New Synthesis of β-Agarofuran and of Dihydroagarofuran

George Büchi* and Hans Wüest

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

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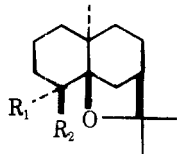
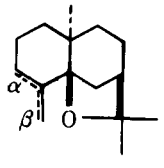
Dihydroagarofuran (1), a constituent of galbanum resin (*Ferula spp.*), and β-agarofuran (3), present in fungus-infected agarwood (*Aquillaria agalocha*), were prepared in a stereoselective manner from (−)-carvone (4) in seven and eight chemical operations, respectively. Alkylation of 8-hydroxy-*p*-menthan-2-one (5) with 5-iodo-1-pentyne gave the highly crystalline acetylene 7, which was converted to the bridgehead chloride 12 with phosphorus pentachloride. Efforts to cyclize 12 reductively with tributyltin hydride failed, but cyclization of the corresponding (trimethylsilyl)acetylene 13 afforded a mixture of diastereomeric vinylsilanes 16 in 72% yield. Both isomers were hydrolyzed to β-agarofuran (3) in wet acetonitrile in the presence of a catalytic amount of *p*-toluenesulfinic acid. Reduction of β-agarofuran (3) with diimide gave dihydroagarofuran (1), exclusively, and similar reduction of vinylsilane 16 gave a single product. The stereoselectivity in these reductions is attributed to a directing effect by the proximate tetrahydrofuran oxygen atom. Reference is made to the unusual ozonization of vinylsilanes.

Galbanum resin, a plant exudation of *Ferula spp.* (Umbelliferae) collected mainly in the mountains of Turkestan and in Iran, is used for the production of fragrances of the oriental type. Dihydroagarofuran (1),[1] one of the many constituents of the resin, is suspected of being an important contributor to the typical odor of galbanum. For an evaluation of its olfactive properties gram quantities of isomer free dihydroagarofuran (1), preferably of synthetic origin, were needed. Although several syntheses of both α- and β-agarofuran (3) have been described,[2-6] these olefins have been poor precursors of their dihydro derivatives. Catalytic reduction of α-agarofuran (3),[1,4,7] using a variety of catalyst–solvent combinations, is invariably accompanied by hydrogenolytic opening of the tetrahydrofuran ring and yields only little isodihydroagarofuran (2) contaminated by minor amounts of dihydroagarofuran (1). β-Agarofuran (3) is reduced more



1, $R_1 = CH_3$; $R_2 = H$
2, $R_1 = H$; $R_2 = CH_3$



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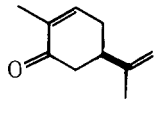
readily, but the dihydroagarofuran (1) obtained contained up to 40% of the isodihydro epimer (2).[1] Since the separation of these epimeric dihydro compounds on a preparative scale is highly impracticable, we decided to search for alternate routes to dihydroagarofuran (1).

Earlier syntheses of the agarofurans, without exception, proceeded from cyclohexanes to decalins and terminated with the construction of the tetrahydrofuran ring. The stereochemical difficulties encountered in this approach prompted us to prepare a suitable oxabicyclo[3.2.1]octane, and to attempt its stereoselective cyclization to dihydroagarofuran (1). Crystalline hydroxydihydrocarvone 5 was prepared by hydration of (−)-carvone (4) with 50% aqueous sulfuric acid. Yields superior to those mentioned in the literature[8] were obtained when unreacted carvone, and other nonpolar products, were first removed by extraction of the reaction mixture with pentane–ether. Continuous extraction of the aqueous phase with ether then led directly to the pure alcohol 5 in 63% yield. Catalytic reduction yielded a mixture of epimeric hydroxy ketones 6. Conversion to the acetylene 7 was effected using 5-iodo-1-pentyne and sodium amide in liquid ammonia. The isolation of this critical intermediate became trivial when it was found that the desired epimer could be crystallized from ether solutions of the crude reaction mixture. The configuration already assigned is based on the assumption of axial alkylation, and in analogy to the well-known synthesis of 10-epi-α-cyperone from dihydrocarvone and ethyl vinyl ketone.[2-4] Our initial plan called for the preparation of olefin 9, which we hoped to convert to dihydroagarofuran (1) by a free-radical cyclization.[9] Accordingly, the triple bond was reduced to a double bond by hydrogenation over a Lindlar catalyst. Treatment of the ketone 8 with phosphorus pentachloride in carbon tetrachloride afforded the chloro ether 9 (64%) accompanied by the dienone 11 (18%). For reductive cyclization the chloro ether was treated with tributyltin hydride. Using cyclohexane as solvent and azoisobutyronitrile as radical initiator this procedure gave a mixture of isodihydroagarofuran (2) and dihydroagarofuran (1) in a ratio of 7:3 (67% yield) in addition to the uncyclized reduction product 10 (20%). In agreement with Walling,[10] who studied the reaction of 6-bromo-1-hexene with tributyltin hydride, we found the ratio of uncyclized to cyclized product to increase when higher concentrations of the reducing agent were used. Thus, when equimolar proportions of chloride and hydride, without added solvent, were caused to react 27% of the reduction proceeded with cyclization and 62% without. Not unexpectedly, the ratio of dihydroagarofurans showed no dependence on hydride concentration. The overall process, undoubtedly, proceeds through the bridgehead radical, which adds to the olefinic bond to produce, contrary to the usual direction of radical addition, a cyclohexylmethyl radical in preference to the energetically less favorable cycloheptyl radical. Clearly, a speculation that the oxygen atom of the tetrahydrofuran ring would have the desired effect on the steric course of the cy-



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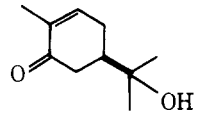

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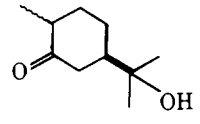

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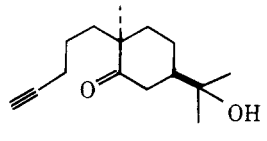

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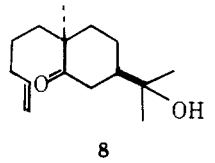

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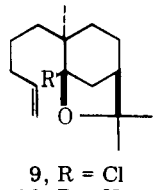
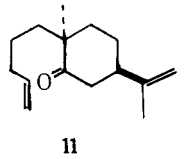


9, R = Cl
10, R = H



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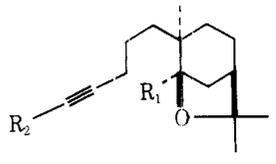
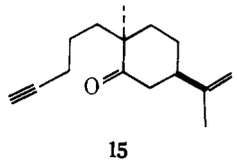
clization and lead to an axially oriented methyl group was not verified by experiment and an alternate route had to be examined.

Treatment of the acetylenic ketone **7** with phosphorus pentachloride afforded the expected bridgehead chloride **12** which again was accompanied by a product **15** (20%) resulting from dehydration. Reductive cyclization of **12** failed, producing only high molecular weight products which were not identified. Perhaps the acetylenic hydrogen caused complications and to prepare a protected acetylene **12** was submitted to the action of ethylmagnesium bromide followed by chlorotrimethylsilane. The acetylenic silane **13** when treated with tributyltin hydride under standard conditions afforded a mixture of products which consisted of the vinylsilanes **16** (72%) and the uncyclized acetylenic silane **14** (13%). Vinylsilane **16** was a 4:1 mixture of geometric isomers separable by gas–liquid chromatography. In contrast to the radical cyclization of 1-ethoxy-6-iodo-1-hexyne-*3,3-d*$_2$ to 2-ethoxymethylene-*1,1-d*$_2$ cyclopentane, which proceeds with 96% anti addition,[11] the radical cyclization used in our synthesis lacks stereospecificity.

To complete the synthesis of β-agarofuran (**3**), vinylsilanes **16** had to be converted to the olefin and this could be accomplished by hydrolysis with aqueous hydriodic acid,[12] but the desired olefin contained impurities that were difficult to remove. We have found that many vinylsilanes can be converted to olefins in wet acetonitrile in the presence of a catalytic amount of *p*-toluenesulfinic acid.[13] β-Agarofuran (**3**) obtained in 92% yield was found to be identical with authentic material. In an alternate synthesis, the vinylsilanes **16** were treated with mercuric acetate in aqueous tetrahydrofuran containing some acetic acid. The resulting acetoxyvinylmercury compound was transformed to the divinyl mercurial, mp 195–197 °C, by sodium borohydride. Reduction of both mercurials with lithium aluminum hydride afforded β-agarofuran (**3**) in good yield. This mild, two-step conversion of vinylsilanes to olefins seems to be new, but its scope was not investigated. For further characterization as the crystalline norketone **19** vinylsilane **16** was submitted to ozonization in methanol, but after reduction of intermediates with dimethyl sulfide only 11% of ketone **19** was isolable, and contrary to a vast body of experience with simple olefins, the α-hydroxyaldehyde **18** (76%) was found to be the major product. In a separate study[14] trimethylsilyldioxetanes and α-trimethylsilyl peroxy ketones or aldehydes were shown to be the initially formed products. Thermal decomposition of the dioxetanes is responsible for the appearance of fragmentation products (**19**) while reduction of both peroxidic intermediates leads to α-hydroxycarbonyl compounds (**18**).





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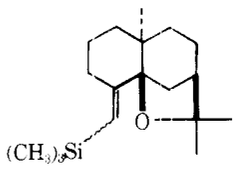
12, R$_1$ = Cl; R$_2$ = H
13, R$_1$ = Cl; R$_2$ = Si(CH$_3$)$_3$
14, R$_1$ = H; R$_2$ = Si(CH$_3$)$_3$



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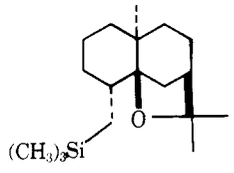

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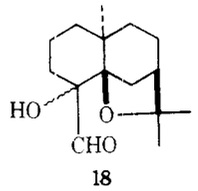

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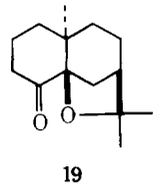

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Three examples seem to show that the steric course of olefin reduction with diimide is dramatically affected by ester or ether groups located in proximity. Due to an, as yet undefined, diimide ester or ether interaction hydrogen addition occurs preferentially cis to these substitutents. The effect was discovered by Baird[15] with two 7-substituted norbornadienes and was later used successfully in a stereoselective synthesis of spirovetivanes.[16] Diimide reduction of β-agarofuran (**3**) (hydrazine, ethanol, hydrogen peroxide, 5–20 °C) afforded 92% dihydroagarofuran (**1**), which according to its nuclear magnetic resonance spectrum contained less than 5% of epimer **2**. Similar reduction of vinylsilane **16** gave a single saturated silane **17**, but its stereochemistry was not verified. Interestingly α-agarofuran (**3**) is not reduced by diimide at room temperature. After 2 h at 140 °C in diglyme using tosylhydrazine[17] as the source of diimide only 40% of the starting material was consumed, and the reduction product contained 70% isodihydroagarofuran (**2**) and 30% dihydroagarofuran (**1**) as determined by nuclear magnetic resonance spectroscopy and gas–liquid chromatography using a capillary column.[18] The substantial difference in the behavior of these two olefins is in agreement with earlier findings because, for instance, methylenecyclohexane was found to be more than 30 times more reactive toward diimide than methylcyclohexene.[19] It also showed that the directing effect of oxygen substituents is lost when reductions have to be performed at elevated temperatures.

Experimental Section

The following spectrometers and solvents were used: IR, Hitachi Perkin-Elmer Model 247 ($CHCl_3$); NMR, Varian T-60 (CCl_4, unless otherwise stated; tetramethylsilane as internal standard); mass spectra, Varian MAT 44 (only molecular ion peak and the three most intense peaks listed); optical rotation, Perkin-Elmer polarimeter (EtOH, unless otherwise stated). Boiling points are uncorrected. Melting points were determined on a hot-stage microscope. GLC analyses were performed on a F&M 720 instrument, using silicon rubber gum SE-30 and Carbowax 20 M columns. Microanalyses were performed by the Robertson Laboratory, Florham Park, N.J.

8-Hydroxy-*p*-6-menthen-2-one (5).[8] A mixture of 300 g of (−)-carvone (**4**) and 2 kg of 50% aqueous sulfuric acid was stirred for 40 h at 22–24 °C. After extraction with 350 mL of pentane–ether (3:1), the aqueous layer was submitted to 24 h of continuous extraction with ether. The ether solution was washed with brine containing sodium bicarbonate, evaporated, and distilled to give 212 g (63%) of **5**: bp 88 °C (0.1 mm); solidifies on cooling. A sample was crystallized from ether: mp 42 °C (lit.[8] mp 40–41 °C); $[\alpha]^{25}_D$ −42° (*c* 6.9) (lit.[8] −43°); IR 3610, 3470, 1660 cm^{-1}; NMR δ 1.20 (6, s), 1.70 (3, s), 3.0 (1, s exchanged with D_2O), 6.7 (1, b), 1.7–2.6 (5, m).

8-Hydroxy-*p*-menthan-2-one (6). A solution of 75.5 g of **5** in 300 mL of ethyl acetate was hydrogenated in the presence of 0.7 g of 10% Pd/C. Hydrogen uptake after 12 h at 20 °C (760 mm) was 10.3 L. Filtration, followed by evaporation and distillation, yielded 71.0 g (93%) of **6**: bp 68 °C (0.1 mm) [lit.[20] bp 81–82 °C (0.05 mm)]; IR 3620, 3470, 1700 cm^{-1}; NMR δ 0.93 (3, d, *J* = 7 Hz). 1.17 (6, s), 2.8 (1, b, exchanged with D_2O), 1.0–2.5 (8, m).

5-Iodo-1-pentyne.[21] A stirred mixture of 82.1 g (0.8 mol) of commercial 5-chloro-1-pentyne, 180 g (1.2 mol) of sodium iodide, and 750 mL of acetone was heated at reflux for 24 h. After removal of most of the acetone in vacuo, water was added, and the mixture was extracted with *n*-pentane. The organic layer was washed with aqueous sodium thiosulfate solution, dried (Na_2SO_4), evaporated, and distilled to give 137 g (88%) of the iodide: bp 58 °C (12 mm); IR 3320, 2130 cm^{-1}.

Hydroxy Ketone 7. Potassium amide was prepared from 27.3 g (0.7 g-atom) of potassium in 1 L of liquid ammonia. Ketone **6** (136 g; 0.8 mol) in 250 mL of dry ether was added within 5 min at −30 °C. A gum precipitated which redissolved. Stirring was continued for 10 min at −30 °C, then 136 g (0.7 mol) of 5-iodo-1-pentyne was added over 5 min at reflux temperature. The ammonia was allowed to evaporate and was gradually replaced with ether. The resulting solution was washed

with water, dried (Na_2SO_4), evaporated, and distilled. A forerun [47 g, bp 82–88 °C (0.1 mm)] consisted of recovered **6**. The product distilling at 110–116 °C (0.1 mm) (100 g) was dissolved in 100 mL of ether, and 300 mL of *n*-hexane was added. The solution was seeded (with a sample obtained previously by column chromatography) and allowed to crystallize for 3 days at 0 °C. Filtration gave 51 g (41%, based on recovered **6**) of **7**: mp 68 °C; $[\alpha]^{25}_D$ +120° (*c* 5.3); IR 3620, 3470, 3320, 1705 cm^{-1}; NMR δ 0.95 (3, s), 1.17 (6, s), 2.6 (1, s, exchanged with D_2O), 0.9–2.5 (14, m); mass spectrum, *m/e* (rel intensity) 236 (4), 152 (100), 110 (54), 43 (53). Anal. ($C_{15}H_{24}O_2$): C, H.

Hydroxy Ketone 8. Ketone **7** (4.72 g, 20 mmol) in 15 mL of ethyl acetate and 80 mL of cyclohexane was hydrogenated in the presence of 100 mg of Lindlar catalyst. After uptake of 1 equiv of hydrogen (80 min), the solution was filtered, evaporated, and distilled to give 4.61 g (97%) of **8**: bp 102 °C (0.1 mm); $[\alpha]^{25}_D$ + 112° (*c* 3.25); IR 3620, 3500, 1700, 1640, 990, 915 cm^{-1}; NMR δ 0.93 (3, s), 1.17 (6, s), 0.9–2.4 (13, m), 2.8 (1, s, exchanged with D_2O), 4.7–6.1 (3, m); mass spectrum, *m/e* (rel intensity) 238 (1), 112 (65), 59 (84), 41 (100). Anal. ($C_{15}H_{26}O_2$): C, H.

Chloro Ether 9. A solution of 5.23 g (22 mmol) of **8** in 20 mL of CCl_4 was added to 5.2 g (25 mmol) of phosphorus pentachloride in 70 mL of CCl_4 over a period of 5 min, without external cooling. Stirring was continued for 10 min, then 20 g of sodium bicarbonate and 100 mL of water were added with ice cooling. After 1 h of being stirred at room temperature, the organic layer was separated, dried (Na_2SO_4), and evaporated. Separation of **9** and **11** was achieved by chromatography on silica gel in benzene. Chloro ether **9**: 3.61 g (64%); bp 82 °C (0.1 mm); $[\alpha]^{25}_D$ −39° (*c* 3.78); IR 1640, 1000, 910 cm^{-1}; NMR δ 1.03 (3, s), 1.33 (6, s), 1.0–2.8 (13, m), 4.8–5.1 (2, m), 5.4–6.1 (1, m); mass spectrum, *m/e* (rel intensity) 256 (5), 82 (48), 81 (51), 41 (100). Anal ($C_{15}H_{26}ClO$): C, H, Cl. Ketone **11**: 0.88 g (18%); bp 66 °C (0.1 mm); $[\alpha]^{25}_D$ +103° (*c* 3.06); IR 1700, 1640, 990, 915, 895 cm^{-1}; NMR δ 0.97 (3, s with fine splitting), 0.9–2.1 (13, m), 4.70 (2, s, with fine splitting), 4.7–5.1 (2, m), 5.4–6.1 (1, m); mass spectrum, *m/e* (rel intensity) 220 (2), 152 (88), 67 (91), 41 (100). Anal. ($C_{15}H_{24}O$): C, H.

Mixture of Isodihydroagarofuran (2) and Dihydroagarofuran (1). A mixture of 1.03 g (4 mmol) of **9**, 1.2 mL (4.5 mmol) of tributyltin hydride, 20 mg of azobis(isobutyronitrile), and 15 mL of cyclohexane was irradiated with a regular 100-W bulb and heated at reflux for 1 h. Evaporation left an oil, which was chromatographed on silica gel containing 10% silver nitrate. *n*-Hexane eluted 0.60 g (67%) of a ca. 7:3 mixture (NMR analysis) of **2** and **1**, bp 51 °C (0.1 mm). Further elution with *n*-hexane–2% ethyl acetate gave 0.18 g (20%) of **10**: bp ca. 65 °C (0.1 mm); $[\alpha]^{25}_D$ −80° (*c* 3.40); IR 1640, 1000, 920 cm^{-1}; NMR δ 0.80 (3, s), 1.10 (3, s), 1.30 (3, s), 0.9–2.2 (13, m), 3.66 (1, d, *J* = 6 Hz), 4.7–5.1 (2, m), 5.4–6.1 (1, m); mass spectrum, *m/e* (rel intensity) 222 (20), 97 (69), 81 (78), 41 (100). Anal. ($C_{15}H_{26}O$): C, H.

Chloro Ether 12. Ketone **7** (7.1 g, 30 mmol) in 25 mL of CCl_4 was treated as described above with 6.8 g (33 mmol) of phosphorus pentachloride in 100 mL of CCl_4. Crystallization from 40 mL of *n*-hexane at −20 °C yielded 4.50 g of **12**: mp 80 °C; $[\alpha]^{25}_D$ −48° (*c* 4.50); IR 3320 cm^{-1}; NMR δ 1.07 (3, s), 1.35 (6, s), 1.2–2.8 (14, m); mass spectrum, *m/e* (rel intensity) 239 (0.2, $M^+ - 15$), 93 (83), 55 (85), 41 (100). Anal. ($C_{15}H_{23}ClO$): C, H, Cl.

Chromatography of the mother liquors in benzene on silica gel afforded an additional 0.90 g (71% combined yield) of **12** and 1.30 g (20%) of **15**: bp 60 °C (0.1 mm); $[\alpha]^{25}_D$ +109° (*c* 3.42); IR 3310, 1700, 1640, 895 cm^{-1}; NMR δ 1.00 (3, s), 1.77 (3, s), 4.72 (2, s), 1.0–2.5 (14, m); mass spectrum, *m/e* 218 (2), 152 (100), 109 (66), 41 (63).

Silane 13. To the Grignard reagent prepared from 0.73 g (30 mg-atom) of magnesium and 2.6 mL (35 mmol) of bromoethane in 20 mL of THF was added 5.1 g (20 mmol) of **12** in 10 mL of THF. After 6 h at 20 °C, 5 mL (40 mmol) of trimethylchlorosilane was added with cooling and stirring was continued for 16 h at room temperature. The reaction mixture was poured into water and extracted with *n*-pentane. The organic layer was washed with water, dried (Na_2SO_4), and evaporated to give 6.4 g (98%) of crystalline **13**. A sample was recrystallized from *n*-hexane: mp 59 °C; $[\alpha]^{25}_D$ −37° (*c* 2.18); IR 2175 cm^{-1}; NMR δ 0.13 (9, s), 1.03 (3, s), 1.30 (3, s), 1.33 (3, s), 1.2–2.8 (13, m); mass spectrum, *m/e* (rel intensity) 326 (1), 73 (100), 69 (50), 41 (57). Anal. ($C_{18}H_{31}ClOSi$): C, H, Cl.

Vinylsilane 16. A mixture of 6.5 g (20 mmol) of **13**, 100 mg of azobis(isobutyronitrile), 6.5 mL (25 mmol) of tributyltin hydride, and 75 mL of cyclohexane was irradiated with a regular 100-W bulb and heated at reflux for 1 h. Evaporation left an oil, which was separated into tributylin chloride, **16**, and **14** by chromatography on 200 g of silica gel using *n*-hexane–2% ethyl acetate as eluant. Silane **16**: 4.23 g (72%), bp 83–85 °C (0.1 mm). GLC indicated the presence of two isomers (ratio ca. 1:4) which were collected. Minor isomer: IR 1620 cm^{-1}; NMR δ 0.12 (9, s), 0.82 (3, s), 1.10 (3, s), 1.31 (3, s), 1.0–2.5 (13, m), 4.97 (1, s); mass spectrum, *m/e* (rel intensity) 292 (20), 73 (93), 43 (92), 41 (100). Anal. ($C_{18}H_{32}OSi$): C, H. Major isomer: IR 1610 cm^{-1}; NMR δ 0.17 (9, s), 0.87 (3, s), 1.08 (3, s), 1.32 (3, s), 1.0–3.0 (13, m), 5.20 (1, s); mass spectrum, *m/e* (rel intensity) 292 (56), 277 (72), 73 (100), 41 (98). Anal. ($C_{18}H_{32}OSi$): C, H. Silane **14**: 0.77 g (13%); bp 84 °C (0.1 mm); IR 2160 cm^{-1}; NMR δ 0.12 (9, s), 0.82 (3, s), 1.10 (3, s), 1.30 (3, s), 1.0–2.2 (13, m), 3.67 (1, d, *J* = 6 Hz); mass spectrum, *m/e* (rel intensity) 292 (42), 97 (61), 73 (100), 69 (96).

β-Agarofuran (3). A. A solution of 1.46 g (5 mmol) of **16** and 0.16 g (1 mmol) of *p*-toluenesulfinic acid in 15 mL of acetonitrile containing 2% of water was heated at reflux for 90 min. Evaporation and filtration through aluminum oxide with *n*-hexane yielded 1.01 g (92%) of **3**: bp 55 °C (0.1 mm); $[\alpha]^{25}_D$ −151° ($CHCl_3$, *c* 3.77) (lit.[7] $[\alpha]^{25}_D$ −127°); IR[7] 1650, 905 cm^{-1}; NMR[7] δ 0.87 (3, s), 1.10 (3, s), 1.33 (3, s), 4.53 (1, s, with fine splitting), 0.9–2.7 (13, m); mass spectrum, *m/e* (rel intensity) 220 (13), 43 (75), 41 (100), 40 (67).

B. A mixture of 1.17 g (4 mmol) of **16**, 1.45 g (4.5 mmol) of mercuric acetate, 20 mL of THF, 5 mL of water, and 1 mL of acetic acid was stirred for 20 h at room temperature. The solution was poured into water, extracted with pentane, washed with 5% $NaHCO_3$, dried (Na_2SO_4), and evaporated. The remaining oil (1.7 g) was dissolved in 20 mL of dry ether. Lithium aluminum hydride (0.25 g) was added, and the mixture was heated at reflux for 1 h. After decomposition with aqueous NH_4Cl, the ether was separated, dried (Na_2SO_4), evaporated, and distilled to give 0.57 g (65%) of β-agarofuran (**3**).

Dihydroagarofuran (1). To a stirred mixture of 1.18 g (5.4 mmol) of β-agarofuran (**3**), 3 mL of 95% hydrazine, and 30 mL of 95% ethanol was added 2.5 mL of 30% hydrogen peroxide over a period of 5 h at 5 °C. Stirring was continued for 16 h at room temperature, then water was added, and the mixture was extracted with *n*-pentane. The organic layer was washed with water, dried (Na_2SO_4), evaporated, and distilled to afford 1.10 g (92%) of **1**: bp 82 °C (0.8 mm); $[\alpha]^{25}_D$ −84° ($CHCl_3$, *c* 4.28) (lit.[7] $[\alpha]^{25}_D$ −77°); NMR ($CDCl_3$) δ 0.98 (3, d, *J* = 7 Hz), 1.07 (3, s), 1.15 (3, s), 1.33 (3, s), 0.9–2.1 (14, m); mass spectrum *m/e* (rel intensity) 222 (8), 137 (89), 43 (91), 41 (100).

Ozonolysis of Vinylsilane 16. A solution of 0.49 g (1.68 mmol) of **16** in 20 mL of methanol and 5 mL of methylene chloride was treated with ozone at −20 to −30 °C. Acetic acid (1 mL) and 2 g of potassium iodide were added, and the stirred mixture was allowed to warm up to room temperature. After 20 min, aqueous sodium thiosulfate was added, and the mixture was extracted with *n*-pentane. Drying (Na_2SO_4) of the organic layer, followed by evaporation, left an oil which was chromatographed on silica gel. *n*-Hexane–2% ethyl acetate eluted 41 mg (11%) of ketone **19**: mp 55 °C (lit.[22] mp 56–57 °C); $[\alpha]^{25}_D$ −115° ($CHCl_3$, *c* 2.86) (lit.[22] $[\alpha]^{25}_D$ −118.86°); IR 1720 cm^{-1} NMR δ 0.87 (3, s), 1.13 (3, s), 1.38 (3, s), 1.0–3.0 (13, m); mass spectrum, *m/e* (rel intensity) 222 (42), 207 (100), 44 (46), 41 (43).

Further elution with *n*-hexane–5% ethyl acetate gave 324 mg (76%) of hydroxy aldehyde **18**. A sample recrystallized from *n*-hexane had mp 52–53 °C: IR 3520, 1740 cm^{-1}; NMR δ 0.88 (3, s), 1.32 (3, s), 1.42 (3, s), 1.0–2.6 (13, m), 2.7 (1, s, exchanged with D_2O), 9.40 (1, s, with fine splitting). Anal. ($C_{15}H_{24}O_3$): C, H.

Silane 17. Reduction of vinylsilane **16** (105 mg) in 2 mL of 95% ethanol with 0.5 mL of 85% hydrazine and 0.3 mL of 30% hydrogen peroxide, as described above, gave 86 mg (82%) of **17**: bp ~80 °C (0.1 mm); IR 1240, 850 cm^{-1}; NMR δ 0 (9, s), 0.4–0.7 (2, m), 1.10 (6, s), 1.28 (3, s), 0.9–2.1 (14, m); mass spectrum, *m/e* (rel intensity) 294 (26), 73 (100), 43 (21), 41 (22). Anal. ($C_{18}H_{34}OSi$): C, H.

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Registry No.—**1**, 5956-09-2; **2**, 20053-66-1; **3** β isomer, 6040-08-0; **4**, 6485-40-1; **5**, 34182-03-1; *trans*-**6**, 35866-66-1; *cis*-**6**, 68566-77-8; **7**, 68524-96-9; **8**, 68568-09-2; **9**, 68524-97-0; **10**, 68524-98-1; **11**, 68524-99-2; **12**, 68525-00-8; **13**, 68525-01-9; **14**, 68525-02-0; **15**, 68525-03-1; **16** isomer A, 68566-78-9; **16** isomer B, 68566-79-0; **17**, 68525-04-2; **18**, 68525-05-3; **19**, 5986-25-4; 5-chloro-1-pentyne, 14267-92-6; sodium iodide, 7681-82-5; phosphorus pentachloride, 10026-13-8; trimethylchlorosilane, 75-77-4; 5-iodo-1-pentyne, 2468-55-5.

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Dipolar Micelles. 8. Hydrolysis of Substituted Phenyl Esters in a Hydroxamic Acid Surfactant

A. Pillersdorf and J. Katzhendler*

Department of Pharmaceutical Chemistry, The Hebrew University, School of Pharmacy, Jerusalem, Israel

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The reactions of hydroxamic acid catalysts of the structure $CH_3(CH_2)_nN^+(CH_3)_2(CH_2)_3CONHOH\ Br^-$ [n = 15 (I3C), n = 0 (I3M)] with substituted phenyl esters have been studied. The kinetics in I3C followed the expression: $k_{obsd} = k_0 + k_cK_a/(K_a + H^+) + k_{OH}[OH^-]$. The water catalysis rates k_0 for all the esters studied were significantly greater than the spontaneous rate constants reported in the literature for esters of identical leaving groups. The magnitude of the water rate constants, and their dependence on microenvironmental factors as displayed by mixed micellar systems, indicated that the reaction proceeds via electrophilic assistance by the onium head groups. Nucleophilic attack by the hydroxamate anion (k_c) in I3C on the esters corresponds to a β Brönsted value of -1.1. The results point out that although I3C is expected to be an α-effector catalyst, the relative enhancement of the rate constants is very small. This was explained in terms of proximity and electrostatic effects in the transition state. The basic hydrolytic rates k_{OH} and the titrimetric behavior of I3C were also discussed.

In order to gain further insight into microenvironmental parameters operating in enzymic reactions, various types of micellar catalyzed reactions have lately been investigated as model systems.[1]

It was proposed that rate acceleration by cationic micelles is generally attained for reactions characterized by a delocalized, negatively charged transition state. Recently, Kunitake[2] has suggested that the remarkable rate enhancement of some anionic nucleophiles in cationic micelles is mainly derived from the formation of hydrophobic ion pairs. The important role of ion pair formation on the reactivity of nucleophiles was also demonstrated in the case of macrocyclic paracyclophane oximes.[3]

In our previous studies[4] we have designed many surfactant models in which the following three features are all covalently bound to the same skeleton: (a) an anionic nucleophile, (b) a positively charged ammonium group, and (c) a hydrophobic long alkyl chain.

This includes a number of betaine- and choline-like derivatives. Similar investigations on the catalytic properties of nucleophilic micelles have been reported in the literature.[5-9]

Continuing the investigation on positively charged functional micelles we became interested in studying the kinetic effects displayed by a structurally related micellar system possessing an α-effector catalyst. Since the hydroxamate anion is known to be highly nucleophilic toward phenyl esters[10-13] and its catalytic reactivity is increased in cationic surfactants, a hydroxamic acid surfactant of type I3C was synthesized.

The present report describes the kinetic results obtained for the hydrolysis of substituted phenyl esters in various micellar[44] systems of I3C, II2 + I3C, I3C + III1, I3C + III2, I3C + III3 and in the analogous nonsurfactant catalyst I3M. The study also includes titrimetric data of homogenous micellar and mixed micellar systems at various ionic strengths.

Detergents:

$CH_3(CH_2)_{15}N^+(CH_3)_2(CH_2)_3CONHOH\ \ Br^-$
I3C

$(CH_3)_3N^+(CH_2)_3CONHOH\ \ Br^-$
I3M

$CH_3(CH_2)_mN^+(CH_3)_2(CH_2)_nH\ \ Br^-$
II1C, II2

$(CH_3(CH_2)_mN^+(CH_3)_2(CH_2)_nCOOH\ \ Br^-$
III1, III2, III3, III3C

III1C, m = 15, n = 1; II2, m = 10, n = 2; III1, m = 0, n = 1; III2, m = 9, n = 2; III3, m = 9, n = 3; III3C, m = 15, n = 3

Esters: Phenyl decanoate (PD), phenyl acetate (PA), tolyl decanoate (PMPD), 4-chlorophenyl decanoate (PCPD) and 3-chlorophenyl decanoate (MCPD).

Experimental Section

Materials. *N*-Cetyl-*N,N*-dimethyl-*N*-(3-hydroxylaminocarbonylpropyl)ammonium Bromide (I3C). *N*-Cetyl-*N,N*-dimethyl-*N*-(3-ethoxycarbonylpropyl)ammonium bromide (III3CE) was prepared by adding 55 g (0.21 mol) of cetyldimethylamine in 100 mL of ethanol to 40 g (0.21 mol) of ethyl 4-bromobutanoate.

The solution was kept at 40 °C for 3 days. Removal of the solvent gave an oil which was crystallized from ethanol–ether, mp 72 °C. Anal. Calcd for $C_{24}H_{50}BrNO_2$: C, 62.01; H, 10.77; N, 3.00; Br, 17.24. Found: C, 62.2; H, 10.88; N, 3.28; Br, 17.53.

A solution of 2.9 g (0.054 mol) of sodium methoxide in 25 mL of methanol was added to 3.8 g (0.054 mol) of hydroxylamine hydrochloride in 25 mL of methanol. After filtration the solution was cooled to 0 °C and 10 g (0.021 mol) of III3CE in 40 mL of methanol was added dropwise over 1.5 h. The solution was kept at 0 °C for 3 weeks. The methanol was removed in vacuo and the remaining viscous oil was dissolved in water, washed with ether, and lyophilized to dryness. The residue was recrystallized from ethanol–ether, mp 180 °C. Anal. Calcd

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