0.20 g. of fine needles of m. p. 118°, obsd. A mixture of the product with that obtained by similar treatment of the dihydroquinazoline (m. p. 121°) melted well at 120°. The bromine split out was weighed as silver bromide: 0.50 g., corresponding to 42.6% bromine, that calculated being 43.5%.

Grateful acknowledgment is made to the Faculty Research Committee of the University of Pennsylvania for a grant to aid this study, and to the following for most of the analytical results reported: W. S. Young (molecular weights), F. W. Landau (nitrogen), and Wm. McClellan (carbon and hydrogen).

Summary

Condensation of *p*-chloroaniline and of *p*-bromoaniline with formaldehyde in cold aqueous solution containing hydrochloric acid yielded as main products the corresponding 3-(halogenophenyl)-6-halogeno-3,4-dihydroquinazolines, of m. p. 192° (corr.) and m. p. 206° (corr.), respectively. The identities of these bases were experimentally established. Formation of these products was accompanied by that of unidentified bases and by methylation of part of the original amines.

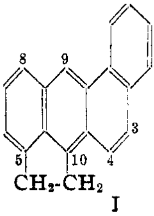
Philadelphia, Penna. Received March 1, 1937

[Contribution from the Chemical Laboratory of Harvard University]

4,10-Ace-1,2-benzanthracene

By Louis F. Fieser and Arnold M. Seligman

The powerfully carcinogenic hydrocarbon cholanthrene[1,2] is the 5,10-ace- (or dimethylene-) derivative (I) of 1,2-benzanthracene and it is one of four possible ace- derivatives of this hydrocarbon. Two of the remaining isomers already have been synthesized and submitted to biological tests. The 8,9-ace- compound (8,9-dimethylene-1,2-benzanthracene[2]) has carcinogenic properties, but it produces tumors less than half as rapidly as cholanthrene.[3] The 3,4′-isomer (acenaphthanthracene[4]), in which both meso positions are unsubstituted, has given only negative results.[5] The synthesis of the fourth isomer, 4,10-ace-1,2-benzanthracene (VIII, below), is described in the present paper. The hydrocarbon is of particular interest because of the indications that substitution at the 10-position in the 1,2-benzanthracene molecule often is particularly favorable for the development of cancer-producing properties,[6] but tests with the new hydrocarbon which are being conducted by Dr. M. J. Shear are not yet complete. The compound produces severe ulceration in mice as rapidly as cholanthrene, but thus far no tumors have been obtained. It is interesting that the three isomeric ace-1,2-benzanthracenes in which the five-membered ring is joined to a meso position of the aromatic system all show some biological activity, while the 3,4′-isomer is completely inactive.



I

The initial step in the synthesis consisted in the condensation of hydrindene with succinic anhydride. As in other Friedel and Crafts reactions, substitution occurred exclusively in the β-position, giving β-(5-hydrindoyl)-propionic acid (II). Reduction to III, cyclization, and reduction to V all proceeded smoothly, and the structure of the tricyclic compounds was established by oxidation of the ketone IV to pyromellitic acid. The structure of the keto acid II follows from that of the ketone. The condensation of 6,7-cyclopentenotetralin (V) with benzoyl chloride gave a liquid product for which only the structure VI is possible, and dehydrogenation of the ketone with selenium gave a liquid of approximately the composition of 1-benzoyl-2,3-cyclopentenonaphthalene, VII. The final step in the synthesis consists in a modified Elbs condensation of the type employed for the preparation of methyl-

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(1) Cook, Haslewood and Robinson, *J. Chem. Soc.*, 667 (1935); Cook and Haslewood, *ibid.*, 767, 770 (1935).

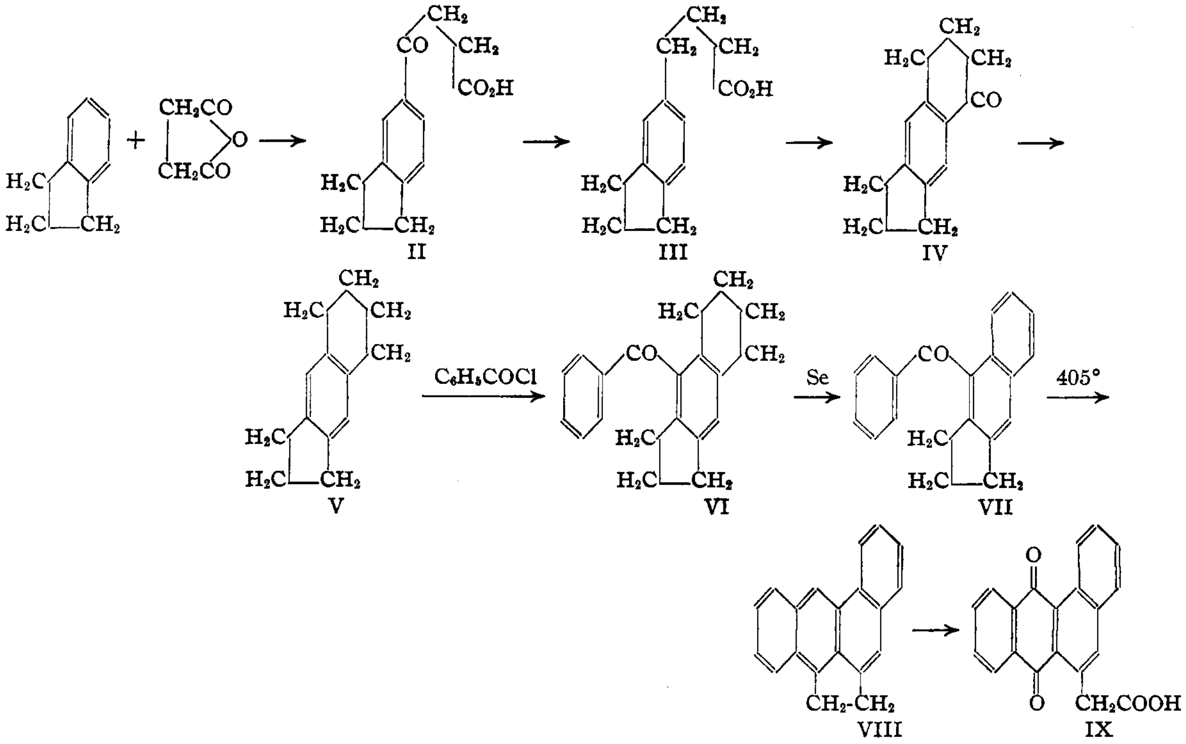
(2) Fieser and Seligman, This Journal, **57**, 2174 (1935).

(3) Shear, *Am. J. Cancer*, **28**, 334 (1936).

(4) Nicodemus, Eng. Patent 251,270 (1926), Ger. Patent 481,819 (1929); Nicodemus and Berndt, U. S. Patent 1,776,925 (1930); Cook, *J. Chem. Soc.*, 1087 (1930); Geyer and Zuffanti, This Journal, **57**, 1787 (1935).

(5) Cook, *Proc. Roy. Soc.* (London), **B111**, 495 (1932).

(6) L. F. Fieser, Mary Fieser, Hershberg, Newman, Seligman and Shear, *Am. J. Cancer*, **29**, 260 (1937).



cholanthrene,[7] but since the ring closure in this case involves substitution in a phenyl, rather than a naphthyl, nucleus, it is not surprising that the hydrocarbon VIII, isolated as the picrate from the oily product of pyrolysis, was obtained in only 10% yield. No difficulty was experienced, however, in obtaining the 4,10-ace-1,2-benzanthracene in a pure condition. Confirmatory evidence of the structure was found in the oxidation of the hydrocarbon to an anthraquinone acetic acid corresponding in properties and analysis to formula IX.

The pyrolysis of the hydrogenated ketone VI also was investigated in order to determine if there is any preference for the participating of the five-membered or six-membered ring in the cyclization. One reaction product was obtained easily in a crystalline and highly pure condition on treating the oily distillate with ether, and a second compound was isolated from the mother liquor through the picrate. The latter compound is a hydrocarbon of the expected composition ($C_{20}H_{18}$), and, as it yielded 4,10-ace-1,2-benzanthracene (VIII) on dehydrogenation, it evidently is the normal product of a cyclization utilizing the cyclopenteno ring, and it can be assigned the formula X. The hydrocarbon which crystallizes from ether has two atoms of hydrogen less than X, or than the hypothetical pyrolysis product XI, and it is resistant to dehydrogenation with selenium. On oxidation, the compound was found to yield the known phenanthrene-8,9-dicarboxylic anhydride, XIII.[8] The hydrocarbon therefore is an 8,9-substituted phenanthrene derivative, and the most probable structure is that of formula XII. The exact location of the alicyclic double bond has not been established. The hydrocarbon evidently is formed as the result of an intramolecular cyclization involving a methylene group of the cyclohexeno ring of the ketone VI, but the anthracene derivative XI, which would result as the primary product of this condensation, does not appear to be stable at the temperature of the reaction. A stabilization possibly is achieved by the migration of one double bond into the angular six-membered ring, followed by the aromatization of this ring through a process of disproportionation, one of the double bonds in the originally aromatic ring remaining at the position between two bridge heads.

That the cyclodehydration proceeds in both possible directions is in keeping with a similar observation[9] concerning a ketone having available for the condensation both an adjacent cyclo-

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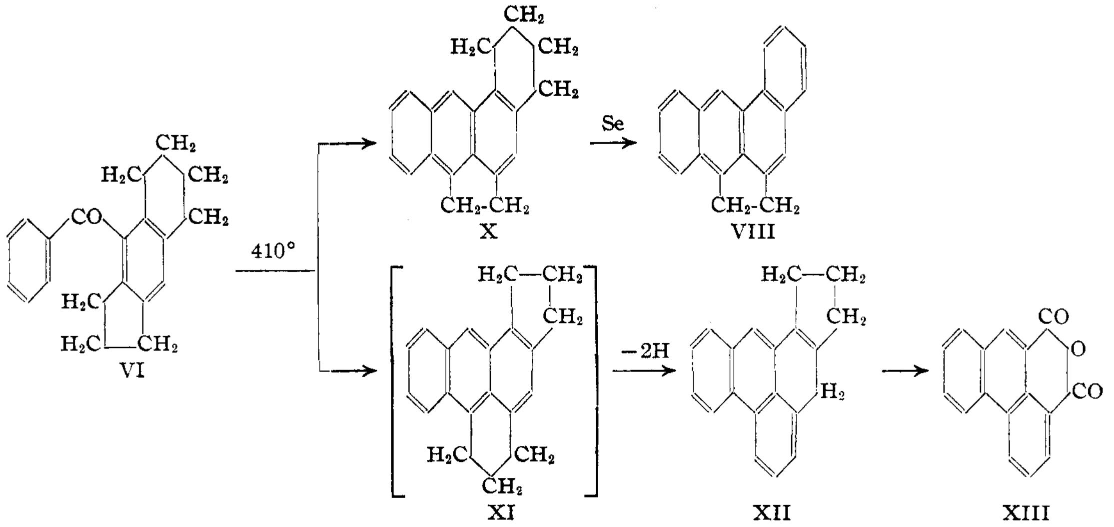
[7] Fieser and Seligman, THIS JOURNAL, **57**, 228, 942 (1935); **58**, 2482 (1936).

[8] Pschorr, *Ber.*, **39**, 3115 (1906).

[9] Fieser and Hershberg, THIS JOURNAL, **59**, 394 (1937).



penteno ring and an *o*-methyl group. The present results find a correlation also with observations concerning the pyrolysis of tetralyl naphthyl ketones,[10] for in two cases phenanthrene derivatives were obtained in place of the expected anthracenoid isomers, and in one instance a dehydro compound was isolated. The controlling factor doubtless is that the angular arrangement of three aromatic rings presents a more stable structure than the linear arrangement, and it is interesting that a readjustment of double bonds and hydrogen atoms occurs without the use of catalysts at the temperature of the pyrolysis.

We are indebted to Mr. Philip A. Shaffer, Jr., for able assistance in the preparative work.

Experimental Part[11]

β-(5-Hydrindoyl)-propionic Acid (II).—The hydrindene employed, b. p. 79.0° (29 mm.), was prepared and carefully fractionated in conjunction with Dr. T. L. Gresham. To a solution of 118 g. of the pure hydrocarbon and 110 g. of succinic anhydride in 500 cc. of tetrachloroethane and 200 cc. of nitrobenzene, cooled to 0°, 270 g. of aluminum chloride was added in portions. The mixture was cooled in an ice-bath for several hours, allowed to stand at room temperature for two days, and then poured onto ice and hydrochloric acid. After removing the solvents with steam, the product was taken into soda solution, and precipitated after clarification with Norite. The crude acid, m. p. 118–120°, uncorr., was satisfactory for use in the next step; yield, 211 g. (97%). After several crystallizations from dilute alcohol and from benzene, the substance was obtained as small needles, m. p. 125–125.5°.

Anal. Calcd. for $C_{13}H_{14}O_3$: C, 71.52; H, 6.47. Found: C, 71.70; H, 6.55.

γ-(5-Hydrindyl)-butyric Acid (III).—Following the general procedure of Martin,[12] a mixture of 211 g. of the acid II, 750 g. of amalgamated mossy zinc, 600 cc. of concentrated hydrochloric acid, 300 cc. of water, and 600 cc. of toluene was refluxed for fifty hours, with the addition of 500 cc. of concentrated acid at intervals. The toluene layer was washed, clarified and distilled, the product being collected as a colorless distillate, b. p. 202° (5 mm.), m. p. 55°; yield, 145 g. (73%). The acid crystallizes from alcohol as colorless needles melting at 54.9–55.2°.

Anal. Calcd. for $C_{13}H_{16}O_2$: C, 76.43; H, 7.90. Found: C, 76.50; H, 8.13.

6,7-Cylopenteno-1-tetralone (IV).—The acid III (145 g.) was refluxed with 200 cc. of thionyl chloride for several hours, and the acid chloride was obtained as a colorless liquid, b. p. 170° (10 mm.); yield, 143 g. (90%). A solution of this material in 250 cc. of carbon bisulfide was added during one hour to a stirred suspension of 130 g. of aluminum chloride in 2 liters of carbon bisulfide at 0°. After being stirred at 0° for one and one-half hours, the mixture was allowed to stand at room temperature for several hours and then decomposed with ice and acid. After removing the solvent with steam, the residual oil was extracted with ether, dried, and distilled. The ketone was obtained as a colorless liquid, b. p. 151–152° (2 mm.); yield, 110.5 g. (92%, based on the acid chloride used). The sample darkened on long standing.

Anal. Calcd. for $C_{13}H_{14}O$: C, 83.83; H, 7.58. Found: C, 83.27, 83.74; H, 7.47, 8.25.

In order to establish the structure, 5 g. of the ketone was heated with 1.5 cc. of concentrated nitric acid and 2.5 cc. of water at 190° for fourteen hours; 1.5 cc. of concentrated acid was added and the heating continued for twelve hours. On concentrating the solution, adding fuming nitric acid, and cooling, 0.7 g. of pyromellitic acid separated. The material was converted into the anhydride at 250°, and this was sublimed and crystallized from dioxane as in a previous experiment.[13] The anhydride melted at 282–283° and did not depress the melting point of an authentic sample.

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[10] Fieser and Seligman, THIS JOURNAL, **58**, 478 (1936).

[11] Melting points are corrected unless otherwise noted. Analyses by Mrs. G. M. Wellwood.

[12] Martin, THIS JOURNAL, **58**, 1438 (1936).

[13] Fieser and Hershberg, *ibid.*, **57**, 2196 (1935).

6,7-Cyclopentenotetralin (V).—To a refluxing mixture of 350 cc. of water, 750 cc. of concentrated hydrochloric acid, 200 cc. of alcohol, and 1100 g. of granulated zinc (amalgamated by contact with a solution of 56 g. of mercuric chloride for five minutes), a solution of 109 g. of the tetralone IV in 300 cc. of alcohol was added over a period of three hours. After refluxing for an additional twelve-hour period, during which time 400 cc. of concentrated acid was added in portions, the mixture was cooled and diluted with an equal volume of water. The liquor was extracted twice with ether, and the bulk of the product was obtained by extraction of the zinc residue with ether. The collected hydrocarbon was steam distilled from a mixture with aqueous alkali, dried, and distilled; b. p. 104–106° (3 mm.); yield, 90 g. (89%). The hydrocarbon is a colorless, mobile liquid which does not alter on storage.

Anal. Calcd. for $C_{13}H_{16}$: C, 90.66; H, 9.37. Found: C, 91.12; H, 9.23.

5-Benzoyl-6,7-cyclopentenotetralin (VI).—A solution of 90 g. of V in 100 cc. of tetrachloroethane was added in the course of one-half hour to a stirred mixture of 80 g. of benzoyl chloride, 90 g. of aluminum chloride, 400 cc. of tetrachloroethane, and 100 cc. of nitrobenzene at 0°. After standing overnight, the mixture was decomposed with 1.5 kg. of ice and 150 cc. of concentrated hydrochloric acid, the solvent was removed with steam, and the residual oil was washed in ethereal solution with water and alkali, dried, and distilled. The ketone was obtained as a very viscous, pale yellow oil, b. p. 183–185° (0.5 mm.) or 215–217° (3.5 mm.); yield, 130 g. (90%).

Anal. Calcd. for $C_{20}H_{20}O$: C, 86.90; H, 7.30. Found: C, 87.04, 86.30; H, 7.76, 7.49.

1-Benzoyl-2,3-cyclopentenonaphthalene (VII).—The above ketone (20 g.) was heated with an equal weight of selenium in an atmosphere of nitrogen at 290° (bath) for twenty-four hours, adding 20 g. of fresh selenium in portions at eight-hour intervals. The material was extracted with benzene and the dark solution was filtered, shaken with a few drops of mercury, allowed to stand overnight, treated with Norite, filtered, and distilled. The product was a yellow, viscous oil, b. p. 215–220° (1.5 mm.); yield, 13.5 g. (69%). The analyses indicate that the material probably contained a small amount of the more highly hydrogenated ketone.

Anal. Calcd. for $C_{20}H_{16}O$: C, 88.20; H, 5.92. Found: C, 88.32, 88.26; H, 6.89, 7.12.

Dehydrogenation of VI with sulfur was investigated without success.

4,10-Ace-1,2-benzanthracene (VIII).—The above oil (13.5 g.) was heated in a bath at 405° for forty-five minutes, and on distillation at 2 mm. pressure there was obtained a viscous yellow oil which failed to solidify or to yield crystals from ether. A hydrocarbon picrate was obtained without difficulty from benzene–ether solution; 5.5 g. of crystalline picrate was collected, and on purification the substance formed clusters of brown-black needles melting at 148–149°. The hydrocarbon recovered from the purified picrate crystallized from ether in the form of stout yellow needles melting at 138.5–140°; yield, 1.3 g. (10%). Further purification by passage through an adsorption tower of alumina and crystallization gave faintly yellow needles of the same melting point. The hydrocarbon gives a deep red solution in concentrated sulfuric acid, and on heating the color changes to violet and then to greenish-black.

Anal. Calcd. for $C_{20}H_{14}$: C, 94.45; H, 5.55. Found: C, 94.17; H, 5.88. *Anal.* (picrate). Calcd. for $C_{20}H_{14}\cdot C_6H_3O_7N_3$: N, 8.69. Found: N, 8.80.

1,2-Benzanthraquinone-4-acetic Acid (IX).—A solution of 0.35 g. of the hydrocarbon VIII in 20 cc. of hot glacial acetic acid was cooled rapidly to give a fine suspension of the material, and on adding 1.8 g. of sodium dichromate and shaking at room temperature the hydrocarbon soon dissolved. The solution was refluxed for twenty minutes and on dilution with water a yellow oxidation product was precipitated. This was dissolved in hot, dilute soda solution and, after clarification and after redissolving some sodium salt which crystallized, reprecipitated. The quinone crystallized from xylene–benzene as small, yellow needles (0.2 g.) melting at 228–229.5° and giving an orange-red vat with alkaline hydrosulfite solution.

Anal. Calcd. for $C_{20}H_{12}O_4$: C, 75.92; H, 3.83. Found: C, 75.81; H. 3.80.

Pyrolysis of 5-Benzoyl-6,7-cyclopentenotetralin.—After heating 13.5 g. of the ketone for one hour at 410°, the residue was distilled in vacuum and the viscous oil obtained was warmed with ether. Before the bulk of the material had dissolved, a crystalline product began to separate, and this substance (A, see below) was easily obtained in a nearly pure condition, m. p. 140–141°, uncorr.; yield, 2.1–2.5 g. (17–21%). After removing this hydrocarbon as completely as possible, the oil recovered from the mother liquor was treated with picric acid in benzene–ether solution, and on standing there was obtained 2.5 g. of a crystalline picrate melting at about 110°. Further crystallization from benzene gave 1 g. (4%) of pure tetrahydro-4,10-ace-1,2-benzanthracene picrate, which formed small, dark red plates melting at 131–132°. The corresponding hydrocarbon is described below.

In one experiment 13.5 g. of ketone was heated as above except for the addition of 1.3 g. of zinc dust. There was little change in the yields, 1.8 g. of hydrocarbon and 3 g. of crude picrate being obtained.

Hydrocarbon A, Probably Δ^3-Dehydro-3,4-trimethylene-isobenzanthrene-2 (XII).—The pyrolysis product separating easily from ether was purified by further crystallization from this solvent and by chromatographic adsorption. It forms faintly yellow-green, fluorescent prisms melting at 144.5–145°. Its solution in sulfuric acid is red, changing to a darker red on heating without showing signs of decomposition. The picrate crystallizes from benzene–ether in the form of crimson needles melting at 136–137°.

Anal. Calcd. for $C_{20}H_{16}$: C, 93.71; H, 6.29. Found: C, 93.68, 93.89; H, 6.34, 6.49. *Anal.* (picrate). Calcd. for $C_{20}H_{16}\cdot C_6H_3O_7N_3$: N, 8.95. Found: N, 9.12.

On attempting to dehydrogenate the hydrocarbon (0.6 g.) with selenium (2 g.) at 295° for twenty-four hours, considerable material was destroyed and the only product isolated was unchanged starting material (0.1 g.).

Oxidation was effected by refluxing a solution of 2 g. of the hydrocarbon and 16 g. of sodium dichromate in 50 cc.

of glacial acetic acid for one-half hour. Yellow needles of the reaction product began to separate from the boiling solution, and the precipitation was completed by the addition of water. The crude oxidation product was dissolved in dilute sodium hydroxide solution at the boiling point and the yellow solution was filtered from a dark sludge of suspended material. When refiltered through a pad of charcoal, the solution was nearly colorless, and on adding acid and boiling, the product separated as a pale yellow precipitate in a nearly pure condition; yield 0.5 g. The substance is insoluble in cold alkali. On crystallization from dioxane, in which it is readily soluble, the substance formed fan-shaped clusters of pale yellow needles, m. p. 280.5–281.5°.

Anal. Calcd. for $C_{16}H_8O_3$: C, 77.41; H, 3.25. Found: C, 77.71; H, 3.39.

The analysis and properties are those of phenanthrene-8,9-dicarboxylic anhydride, for which Pschorr[8] reports the corrected melting point 283–284°. No depression was observed in the melting point on admixture with a slightly less pure sample of the anhydride previously prepared in this Laboratory.[14]

1′,2′,3′,4′-Tetrahydro-4,10-ace-1,2-benzanthracene (X).—This hydrocarbon was recovered from the purified picrate, m. p. 131–132°, described above, by distribution between ammonia water and ether. The compound crystallizes well when an ethereal solution is diluted with methanol and concentrated to the point of saturation. The sample for analysis was distilled in vacuum and recrystallized, forming silky, colorless needles melting at 106–107°. The solutions are beautifully fluorescent.

Anal. Calcd. for $C_{20}H_{18}$: C, 92.98; H, 7.02. Found: C, 92.69; H, 7.24. *Anal.* (picrate). Calcd. for $C_{20}H_{18}\cdot C_6H_3O_7N_3$: N, 8.62. Found: N, 8.78.

Dehydrogenation of the hydrocarbon with a large excess of selenium was conducted at 300–320° for twenty hours. The product was extracted with benzene, the solution was passed through a tower of alumina, and the recovered material on crystallization from methanol gave pale yellow needles melting at 135–137° and showing no depression when mixed with 4,10-ace-1,2-benzanthracene.

Summary

The synthesis of 4,10-ace-1,2-benzanthracene, an isomer of the carcinogenically active cholanthrene, has been accomplished by the use of the modified Elbs reaction. This pyrolytic reaction, applied in another case where both a five-membered and a six-membered ring are available for condensation, was found to proceed in both possible directions. Further evidence was found of the tendency of 1,9-trimethylene derivatives of anthracene to undergo transformation to phenanthrene derivatives in the course of the pyrolysis.

CONVERSE MEMORIAL LABORATORY
CAMBRIDGE, MASSACHUSETTS RECEIVED MARCH 17, 1937

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[14] Fieser and Peters, THIS JOURNAL, **54**, 4373 (1932).

[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY, HARVARD UNIVERSITY]

The Tautomerism of Certain Derivatives of Acetomesitylene

BY E. P. KOHLER AND R. B. THOMPSON

In a recent study of the structure of the magnesium derivatives of mono ketones[1] it was found that the derivative of benzhydryl acetomesitylene is an enolate and that the corresponding enol is sufficiently persistent in solution to be detectable as peroxide. This observation is important because at present the only reliable evidence that a substance obtained by adding a metallic derivative to an unsaturated ketone or ester is an enolate, is its conversion into an enol by a process which does not enolize the corresponding ketone or ester.

It was found, also, that in a series of related mono ketones the mode of acylation of the magnesium derivatives appeared to be associated with the relative persistence of the enolic modifications. At the time this observation was made it was not possible to study the behavior of these enolates in reactions involving alkylation because they failed to react with any of the alkylating agents that were available. Having found, in the meanwhile, that magnesium derivatives of this type react very readily with chloromethyl ether we have now compared the mode of alkylation of the enolates which differed most in the mode of acylation, namely, the magnesium derivatives of benzhydryl acetophenone and benzhydryl acetomesitylene. We have also compared the tautomerism of a number of other ketonic derivatives of mesitylene with that of the corresponding derivatives of benzene. The results are embodied in the present paper.

When the magnesium derivative of benzhydryl acetophenone reacts with chloromethyl ether the result is a mixture composed of 30% of the

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[1] Kohler, Tishler and Potter, THIS JOURNAL, **57**, 2517 (1935).