[Contribution from the School of Chemistry of the University of Minnesota]

Electrophilic Properties of Ethyl 3-Phenylindone-2-carboxylate

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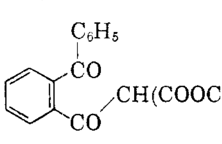
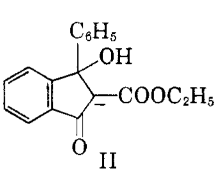
In spite of presumed steric hindrance and electronic deactivation, the 2,3-double bond in ethyl 3-phenylindone-2-carboxylate is quite reactive. The compound adds amines or alcohols to give products stable only in basic solution, but it adds many other types of active hydrogen compounds including hydrogen cyanide, nitromethane, ethyl malonate, or acetone to give relatively stable products.

When *o*-benzoylbenzoyl malonic ester (I)[1] is warmed with dilute sodium carbonate, a clear nearly colorless solution is formed. Acidification of this solution then precipitates ethyl 3-phenylindone-2-carboxylate (III).[2]


I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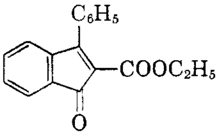
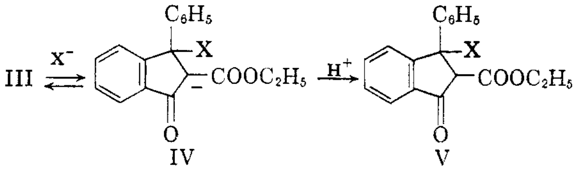

III

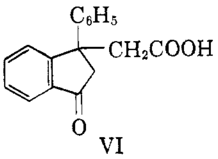
The product is insoluble in aqueous sodium hydroxide, and it is therefore unlikely that the original alkaline solution contains II. Investigation of this situation has disclosed that III is remarkably reactive toward most nucleophilic reagents other than OH^-. The solution referred to may contain an anion (IV, $X = OC_2H_5$) formed by addition of alkoxide, the alcohol involved resulting from hydrolysis of one ester group of I.

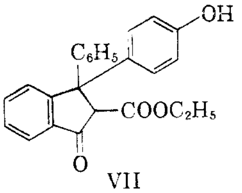


When III is suspended in dilute aqueous alkali and a little alcohol is added, solution rapidly takes place. Acidification of this solution at 0° yields a colorless precipitate which changes within a few seconds to the bright yellow characteristic of III. Similarly, the indone III reacts with dilute aqueous ammonia, piperidine, or sodium phenoxide. Neutralization of the resulting solutions or the solids obtained by concentrating them yields colorless substances which are stable enough to be removed by filtration, but which rapidly revert to III when they are moistened with organic solvents. If an ether solution of III is shaken with aqueous sodium bisulfite, an oily sodium salt is deposited, presumably the addition product IV, $X = SO_3Na$.

Other nucleophilic reagents give addition products of somewhat greater stabilities. Aqueous sodium cyanide reacts rapidly, and acidification precipitates V ($X = CN$), which can be recrystallized easily. Similarly, III in presence of dilute potassium hydroxide and aqueous acetone, cyclohexanone, ethyl malonate, ethyl cyanoacetate, nitromethane, or sodium thioglycollate yields IV (X = respectively CH_2COCH_3, C_6H_9O, $CH(COOC_2H_5)_2$, $CH(CN)COOC_2H_5$, CH_2NO_2, SCH_2COO^-). In all cases acidification of the resulting basic solutions is a critical procedure; it must be carried out rapidly and in the cold if reversion is to be avoided.

The products (V) are fairly strong acids, soluble in aqueous carbonate, and they give deep colors with ferric chloride. They are degraded to III by solution in alkali and subsequent hot acidification, but the addition products are stable to acids. Thus it was possible to convert the malonic ester product to VI by use of hot 48% hydrobromic acid. Hydrolysis and decarboxylation of the acetone product were effected similarly.


VI


VII

Although phenol yields an unstable adduct (IV, $X = OC_6H_5$) under usual conditions, at 160° III reacts with potassium phenoxide to form a stable product (VII). Structure of this substance was proved by comparison of the methyl ether (X) of its hydrolysis product with a sample synthesized by reactions involving compounds VIII and IX.

Preparation of β-*p*-anisyl-β,β-diphenylpropionic acid (IX) by the method indicated[3] was done only after attempts by the method of Huston and Jackson,[4] using pure crystalline anisyldiphenylcarbinol,

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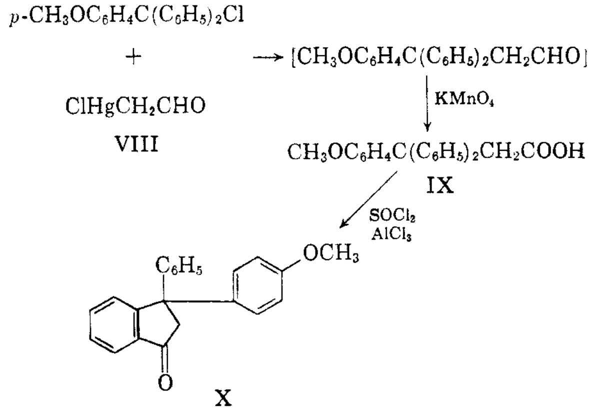
[1] C. F. Koelsch, *J. Org. Chem.*, **25**, 642 (1960).

[2] W. L. Yost and A. Burger, *J. Org. Chem.*, **15**, 1113 (1950).

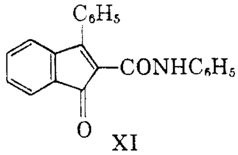
[3] *Cf.* D. Y. Curtin and M. J. Hurwitz, *J. Am. Chem. Soc.*, **74**, 5381 (1952).

[4] R. C. Huston and R. L. Jackson, *J. Am. Chem. Soc.*, **63**, 541 (1941).

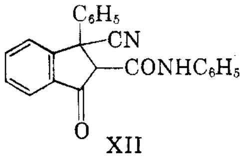


gave yields of less than 1%. It is to be noted that the 85% yield claimed for this method refers to an oily material that was not analyzed, whereas in the present work the acid was found to crystallize easily, m.p. 156–157°.

The nucleus of dimethylaniline is not as active as that of the phenoxide anion, and III was recovered unchanged after a mixture of it with dimethylaniline had been kept at 190° for ten minutes. When III is boiled with aniline, only ammonolysis of the ester group takes place, with formation of the anilide XI. This substance retains the high electrophilic property of III, indicated by its ready reaction with cyanide to form a stable adduct XII.

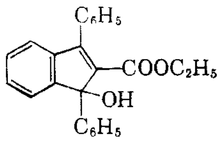


XI

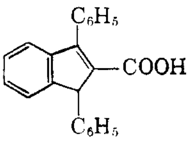


XII

Compared with the reactions of III with active hydrogen compounds, the course of its reaction with phenylmagnesium bromide is surprising. This reagent yields XIII. Structure of the product was proved by reduction and hydrolysis to XIV, a compound which is identical with one synthesized by action of oxalyl chloride on 1,3-diphenylindene. Formation of IV and its analogs is thermodynamically controlled, whereas formation of XIII is kinetically controlled.



XIII



XIV

EXPERIMENTAL

Ethyl 3-phenylindone-2-carboxylate was made by the published method,[2] which yields the solution discussed above, or by a similar but more efficient method which yields the compound directly. A mixture of 37 g. of benzoylbenzoylmalonic ester with 100 ml. of 5% sodium carbonate was boiled under reflux for 10 min., and then cooled. The aqueous solution was removed by decantation (acidification of it yielded only a slight cloudiness) and the product was boiled out once with 100 ml. of water and dried at 100° under reduced pressure; yield 26.5 g. (96.5%), m.p. 88–89°.

2-Carbethoxy-3-cyano-3-phenylhydrindone. A mixture of 0.5 g. of III with 2 ml. of water containing 0.2 g. of sodium cyanide and a few drops of alcohol became colorless within 1 min. when it was warmed. Cooling and acidification precipitated 0.5 g. of nearly pure product, faintly pink plates from dilute alcohol, m.p. 99–101°. The compound gave a purple color with alcoholic ferric chloride; its sodium salt was difficultly soluble in 10% sodium hydroxide and not affected by boiling with this for 1 hr.

Anal. Calcd. for $C_{19}H_{15}NO_3$: C, 74.7; H, 4.95. Found: C, 75.0; H, 4.93.

3-Acetonyl-2-carbethoxy-3-phenylhydrindone. A mixture of 1 g. of III with 3 ml. of acetone and 10 ml. of 10% potassium hydroxide was shaken for 10 min. or until it had become colorless. Excess acetone was removed under reduced pressure, leaving an oily salt which soon solidified (use of sodium hydroxide gave a permanently oily salt, and the final product was difficult to purify). This salt was easily soluble in toluene, and by addition of 2 drops of this solvent it became crystalline and easily removable by filtration. The salt was suspended in cold ether and shaken with iced hydrochloric acid. Evaporation of the ether left 1 g. of product, colorless needles from dilute alcohol, m.p. 96–99°, red-purple with alcoholic ferric chloride.

Anal. Calcd. for $C_{21}H_{20}O_4$: C, 75.0; H, 5.99. Found: C, 75.0; H, 6.01.

When a mixture of 2.7 g. of this compound with 10 ml. of 48% hydrobromic acid was boiled for 10 min. and then evaporated, there was left 2.1 g. of crude *3-acetonyl-3-phenylhydrindone.* Crystallization from methanol and then ethyl acetate–ligroin gave large faintly tan prisms, m.p. 95–96°.

Anal. Calcd. for $C_{18}H_{16}O_2$: C, 81.7; H, 6.10. Found: C, 81.4; H, 6.10.

2-Carbethoxy-3-(2-cyclohexanonyl)-3-phenylhydrindone. A mixture of 3 g. of III with 3 g. of cyclohexanone, 6 ml. of *tert*-butyl alcohol, and 10 ml. of 10% sodium hydroxide became colorless when it was shaken for a few minutes. The mixture was then evaporated to dryness at 100° under reduced pressure and treated with water and ether, giving a bulky mass of a difficultly soluble sodium salt. This was washed with a little water and ether, dissolved in 20 ml. of alcohol, cooled to 0°, and made slightly acid with alcoholic sulfuric acid. The solution was filtered and concentrated under reduced pressure, and the crystalline product was recrystallized from alcohol, giving 2 g. of colorless plates, m.p. 126–136°; blue with alcoholic ferric chloride.

Anal. Calcd. for $C_{24}H_{24}O_4$: C, 76.6; H, 6.43. Found: C, 76.4; H, 6.56.

2-Carbethoxy-3-nitromethyl-3-phenylhydrindone. A solution of 3 g. of III and 3 g. of nitromethane in 6 ml. of *tert*-butyl alcohol was treated with 5 ml. of 10% sodium hydroxide, added dropwise and with shaking. The yellow color deepened at first but rapidly became lighter. The mixture was then cooled and acidified, and the precipitated product was crystallized from alcohol giving 3 g. of slightly pink prisms, m.p. 105–107°; purple with ferric chloride.

Anal. Calcd. for $C_{19}H_{17}NO_5$: C, 67.3; H, 5.05. Found: C, 67.5; H, 5.10.

Ethyl 2-carbethoxy-3-phenylhydrindone-3-malonate. A solution of 8.4 g. of III and 5 g. of ethyl malonate in 10 ml. of warm *tert*-butyl alcohol was mixed with 15 ml. of 10% sodium hydroxide and shaken. The mixture rapidly became dark orange, then pale yellow, and on cooling set to a solid crystalline mass. Addition of 30 ml. of ether gave a clear solution. This was mixed with 50 g. of ice containing 5 ml. of sulfuric acid and shaken for 30 min. The ether layer was then separated, washed with water, and evaporated under reduced pressure. The crystalline residue (13.2 g.) was nearly pure; recrystallization from alcohol gave coarse colorless needles, m.p. 89–91°.

Anal. Calcd. for $C_{25}H_{26}O_7$: C, 68.5; H, 5.98. Found: C, 68.2; H, 5.96.

A mixture of 13 g. of this ester with 50 ml. of 48% hydrobromic acid was boiled for 2 hr., then evaporated to dryness at 100° under reduced pressure. The residue was boiled for 90 min. more with 25 ml. of fresh hydrobromic acid and 10 ml. of acetic acid, and evaporated again. The resulting gum (9.4 g.) was heated at 185° until gas evolution ceased, then cooled, giving a crystalline mass of crude acid (8.2 g.). This was taken up in 40 ml. of methanol containing 2 ml. of sulfuric acid and boiled for 1 hr. The resulting *methyl 3-phenylhydrindone-3-acetate* (7.6 g.) was distilled, b.p. 230–235° (15 mm.) and recrystallized from ethyl acetate–ligroin giving 5.7 g. of colorless needles, m.p. 88–89°.

Anal. Calcd. for $C_{18}H_{16}O_3$: C, 77.1; H, 5.75. Found: C, 77.5; H, 5.78.

Saponification of the ester by boiling 5 min. with 2% potassium hydroxide in methanol gave *3-phenylhydrindone-3-acetic acid,* colorless solvated needles from ethyl acetate–ligroin, m.p. 91–92°.

Anal. Calcd. for $C_{17}H_{14}O_3 + CH_3COOC_2H_5$: C, 71.2; H, 6.2. Found: C, 71.5; H, 5.8.

From methylene chloride, the acid separated solvent-free, m.p. 128–130°.

Anal. Calcd. for $C_{17}H_{14}O_3$: C, 76.7; H, 5.3. Found: C, 76.7; H, 5.5.

Ethyl 2-carbethoxy-3-phenyl-3-cyanoacetate. A mixture of 0.5 g. of III with 0.5 ml. of ethyl cyanoacetate was treated with 1 drop of 50% aqueous potassium hydroxide and kept overnight. Cooling and acidification gave an oil that soon solidified. Recrystallization from alcohol gave colorless needles, m.p. 121–124° that gave a purple ferric chloride test.

Anal. Calcd. for $C_{23}H_{21}NO_5$: C, 70.6; H, 5.41. Found: C, 70.8; H, 5.47.

2-Carbethoxy-3-phenylhydrindone-3-thioglycollic acid. A mixture of 1 g. of III with 10 ml. of 10% sodium hydroxide and 1 ml. of 75% thioglycollic acid became homogeneous when it was boiled for 1 min. Acidification at 0° gave a colorless product that formed colorless prisms from benzene-ligroin. The compound became yellow at 95° and melted at 105° to a bright yellow liquid; to avoid decomposition it had to be dried at room temperature. It gave a purple color with ferric chloride. It was soluble in cold dilute bicarbonate, but this solution became yellow and cloudy when it was warmed.

Anal. Calcd. for $C_{20}H_{18}O_5S$: C, 64.9; H, 4.90. Found: C, 64.7; H, 5.20.

Reaction with phenol. A solution of 0.5 g. of potassium hydroxide in 5 ml. of phenol was distilled to $^2/_3$ volume under reduced pressure to remove water, then cooled and treated with 1 g. of III. The mixture was heated to 160° and cooled within 0.5 min., then diluted with ether and washed with dilute hydrochloric acid. Ether and excess phenol were removed by heating at 160° (10 mm.) for 15 min., and the residue was dissolved in ether and extracted with 5% sodium hydroxide. This left 0.05 g. of III and removed 1.2 g. of phenolic product which crystallized when it was dried and kept for several days under ether-ligroin. *Ethyl 3-p-hydroxyphenyl-3-phenylhydrindone-2-carboxylate* formed solvated plates from ether, m.p. 68–72° with frothing. When it was dried at 65° under reduced pressure it fell to a white powder, m.p. 155–160°; it gave a purple-blue color with ferric chloride.

Anal. Calcd. for $C_{24}H_{20}O_4$: C, 77.4; H, 5.41. Found: C, 77.6; H, 5.31.

The foregoing ester was easily hydrolyzed and decarboxylated, but it was much simpler to prepare *3-p-hydroxyphenyl-3-phenylhydrindone* directly. A solution of 1 g. of potassium hydroxide in 10 g. of phenol was treated with 2 g. of III, then boiled for 5 min. under reflux; the mixture became deep red, then pale yellow, and alcohol was evolved. Isolated in the same way as the carbethoxy derivative, this compound formed colorless prisms and needles (1.75 g.) from ethyl acetate–ligroin, m.p. 136–139°. It gave no color with ferric chloride but was soluble in dilute sodium hydroxide.

Anal. Calcd. for $C_{21}H_{16}O_2$: C, 84.0; H, 5.37. Found: C, 84.3; H, 5.47.

With methyl sulfate in aqueous sodium hydroxide, the phenol gave *3-p-anisyl-3-phenylhydrindone,* prisms from methanol, m.p. 86–88°.

Anal. Calcd. for $C_{22}H_{18}O_2$: C, 84.0; H, 5.77. Found: C, 84.1; H, 5.76.

β-p-Anisyl-β,β-diphenylpropionic acid. A solution of 22 g. of *p*-anisyldiphenylchloromethane in 65 ml. of benzene was mixed with 20 g. of chloromercuriacetaldehyde, stirred 4 hr. at room temperature and boiled under reflux for 2 hr. Water was then added, the mixture was filtered, and the benzene solution was separated and evaporated at 100° under 20 mm. When the residual brown gum was dissolved in 50 ml. of acetone and stirred under reflux with 10 g. of powdered potassium permanganate, a smooth reaction occurred which kept the mixture boiling for 15 min. After an additional 45 min., the acetone was evaporated, replaced with ether and dilute sodium carbonate, and the manganese dioxide was removed by filtration. The ether contained 11.5 of neutral material, which was discarded, while from the aqueous extract there was obtained 8.6 g. of solid acid, colorless plates from dilute acetic acid, m.p. 156–157°.

Anal. Calcd. for $C_{22}H_{20}O_3$: C, 79.5; H, 6.06. Found: C, 79.5; H, 6.15.

Treatment of the acid with polyphosphoric acid gave only gummy products, but the desired cyclization was achieved as follows. Addition of a droplet of pyridine to a mixture of 1 g. of the acid with 5 ml. of thionyl chloride initiated a smooth reaction which was completed by warming for 5 min. Excess thionyl chloride was removed, and the residue was taken up in 5 ml. of benzene and treated with 1 g. of powdered aluminum chloride. After it had been kept for 15 min. at room temperature, the mixture was hydrolyzed, and the neutral product was kept for some time with ether-ligroin. There was obtained 70 mg. of crystalline material; recrystallization from ligroin gave 20 mg. of prisms, m.p. 87–88°, identified as 3-*p*-anisyl-3-phenylhydrindone by mixed melting point and infrared spectrum.

Reaction with aniline. A mixture of 1 g. of III with 1.5 g. of aniline was boiled 5 min. while alcohol was allowed to escape. The deep red solution was cooled and treated with 5 ml. of alcohol, giving 1.1 g. of deep red needles. From dilute acetic acid, *3-phenylindone-2-carboxanilide* (XI) formed bright red prisms, m.p. 178–179°. It was insoluble in hot aqueous sodium hydroxide. Addition of a few drops of alcohol to this gave a colorless solution which deposited unchanged anilide when it was acidified.

Anal. Calcd. for $C_{22}H_{15}NO_2$: C, 81.2; H, 4.65. Found: C, 80.8; H, 4.80.

If boiling III with aniline was prolonged to 10 min., part of the product was *3-phenylindone-2-carboxanilide anil.* Separation of the anil was most easily effected by warming the once crystallized product with 5% sodium hydroxide in 25% alcohol. The anilide dissolved as its alcohol addition product, and was regenerated by acidification, whereas the anilide-anil remained insoluble. Crystallization from *n*-butyl alcohol gave deep yellow needles, m.p. 217–218°. When the anil was suspended in alcohol and treated with a drop of hydrochloric acid, it gave a deep red solution which almost at once deposited the anilide.

Anal. Calcd. for $C_{28}H_{20}N_2O$: C, 84.0; H, 5.03. Found: C, 84.2; H, 5.00.

When 1 g. of the anilide was suspended in 7 ml. of alcohol and treated with 0.5 g. of sodium cyanide in a little water, rapid solution and decolorization occurred. Cooling to 0° and acidification gave 1.0 g. of *3-cyano-3-phenylhydrindone-2-carboxanilide,* faintly tan prisms from alcohol, m.p. 157–159°; purplish-red ferric chloride test.

Anal. Calcd. for $C_{23}H_{16}N_2O_2$: C, 78.4; H, 4.58. Found: C, 78.4; H, 4.44.

Reaction with phenylmagnesium bromide. A solution of 2.5 g. of III in 10 ml. of benzene was treated with 6 ml. of 2*N* ethereal phenylmagnesium bromide, giving a deep purple solution and a gummy black precipitate that dissolved when the mixture was kept overnight. Addition of dilute hydrochloric acid, etc. gave 2.9 g. of a pale tan oil that could not be obtained crystalline. This was treated with 10 ml. of 20% methanolic potassium hydroxide, rapid solution occurring, followed by separation of a colorless crystalline potassium salt. This salt was washed with methanol and then ether, then dissolved in water and acidified. The resulting *1,3-diphenyl-1-hydroxyindene-2-carboxylic acid* separated as an oil, which crystallized after it had been kept under ether-ligroin for several days. Recrystallization from dilute alcohol gave fine colorless needles, m.p. 163–164°. The compound gave a deep purple color with concd. sulfuric acid.

Anal. Calcd. for $C_{22}H_{16}O_3$: C, 80.5; H, 4.91. Found: C, 80.6; H, 4.92.

A solution of 0.5 g. of this acid in 5 ml. of acetic acid and 1 ml. of acetyl chloride was treated with 0.5 g. of zinc dust and boiled for 10 min. Water and ether were then added, and the ether solution was extracted with dilute sodium carbonate. This removed 50 mg. of *1,3-diphenylindene-2-carboxylic acid*, flat yellow needles from dilute acetic acid, m.p. 195–196° that gave no color with concd. sulfuric acid.

Anal. Calcd. for $C_{22}H_{16}O_2$: C, 84.6; H, 5.16. Found: C, 84.4; H, 5.16.

The same compound was synthesized by boiling 2 g. of 1,3-diphenylindene with 2 ml. of oxalyl chloride for 1 hr. The acidic product (500 mg.) from this reaction formed colorless needles, m.p. 173–181°, that gave a deep orange color with sulfuric acid; solution in dilute sodium carbonate and warming with 3 ml. of 3% hydrogen peroxide followed by reprecipitation and crystallization from dilute acetic acid gave yellow needles, m.p. 194–196° alone or mixed with the previously described acid; infrared spectra of the two samples were identical.

Acknowledgment. The author thanks Mrs. O. Hamerston for analytical data.

MINNEAPOLIS, MINN.

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE VIRGINIA POLYTECHNIC INSTITUTE]

The Synthesis and Cyclization of Some 2'-Substituted 2-Benzylbenzophenones[1,2]

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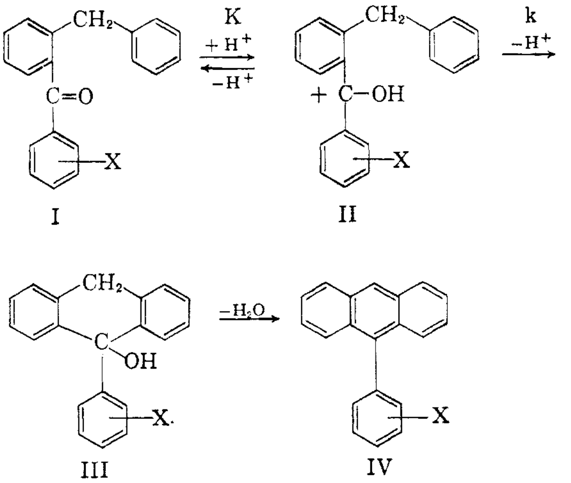
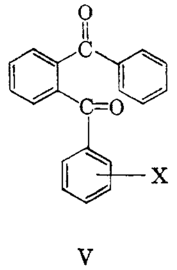
A series of new 2'-substituted 2-benzylbenzophenones has been prepared. These ketones have been cyclized to their corresponding 9-substituted phenylanthracenes. The rates of cyclization were measured and correlated with a mechanism proposed for aromatic cyclodehydration.

In 1940 Bradsher[3] introduced a new method of synthesis for the 9-alkyl- and 9-arylanthracenes. This method has been found to be of considerable value and to have a wide range of application.[4] Quite a few derivatives of 9-phenylanthracene have been prepared by this method in connection with rate studies.[5,6] Compounds of the type I were reported where X was in either the *para* or *meta* positions. The present investigation reports the synthesis of four new ketones of type I, in which X is an *ortho* substituent, and their subsequent cyclization to derivatives of 9-phenylanthracene.

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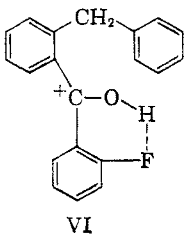
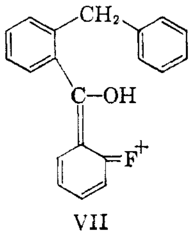

VI


VII

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[1] Presented before the Chemistry Section at the Southeastern Regional Meeting of the American Chemical Society, Durham, N. C., Nov. 1957.

[2] This paper has been abstracted in part from the Masters thesis of Mr. James Bondurant presented to the Virginia Polytechnic Institute in 1955 and in part from the Doctorate thesis of Mr. M. O. L. Spangler presented to the Virginia Polytechnic Institute in 1958.

[3] C. K. Bradsher, *J. Am. Chem. Soc.*, **62**, 486 (1940).

[4] C. K. Bradsher, *Chem. Rev.*, **38**, 447 (1946).

[5] C. K. Bradsher and F. A. Vingiello, *J. Am. Chem. Soc.*, **71**, 1434 (1949).

[6] F. A. Vingiello, J. G. Van Oot, and H. H. Hannabass, *J. Am. Chem. Soc.*, **74**, 4546 (1952).