_2 group is present in cyclobutane, and a comparison of the heat of combustion of cyclobutane with that of cyclohexane gives 7.5 kcal. per methylene group as the approximate translation of this strain into heat units. This suggests that the energy of activation for the unimolecular solvolysis of 1-chlorobicyclo-[2,2,2]-octane (assuming the ionization mechanism) should be higher than that of an acyclic analog by at least $3 \times 7.5 = 22.5$ kcal. This corresponds to a factor of more than 10^{14} in the rates of reaction at 350°K. and hence is an important enough effect to take account of the experimental observations. Incidentally, this 22.5 kcal. is the same approximate amount by which such a bicyclic compound with a double bond at the bridge-head would be more strained than an isomer with the double bond in the 2-position. Bredt's rule is thus seen to embody a high degree of probability in thermodynamic terms.

There exists, therefore, an hypothesis which would reconcile our present results with the general theory of solvolytic reactions which postulates ionization of the tertiary halide as a rate-controlling step. The evidence for this hypothesis is obviously far from complete, but we feel that the absolute rates of solvolysis of the tertiary halides in alcohol–water mixtures are not without significance in this connection. When a model of *t*-butyldiethylcarbinyl chloride is constructed out of atomic calotte models according

(14) The semiquantitative arguments recently presented by Ogg (ref. 2) against this mechanism apply only to methyl and, less strongly, to ethyl halides. These and other primary halides, of course, are the very ones which *do not* hydrolyze by the unimolecular or pseudo-unimolecular mechanism in the presence of basic ions.

(15) For example, the work of Roberts and Hammett, THIS JOURNAL, **59**, 1063 (1937).

(16) Levy and Brockway, *ibid.*, **59**, 2085 (1937).

to H. A. Stuart,[17] even the most favorable orientation of the atoms seems to offer little opportunity for a solvent molecule to approach within bond-forming distance of the central carbon atom on the side opposite to the halogen. If this kind of participation of the solvent is necessary to solvolysis, we should expect this compound to occupy a position intermediate between *t*-butyl chloride and 1-chloroapocamphane with respect to its ease of solvolysis. Instead, it gives no indication that mere hindrance to the back side of the central carbon atom, unattended by restriction of the bond angles, is of the slightest inhibitory influence in the solvolytic reaction. Another case in point is that of dimesitylchloromethane.[18] It is impossible to make a Stuart model of a transition state in which both the chlorine atom of this compound and the oxygen of an alcohol molecule are within bond-forming distance, and on opposite sides, of the central carbon atom, assigning to the atoms their commonly accepted interference radii. Nevertheless, the chlorine of dimesitylchloromethane is replaced by alkoxyl as readily as would be expected in a substituted benzhydryl chloride. This case is free from the possibility of an olefinic intermediate. Thus the balance of the present evidence seems to us in favor of the ionization mechanism for the solvolysis of tertiary chlorides and its reverse reaction, with the carbonium ion having a planar arrangement of its central carbon atom with the three atoms attached to it.

Experimental

***dl*-Ketopinic acid** was prepared by the direct oxidation of *dl*-camphor-10 sulfochloride. This eliminates a step in the procedure of Wedekind and Weindand[19] without loss in yield. The use of racemic camphor as the starting material is advantageous, as the racemic forms of compounds in this series have better crystallizing properties than the optically active forms. The camphorsulfochloride (100 g.) was added in three portions with stirring to 1000 g. of a 10% solution of sodium carbonate, heated on the steam-bath, together with the three corresponding portions of a hot solution of 100 g. of potassium permanganate in 600 cc. of water. Heating was continued for an hour, after which the excess permanganate and manganese dioxide were destroyed with bisulfite. Long needles of ketopinic acid separated when the clear solution was cooled. The remainder of the acid was obtained by ether extraction of the cold solution. Recrystallization from water yielded 28–32 g. of the pure acid (38.4–42.7% of the theoretical) melting at 233–234°.

Anal. Calcd. for $C_{10}H_{14}O_3$: C, 65.89; H, 7.75. Found: C, 65.95, 66.20; H, 8.21, 8.03.

The reduction of ketopinic acid to apocamphane-1-carboxylic acid was carried out by both the Wolff–Kishner method[20] and the method of Clemmensen as modified by Martin.[8] The latter method is preferable for working in quantity. From 50 g. of ketopinic acid the product, after four recrystallizations from water, amounted to 28 g. (60.4%) and melted at 217–218°.

Anal. Calcd. for $C_{10}H_{16}O_2$: C, 71.39; H, 9.58. Found: C, 71.00; H, 9.53.

A mixed melting point with the acid obtained by the Wolff–Kishner method showed no depression.

Amide of Apocamphane-1-carboxylic Acid.—The acid (28 g.) was refluxed with thionyl chloride (80 g.) for one hour. After removal of the excess thionyl chloride under diminished pressure the acid chloride was taken up in dry ether and ammonia gas passed in. The yield of amide, after crystallization from ligroin, was 25.5 g. (92.1%). The melting point was 185°.

Anal. Calcd. for $C_{10}H_{17}NO$: C, 71.81; H, 10.23. Found: C, 71.67; H, 10.12.

Methyl 1-Apocamphylcarbamate.—To a solution of 7 g. of sodium in 385 cc. of methyl alcohol was added 25 g. of the amide. To the ice-cold solution 24 g. of bromine was added dropwise with stirring. The mixture was refluxed on the steam-bath for fifteen minutes, cooled, and diluted with a liter of water. A white solid precipitated which was separated by three extractions with 100-cc. portions of petroleum ether. After drying with anhydrous sodium sulfate and removal of the solvent, the urethan was obtained as an oil which crystallized on cooling. The yield was 8.3 g. (60.2%). Recrystallization from petroleum ether gave a product melting at 93–94°.

Anal. Calcd. for $C_{11}H_{19}O_2N$: C, 66.95; H, 9.71. Found: C, 66.97; H, 9.39.

1-Aminoapocamphane was obtained in 82.7% yield (8.5 g.) by refluxing the urethan (14.5 g.) with a solution of 50 g. of potassium hydroxide in 117 cc. of methyl alcohol and 33 cc. of water for forty-three hours. The product was isolated by diluting with water, extracting with petroleum ether, and purifying through the hydrochloride. The amine is very volatile and melts at 175° in a sealed tube.

Anal. Calcd. for $C_9H_{17}N$: C, 77.64; H, 12.28. Found: C, 77.69; H, 12.79.

The hydrochloride began to discolor at 235–240°, but did not melt below 320°.

N-Acetyl-1-apocamphylamine crystallizes from ligroin in long, slender needles melting at 132°.

Anal.[20a] Calcd. for $C_{11}H_{19}ON$: C, 72.88; H, 10.56. Found: C, 73.09; H, 10.79.

After refluxing 0.7 g. of this amide with 15 g. of potassium hydroxide in 25 cc. of 80% aqueous ethyl alcohol for twenty-four hours, we recovered 0.6 g. (85.7%) of the amide. There was an odor of the amine, but none could be isolated.

(17) Stuart, *Z. physik. Chem.*, **27B**, 354 (1934). Models of this type are now obtainable from the Fisher Scientific Co.

(18) Nauta and Wuis, *Rec. trav. chim.*, **56**, 535 (1937).

(19) Wedekind and Weindand, *Ber.*, **55**, 946 (1922).

(20) Wedekind, *ibid.*, **57**, 664 (1924).

(20a) Starred analyses (*) were performed by H. S. Wight.

N-Benzoyl-1-apocamphylamine melts at 112° after crystallization from ligroin.

Trimethylacetamide, m. p. 154–156°, was prepared in 73.5% yield by the procedure of Whitmore and Langlois.[21]

***t*-Butylamine,** b. p. 46.4°, was prepared in 64% yield (as the hydrochloride) by the action of aqueous sodium hypobromite on the amide at 0°.

N-*t*-Butylacetamide, prepared from the amine and acetic anhydride, melted at 97°, was volatile with steam and very hygroscopic. A mixture of 25 cc. of a 25% aqueous solution of potassium hydroxide and 2.32 g. of the amide was heated to reflux in an apparatus with a trap for collecting vapors of the amine which might escape. After twenty and one-half hours 1.7 g. of the amide was recovered and 0.11 g. of *t*-butylamine hydrochloride was isolated from the trap.

Reaction of 1-Aminoapocamphane with Nitrous Acid.—In dilute solution no reaction of 1-aminoapocamphane with nitrous acid could be detected even on long standing at room temperature. In an experiment carried out at 80°, in which the nitrogen evolved could be estimated quantitatively, 0.0039 mole of amine hydrochloride was used, 0.0021 mole was recovered, and 0.0018 mole of nitrogen was evolved (calcd., 40.30 cc.; found, 40.00 cc., at S. T. P.). The apocamphanol-1 isolated from this experiment amounted to 0.0011 mole.

Apocamphanol-1.—To a solution of 5 g. of 1-apocamphylamine in 70 cc. of 10% sulfuric acid (five times the calculated amount) 5 g. of sodium nitrite (twice the calculated amount) in concentrated aqueous solution was added. When the vigorous reaction had abated, the reaction flask was warmed for ten to fifteen minutes on the steam-bath. After cooling, the product was isolated by ether extraction and recrystallization from petroleum ether. The yield was 1.58 g. (66.6% of the unrecovered material) of silky white needles melting at 161–162° in a sealed tube and subliming readily.

*Anal.** Calcd. for $C_9H_{16}O$: C, 77.03; H, 11.50. Found: C, 76.80; H, 11.44.

By making the mother liquor from the diazotization alkaline and extracting with ether, 2.63 g. of the free amine was recovered.

1-Apocamphyl *p*-toluenesulfonate, crystallized from 50% ethanol, melts at 93°.

*Anal.** Calcd. for $C_{16}H_{22}O_3S$: C, 65.27; H, 7.53. Found: C, 65.36; H, 7.52.

Behavior of Apocamphanol-1 toward Hydrogen Bromide.—Dry hydrogen bromide was passed into a solution of 1 g. of the alcohol in 75 cc. of dry ether, cooled in an ice-bath. Evaporation after half an hour yielded a yellow oil from which crystals slowly deposited. Both the oil and the crystals were insoluble in petroleum ether, but in contact with water a white solid was formed immediately which proved identical with the alcohol and amounted to 0.7 g.

In another experiment, hydrogen bromide was passed into a petroleum ether solution of the alcohol for two hours. After several hours of standing the oil which was at first deposited solidified. By decantation of the mother liquor the solid residue of brittle crystals was isolated. These fumed strongly in air and melted at 83–84°. A further crop was deposited slowly from the mother liquor.

Anal. Calcd. for $C_{18}H_{33}O_2Br$: Br, 22.14. Found: Br, 24.46.

The sample was stored in a desiccator over anhydrous calcium chloride. The melting point rose from day to day, and after several weeks it had reached 157–160° and this melting point was not lowered by mixture with apocamphanol-1. In contact with water, this alcohol was immediately produced, as shown by a mixed melting point.

Behavior of Apocamphanol-1 toward Phosphorus Pentachloride.—A solution of 1 g. of the alcohol in 40 cc. of petroleum ether (b. p. 20–40°) was treated with 2 g. of phosphorus pentachloride. The mixture was allowed to stand overnight in a glass-stoppered Erlenmeyer flask and was then washed carefully with ice water and the petroleum ether solution was dried and evaporated. Since we expected to get the chloride, the solid residue was next sublimed. The sublimed material melted unreliably between 157 and 168°.

*Anal.** Calcd. for $C_{18}H_{33}O_2Cl$: C, 68.21; H, 10.49; Cl, 11.19. Found: C, 67.79; H, 10.49; Cl, 11.04.

An attempt to determine the molecular weight of this substance by the Rast method was unsuccessful, since no depression of the melting point of camphor was obtained.

Nitrosyl Chloride.—Dry sulfur dioxide was passed for several hours into 150 cc. of fuming nitric acid cooled in ice. The resulting crystalline mass was freed of adhering liquid by suction filtration and stored in a desiccator over sulfuric acid. Equivalent amounts of this nitrosylsulfuric acid and sodium chloride were warmed gently and the nitrosyl chloride condensed in a U-tube surrounded by dry-ice. A stream of dry nitrogen was passed through this liquid to remove as much dissolved hydrogen chloride as possible. The nitrosyl chloride was stored in the dark.

1-Chloroapocamphane.—A solution of 5 g. of 1-aminoapocamphane in 100 cc. of dry ether was cooled below −10° in a 250-cc. three-necked flask fitted with a mercury-sealed stirrer, dropping funnel, and gas exit tube for collecting the gaseous products of the reaction over water. An ethereal solution of nitrosyl chloride was added dropwise until the orange-yellow color of the reagent persisted and nitrogen ceased to be evolved. The volume of nitrogen collected was roughly estimated at between 450 and 500 cc. When the reaction mixture had come to room temperature a little cold water was added to dissolve the amine hydrochloride precipitated by the hydrogen chloride remaining in the reagent. The ether layer was removed, dried, and concentrated. The yellow, semi-solid residue was taken up in 25 cc. of low-boiling petroleum ether and extracted with three 5-cc. portions of 95% sulfuric acid. The petroleum ether solution was then washed with cold water, dried with sodium sulfate, and concentrated. White crystals (1.7 g.) were obtained melting at 154–156°. Mixture with apocamphanol-1 depressed the melting point to 145–148°.

Anal. Calcd. for $C_9H_{15}Cl$: C, 68.13; H, 9.53; Cl, 22.35. Found: C, 67.71; H, 9.72; Cl, 21.95.

1-Aminoapocamphane (1.8 g.) was recovered from the aqueous extract from the original reaction by the addition of sodium hydroxide and extraction with ether. The yield

(21) Whitmore and Langlois, THIS JOURNAL, **54**, 3438 (1932).

of 1-chloroapocamphane, based upon the amount of amine consumed, was 45% of the theoretical. Its great volatility may have been responsible for some loss in isolation.

Attempted Hydrolysis of 1-Chloroapocamphane.—A solution of 0.096 g. of the chloride and 1.5 g. of potassium hydroxide in 5 cc. of 80% ethyl alcohol by volume was refluxed for twenty-one hours. The solution became discolored. It was diluted with water and extracted with several portions of petroleum ether. The aqueous extract was acidified with pure nitric acid and an excess of 10% silver nitrate solution added. A brownish opalescence was produced. After standing for thirty-six hours the mixture was filtered, yielding 0.0256 g. of solid having the appearance of discolored glass. This was digested with concentrated aqueous ammonia and again filtered. A colorless glassy precipitate remained, weighing 0.0221 g., which was evidently not silver chloride. These residues were dried at 120°. Acidification of the ammoniacal solution gave a precipitate weighing 0.0020 g. Extraction of the petroleum ether solution with concentrated sulfuric acid removed no organic matter which could be precipitated by dilution; hence no detectable amounts of alcohol or ether were produced. From the petroleum ether extract 0.067 g. of unchanged chloride was recovered, which depressed the melting point of the alcohol and not that of the chloride.

Behavior of 1-Chloroapocamphane toward Silver Nitrate.—A solution of 0.1 g. of the chloride and 0.54 g. of silver nitrate in 2 cc. of water and 7 cc. of absolute ethyl alcohol was refluxed for forty-eight hours. At the end of this time the solution was still perfectly clear, and remained free of opalescence on cooling to room temperature. By the usual procedure 60% of the chloride was recovered and its identity checked by mixed melting points with both pure 1-chloroapocamphane and apocamphanol-1.

Behavior of Bornyl Chloride toward Silver Nitrate.—A solution of 0.10 g. of bornyl chloride and 0.54 g. of silver nitrate in 2 cc. of water and 7 cc. of absolute ethyl alcohol was refluxed for a measured length of time and the precipitate of silver chloride collected on a sintered glass funnel and weighed. Three such samples were run for different lengths of time, with the following results.

Weight of bornyl chloride	Time of reflux, min.	Weight of AgCl	% reaction
0.10	5	0.0182	22
.1013	10	.0256	30
.1021	60	.0711	84

An approximate calculation of the bimolecular velocity constant k, neglecting any heterogeneous reaction or autocatalysis, on the basis of the sixty minute point, gives

$$k = \frac{2.3}{0.3542} \log_{10} \frac{0.3648 \times 0.0658}{0.0106 \times 0.420} = 11.25$$

time being expressed in hours.

2,2-Dimethyl-3-ethylpentanol-3 (*t*-**butyldiethylcarbinol**) was prepared from ethylmagnesium bromide and trimethylacetyl chloride, as described by Whitmore and coworkers.[22] The yield was supplemented by oxidizing the *t*-butylethylcarbinol produced in the reaction and treating the ketone again with the ethyl Grignard reagent. In the preparation of trimethylacetyl chloride use was made of the excellent method described by Brown.[23] The *t*-butyldiethylcarbinol, obtained in 22.9% yield from the direct reaction of Grignard reagent and acid chloride, boiled at 118–119.6° under 160 mm. pressure.

2,2-Dimethyl-3-ethyl-3-chloropentane.—Dry hydrogen chloride was passed into 20 g. of the carbinol at 0° until no further increase in the water layer was apparent. The water layer was then removed and the organic layer again saturated with hydrogen chloride. After washing and drying of the chloride it was distilled, giving 12.5 g. of colorless liquid boiling at 53–54° under 6 mm. pressure.

Anal. Calcd. for $C_9H_{19}Cl$: Cl, 21.97. Found: Cl, 21.54.

In an earlier preparation the distillation of the product under 150 mm. pressure yielded a considerable amount of olefin, boiling at 80.6–81° (150 mm.).

*Anal.** Calcd. for C_9H_{18}: C, 85.64; H, 14.36. Found: C, 85.09; H, 14.46.

Hydrolysis of the Acyclic Chloride.—A kinetic study of the hydrolysis at 25° in 80% ethyl alcohol by volume was carried out in order to have results comparable with those in the literature on other tertiary chlorides. The chloride (0.6220 g.) was weighed into a glass-stoppered Erlenmeyer flask and diluted to 50 cc. with the solvent, which had already been brought to temperature in a thermostat bath. Five-cc. portions were removed at suitable intervals, swirled with carbon tetrachloride, and the acid in the aqueous layer titrated with sodium hydroxide solution. The logarithms of the molar concentrations of the remaining chloride were plotted against time, yielding a fairly good straight line. From the slope of this line the unimolecular velocity constant was found to be 0.4206 (time in hours).

Summary

Apocamphane-1-carboxylic acid amide has been converted by the Hofmann reaction into 1-aminoapocamphane. Although the amino group is so situated that it cannot possibly be replaced in any reaction involving a Walden inversion, this compound readily reacts with nitrous acid to yield apocamphanol-1 and with nitrosyl chloride to yield 1-chloroapocamphane. This alcohol and chloride cannot be interconverted. The alcohol forms loose molecular compounds with hydrogen chloride and hydrogen bromide, while the 1-chloroapocamphane withstands forty-eight hours of boiling with silver nitrate in water–alcohol solution without producing any opalescence.

It is concluded from the reactions of the amide and amine that the Walden inversion, in which one negative substituent replaces another on the opposite side of the same carbon atom, is not a universal necessity for the occurrence of a "negative substitution" reaction.

(22) Whitmore, Meyer, Pedlow and Popkin, THIS JOURNAL, **60**, 2788 (1938).

(23) H. Brown, *ibid.*, **60**, 1325 (1938).

The inertness of the bridge-head hydroxyl group and chlorine atom may be interpreted as indicating either (1) that a Walden inversion is absolutely necessary in the replacement of these groups, or (2) that in a carbonium ion the central carbon atom and the three atoms forming bonds with it must be coplanar. Certain drawbacks to the former of these interpretations are pointed out.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF NEW HAMPSHIRE]

Synthesis of α-2-Methoxyphenyl-β,β,β-triphenylethane

BY H. A. IDDLES, K. S. FRENCH AND E. F. MELLON

In 1932 Parsons and Porter[1] reported a synthesis of the methyl ether of α-2-hydroxyphenyl-β,β,β-triphenylethane (m. p. 172°) and used the product in establishing the probable structure for the methylation product (m. p. 172°) which they had prepared from Schorigin's[2] so-called "kryptophenol." Schorigin had obtained this rearrangement product as a by-product during the synthesis of triphenylmethyl *o*-tolyl ether and by a direct rearrangement of the ether when it was heated with metallic sodium. He postulated a structure, α-2-hydroxyphenyl-β,β,β-triphenylethane, from a somewhat analogous case in which benzyl *o*-tolyl ether was rearranged to give *o*-hydroxydibenzyl[2] by heating with metallic sodium. Van Alphen[3] also reported results on the preparation and rearrangement of this triphenylmethyl *o*-tolyl ether but gave no proof of structure of the product obtained.

However, the work of Boyd and Hardy[4] has questioned the unusual and special interpretation of Schorigin[2,5,6] which postulates the migration of the triphenylmethyl group to the side chain of *o*-cresol. They distilled the triphenylmethyl rearrangement products from the three cresols and phenol with soda lime, obtaining triphenylmethane in each case, and warmed each product with sulfuric acid, producing triphenylcarbinol. Consequently they conclude there is no evidence for postulating a different constitution for the ortho derivative.

To aid in clarifying these opposing points of view, further syntheses of "kryptophenol" as its methyl ether have been carried out. This seemed particularly desirable since the one direct synthesis of Parsons and Porter[1] has one unusual step in which the hydrolysis of the Grignard addition compound gave a hydrocarbon instead of the expected secondary alcohol.

For use in two separate syntheses, *o*-methoxybenzyl chloride was prepared by methylation of salicylic acid, electrolytic reduction to methoxybenzyl alcohol and treatment of the alcohol with thionyl chloride. In the first method the methoxybenzyl chloride was treated with triphenylmethylsodium in an atmosphere of nitrogen according to the procedure of Schlenk and Marcus,[7] who similarly produced unsymmetrical tetraphenylethane from triphenylmethylsodium and benzyl chloride. The product melted at 142–143°. In a second sequence a Grignard reagent was prepared from the *o*-methoxybenzyl chloride and this was coupled with triphenylchloromethane following an analogous reaction of Gomberg and Cone,[8] who reported an almost quantitative yield of unsymmetrical tetraphenylethane from benzylmagnesium bromide and triphenylchloromethane. The product in this case melted at 140–142° and there was no depression in a mixed melting point of the two synthetic products. However, neither agreed with the m. p. of 172° recorded by Parsons and Porter[1] for their synthetic product and a depression in melting point occurred when each of these synthetic samples was mixed with the methylated rearranged product of m. p. 162–163°.

The non-agreement between these synthetic samples and the methylated rearranged compound supports the interpretation of mechanism of Boyd and Hardy[4] which maintains that the original rearrangement of the triphenylmethyl group involves a ring position instead of the side

(1) Parsons and Porter, THIS JOURNAL, **54**, 363 (1932).
(2) Schorigin, *Ber.*, **58**, 2028 (1925); **59**, 2502 (1926).
(3) Van Alphen, *Rec. trav. chim.*, **46**, 287 (1927).
(4) Boyd and Hardy, *J. Chem. Soc.*, 630 (1928).
(5) Porter, "Molecular Rearrangements," Chemical Catalog Co., New York, N. Y., 1928, p. 118.
(6) Houben, "Die Methoden der organischen Chemie," Vol. III, 1930, p. 184.
(7) Schlenk and Marcus, *Ber.*, **47**, 1664 (1914).
(8) Gomberg and Cone, *ibid.*, **39**, 1461 (1906).