

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

Synthetic Applications of the Abnormal Reimer-Tiemann Reaction

HANS WYNBERG¹ AND WILLIAM S. JOHNSON

Received March 20, 1959

trans-9-Methyl-1-decalone (VI) has been prepared by the Woodward method from *ar.* α -tetralol IV *via* the dienone V. β -(*p*-Hydroxyphenyl)-propionic acid (XI) was similarly converted to the dienone XII and thence to XIII. Mesityl was found to furnish the two isomeric dienones XVIII and XIX. The relationship of these studies to the synthesis of nonaromatic steroids is discussed.

Since aromatic steroid types such as VII² and IX or its precursor X³ are available by total synthesis, their conversion to nonaromatic steroids containing two angular methyl groups becomes a subject of considerable interest.

Woodward's⁴ ingenious method for producing *trans*-10-methyl-2-decalone III⁵ from *ar.* β -tetralol I *via* the product II of abnormal Reimer-Tiemann reaction promised, *a priori*, to be applicable to the formation of 9-methyl-1-decalone (VI) from *ar.* α -tetralol (IV) *via* the dienone V. This extension of Woodward's scheme thus serves as a model for

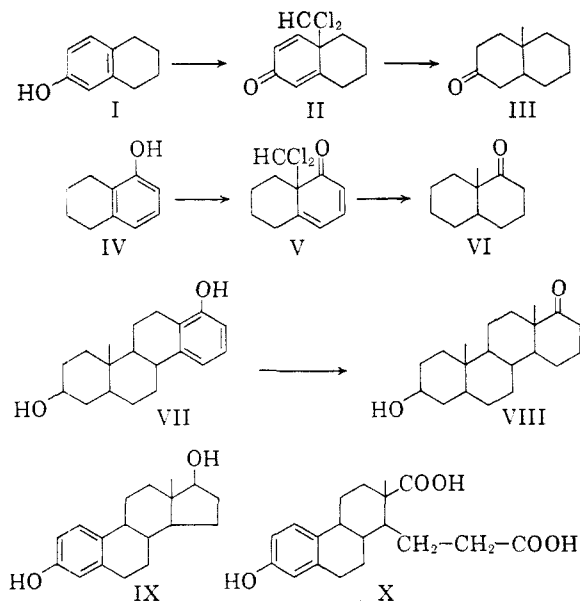
conversion of the readily available phenol VII² into a D-homo-17-keto steroid VIII. Although this ultimate objective was not realized, the conversion of IV \rightarrow VI has been successful and an account of this study is the subject of Part I of this paper.

Since attempts by Woodward to apply his scheme to estradiol (IX) failed,⁶ we were prompted to examine the applicability of the method to D-homomarrionolic acid (X)⁷ in the hope that its greater compatibility, by virtue of the carboxyl groups, with the aqueous-alkaline phase of the reaction mixture would be beneficial. Although this hope was not realized, the model conversion of β -(*p*-hydroxyphenyl)-propionic acid (XI, R=H) to the abnormal Reimer-Tiemann product XII was successful and is reported in Part II.

Part III of this paper deals with a study of the abnormal Reimer-Tiemann reaction with mesityl (XVII) as an interesting example where normal reaction is precluded.

PART I

Treatment of *ar.* α -tetralol with chloroform and 50% aqueous potassium hydroxide afforded a mixture separable into an acidic and neutral fraction by virtue of the insolubility of the sodium salt of the former. The neutral fraction could be separated into two components by chromatography. The first product obtained in 1.5% yield was a crystalline solid which, after purification, melted at 164.5–165°. The analysis was compatible with the formula C₂₁H₃₄O₂ which corresponds to the orthoformate structure XVI, an expected product.⁸ The second neutral product, obtained in 2.5% yield as a pale yellow crystalline solid melting at 149–150.5° after purification, was identified through compositional analysis and the ultraviolet spectrum, λ_{\max} 320 m μ ,⁹ as the dichloroketone V.



(1) Sterling-Winthrop Research Institute Fellow, Spring 1951; Allied Chemical and Dye Fellow, 1951–52. Present address: Department of Chemistry, Tulane University, New Orleans, La.

(2) W. S. Johnson, E. R. Rogier, J. Szmuszkowicz, H. I. Hadler, J. Ackerman, B. K. Bhattacharyya, B. M. Bloom, L. Stalman, R. A. Clement, B. Bannister, and H. Wynberg, *J. Am. Chem. Soc.*, **78**, 6289 (1956).

(3) J. E. Cole, W. S. Johnson, P. A. Robins and J. Walker, *Proceedings Chem. Soc.*, 114 (1958).

(4) R. B. Woodward, *J. Am. Chem. Soc.*, **62**, 1208 (1940).

(5) For the matter of configuration see M. Yangita, K. Yamakawa, A. Tahara, and H. Dgura, *J. Org. Chem.*, **20**, 1767 (1955).

(6) Private communication from Prof. R. B. Woodward.

(7) For the synthesis of homomarrionolic acid and its conversion to estrone see ref. (3) and articles cited therein.

(8) Cf. A. Weddige, *J. prakt. chem.*, (2) **26**, 444 (1882); G. Keil as quoted by K. Auwers and M. Hessenland, *Ann.*, **352**, 273 (1907); H. Baines and J. E. Driver, *J. Chem. Soc.*, **125**, 907 (1924); J. E. Driver, *J. Am. Chem. Soc.*, **46**, 2090 (1924).

Additional proof of this structural assignment was obtained by conversion of V to 9-methyl-1-decalone (VI) and comparison of the latter with an authentic sample.¹⁰ This conversion was achieved by reduction and hydrogenation of the olefinic, carbonyl and dichloromethyl functional groups followed by reoxidation to the ketone. In agreement with the previous observations in the β -tetralol series,⁵ mild conditions at the first reduction stage, namely atmospheric pressure hydrogenation in the presence of 5% palladium-on-carbon, effected highly stereoselective reduction of the olefinic bonds of V to give a *trans*-fused ring system. The use of highly active platinum oxide¹¹ at the first stage of reduction led to a mixture of *cis*- and *trans*-isomers.

Two aldehydes were isolated from the acidic fraction of the reaction mixture. One of these, purified *via* the sparingly soluble sodium salt, was obtained in 9% yield as shiny plates melting at 29.6–30.1° after purification. The other aldehyde, obtained in 2% yield, melted at 141.5–142.5°. This melting point was not depressed on admixture with the aldehyde, m.p. 141–142° obtained from the reaction of *ar.* α -tetralol with zinc cyanide and dry hydrogen chloride. On the basis of the orientation rules in the Reimer-Tiemann and Gattermann reactions, the lower melting aldehyde is assigned the *o*-hydroxy structure XIV, while the 141–142° melting aldehyde is considered to be the *para* isomer XV.

All attempts to obtain a neutral chlorine-containing product from the phenol VII failed.

PART II

Treatment of β -(4-hydroxyphenyl)-propionic acid, (XI R=H) with excess chloroform in the presence of 42% potassium hydroxide furnished a mixture which could be separated into the phenolic and neutral components conveniently after esterification of the carboxylic acid function. The neutral fraction thus obtained in 17% yield as a pale yellow powder melting at 51.4–52.0° after purification, was assigned the dichlorocyclohexadienone structure XII (R=C₂H₅), on the basis of its compositional analysis, ultraviolet absorption maxi-

(9) The ultraviolet spectrum of 2-dichloromethyl-2-methyl-3,5-cyclohexadienone, prepared according to K. Auwers and G. Keil, *Ber.*, **35**, 4207 (1902) showed an absorption maximum at 300 m μ (log ϵ 3.6). R. C. Cookson and N. S. Wariyar, *J. Chem. Soc.*, 2302 (1956) reported the maximum at 303 m μ (log ϵ 3.6) while C. LaLane, *J. Chem. Soc.*, 3217 (1953) observed a maximum at 297–299 m μ . D. C. Curtin and R. R. Fraser, *J. Am. Chem. Soc.*, **80**, 6016 (1958) reported λ_{\max} 299 m μ for 2,2-dimethyl-3,5-cyclohexadienone. These observations indicate that the λ_{\max} at 228 m μ reported by E. N. Marvel and E. Magoon, *J. Am. Chem. Soc.*, **77**, 2542 (1955) for the same substance is incorrect.

(10) (a) W. S. Johnson, *J. Am. Chem. Soc.*, **65**, 1317 (1943); (b) W. S. Johnson and H. Posvic, *J. Am. Chem. Soc.*, **69**, 1361 (1947).

(11) V. L. Frampton, J. D. Edwards, Jr., *J. Am. Chem. Soc.*, and R. R. Henze, **73**, 4432 (1957).

mum at 233 m μ ¹² (log ϵ 4.2) and by analogy to the behavior of other *p*-alkyl substituted phenols. The *o*-hydroxyaldehyde XXI was isolated from the acidic fraction in 13% yield as fine colorless plates melting at 119–121.2° after purification. The dichloroketone XII (R=C₂H₅) was converted by reduction over platinum oxide¹¹ followed by oxidation with chromic oxide in glacial acetic acid into ethyl (1-methyl-4-ketocyclohexyl)-propionate (XIII) isolated as the yellow-orange 2,4-dinitrophenylhydrazone melting at 189–190°.

Attempts to obtain a chlorine-containing cyclohexadienone from homomarrinolic acid (X) failed. A significant difference between the model phenol, β -(*p*-hydroxyphenyl)-propionic acid (XI, R=H), which could be converted successfully into a cyclohexadienone, and *D*-homomarrinolic acid (X) consists in the presence of ring C in the letter. The steric interference of the axial hydrogen atoms attached to C₃, C₉ and C₁₁ (formula X) evidently precludes reaction at C₁₀ with a fragment even as small as dichlorocarbene.¹³

PART III

Although both *ortho*- and *para*-substituted phenols have been converted to the corresponding *ortho*- and *para*-substituted dichloromethyl cyclohexadienones there appears to have been no case recorded where both possible dienones have been isolated¹⁴ from the reaction with one phenol.

Treatment of mesitol (XVII) with chloroform and 50% aqueous potassium hydroxide solution for 12 hours afforded in our hands a mixture from which the starting phenol was separated by extensive extractions with Claisen's alkali. The neutral straw-colored liquid thus obtained in 67.5% yield boiled at 73–74° (0.17 mm.). Its compositional analysis was in agreement with the dichloroketone structure XVIII and XIX. Upon attempted

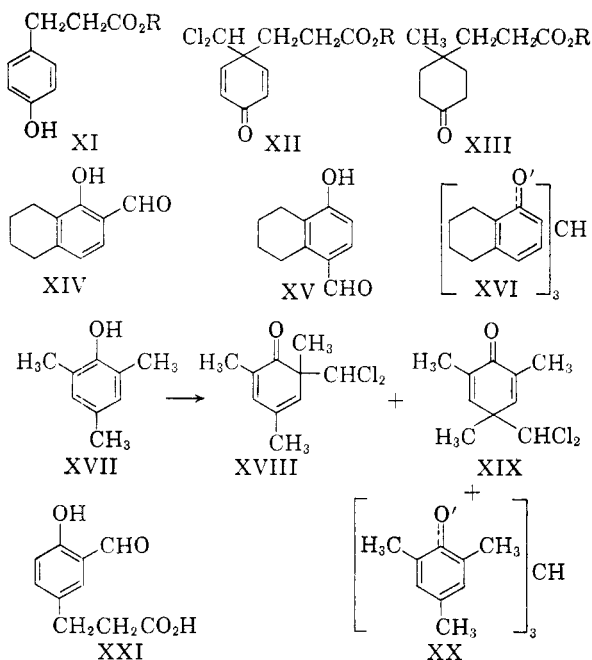
(12) Cf. the λ_{\max} at 235 m μ (log ϵ 4.1) for compound II (ref. 4). M. Yanagita and S. Inayama, *J. Org. Chem.*, **19**, 1724 (1954) report λ_{\max} 237 m μ (log ϵ 4.0) for 2,4,4-trimethyl-2,5-cyclohexadienone. 4-Dichloromethyl-4-methyl-2,5-cyclohexadienone has been found in the present work to absorb at 232 m μ (log ϵ 4.2).

(13) Cf. H. Wynberg, *J. Am. Chem. Soc.*, **76**, 4998 (1954). Note, however, that dichlorocarbene may well be associated with solvent molecules.

(14) K. Auwers and F. Winternitz, *Ber.*, **35**, 465 (1902) isolated a neutral chlorine-containing oil from 2,4-dimethylphenol, which may have contained both isomers. The separation and isolation of these isomers was reported to be unsuccessful. Auwers further reported the Reimer-Tiemann reaction with mesitol as furnishing a neutral chlorine containing oil (elemental analysis 10% low in chlorine) without experimental details. No characterization of this neutral substance has been reported. W. J. Hickinbottom and B. H. M. Thompson are quoted in E. H. Rodd, *Chemistry of Carbon Compounds*, Elsevier Publishing Co., Amsterdam, Holland, Vol. III B, p. 738 as having obtained a 70% yield of dichloromethyl cyclohexadienone from mesitol. Added in proof: after our paper was in press we learned from Prof. D. H. R. Barton that he and P. T. Gilham had obtained results with mesitol essentially the same as our own described here.

crystallization from methanol a 1% yield of a chlorine-free product was isolated as small colorless prisms, melting at 188.0–188.5° after purification, which as shown by compositional analysis, corresponded to the expected mesityl orthoformate (XX). The remaining oil furnished, upon chromatography, an oily fraction in 63% yield which exhibited a sharp maximum at 317 $m\mu$ ($\log \epsilon$ 3.75) in the ultraviolet spectrum.

This absorption maximum and extinction coefficient is that expected for a 2,2-dialkylcyclohexadienone.^{9,15} The second fraction, eluted in 6% yield from the column, was obtained as a white crystalline solid melting at 37.5–38.5° after crystallization from methanol. The ultraviolet spectrum, λ_{max} 240 $m\mu$ ($\log \epsilon$ 4.0), and compositional analysis were compatible with the *para* dichloroketone structure XIX. From the absorption coefficients of XVIII and XIX at 240 and 317 $m\mu$ respectively it was possible to calculate the ratios of isomers as 7 to 3 (*ortho* to *para*) in the original neutral oil. Reduction of the reaction time from twelve hours to one hour caused a decrease in the yield of neutral material from 67.5 to 47.5%. It is noteworthy that the ratio of *ortho* to *para* isomers in this product was changed to 40 to 1 under these conditions.



EXPERIMENTAL¹⁶

Reimer-Tiemann reaction with ar. α -tetralol (IV). To a solution of 20.0 g. *ar. α -tetralol* IV, m.p. 69–70°¹⁷ in 875 ml.

(15) It is noteworthy that the abnormal product from *o*-cresol (ref. 8) can be obtained pure with relative ease. Its dimerization was observed by us after a period of two years (see Experimental). Curtin (ref. 9) also reported the isolation of 2,2-dialkylcyclohexadienones as their dimers.

(16) All melting points are corrected for stem exposure. Ultraviolet spectra were determined on a Beckmann DU Spectrophotometer, and 95% ethanol was used as a solvent.

of 50% aqueous potassium hydroxide solution was added in an atmosphere of nitrogen, with vigorous stirring, 450 ml. of chloroform (Eastman Kodak, Pract.) over a period of 1.5 hr. Some external cooling was necessary to moderate the vigorous reaction. The mixture was allowed to reflux for an additional 1 hr., whereupon it was cooled and acidified with dilute sulfuric acid. The aqueous layer was extracted once with chloroform and the combined organic layers were stirred with a 20% sodium hydroxide solution. The insoluble sodium salts of the phenolic aldehydes which precipitated were removed by filtration and washed with chloroform. The chloroform solution was washed free of alkali with water, dried over magnesium sulfate and concentrated. The residue was dissolved in 100–200 ml. of 1:1 ether-petroleum ether (b.p. 60–68°) and passed through 75 g. of activated alumina (Alcoa, F-20 grade). The first 200 ml. of eluate afforded 930 mg. (1.5%) of *ar. α -tetralol orthoformate* (XVI), m.p. 160–162° as well formed white crystals. Three recrystallizations from benzene-methanol furnished the analytical sample as colorless prisms, m.p. 164.5–165.0°.

Anal. Calcd. for $C_{21}H_{34}O_3$: C, 81.90; H, 7.54. Found: C, 82.0; H, 7.56.

The next 600 ml. eluted 938 mg. (3.0%) of yellow crystals melting at 145–151°. An analytical sample of *9-dichloromethyl-1-keto- $\Delta^{2,4}$ -hexahydronaphthalene* m.p. 149.0–150.5° was obtained by crystallization from dilute ethanol followed by two sublimations at 145° and (0.01 mm.), λ_{max} 320 $m\mu$ ($\log \epsilon$ 3.6).

Anal. Calcd. for $C_{11}H_{12}OCl_2$: C, 57.16; H, 5.24. Found: C, 57.2; H, 5.33.

Each of the two isomeric aldehydes was isolated from separate runs. When 14.8 g. of the phenol IV, 350 g. of potassium hydroxide, 300 ml. of water, and 200 ml. of chloroform were employed, 1.5 g. (9%) of an oil, b.p. 140–150° (8–10 mm.) was obtained upon acidification of the sodium salts. The oil was reconverted to the sodium salts, washed with ether, and the hydroxy aldehyde liberated with dilute acetic acid. Upon cooling and scratching the aldehyde crystallized as colorless shiny plates, turning yellow on exposure to air. One crystallization from dilute alcohol followed by another crystallization from petroleum ether (b.p. 35–40°) yielded pure *6-formyl-5-hydroxy-1,2,3,4-tetrahydronaphthalene* (XIV) as nearly colorless shiny plates, m.p. 29.6–30.1°.

Anal. Calcd. for $C_{11}H_{12}O_2$: C, 74.98; H, 6.87. Found: C, 74.7; H, 6.94.

In another experiment in which 5.0 g. of the phenol IV in 5 ml. of chloroform and 15 ml. of ethanol were added to 10 g. of sodium hydroxide in 16 ml. of water at 60° over a period of 2 hr., a fraction b.p. 125–175° (0.1 mm.) was collected. This fraction crystallized to a white solid which furnished 135 mg. (2%) of the *p*-hydroxyaldehyde m.p. 141.5–142.5° undepressed on admixture with the aldehyde, m.p. 141–142° obtained from a Gattermann reaction described below. Although analysis of this aldehyde was not entirely satisfactory. (Calcd. for $C_{11}H_{12}O_2$: C, 74.98; H, 6.87; Found: C, 74.2; H, 7.21.) *The semicarbazone of 8-formyl-5-hydroxy-1,2,3,4-tetrahydronaphthalene* (XV), melting at 214–215° after one crystallization from dioxane gave satisfactory analytical results.

Anal. Calcd. for $C_{12}H_{15}O_2N_3$: C, 61.78; H, 6.45. Found: C, 62.1; H, 6.42.

Treatment of 5 g. of α -tetralol (IV) in 50 ml. of ether with 6.0 g. of anhydrous zinc cyanide and dry hydrogen chloride for 2 hr. furnished a red oil which was decomposed by heating for 35 min. on the steam bath with 50 ml. of water and 10 ml. of 95% alcohol. Extraction with ether followed by washing with water, drying and removal of the ether left 1.75 g. (29.4%) of tan solid. Two recrystallizations from

(17) Prepared by S. Kraychy and O. R. Rodig according to the procedure of Musser and H. Adkins, *J. Am. Chem. Soc.*, 60, 664 (1938).

benzene furnished 8-formyl-5-hydroxy-1,2,3,4-tetrahydronaphthalene (XV) m.p. 140.5–142.0° undepressed on admixture with the aldehyde obtained from the Reimer-Tiemann reaction.

cis- and trans-4-Methyldecalone-1 (VI). A 230 mg. sample of 9-dichloromethyl-1-keto- $\Delta^{2,4}$ -hexahydronaphthalene (V), m.p. 149–151°, in 25 ml. of 95% alcohol (purified by distillation from Raney nickel) was added to a suspension of 100 mg. of pre-reduced platinum oxide¹¹ in 15 ml. of alcohol. The mixture was stirred in an atmosphere of hydrogen at 25° and 731 mm. until 3 mole-equivalents of hydrogen were absorbed. The catalyst was removed by filtration and hydrogenation was continued over 2.00 g. of 30% palladium-on-strontium carbonate.¹⁸ When no further uptake of hydrogen occurred (total absorption 1.8 mole-equivalents) the mixture was filtered, and the filtrate diluted with water and extracted with ether. The ether solution was washed with water and dried over anhydrous magnesium sulfate. The residue obtained on evaporation of the ether was dissolved in 8.35 ml. of glacial acetic acid, then a solution of 0.336 g. of potassium chromate in 0.62 ml. of water was added and the mixture allowed to stand for 21 hr. at room temperature. The mixture was diluted with water and extracted with benzene and with ether. The combined organic layers were washed free of acetic acid with water and with saturated sodium bicarbonate solution, then dried over anhydrous potassium carbonate. The residue obtained on removal of the solvent was evaporatively distilled at 100–130° (8–10 mm.) to give an oily product with a camphor-like odor which was dissolved in 10 ml. of methanol. A 3-ml. aliquot was used to prepare the semicarbazone and the yield was 22 mg. (corresponding to a 33% over-all yield from the dienone), m.p. 227.5–228° (introduced at 215°). This derivative evidently consisted mainly of the *cis*-isomer since on admixture with an authentic specimen m.p. (222–224°¹⁹) the m.p. of the latter was not depressed. The m.p. of an authentic specimen of the *trans* semicarbazone, in contrast, was markedly depressed on admixture with the specimen of the present study. When the oxime and 2,4-dinitrophenylhydrazone were prepared from the crude ketone solution, mixtures were obtained which on exhaustive recrystallization afforded, in low yield, pure derivatives of *trans*-9-methyl-decalone, m.p. 138–139° and 170.5–171.5°, respectively, undepressed on admixture with the appropriate derivatives of the *trans* series,^{10a} but depressed by those of the *cis*.

In another experiment 100 mg. of 5% palladium-on-carbon catalyst²⁰ was used for the first reduction stage during which 1.8 mole equivalents of hydrogen were absorbed. After removal of the catalyst, the reduction (of the carbonyl group) was then continued, over 200 mg. of platinum oxide,¹¹ then finally over 0.25 teaspoonful of W-1 Raney nickel catalyst in the presence of added solid potassium hydroxide (3 pellets). This last reduction stage required 23 hr. at atmospheric pressure and room temperature, 2.06 mole equivalents of hydrogen being absorbed. After oxidation as described above, part of the crude product was converted into the semicarbazone which, after a single recrystallization, melted at 217–218°, undepressed on admixture with authentic *trans* derivative, but depressed by the *cis*. The 2,4-dinitrophenylhydrazone was obtained in 26% over-all yield from the dienone, and after a single recrystallization melted at 171–171.5°, undepressed on admixture with authentic *trans* derivative but depressed by the *cis*.

Attempted Reimer-Tiemann reaction with the phenol VII. One g. of the phenol VII,² m.p. 195–197.5° (vac.) and 25 g. of potassium hydroxide in 20 ml. of water was treated with 30 ml. of chloroform just as described above for the reaction with α -tetralol (IV). Chromatography of the neutral fraction furnished 2 mg. of oily material, λ_{\max} 318 m μ (ϵ 1000).

(18) Cf. ref. 2 and footnote 39 cited therein.

(19) See footnote 15 of reference 10(b).

(20) R. Mozingo, *Org. Syntheses*, Coll. Vol. III, 685, (1955).

This absorption corresponds to a maximum of 0.5 mg. of possible abnormal ketone in the reaction product. All attempts to increase the yield were unsuccessful.

*Reimer-Tiemann reaction with β -(*p*-hydroxyphenyl)-propionic acid (XI, R = H).* Five g. of β -(*p*-hydroxyphenyl)-propionic acid (XI)²¹ m.p. 127–128.5° in 35 ml. of chloroform was treated with a solution of 35 g. of potassium hydroxide in 35 ml. of water in an atmosphere of nitrogen. The mixture was vigorously stirred under reflux for 1 hr., cooled, diluted with 40 ml. of water and stirred rapidly into an excess of cold dilute hydrochloric acid. The aqueous layer was extracted with ether and the combined organic layers washed with water and dried over anhydrous magnesium sulfate. The residue obtained on evaporation of the solvent was esterified by heating under reflux for 4 hr. with 65 ml. of absolute ethanol containing 4 drops of concentrated sulfuric acid. One half of the alcohol was then removed under reduced pressure, 65 ml. of water added, and the mixture extracted with ether. Unesterified material (4.5%) was separated by washing the ethereal layer with 5% sodium bicarbonate solution. The phenolic material was extracted with 10% sodium hydroxide solution. The ether solution was washed with water and dried over anhydrous magnesium sulfate. The neutral material left after removal of the ether was obtained as an oily solid weighing 1.42 g. (17% yield) and was purified by two successive evaporative distillations at 50° (0.1 mm.) to furnish *ethyl β -(1-dichloromethyl-4-ketocyclohexa-2,5-dienyl)-propionate* (XII, R = C₂H₅) as a pale yellow powder, m.p. 51.5–52°.

Anal. Calcd. for C₁₂H₁₄O₂Cl₂: C, 52.00; H, 5.09. Found: C, 52.3; H, 5.03.

The normal product could be isolated from the reaction mixture by fractional crystallization before the esterification step. Thus from an experiment like that described above (2-g. scale) there was obtained 0.3 g. (13%) of aldehydic material m.p. 117–121.5° after crystallization from benzene-petroleum ether (60–68°). A pure sample of β -(*3*-formyl-4-hydroxyphenyl)-propionic acid (XXI) was obtained, after 2 recrystallizations from ether-petroleum ether (60–68°) as fine, colorless plates, m.p. 119–121.2°, λ_{\max} 257.5 m ($\log \epsilon$ 4.03), 335 (3.53).

Anal. Calcd. for C₁₀H₁₀O₃: C, 61.87; H, 5.19. Found: C, 62.0; H, 5.34.

An 830-mg. sample of the keto-ester XII (R = C₂H₅) was reduced as described for V (initial reduction stage with platinum oxide) and oxidized with 400 mg. of chromic oxide in 15 ml. of glacial acetic acid containing 12 ml. of water. The crude oily product, isolated by continuous extraction with ether, was evaporatively distilled at 80° (0.3 mm). The distillate upon treatment with 500 mg. of 2,4-dinitrophenylhydrazine in 15 ml. of 95% ethanol furnished after 3 crystallizations from 95% ethanol, 53.5 mg. of the 2,4-dinitrophenylhydrazone of β -(1-methyl-4-ketocyclohexanyl)-propionic acid (XIII, R = H) as very fine yellow-orange needles m.p. 189–190°.

Anal. Calcd. for C₁₃H₂₀O₂N₄: C, 52.80; H, 5.50. Found: C, 52.9; H, 5.70.

Attempted Reimer-Tiemann reaction with homomarrionolic acid (X). A 500 mg. sample of *D*-homomarrionolic acid⁶ m.p. 233–238° was treated with 5 ml. of chloroform and 4 ml. of 50% potassium hydroxide solution (nitrogen atmosphere) in exactly the manner as described above for the phenolic acid XI. Acidification of the cooled reaction mixture furnished 541 mg. of crude organic material which had been washed completely free of ionic chloride. Three 50-mg. samples were submitted to sodium fusion and chlorine deter-

(21) E. Bowden and H. Adkins, *J. Am. Chem. Soc.*, **62**, 2422 (1940), reported m.p. 128–129°. This substance was prepared in the present work by hydrogenation over platinum oxide of *p*-hydroxycinnamic acid [G. C. Overberger, E. J. Luhrs, and P. K. Chien, *J. Am. Chem. Soc.*, **72**, 1201 (1950)].

mined by the Volhard method. The results in each case were negative within the experimental error.

Reimer-Tiemann reaction with mesitol (XVII). Ten g. of mesitol, m.p. 71–72° was heated under reflux for 12 hr. with 200 ml. chloroform, 200 g. of potassium hydroxide, and 170 ml. of water. Upon cooling, the organic layer was extracted with five 50-ml. portions of Claisen's alkali,²² then dried over magnesium sulfate and the solvent removed under reduced pressure leaving 10.86 g. (67.5%) of neutral oil. Upon standing in the refrigerator overnight in absolute methanol, 0.90 g. (1%) of white crystals m.p. 185–186° had separated. Colorless prisms of *mesityl orthoformate* (XX), m.p. 188.0–188.5° were obtained after three recrystallizations from benzene-methanol.

Anal. Calcd. for C₂₃H₃₄O₂: C, 80.35; H, 8.19. Found: C, 80.3; H, 8.19.

Distillation of the remaining oil furnished a mixture of the two cyclohexadienones as a faintly straw colored liquid, b.p. 73.8–74.0° (0.17 mm.), λ_{max} 239 mμ (log ε 3.66) 317 (3.51).

Anal. Calcd. for C₁₀H₁₃OCl₂: C, 54.84; H, 5.52. Found: C, 54.7; H, 5.67.

Assuming λ_{max} 239 mμ (ε 12,100) 317 (ε 1000) for the *para* isomer¹² and λ_{max} 317 (4500) 239 (200) for the *ortho* isomer⁹ the following calculations can be made:²³

$$\textit{para isomer} \frac{4600 - 1000}{12,100 - 1000} \times 100 = 32\% \text{ and}$$

$$\textit{ortho isomer} \frac{3240 - 200}{4500 - 200} \times 100 = 70\%$$

(22) L. F. Fieser, *Experiments in Organic Chemistry*, C. D. Heath and Co., Boston, Mass. 3rd Ed. p. 310.

(23) M. J. S. Dewar and D. S. Urch, *J. Chem. Soc.*, 345 (1957) describe a general method for the analysis of mixtures using ultraviolet spectroscopy.

One g. of this distillate was chromatographed over 70 g. of alumina using 1:10 ether-petroleum ether (b.p. 34°) as the eluant. The first nine 50-ml. fractions furnished 650 mg. of oil. Fractions 3, 6, and 8 exhibited sharp maxima at 317 mμ with log ε 3.7, 3.7, and 3.75 respectively. Crystallization of this oil was unsuccessful, while attempted purification by evaporative distillation at 120–150° (8–10 mm.) resulted in some decomposition as indicated by a shift of the absorption maximum in the ultraviolet to 305 mμ. The next four 50-ml. fractions eluted from the column furnished 60 mg. of solid which, after recrystallization from dilute methanol, yielded 20 mg. of colorless crystals of *4-dichloromethyl-2,4,6-trimethyl-3,5-cyclohexadienone* (XIX), m.p. 37.5–38.5° with softening at 36°, λ_{max} 240–242 mμ (log ε 4.0).

Anal. Calcd. for C₁₀H₁₃OCl₂: C, 54.84; H, 5.52. Found: C, 54.7; H, 5.45.

In another experiment in which 5.0 g. of mesitol was refluxed for 1 hr. with 25 ml. of chloroform, .25 g. of potassium hydroxide, and 20 ml. of water, 3.85 g. (47.5%) of neutral oil was obtained. Its λ_{max} 317 mμ (log ε 3.58) 240 (3.15) allowed the percentage of isomers to be determined in the manner described above: *para*-isomer 4%, *ortho*-isomer 84%.

Dimer of 2-dichloromethyl-2-methyl-3,5-cyclohexadienone. When 6.0 g. of the abnormal Reimer-Tiemann product¹⁴ of *o*-cresol, m.p. 30.5–32.0°, was allowed to stand in a stoppered flask at room temperature for 2 years, 250 mg. of a white crystalline solid m.p. 188.5–189.5° could be obtained with petroleum ether (b.p. 60–68°). Two crystallizations from methanol-acetone furnished colorless prisms, m.p. 190–190.5°.

Anal. Calcd. for C₈H₈OCl₂: C, 50.29; H, 4.22. Found: C, 50.2; H, 4.29.

MADISON, WIS.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING, STANFORD UNIVERSITY]

Bicyclic Sulfonium Salts with Sulfur at a Bridgehead¹

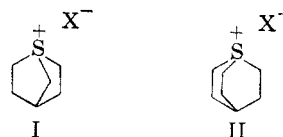
RICHARD H. EASTMAN AND GENE KRITCHEVSKY

Received March 12, 1959

By treatment of the appropriate mercaptans or tetrahydrothiophene derivatives with hydrogen halides, bicyclic sulfonium salts of the bicyclo[3.3.0]octane-1-thianium, bicyclo[4.3.0]nonane-1-thianium, and bicyclo[4.4.0]decane-1-thianium types have been prepared.

A few bicyclic sulfonium compounds in which the sulfonium function is located at a bridgehead have been prepared. In addition to the interest inherent in such structures, the compounds of this type are frequently pharmacologically active. The most active are the bicyclo[2.2.1]heptane-1-thianium (I) and bicyclo[2.2.2]octane-1-thianium (II) halides reported by Prelog,² the former having a minimum lethal dose of 30γ in white mice. A few other compounds have been prepared.³ The compounds which were tested exhibited a lower order of activity, the activity apparently being

related to the ability of the bicyclic sulfonium function to act as an alkylating agent.



In connection with the question of valence-shell expansion to 10 electrons in the sulfur atom,⁴ we have prepared the bicyclo[3.3.0]octane-1-

(3) B. R. Baker, M. Query, S. Safir, and S. Berstein, *J. Org. Chem.*, 12, 138 (1947); M. W. Goldberg and L. H. Sternbach, U.S. Patent 2,489,232, U.S. Patent 2,489,235; W. F. Cockburn and A. F. McKay, *J. Am. Chem. Soc.*, 76, 5703 (1954); 77, 397 (1955).

(4) For recent work and a bibliography see W. E. Doering and A. K. Hoffmann, *J. Am. Chem. Soc.*, 77, 521 (1955).

(1) Taken from the Ph.D. dissertation of Gene Kritchevsky in the Department of Chemistry at Stanford University.

(2) V. Prelog and E. Cerkovnikov, *Ann.*, 537, 214 (1939); V. Prelog and D. Kohlbach, *Ber.*, 72, 672 (1939).