

AN ABSTRACT OF THE THESIS OF

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Title: IDENTIFICATION OF A PRODUCT OF THE FRIEDEL-
CRAFTS CYCLIZATION OF β -(3-CYCLOHEXENYL)-
PROPIONYL CHLORIDE

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Elliot N. Marvell

An improved procedure for the preparation of β -(3-cyclohexenyl)propionic acid from 4-vinylcyclohexene was developed. The Friedel-Crafts cyclization of β -(3-cyclohexenyl)propionyl chloride with aluminum chloride was shown to give one bicyclic chlorine containing ketone in 41% yield. This ketone was identified by a combination of spectral and chemical methods as a mixture of exo- and endo-6-chlorobicyclo[3.3.1]nonan-2-ones. Useful synthetic procedures for the conversion of this ketone to 6-bicyclo[3.3.1]nonen-2-one and to 2-bicyclo[3.3.1]nonanols were developed.

A logical route to 6-chlorobicyclo[3.3.1]nonan-2-one from β -(3-cyclohexenyl)propionyl chloride must involve 2-oxo-8-bicyclo[3.3.1]nonyl carbonium ion as an intermediate. In support of this idea it was shown that 8-chlorobicyclo[3.3.1]nonan-2-one can be

converted to 6-chlorobicyclo[3.3.1]nonan-2-one under the conditions of the Friedel-Crafts cyclization.

Identification of a Product of the
Friedel-Crafts Cyclization of
 β -(3-Cyclohexenyl)propionyl Chloride

by

Terry Earl McEwen

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IDENTIFICATION OF A PRODUCT OF THE
FRIEDEL-CRAFTS CYCLIZATION OF
 β -(3-CYCLOHEXENYL)PROPIONYL CHLORIDE

INTRODUCTION

Recent improvement in the understanding of cyclohexane ring chemistry has been mainly due to development of an effective conformational analysis of cyclohexane derivatives. An equivalent understanding of medium ring chemistry has been limited by the conformational mobility of these rings. A program aimed at using bridged medium rings as conformationally restricted models for medium rings has been underway at Oregon State for several years.

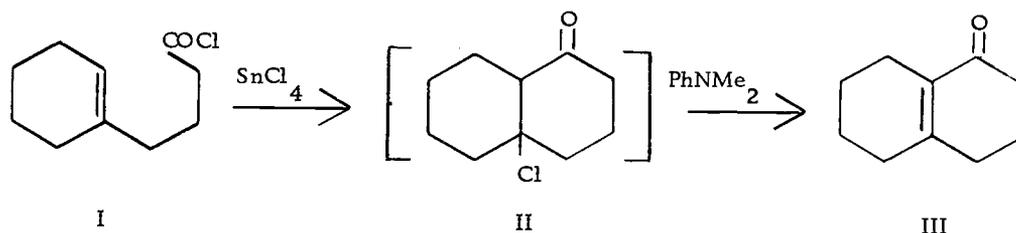
For this purpose the synthesis of bicyclo[3.3.1]nonane derivatives, especially those containing functional groups in both rings, has been investigated. It had been found previously in our laboratory that at least seven different products can be obtained from the Friedel-Crafts cyclization of β -(3-cyclohexenyl)propionyl chloride depending on the temperature, the catalyst and the solvent used. Only one of the seven, 7-bicyclo[3.3.1]nonen-2-one, had been completely identified when this work was initiated. Cyclization in 1,2-dichloroethane at room temperature with aluminum chloride as the catalyst gave one major product in 41% yield. The identification of this compound as 6-chlorobicyclo[3.3.1]nonan-2-one is the subject of the research described in this thesis.

HISTORICAL

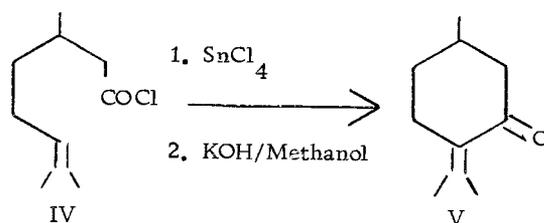
The Friedel-Crafts reaction has a long history of successful use in synthesis. The intramolecular reaction of acyl halides with aromatic substituents appropriately placed on the aliphatic chain has been one step of the standard routes to annellation of fused ring systems. Similarly the internal acylation of an unsaturated acid chloride constitutes a useful route to alicyclic molecules.¹

The first such reaction was described in 1935 by Cook and Lawrence (5) who prepared $\Delta^{9,10}$ -1-octalone (III) from γ -(1-cyclohexenyl)butyryl chloride (I) using stannic chloride in carbon disulfide. The Friedel-Crafts reaction was followed by dehydrochlorination of the intermediate. Presumably the initial product of the reaction was 5-chloro-1-decalone (II).

Citronellic acid chloride (IV) has also been cyclized under these same conditions to give, after dehydrochlorination, the terpene pulegone (V) (3)

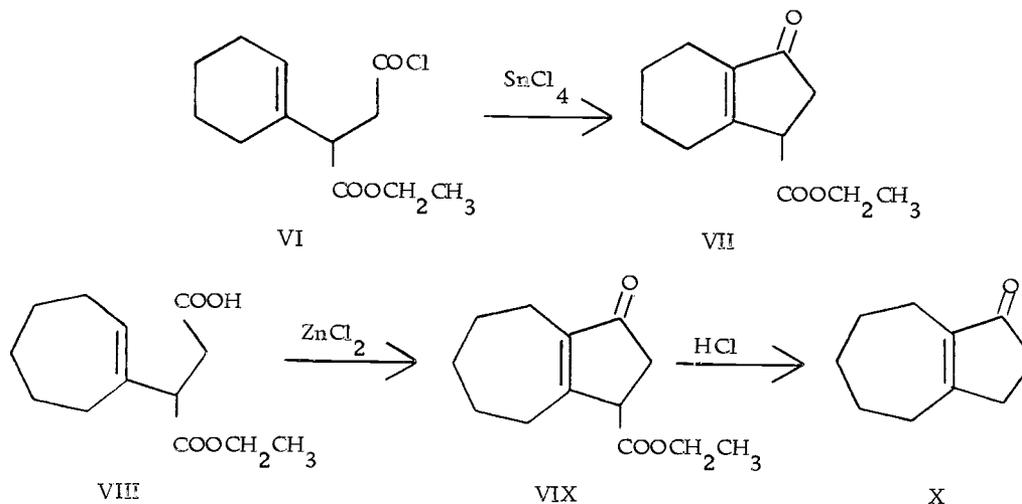


¹ For a review of intramolecular acylation, see G. A. Olah, ed. "Friedel-Crafts and Related Reactions," Vol III part 2, Interscience Publishers, John Wiley and Sons, Inc., New York, N. Y., 1964. pp. 1054-1069.



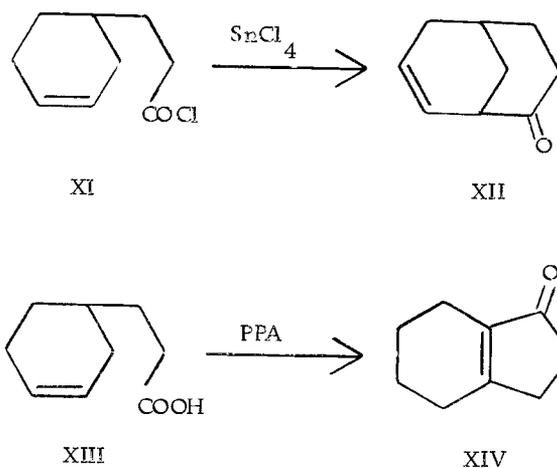
In 1953 Mathieson (20) prepared ethyl 4, 5, 6, 7-tetrahydro-3-oxoindane-1-carboxylate (VII) by treating β -carbethoxy- β -cyclohexenylpropionyl chloride (VI) with stannic chloride in 1, 2-dichloroethane.

In a similar manner, Plattner and Büchi (28) cyclized β -carbethoxy- β -cycloheptenylpropionic acid (VIII) with zinc chloride and obtained the unsaturated ketone X after hydrolysis of the intermediate keto ester VIX.

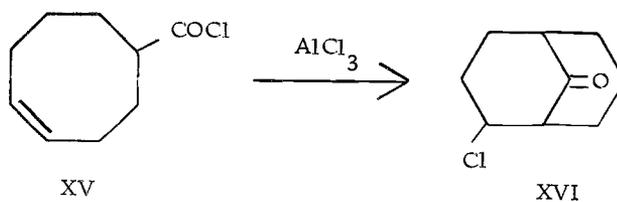


Another intramolecular acylation resulted when β -(3-cyclohexenyl)propionyl chloride (XI) was treated with stannic chloride in chloroform. In this case the product was shown to be 7-bicyclo[3.3.1]nonen-2-one (XII). However, treatment of the free acid

with polyphosphoric acid gave 4, 5, 6, 7-tetrahydroindanone (XIV) in 74% yield (30).



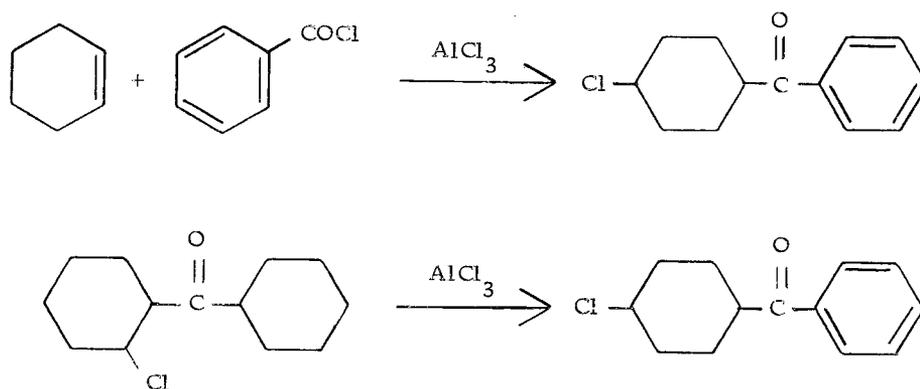
Erman and Kretschmer (8) have recently shown (1968) that treatment of the acid chloride XV with aluminum chloride in diglyme at 100°C for 16 hrs results in a 26% yield of exo-2-chlorobicyclo[3.3.1]nonan-9-one (XVI).



As the preceding examples have shown, the interaction of the olefin and the electrophilic acyl species results in an intermediate which can either add a halide ion to produce a β -haloketone or eliminate a β -proton to produce an unsaturated ketone. Another possibility, first observed by Nenitzescu and Gavăţ in 1935 (22) is a hydride shift. These workers noticed that in the aluminum

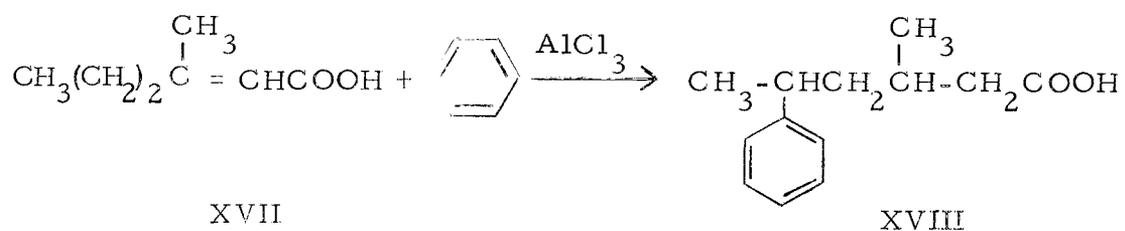
chloride catalyzed reaction between acetyl chloride, cyclohexene, and benzene in carbon disulfide the expected 1-acetyl-2-phenylcyclohexane was not formed. Instead, the 4-phenyl isomer was obtained in 34% yield. No trace of other isomeric phenylacetylcyclohexanes was found.

Hydride shifts are also indicated by the detection of isomeric chloroketones formed during Friedel-Crafts acylations. For example, the reaction of cyclohexene with benzoyl chloride in the presence of aluminum chloride results in a 5% yield of 4-chlorobenzoylcyclohexane (33). Furthermore, the 2-chlorobenzoylcyclohexane expected as a normal product of this reaction has been shown to isomerize to the 4-chloro isomer under the reaction conditions (33).



Nenitzescu and co-workers (25) have studied the products arising from aluminum chloride catalyzed acetylation of a variety of cyclic olefins. Chloroketones were formed in good yield with chlorine being found in either β or γ positions. With cyclopentene for example 96% of the chlorine appeared in the γ position and only 4% at the β carbon.

In general it seems that the migrating group terminates at a secondary carbon atom that is as far removed from the inductive influence of the carbonyl group as possible. Even a tertiary carbon atom does not halt this migration. Thus the aluminum chloride catalyzed reaction between 3-methyl-2-hexen-1-oic acid (XVII) and benzene produces 5-phenyl-3-methylcaproic acid (XVIII) (23).



In order to determine how far this migration can be forced along a saturated carbon chain, 2-nonenoic acid was condensed with benzene in the presence of aluminum chloride. Only 8-phenyl-nonanoic acid was obtained (24). Even when oleic acid was condensed with benzene under these conditions 50% of the product was 17-phenylstearic acid and the remainder of the product consisted of acids with the phenyl group appearing at positions 10-16 (24).

DISCUSSION

Friedel-Crafts cyclization of β -(3-cyclohexenyl)propionyl chloride has been found to give a number of products depending on the catalyst, the solvent and the temperature. Reaction at room temperature with aluminum chloride in 1,2-dichloroethane is of particular interest because one compound comprises about 80% of the monomeric material. This product, having the composition $C_9H_{13}OCl$, can be isolated in about 40% yield. It will be referred to here as chloroketone-A.

The spectral data for chloroketone-A are not sufficient to delineate its structure in the absence of further information. However, the absence of absorption in the olefinic proton region of the nmr in conjunction with the elemental composition and the presence of a carbonyl absorption at 1710 cm^{-1} confirms the bicyclic nature of the molecule. The carbonyl band at 1710 cm^{-1} indicates that the ring bearing the ketone must have at least six carbon atoms. Nmr resonance at 4.28 ppm shows that this is a secondary chloride and the chlorine is not alpha to the ketone. Absence of bands in the nmr at higher fields than 1.4 ppm suggested the lack of C-methyl groups. Though high frequency C-H stretching and bending bands are not observed this is not indicative since these bands are generally absent in bicyclo[3.3.1]nonanones. If skeletal

rearrangements are excluded, these data limit the possible carbon skeletons to two, viz. bicyclo[3.3.1]nonane and bicyclo[3.2.2]nonane.

Determination of the Carbon Skeleton

Since at least four of the six possible ketones of the bicyclo[3.3.1] or bicyclo[3.2.2]nonanes are known our initial effort was directed towards removal of the chlorine from chloroketone-A, hopefully giving an identifiable product. Hydrogenolysis with palladium on charcoal, which had previously been used to remove halogen from bicyclic chloroketones (34), was unsuccessful with chloroketone-A as was hydrogenolysis with Raney-nickel. Further attempts to remove the chlorine reductively using nickel-aluminum alloy in base (27), and sodium in alcohol were also unsuccessful. Finally, an attempt to dehydrochlorinate chloroketone-A with sodium ethoxide was also unfruitful.

Failure to remove the chlorine forced us to consider removal of the ketone assuming that the resulting cyclic chloride could then be converted to a known hydrocarbon. Our first attempt involved use of the Wolff-Kishner reduction. This gave directly in 32% yield an unsaturated hydrocarbon. The product was identified as 2-bicyclo[3.3.1]nonene by comparisons with the ir and nmr spectra of authentic 2-bicyclo[3.3.1]nonene (9). A mixture of the product

with an authentic sample (2) showed only one peak in the vapor-phase chromatogram. Clearly the strongly basic conditions at high temperature had led to dehydrochlorination as well as removal of the ketone function.

Raney-nickel desulfurization of the ethylenethioketal of chloroketone-A also reduced the ketone and removed the chlorine. In this case a saturated compound was obtained. The nmr spectrum of this compound showed only a broad singlet centered at 1.74 ppm and its infrared spectrum proved identical with that reported for bicyclo[3.3.1]nonane (34). A mixture of the product and an authentic sample of bicyclo[3.3.1]nonane gave a single peak in the vpc. The melting point of this hydrocarbon (143-146°) is in accord with the literature value for bicyclo[3.3.1]nonane (21) and is quite different from the recorded melting point (157-159°) for bicyclo[3.2.2]nonane (12).

These results clearly suggest that chloroketone-A possesses a bicyclo[3.3.1]nonane skeleton. However the specter of molecular rearrangement must always be considered. The most likely intermediate giving rise to facile rearrangements, the carbonium ion, is not a likely intermediate in these reactions. It also seems improbable that two such diverse sets of conditions would both lead exclusively to a rearranged skeleton. Thus these results are assumed to provide adequate evidence for the correct skeleton. This assumption

is in accord with the expectation that cyclization would be more likely to give a six-membered ring than a seven-membered one. It will also be confirmed by some of the results noted below.

Determination of the Ketone Position

Although all previous attempts to remove the chlorine by hydrogenolyses had failed, the results of the reaction of the dithioketal with Raney-nickel made it evident that such a reaction could be effected. The correctness of the supposition was illustrated by treatment of chloroketone-A with a large excess of Raney-nickel. A halogen-free product was obtained which was identified as 2-bicyclo[3.3.1]nonanol. The structural assignment was based on the spectral properties of the product and its melting point. The nmr spectrum of 3-bicyclo[3.3.1]nonanol shows an apparent septet for the CHOH proton, while the equivalent proton in 2-bicyclo[3.3.1]nonanol is not clearly resolved but appears as a broad singlet. The nmr spectrum of the product from this reaction was identical to that from authentic samples of either exo- or endo-2-bicyclo[3.3.1]nonanol (18). A vpc comparison of the product with samples of the two possible epimers showed it to be a mixture composed of about 70% endo- and 30% exo-2-bicyclo[3.3.1]nonanol. This ratio is about the same as the equilibrium ratio of the two epimers (18). Thus,

as expected on the basis of the mode of synthesis, the ketone function in chloroketone-A is at C-2.

Determination of the Chlorine Position

The positioning of the chlorine proved to be the most difficult part of the structural determination.

Owing to the symmetry of the carbon skeleton and the scarcity of reference molecules, any procedure devised must alter the chlorine while leaving the ketone as a reference site. The data already in hand permit elimination of four positions, C-1, C-3, C-4, and C-5 as possible sites for the chlorine atom. Positions C-1, C-3 and C-5, the two bridgehead positions and the alpha position, were eliminated by the nmr absorption at 4.28 ppm of chloroketone-A and position C-4, the beta position, by the inertness of chloroketone-A to sodium ethoxide at 55°. Beta chloroketones are very labile to dehydrochlorinating conditions. For example, 2-chloro-1-benzoylcyclohexane can be easily dehydrohalogenated with sodium ethoxide whereas the 4-chloro isomer cannot (33). Thus the only positions left for consideration are at C-6, C-7, C-8 and C-9. If dehydrochlorination could be effected the resulting unsaturated ketone would establish the location of the chlorine. If the chlorine were at C-6, 6-bicyclo[3.3.1]nonen-2-one would be formed. If it were at C-8, 7-bicyclo[3.3.1]nonen-2-one would

result. Both of these unsaturated ketones are known. If the chlorine were at C-7, a mixture of these two compounds would be expected. A chlorine at C-9 should be inert because a double bond cannot form between C-1 and C-9.

Initially elimination was carried out on the ethyleneketal of chloroketone-A to protect the ketone from rather rigorous treatment with strong base. Double bond formation was found to proceed slowly and use of sodium glycolate at 155° was needed to obtain a reasonable yield. Hydrolysis of the ketal gave a single unsaturated ketone identified by comparison of its ir and nmr spectra with those of authentic 6-bicyclo[3.3.1]nonen-2-one (29). The distinguishing feature of the nmr spectrum of 6-bicyclo[3.3.1]nonen-2-one compared to that of 7-bicyclo[3.3.1]nonen-2-one is the absence of a peak at 2.82 ppm corresponding to the bridgehead proton between the olefinic carbon and the carbonyl carbon. These two unsaturated ketones also have characteristically different ultraviolet spectra. The product from this reaction, 6-bicyclo[3.3.1]nonen-2-one has its λ_{\max} at 293 m μ (ϵ 41) whereas the 7-ene has a λ_{\max} at 298 m μ (ϵ 181) (34). The product from this dehydrochlorination gave no indication of being a mixture. It shows no trace of a peak in its nmr spectrum at 2.82 ppm, and no inflection at 298 m μ in its uv spectrum. Finally it has a sharp melting point, a further criterion of purity.

A second method for attaining dehydrochlorination was developed. Chloroketone-A reacts with silver trifluoroacetate in trifluoroacetic acid at room temperature giving a mixture of 54% of unchanged chloroketone-A and 46% of 6-bicyclo[3.3.1]nonen-2-one. The physical and spectral properties of the unsaturated ketone were the same as those of the product from the previous dehydrochlorination.

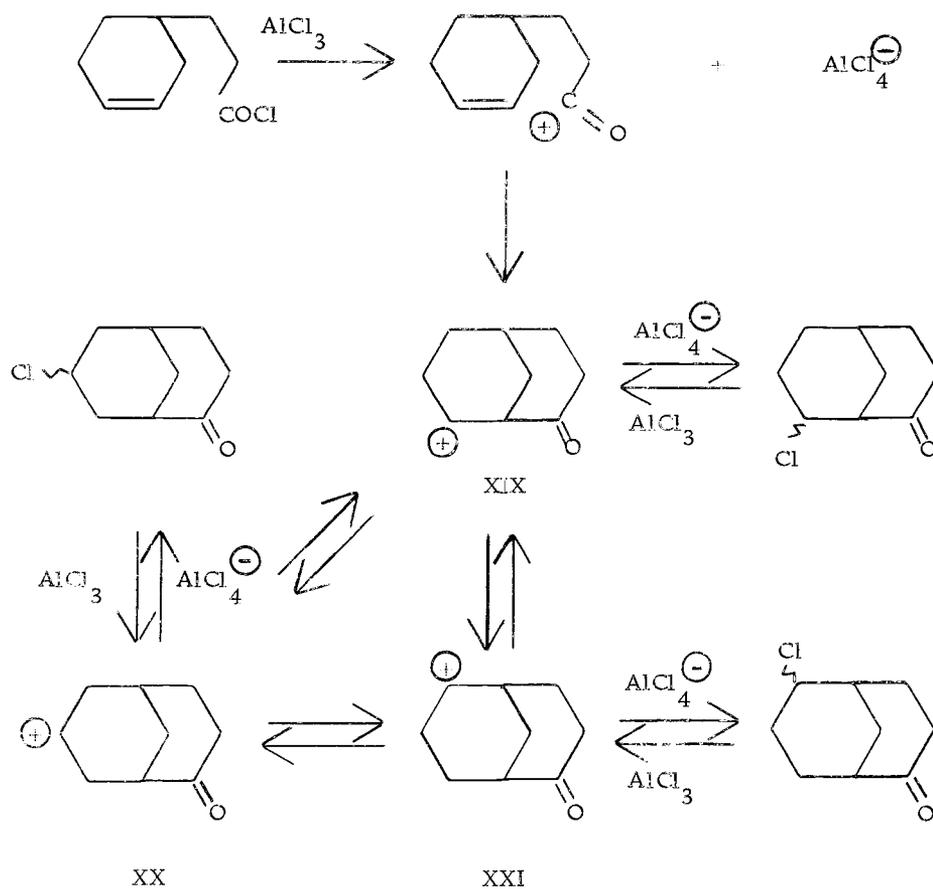
These reactions again confirm the nature of the carbon skeleton. They also provide reasonable evidence that the chlorine atom is attached to C-6. Unless the product of both reactions is the thermodynamic rather than the kinetic product, and the 6-en-2-one is more stable than the 7-en-2-one by about 2 kcal/mole, the chlorine must be at C-6. We do not consider it likely that the equilibrium between a 6-en-2-one and a 7-en-2-one should be so heavily weighted in favor of the former. Furthermore the latter does not rearrange to the 6-en-2-one in trifluoroacetic acid. Finally the resonance peak for the CHCl proton at 4.28 ppm is a broad singlet similar to those observed for the CHOH protons in the 2-bicyclo[3.3.1]nonanols, but very different from the clearly resolved pattern for the equivalent proton of the 3-ol. We conclude that chloroketone-A is thus 6-chlorobicyclo[3.3.1]nonan-2-one.

There exists one final problem; 6-chlorobicyclo[3.3.1]nonan-2-one has two stereoisomeric forms depending on the orientation of the chlorine. Considering the reaction conditions under which

chloroketone-A is formed, it seems reasonable to expect it to be an equilibrium mixture of exo and endo isomers. The infrared spectrum of chloroketone-A suggests that this is indeed the case. Allinger and Liang (1) have shown that the orientation of a chlorine on a cyclohexane ring can be deduced from the position of the C-Cl stretching band. According to their correlations the C-Cl stretch of chloroketone-A should lie between 661-678 cm^{-1} if the chlorine is axial and between 749-758 cm^{-1} if the chlorine is equatorial. Chloroketone-A shows two bands in this region, one at 768 cm^{-1} , roughly corresponding to an equatorial chlorine, and a smaller peak at 715 cm^{-1} corresponding to an axial chlorine. In our case nmr does not help distinguish the conformation of the chlorine even though the nmr chemical shifts for axial and equatorial protons of the CHCl group in cyclohexyl chlorides are different enough to be useful e. g. 3.73 ppm for axial and 4.43 ppm for equatorial (26). For bicyclo[3.3.1]nonanes the chemical shifts for epimeric protons of this type are very similar. For example, the positions of these protons in both endo- and exo-bicyclo[3.3.1]nonan-2-ol appear at 3.80 ppm (18).

Thus the appearance of a single CHCl resonance in the nmr spectrum of chloroketone-A does not indicate that only a single epimer is present. The best evidence available at present indicates that both exo- and endo-epimers are present in chloroketone-A.

Having solved the structural problem, we may now inquire about the mode of formation of this interesting product. As was noted in the historical section there are numerous references to migration of chlorine during cyclizations of unsaturated acid chlorides by Friedel-Crafts catalysts. These indicate that the preferred position taken by the chlorine is that one furthest from the carbonyl group. Though definitive evidence is not available it appears that the rearrangement process involves a series of 1,2-hydride shifts. A similar route is possible in the present case also. Thus the carbonium ion XIX



should be the direct result of cyclization of the acyl carbonium ion. A series of 1,2 hydride shifts leads through XX to XXI which gives the observed product. It is surprising that the ion XX does not give rise to any observable product. This might suggest that a 1,3-hydride shift converting XIX directly to XXI is operative.

A 1,3 hydride shift has been shown by Howe et al. (16) to be much faster than a 1,2 hydride shift in bicyclo[2.2.1] heptane systems. In eight-membered rings both 1,3 and 1,5 hydride shifts can occur. For example, in the formolysis of cis-cyclooctene oxide a 1,5 hydride shift is 22% faster than a 1,3 hydride shift. However in the solvolysis of cyclooctyl brosylate, 1,5 hydride shifts were almost the exclusive path of the reaction (7). A 1,3 shift in a six-membered ring is not very probable as was shown from the reaction of cyclohexene with peroxyformic acid. The 1,3 rearranged product (1,4 cyclohexanediol) was found in only 0.03% yield (6). The route in the present example deserves further study.

Evidence bearing on the ease of conversion of XIX to XXI was obtained experimentally. A sample of 8-chlorobicyclo[3.3.1] nonan-2-one was treated with aluminum chloride under the conditions of the synthesis. Vpc analysis of the product showed that it contained 90% chloroketone-A and 10% of an unsaturated ketone which was not further identified.

EXPERIMENTAL

 β -(3-Cyclohexenyl)propionic Acid

This reaction was carried out using a modification of the method of Finkbeiner and Cooper (10).

To 32.1 g (1.32 g-atom) of magnesium in 175 ml of dry tetrahydrofuran was added 147.8 g (1.2 moles) of n-propyl bromide under dry nitrogen. When visible evidence of initiation was noted, 100 ml more of tetrahydrofuran was added. After addition of n-propyl bromide had been completed (ca. 2 hrs) the mixture was heated under reflux for 30 min. The warm solution was diluted with 500 ml of tetrahydrofuran and to it was added very slowly 2.9 ml of titanium tetrachloride. A vigorous reaction ensued and a yellow gas was evolved. To the resulting solution was added 108 g (1 mol) of 4-vinyl-1-cyclohexene and the solution was stirred and heated at reflux for 16 hrs. The mixture was diluted with 100 ml of dry diethyl ether and cooled to -5° . Dry carbon dioxide was then passed over the stirred solution at a rate which permitted maintenance of the temperature below 10° . When the solution temperature fell to that of the cooling bath the flow of carbon dioxide was stopped, and a mixture of 550 ml of 10% sulfuric acid and ice chips was added cautiously. The aqueous layer was extracted with ether and the

combined organic layers extracted in turn with four 60 ml portions of 20% sodium hydroxide. The basic solution was cooled to 0° and neutralized carefully with concentrated hydrochloric acid. The yellow oil was separated and the aqueous phase extracted with ether. The desired product was isolated by distillation giving 76 g (0.49 mol) of β -(3-cyclohexenyl)propionic acid (49%): bp 89-90° (0.05 mm); mp 33-35° (reported: 33-35°, 34).

6-Chlorobicyclo[3.3.1]nonan-2-one: Chloroketone-A

A mixture of 12 g (0.076 mol) of β -(3-cyclohexenyl)propionic acid and eight drops of pyridine in 120 ml of dry benzene was cooled to 10-15° and 20 ml (0.23 mol) of oxalyl chloride was added over a 2 hr period. The reaction mixture was kept at 10-15° for 6 hrs after addition was complete. The solvent was removed and the residue taken up in 100 ml of n-hexane. After removal of any insoluble material by filtration, distillation gave 12.6 g (0.073 mol) of β -(3-cyclohexenyl)propionyl chloride (94%): bp 76° (2 mm).

Anhydrous aluminum chloride (17.2 g., 0.129 mol) was added to a well stirred solution of 10.1 g (0.059 mol) of β -(3-cyclohexenyl)propionyl chloride in 240 ml of dry 1,2-dichloroethane. The mixture was stirred for 5 hrs at room temperature, then cooled in an ice bath and 120 ml of 10% hydrochloric acid was added. The organic layer was separated and the aqueous layer was extracted with 1,2-dichloroethane. The organic solutions were washed in turn with sodium bicarbonate and water, dried (MgSO_4), and concentrated. A forerun

(2.02 g) was removed from this residue by distillation through a 10 cm column packed with glass helices. The bath temperature was raised from 70 to 166° and the pressure was lowered to 0.005 mm. The tarry residue was heated at 170° for 2 to 3 hrs after which the waxy solid that coated the helices and distillation head was washed off with dichloromethane and sublimed. After a second sublimation at 45° (0.1 mm) 4.12 g (41%) of chloroketone-A was obtained; mp 78-81°; ir (carbon disulfide) 2860, 1710, 986, 768, 715 cm^{-1} ; nmr (CCl_4) 1.40-2.67 (m,12), 4.28 (s, broad, 1) ppm.

Anal. Calcd for $\text{C}_9\text{H}_{13}\text{OCl}$: C, 62.61; H, 7.54; Cl, 20.57.

Found: C, 62.54; H, 7.62; Cl, 20.42.

A semicarbazone was prepared according to the method of Cheronis and Entrikin (4, p. 320): mp 184-185°.

Attempted Reductive Dechlorination of Chloroketone-A

Palladium on Charcoal

A mixture of 100 mg (0.58 mmol) of chloroketone-A, 658 mg (11.7 mmol) of potassium hydroxide, 15 ml of methanol and 188 mg of 5% palladium on charcoal was shaken in an atmosphere of hydrogen at 40 psi for 4 hrs at room temperature. The catalyst was removed by filtration and the filtrate poured into 15 ml of water. This solution was brought to about pH 6 with 10% hydrochloric acid and

extracted with dichloromethane. The extract was concentrated to about 1 ml, and vapor phase chromatographic (vpc) analysis of the residue showed it to contain mainly starting material.

Raney-nickel

The conditions used were similar to those described by Horner, Schläfer, and Kämmerer for the reduction of 2-chlorocyclohexanol to cyclohexanol (14).

To a solution of 100 mg (0.58 mmol) of chloroketone-A and 33.6 mg (0.60 mmol) of potassium hydroxide in 15 ml of methanol was added 150 mg of Raney-nickel catalyst (W-4). The mixture was treated with hydrogen for 16 hrs at 32 psi. After removal of the catalyst the solution was diluted with water and acidified with 5% hydrochloric acid. This solution was extracted with dichloromethane and concentrated. The residue was separated by preparative thin-layer chromatography (Silica gel PF₂₅₄ and benzene/ethyl acetate 95:5). Four components were obtained (total isolated weight 60 mg). The main component (42 mg) gave a positive test for halogen: ir (CCl₄) 3650, 3400, 1120 cm⁻¹; nmr (CCl₄) δ 4.30 (s, 1), 3.82 (s, 1), 2.82 (s, 1), 2.5-1.1 (m, 12) ppm. A second component (12 mg) showed a negative test for halogen and its nmr spectrum had a multiplet centered at 1.15 ppm with a strong absorption at 0.96 ppm.

Nickel-aluminum Alloy

A solution of 0.501 g of sodium hydroxide (12.5 mmol) and 200 mg (1.16 mmol) of chloroketone-A in 25 ml of 60% ethanol was stirred at 70° while 0.334 g of Raney Nickel Catalyst Powder was slowly added over 4 hrs. The solution was heated and stirred for 1 hr longer, then was cooled and acidified with concentrated hydrochloric acid. The mixture was extracted with dichloromethane, and the extracts washed with water, dried (MgSO_4) and the solvent removed giving 131 mg (65%) of a mixture containing at least four compounds. All fractions isolated from the mixture contained chlorine.

Sodium Metal

This reaction was carried out according to the method described by Houben and Pfankuch for the reduction of 1-chloro-camphene to camphene (15).

A solution of 150 mg (0.87 mmol) of chloroketone-A in a mixture of 18 ml of xylene and 2 ml of n-propanol was maintained at 145° while 554 mg (24.1 mg-atoms) of sodium was added over 3.5 hrs. No volatile material could be isolated from the tarry reaction product.

2-Bicyclo[3.3.1]nonene

Chloroketone-A (250 mg; 1.45 mmol) was mixed with 0.146 ml (3.01 mmol) of hydrazine hydrate and 0.24 g of potassium hydroxide in 2.5 ml of diethylene glycol. The solution was placed in a 10 ml flask fitted with a cold-finger condenser. The solution was heated for 4 hrs at 50° then heated to 200° for 4 hrs. The solid that collected on the cold-finger was separated by preparative vpc (Aerograph A90-P3, 100°, 5' x 1/4" 20% SF-96 column, 75 ml He/min) into two components. The first component weighing 80.4 mg (0.66 mmol) was 2-bicyclo[3.3.1]nonene (32%): mp 99.5-100.5° (reported: 96-100°, 11) halogen test negative, ir (CCl₄) 3025, 1645, 916 cm⁻¹; nmr (CCl₄) δ 5.72 (s, 2), 1.2-2.5 (m, 12) ppm.

The second component (8.8 mg, 3.5%) gave a positive test for halogen and its infrared spectrum showed no bands for hydroxyl, carbonyl, or unsaturation.

Bicyclo[3.3.1]nonane

The conditions used were similar to those described by Sondheimer and Rosenthal for the formation of 9-methyldecalin from 9-methyl-1-decalone (32).

A solution of 500 mg (2.90 mmol) of chloroketone-A in a few drops of dry ether was combined with 0.54 ml (6.4 mmol) of

1,2-ethanedithiol. To this solution was added eight drops of boron trifluoride-etherate. After 2 hrs at room temperature excess 1,2-ethanedithiol was removed by addition of 2 mls of dry ethanol followed by distillation of the azeotrope (repeated twice). The residue (ethylenethioketal of chloroketone-A) was diluted with 5 ml of dry ethanol and heated at reflux for 10 hrs with 5.5 g of Raney-nickel catalyst (W-2). The catalyst was removed by filtration and the filtrate was diluted with water and extracted with pentane. The extract was dried (CaCl_2) and concentrated by distillation. Isolation of the main component (95% of the total by vpc analysis) by preparative vpc (Aerograph A90-P3, 100° , $5' \times 1/4''$ 20% SF-96 column, 75 ml He/min.) gave 102 mg (28%) of bicyclo[3.3.1]nonane: mp $143-145^\circ$, (reported mp $145-146^\circ$, 21); ir (CCl_4) 2998, 2920, 1470 cm^{-1} ; nmr (CCl_4) 1.74 ppm. A Beilstein test for halogen was negative.

2-Bicyclo[3.3.1]nonanol

To a solution of 311 mg (1.81 mmol) of chloroketone-A in 5 ml of dry methanol was added 3 g of Raney-nickel catalyst (W-2). This mixture was stirred vigorously while being heated at reflux for 10 hrs. The catalyst was removed by filtration and extracted 4 hrs with methanol in a Soxhlet apparatus. The combined methanol solutions were concentrated, diluted with water, extracted with pentane and dried (MgSO_4). Evaporation of the pentane gave 146.6 mg

(47%) of 2-bicyclo[3.3.1]nonanol (ca. 70% endo- and 30% exo- by vpc comparison with authentic samples). A pure sample, isolated by preparative vpc (Aerograph A90-P3, 145°, 5' x 1/4" 20% SF-96 column, 75 ml He/min) gave a negative test for halogen. This sample melted at 178-182° (reported mp 185°, 21); ir (CCl₄) 3625, 3500 cm⁻¹; nmr (CCl₄) δ 1.70 (m, 14), 3.82 (s, 1), 2.72 (s, 1) ppm.

6-Bicyclo[3.3.1]nonen-2-one

Method A

The conditions used for preparing the ethyleneketal of chloroketone-A were similar to those described by Johnson et al. (17).

A mixture of 500 mg (2.9 mmol) of chloroketone-A, 16 ml of dry benzene, 5 ml (90 mmol) of 1,2-ethanediol, and 19.3 mg of p-toluenesulfonic acid was heated at reflux for 5.5 hrs. Water was removed by means of a Dean-Stark separator. The mixture was added to 10 ml of 1% sodium hydroxide and extracted with ether. The ether-benzene solution was washed with water and distilled until the boiling point of the distillate was 80°. At this point 5 ml of solution remained. The infrared spectrum of the residue showed no carbonyl or enol ether bands but did show a strong band at 1110 cm⁻¹.

The above residue was added to 20 ml of a solution prepared by adding 670 mg (29.1 mmol) of sodium to 20 ml of dry

1,2-ethanediol. The solution was heated to 155° for 4 hrs, cooled, acidified with 10% sulfuric acid, and extracted with pentane. This solution was concentrated to 1 ml and the residue was then heated at reflux for 1 hr with 10 ml of acetone and 7 ml of 4% sulfuric acid. The solution was diluted with 20 ml of water, extracted with pentane and concentrated. The main component (99% by vpc) of this solution was isolated by preparative vpc (Aerograph A90-P3, 135°, 5' x 1/4" 20% SF-96 column, 100 ml He/min). Collection gave 134.3 mg (34%) of 6-bicyclo[3.3.1]nonen-2-one: mp 61.5-62.5°; halogen test negative; ir (CCl₄) 3050, 1710, 1105 cm⁻¹; nmr (CCl₄) δ 5.84 (d, 2, J-3Hz), 2.66-1.60 (m, 10) ppm; λ_{max} (methanol) = 293 mμ (41). A semicarbazone was made using the directions of Cheronis and Entrikin (4, p. 320): mp 191-192°.

Anal. Calcd for C₁₀H₁₅N₃O: C, 62.12; H, 7.82.

Found: C, 61.98; H, 7.69.

Method B

Silver trifluoroacetate was prepared by a method described by Janssen and Wilson (19, Vol. 36, p. 47).

A solution containing 506 mg (2.32 mmol) of silver trifluoroacetate in 10 ml of trifluoroacetic acid was mixed with 200 mg (1.16 mmol) of chloroketone-A. The solution was stirred for 12 hrs at room temperature after which the white precipitate was removed

by filtration. The filtrate was diluted with water and extracted with pentane. The extract was washed with water until free from acid and silver ion, then concentrated to about 1 ml. Isolation of one peak (46% of the total by vpc) by preparative vpc (Aerograph A90-P3, 160°, 5' x 1/4" 20% SF-96 column, 100 ml He/min) furnished 26.3 mg (16.7%) of 6-bicyclo[3.3.1]nonen-2-one. The spectral and physical data of this compound were identical with those of the product from method A.

Attempted Dehydrochlorination with Sodium Ethoxide

A solution of 2.9 mmol of the crude ethyleneketal of chloro-ketone-A (prepared as previously described) and 20 ml of 4% sodium ethoxide in dry ethanol was heated at 55° for 5 hrs. When the solution was cool, 5 ml of 1% sulfuric acid was added and the solution was extracted with pentane. The organic solution was washed consecutively with water and saturated sodium chloride then concentrated. The concentrate was heated to reflux for 1 hr with 20 ml of acetone and 7 ml of 4% sulfuric acid. Subsequent extraction with pentane, concentration, and vpc analysis (Perkin Elmer, 190°, 14' x 1/8" 10% Carbowax 20 M, 17 psi helium) of the product indicated that the major component (94% of the total vpc area) was unchanged chloro-ketone-A.

Attempted Preparation of 6-Hydroxybicyclo[3.3.1]nonan-2-one

The conditions used were similar to those described by Hesse for the preparation of borneol from bornyl chloride (13).

The crude ethyleneketal was prepared from 500 mg (2.9 mmol) of chloroketone-A in the manner previously described. This solution (ca. 2 ml) was mixed with 0.221 ml (2.9 mmol) of ethyl bromide and 25 ml of dry ether and dropped onto 141.4 mg (5.82 mg-atoms) of magnesium. After having been heated at reflux for 10 hrs the mixture was cooled to 0° and dry oxygen bubbled through it for 6 hrs. This mixture was concentrated and heated at reflux for 1 hr with 20 ml of acetone and 3 ml of 5% sulfuric acid then extracted with ether. Concentration and comparative vpc analysis (Perkin Elmer, 190°, 14' x 1/8", 10% Carbowax 20M, 17 psi helium) of the extracts indicated that the volatile material in the product was composed of bicyclo[3.3.1]nonan-2-one (95%) and chloroketone-A (5%).

Isomerization of 8-Chlorobicyclo[3.3.1]nonan-2-one

A solution of 50 mg (0.29 mmol) of 8-chlorobicyclo[3.3.1]nonan-2-one in 2.5 ml of 1,2-dichloroethane was stirred with 86 mg (0.65 mmol) of anhydrous aluminum chloride at room temperature for 5.5 hrs. The mixture was hydrolyzed with 2 ml of water and extracted with pentane. The extracts were concentrated and the

main component (95% by vpc analysis) was collected in carbon tetrachloride (Aerograph A90-P3, 150°, 5' x 1/4" 20% SF-96 column, 75 ml He/min). This component was identified as 6-chlorobicyclo-[3.3.1]nonane-2-one by its vpc retention time and its infrared spectrum.

Spectral Measurements

Infrared spectra were measured on a Beckman IR8 infrared spectrophotometer. Nuclear magnetic resonance spectra were determined on a Varian A-60 NMR Spectrometer. Tetramethylsilane was used as an internal standard. The ultraviolet spectra were taken in methanol using a Cary 15 spectrophotometer.

Melting Points

Melting points were measured using a Büchi melting point apparatus and are corrected.

Elemental Analysis

Quantitative elemental analyses were done by Alfred Bernhardt Analytical Laboratories, Mulheim/Ruhr, Germany.

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