Synthesis of 1,5-Dimethylalkanes, Components of Insect Hydrocarbons

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ABSTRACT

Two general routes to 1,5-dimethylalkanes were developed. One of these uses 5-hydroxy-2-pentanone, the other 6-methyl-5-hepten-2-one, as a starting material. Although overall yields are only fair, the chemicals employed are inexpensive and the procedures are easily reproduced, thus making such compounds available for study.

INTRODUCTION

The cuticular hydrocarbons of insects serve to protect the organism from desiccation and bacterial infection. These materials, however, can serve as chemical messengers as well. For example, 13-methylhentriacontane has been identified in the feces and larvae of the corn earworm, *Heliothis zea* Boddie, as the major constituent that triggers a short range host seeking response of the parasitic wasp *Microplitis croceipes* Cresson (1). The sex pheromones of the house fly, *Musca domestica,* L. ([*Z*]-9-tricosene) (2), and the face fly, *Musca autumnalis* deGeer ([*Z*] 14-nonacosene) (3), are likewise a part of the external hydrocarbon complex of these flies. Also, examination of the cuticular hydrocarbon content of the stable fly, *Stomoxys calcitrans*, L., indicated that the male was aroused to mating behavior by the externally borne saturated hydrocarbons of the female fly (4). These included 1,5-dimethylalkanes such as [5] for which no general synthetic routes had been developed. A need exists to routinely prepare such compounds for identifications and bioassays. Additionally, such hydrocarbons which are apparently hydrids of terpenoid and fatty acid biosynthesis also have been found in the ant, *Atta colombica* Guerin (1,5,9-trimethylalkanes) (5); the tobacco hornworm (a moth), *Manduca sexta* Johannson (mono-, 1,5-di-, and 1,5,9-trimethylalkanes) (6); the grasshopper, *Schistocerca vaga* Scud. (again mono-, di-, and tri-) (7); and the Japanese beetle, *Popillia japonica* Newman (mono- and di-) (8).

EXPERIMENTAL PROCEDURES

IR spectra were taken on a Perkin Elmer 137 Infracord as films, and also as 3% carbon tetrachloride solutions on a Perkin Elmer 457A Spectrophotometer (bands assigned are from 457A spectra). Nuclear magnetic resonance (NMR) spectra were obtained in carbon tetrachloride solution with a Varian T-60 spectrometer, and chemical shifts are reported in ppm (δ) downfield relative to tetramethylsilane as internal standard. Gas liquid chromatography (GLC) analyses were performed with a Hewlett-Packard 7620A chromatograph employing an OV-1 column (0.92 m x 0.63 cm 3% on Gas Chrom Q) at temperatures ranging from 130 to 280 C. Mass spectrometric data were obtained with a Finnigan Corp. 1015 quadrupole mass spectrometer interfaced with a glass Gohlke separator to a gas chromatograph equipped with a glass column containing 3% OV-1 on Varaport. Elemental analyses were obtained from Galbraith Laboratories, Inc. (Knoxville, TN). Phosphonium salts were prepared from alkyl bromides and triphenylphosphine in the usual manner (9).

5-Hydroxy-2-pentanone Tetrahydropyranyl Ether [1]

Dihydropyran (68.0 ml, 0.75 mol) and hydrochloric acid (3 drops) were stirred in an ice bath while 5-hydroxy-2-pentanone (51.0 g, 0.50 mol) was added dropwise over 0.5 hr. The addition funnel was rinsed with a few ml of ether. The mixture was allowed to stand at ambient temperature overnight. Powdered potassium carbonate (ca. 3 g) was added, and the mixture was stirred for 0.5 hr. Magnesium sulfate (a few g) was added, and the mixture was then filtered, concentrated, and distilled through a Vigreaux column. A fraction (81.0 g, 87%) was collected: bp 79-87 C at 2 mm; $n^{28}D$ 1.4495; IR 1720 (C=O); NMR δ 2.08 (s, CH_3), 2.47 (t, CH_2CO), 3.2-4.0 (m, CH_2O), 4.47 (bs, OCHO), also 1.33 (s, CH_3 of ketol tetrahydropyranyl ether). Analysis calculated for $C_{10}H_{18}O_3$: C, 64.48; H, 9.74. Found: C, 64.32; H, 9.64.

Wittig Condensations

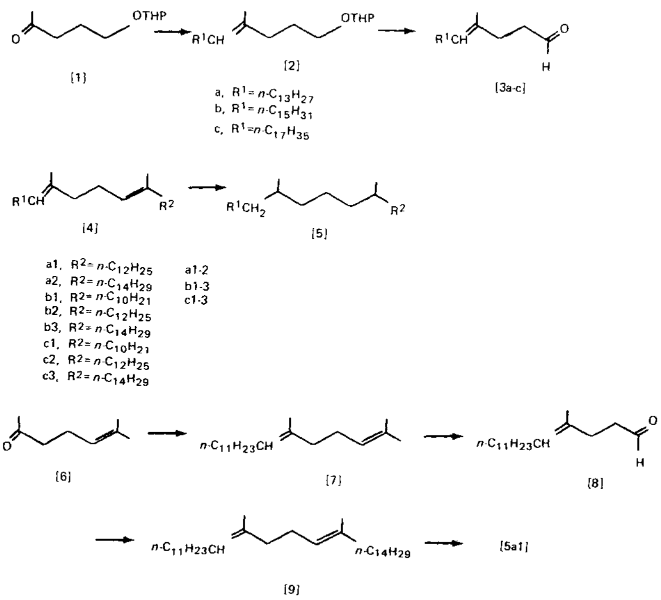
Syntheses of [2a-c]: A mixture of the alkyltriphenylphosphonium salt (43 mmol) and dry tetrahydrofuran (THF) (120 ml) was stirred under nitrogen while its temperature was maintained at 5-10 C with an ice bath. The ylid was prepared by injecting *n*-butyllithium (2.0 M hexane solution, 21.5 ml, 43 mmol) beyond the point of permanent coloration of the mixture. The ketoether [1] (7.2 ml, 40 mmol) was injected and the ice bath removed. After 1 hr, the mixture was worked up in the usual manner. Much of the triphenylphosphine oxide was removed by extraction of the product with petroleum ether. The crude product was deposited onto alumina (30 g) and placed on top of a column of silica gel (100 g). Elution with petroleum ether (200 ml) and 15:85 ether:petroleum ether (200 ml) yielded the olefinic ethers [2a-c] in the latter eluant. The yields were 30-40%, and purity was assessed by thin layer chromatography (TLC). [2a]: $n^{25}D$ 1.4634. Analysis calculated for $C_{24}H_{46}O_2$: C, 78.86; H, 12.84. Found: C, 78.62; H, 12.65. [2b]: $n^{25}D$ 1.4643. Analysis calculated for $C_{26}H_{50}O_2$: C, 79.16; H, 12.57. Found: C, 79.12; H, 12.77. [2c]: $n^{25}D$ 1.4658. Analysis calculated for $C_{28}H_{54}O_2$: C, 79.95; H, 12.80. Found: C, 79.55; H, 12.88.

Syntheses of the dienes [4], [7], and [9]: The required 1-methylalkyltriphenylphosphonium salts were prepared by generating an ylid from ethyltriphenylphosphonium bromide (5.56 g, 15 mmol) with *n*-butyllithium (8.0 ml, 16 mmol) in THF (25 ml) as described above. The 1-bromoalkane (16.5 mmol) was added to the ylid followed by hexamethylphosphoric triamide (6 ml). The mixture was stirred under nitrogen at room temperature for 20-24 hr, diluted with water, and extracted with 1,2-dichloroethane. The solvent was removed, and the residue was washed several times with petroleum ether and then freed of solvent. A solution was prepared in THF and stored.

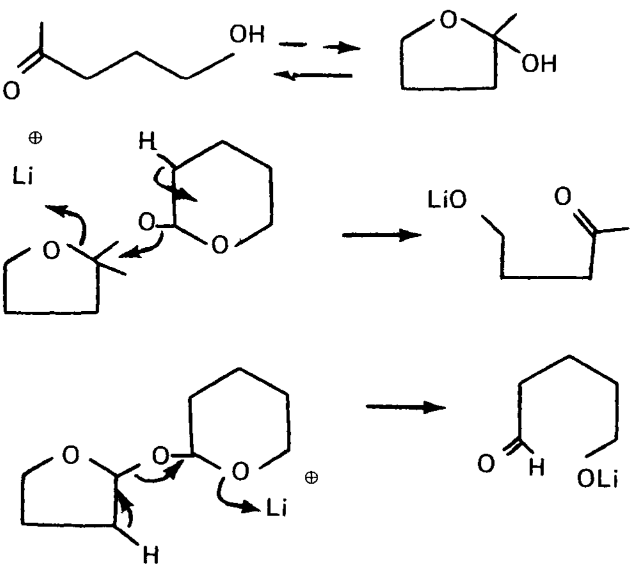
The salt solution was injected into a reaction vessel containing THF (4 ml per mmol of salt) under nitrogen. Conversion to the ylid was affected in the manner described above, and then the aldehyde [3a-c] (1.5 mmol of carbonyl component per 2.5 mmol of salt) or the ketone [6] (1 equivalent) was added. The mixture was worked up as previously described and also chromatographed as described above using similar proportions of adsorbents and eluting solvents. The dienes [4] were obtained by elution with petroleum ether. They were judged pure by TLC and were not further characterized (yields ca. 60%).

Syntheses of the Aldehydes [3] and [8]

Conversion of tetrahydropyranyl ethers [2] to alde-



SCHEME 1. Syntheses of internally branched 1,5-dimethylalkanes.



SCHEME 2. Possible mechanism for formation of isomeric alkanes as by-products.

hydes [3]: The ether [2] (9 mmol), propionic acid (50 ml), and water (6 ml) were stirred at 60-70 C for 20-22 hr. The mixture was diluted with water and then was extracted with petroleum ether, and the organic phase was washed to neutrality (aqueous sodium bicarbonate). The solution was dried (magnesium sulfate) and concentrated. The alcohols thus obtained were used directly.

A solution of chromic oxide (5.5 g, 55 mmol) and pyridine (8.85 ml, 110 mmol) in methylene chloride (145 ml) was prepared and used for the oxidation of the alcohols to the aldehydes [3]. The procedure for this oxidation and the product work-up has been described (10). The crude aldehydes were purified by column chromatography using silica gel (100 g) and 200 ml each of petroleum ether and 15% ether:petroleum ether; the aldehydes eluted with the latter solvent (70-80% yields from the ethers [2]). The products obtained were sufficiently pure to proceed with condensations; the physical data, including partially resolved GLC peaks for the *Z* and *E* isomers, confirmed their identities. Compound [3a]: IR 2740 (HC=O), 1735 (C=O); NMR δ 5.10 (bt, vinyl H), 9.63 (bs, CHO).

Conversion of diene [7] to aldehyde [8]: Diene [7] (6.4 g, 23 mmol) was added to a solution of *N*-bromosuccinimide (4.5 g, 24 mmol) in 1,2-dimethoxyethane (85 ml). Water was added till saturation occurred, and the resulting homogeneous mixture was allowed to stand for 5 hr. The mixture was diluted, the bromohydrin was extracted with ether, and the organic phase was dried and concentrated. The crude bromohydrin was dissolved in isopropanol (100 ml) containing sodium isopropoxide (from 45 mmol of sodium hydride), and the mixture was allowed to stand overnight. The mixture was diluted and extracted with petroleum ether. The crude epoxidized product was placed onto silica gel (100 g) and eluted with petroleum ether (300 ml), whereupon diene [7] was recovered (0.9 g, 14%). Elution with 15% ether (300 ml) provided the epoxide (3.2 g, 47%) in suitable purity for further transformation (TLC indicated both possible epoxides had been generated).

The epoxide (3.0 g, 10 mmol) was dissolved in THF and water (15 ml each). THF was added till homogeneity was achieved, perchloric acid (5 drops of 70%) was added, and the mixture was allowed to stand overnight at room temperature. The product diol was worked up in the usual manner. Lead tetraacetate (5.15 g, 11 mmol) was slurried in dry benzene (50 ml), and the diol was added. The resulting mixture was stirred at 40 C for 0.75 hr and then transferred to a beaker with ether and diluted with 200 ml of 20% aqueous acetic acid. The resulting emulsion was satisfactorily handled by filtering the mixture through celite. The phases were separated, and the product was worked up in the usual fasion. The TLC indicated good purity of the aldehyde (1.4 g, 54%: IR 2740, 1735; NMR δ 5.10 (bt vinyl H), 9.65 (bs, CHO); GLC analysis revealed the presence of dodecanal which indicated that internal epoxidation had occurred to the extent of about 4%.

Synthesis of the 1,5-Dimethylalkanes [5]

The dienes [4] and [9] (ca. 0.4 g) were each hydrogenated using 10% palladium on charcoal (ca. 0.1 g) and hexane (15 ml) at atmospheric pressure. Hydrogenation was followed by GLC, the overlapping peaks of the diene isomers giving way to a sharp single peak with slightly greater retention. Low temperature (-20 C) recrystallization from acetone (ca. 50 ml per 0.25 g) was performed. The products were semisolids, pure by GLC and TLC analyses. Chemical analyses of one 1,5-dimethylalkane derived from each of the ethers [2] follows. Compound [5a1]: $n^{25}D$ 1.4525. Analysis calculated for $C_{33}H_{68}$: C, 85.26; H, 14.74. Found: C, 85.17; H, 14.80. Compound [5b2]: $n^{25}D$ 1.4535. Analysis calculated for $C_{35}H_{72}$: C, 85.28; H, 14.72. Found: C, 85.22; H, 14.80. Compound [5c2]: $n^{25}D$ 1.4543. Analysis calculated for $C_{37}H_{76}$: C, 85.30; H, 14.70. Found C, 85.49; H, 14.67.

RESULTS AND DISCUSSION

The ketone, 5-hydroxy-2-pentanone, was converted to its tetrahydropyranyl ether (Scheme 1). Although 5-hydroxy-2-pentanone gave NMR evidence for the ketol (Scheme 2), the mixture being 1:1, the tetrahydropyranyl ether was 80-85% [1] judging by both NMR and GLC data. Condensation of this material with alkylidenetriphenylphosphoranes afforded the alkylidene ethers [2] after filtration of the crude product through silica gel. The ethers [2] were not soluble in acetic acid and were therefore best hydrolyzed in warm aqueous propionic acid. The crude alcohols were then oxidized by Collins reagent using the modification of Ratcliffe and Rodehorst (10). The aldehydes were obtained by column chromatography (alumina, or silica gel) and were stored cold. (1-Methylakylidene)triphenylphosphoranes were prepared by allowing ethylidenetriphenylphosphorane to react with 1-

bromoalkanes in tetrahydrofuran-hexamethylphosphoric triamide at room temperature for a day. The crude oily salt was recovered and stored as a solution (ca. 1N) in tetrahydrofuran. Treatment of such salt solutions with *n*-butyllithium generated the required α-methyl phosphoranes which, upon reacting with the aldehydes [3], produced the dienes [4]. The dienes, undoubtedly mixtures of geometrical isomers, were obtained by filtration through silica gel. Hydrogenation over a palladium catalyst gave the 1,5-dimethylalkanes [5] as mixture of diastereomers.

A by-product of these preparations constituting a few percent of the product was identified as a hydrocarbon with the same number of carbon atoms and one less methyl substituent. For example, 13,17-dimethylhentriacontane [5a1] contained 5% of 13-methyldotriacontane, which was identified by mass spectrometry (P^+ m/e = 464, α-cleavages m/e 176, 295). A likely source of this by-product is the tetrahydropyranyl ether of the ketol (Scheme 2) which might react with phosphoranes, perhaps because lithium chloride is present, as either the ketoether [1] or the tetrahydropyranyl ether of 5-hydroxyvaleraldehyde.

Ketone [6] was allowed to react with 1-dodecylidene triphenylphosphorane to give the diene [7]. Such dienes are known to undergo selective electrophilic addition at the exposed (terminal) double bond (11). Treatment of [7] with N-bromosuccinimide in aqueous tetrahydrofuran followed by cyclization of the resulting bromohydrin with sodium isopropoxide/isopropanol provided and epoxide after chromatographic purification. Hydrolysis to the diol was followed by cleavage with lead tetraacetate to give the aldehyde [8]. The degree to which this compound was contaminated with shorter chain aldehyde (dodecanal) and ketone [6] derived from internal epoxidation was determined by GLC. Internal epoxidation accounted for 4% of the product. Reaction of the aldehyde [8] with 1-methyl-1-pentadecylidenetriphenylphosphorane (from ethylidenetriphenylphosphorane and 1-bromotetradecane followed by *n*-butyllithium) produced the diene [9]. Hydrogenation as before gave 13,17-dimethylhentriacontane [5a1]. Only a small amount of materials of shorter GLC retention were present, further confirming that the epoxidation of [7] had indeed been very selective.

Although overall yields of internally branched 1,5-dimethylalkanes are only 10-20%, the processes described involve readily available chemicals and are easily reproduced. The availability of such hydrocarbons should aid in natural product identifications and make materials available for insect bioassays and applications studies.

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