## Synthesis of $\beta$ - and $\gamma$ -Phenyltropolones from 1,4-Cyclohexanedione

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#### Received August 18, 1960

In the course of the synthesis of  $\beta$ - and  $\gamma$ -phenyltropolones by the ring-enlargement of 4-hydroxy-4-phenylcyclohexanone (II), the intermediate, 1-hydroxy-4-phenyl-8-oxabicyclo[3.2.1]octane (III) was isolated and found to exist exclusively in the cyclic hemiketal form.

There are two methods available for the synthesis of  $\beta$ - and  $\gamma$ -substituted tropolones. That of Doering and Knox<sup>2</sup> involves the production of tropilidenes by the photochemical reaction of diazomethane and substituted benzenes, and their oxidation to tropolones by permanganate. This method is limited by the need for large quantities of readily available substituted benzenes as starting materials, by the indiscriminate reactivity of methylene and by the low yield of tropolones in the oxidation. The method developed by Nozoe, et al.<sup>3</sup> and Cook, et al.<sup>4</sup> involves the oxidation of 3or 4-substituted cycloheptanones with selenium dioxide to the  $\alpha$ -diketones followed by dehydrogenation with bromine or N-bromosuccinimide. The required substituted cycloheptanones are obtained by the conventional diazomethane ring enlargement of the corresponding cyclohexanones. The method appears to be limited by the comparative inaccessibility of the starting 4-substituted cyclohexanones and by the mediocre yields obtained in the ring enlargement. In the present work, we have attempted to point the way to an extension



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of the scope and convenience of the Nozoe-Cook method by developing an alternative synthesis of 4-substituted cycloheptanones. We have chosen the phenyl group as the illustrative substituent.

In the first step, 1,4-cyclohexanedione (I), readily available from diethyl succinate,<sup>5</sup> is treated with phenylmagnesium bromide to afford 4-phenyl-4-hydroxycyclohexanone (II) in 48% yield, together with the known 1,4-diphenylcyclohexanediol-1,4.<sup>6</sup>

In the second step, ring enlargement is effected by means of diazomethane.<sup>7</sup> This reaction has been applied to many cyclohexanones<sup>4,8-11</sup> with yields of substituted cycloheptanones being relatively low. The ring enlargement of 2-chlorocyclohexanone with nitrosomethylurethan, examined by both Steadman<sup>12</sup> and Gutsche,<sup>11</sup> gave a mixture of 2- and 3-chlorocycloheptanone in 50-60% of the theoretical yield. 2-Phenylcyclohexanone<sup>11</sup> gave 2- and 3-phenylcycloheptanone (49.5%) while 4phenylcyclohexanone<sup>13</sup> gave the corresponding 4-phenylcycloheptanone in 80% yield (the reported m.p. is much lower (23-25°) than that of the pure material (m.p. 52-53°) described in the experimental section). 2-Phenylcycloheptanone has also been prepared by the expansion of cyclohexanone with nitrosobenzylurethan<sup>14</sup> in 41-56% yield.

The ring enlargement of 4-hydroxy-4-phenylcyclohexanone (II) with diazomethane generated from nitrosomethylurethan proceeds in excellent yield (about 90%) to give exclusively 1-hydroxy-4phenyl-8-oxabicyclo[3.2.1]octane (III). This significant improvement in yield is presumably due to intramolecular catalysis by the strategically

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located hydroxyl group. Strong catalysis by water and methanol has been demonstrated by Meerwein and Burneleit,<sup>16</sup> who also mention catalytic activity by other alcohols, although in amount decreasing with molecular weight and degree of substitution. The phenomenon is also shown clearly by Gutsche and Jason<sup>14</sup> in their work on the reaction of phenyldiazomethane with cyclohexanone.

For conversion to the phenvltropolones. 1-hvdroxy-4-phenyl-8-oxabicyclo[3.2,1]octane (III) was converted to the chloride with dry hydrogen chloride in ether-benzene and reduced directly without isolation to 4-phenylcycloheptanone(IV). Oxidation with selenium dioxide in ethanol afforded a mixture of 4-ethoxy-4-phenylcycloheptanedione-1,2 and the corresponding 3-ethoxy-3-phenyl isomer. Analogy for the ethoxylation is to be found in the conversion of 2-isopropylcycloheptanone to 2ethoxy-2-isopropylcycloheptanone reported by Cook, Raphael and Scott.<sup>4</sup> Bromination according to Cook, et al.,<sup>16</sup> afforded a mixture of  $\beta$ -phenyltropolone (V) and  $\gamma$ -phenyltropolone (VI), in 9 and 5% yields respectively by the procedure of Doering and Knox.<sup>2</sup> Infrared analysis of the crude phenyltropolones indicated ca. 60% of the  $\beta$ isomer and 40% of the  $\gamma$ -isomer.

Returning to 1-hydroxy-4-phenyl-8-oxabicyclo-[3.2.1] octane (III) we are confident of the relation of the phenyl group and oxygen atoms and of the presence of the cycloheptane ring on the basis of the method of synthesis and the subsequent conversion to  $\beta$ - and  $\gamma$ -phenyltropolones. Evidence for the hemiketal structure<sup>17</sup> includes the total absence of infrared absorption in the carbonyl region accompanied by the ability to form easily a crystalline semicarbazone derivative, from which the hemiketal is regenerated by acid hydrolysis. Although it is easy to rationalize the predominence of the cyclic tautomer by noting that the bicyclo-[3.2.1]octane system is essentially free of angular strain and that the entropy change involved in proceeding from the ketol tautomer to the cyclic hemiketal is certainly more favorable than in related intermolecular cases, the more critical problem of comparing nonbonded interactions in the monocyclic hydroxycycloheptanone tautomer with those in the hemiketal oxabicyclo[3.2.1]octane tautomer defies reliable analysis.

It is relevant to point out that 4-hydroxy-4phenylcyclohexanone shows strong absorption in the carbonyl region and must exist as the hydroxy ketone. Here, angular strain of the oxabicyclo-[2.2.1]heptane system and the more favorable nonbonded interactions in the hydroxycyclohex-

anone system relative to the unfavorable situation in the 7-oxabicvclo[2.2.1]heptane system, combine to render the bicyclic hemiketal form unlikely. The absorption in the OH stretching region  $[2.81\mu]$  $(3560 \text{ cm}, ^{-1})$  and  $2.94\mu$   $(3405 \text{ cm}, ^{-1})$ ] remains unchanged in relative intensity over the concentration range of 1.0, 0.5 and 0.2% in tetrachloroethylene. By contrast the ratio of the intensities of the  $2.80\mu$  and  $2.92\mu$  absorptions in 1-phenylcyclohexanol increases rapidly with increasing dilution over the same concentration range. This evidence for intramolecular hydrogen bonding in 4-hydroxy-4-phenylcyclohexanone affords some physical confirmation of the hypothesis that intramolecular catalysis is an important factor in causing the high yield in the diazomethane ring enlargement.

The unsubstituted analogue, 4-hydroxycycloheptanone (VII) may also be prepared in excellent yield by ring enlargement with diazomethane from 4-hydroxycyclohexanone. Infrared evidence indicates that VII exists mainly in the cyclic hemiketal tautomer, 1-hydroxy-8-oxabicyclo[3.2.1]octane: the carbonyl absorption at  $5.88\mu$  (1701 cm.<sup>-1</sup>) is of low intensity [cycloheptanone:  $5.90\mu$  (1696 cm.<sup>-1</sup>)]; bands at  $2.81\mu$  (3560 cm.<sup>-1</sup>) and  $2.97\mu$  (3365 cm.<sup>-1</sup>) are consistent with free and intermolecular hydrogen bonds<sup>18</sup>; absorption at  $7.41\mu$  (1350 cm.<sup>-1</sup>) corresponds to the C-O stretching absorption of tertiary alcohols (1310-1410 cm.<sup>-1</sup>) while the absorption at  $8.81\mu$  (1133 cm.<sup>-1</sup>) is within the range (about 1140 cm.<sup>-1</sup>) reported for the OH deformation in tertiary alcohols<sup>19</sup>; a band at  $9.17\mu$  (1090  $cm.^{-1}$ ) is consistent with ether oxygen (range 1060–1150 cm.<sup>-1</sup>). Recently, van Tamelen *et al.*,<sup>20</sup> observed a similar case of partial hemiketal formation in the course of their total synthesis of colchicine.

By contrast, 4-hydroxycyclohexanone is in the ketonic form and is, perhaps, intramolecularly hydrogen bonded. Absorption of the carbonyl group at  $5.85\mu$  (1710 cm.<sup>-1</sup>) is very strong as is the absorption at 9.37 $\mu$  (1068 cm,<sup>-1</sup>) attributable to the cyclohexanol OH deformation  $[9.40\mu$  (1064 cm.<sup>-1</sup>].<sup>19</sup> Absorption at 2.80 $\mu$  (3575 cm.<sup>-1</sup>) and  $2.92\mu$  (3425 cm.<sup>-1</sup>) is not inconsistent with free OH and intramolecular hydrogen bonding. Better indication of the existence of an intramolecular hydrogen bond is given by the fact that the relative intensities of the two bands do not change with dilution. Although an intramolecular hydrogen bonded conformation might at first sight seem unlikely because it demands a boat conformation for the ring, the strength of a favorable hydrogen bond (6-8 kcal.) is slightly greater than the re-

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<sup>(17)</sup> For a general reference, see W. Hückel, Theoretical Principles of Organic Chemistry, Elsevier, Amsterdam, 1955, Vol. I, pp. 275-290.

<sup>(18)</sup> L. J. Bellamy, The Infrared Spectra of Complex Molecules, Methuen, London, 1958.

<sup>(19)</sup> H. H. Zeiss and M. Tsutsui, J. Am. Chem. Soc., 75, 897 (1953).

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cently reported difference in enthalpy of the chair and boat form of cyclohexane (5.3 kcal.).<sup>21</sup>

In a vain attempt to prepare 4-hydroxytropone, 4-hydroxycycloheptanone (VII) was oxidized to 1,4-cycloheptanedione (identical in all respects to a sample prepared by Cope, *et al.*,<sup>22</sup>) and brominated in glacial acetic acid. The resulting bromo-4hydroxytropone is not identical with the 5-bromo-4-hydroxytropone of Coffey and Johnson<sup>23</sup> nor could it be reduced to 4-hydroxytropone.

### EXPERIMENTAL<sup>24</sup>

1,4-Cyclohexanedione (I). Ethyl succinylsuccinate (48 g.), prepared according to the procedure of Hauser and Hudson,<sup>5</sup> was suspended in a solution consisting of 160 g. of 85%phosphoric acid, 1.2 l. of water and 20 ml. of ethanol and refluxed for 5 days when all the starting material had dissolved. The solution was continuously extracted with chloroform, dried, and concentrated by distillation through a Vigreux column. The 1,4-cyclohexanedione (I), obtained in a quantitative yield, was purified by sublimation at 100° (15 mm.); m.p. 77-78°; reported 78-79.5°.<sup>25</sup>

4-Hydroxy-4-phenylcyclohexanone (II). 1,4-Cyclohexanedione (30 g., 0.267 mole) in 1 l. of dry ether, was placed in a 2-l., three necked, round bottom flask, equipped with a mercury-sealed stirrer, condenser, and equilibrating addition funnel. In an atmosphere of dry nitrogen, an ethereal solution (300 ml.) of phenylmagnesium bromide (0.267 mole by titration) was added dropwise with stirring over a period of 2 hr. After being refluxed for 1 hr., the reaction mixture was decomposed with aqueous (130 ml.) ammonium chloride (50 g.) with cooling. The ether layer was separated and the aqueous layer extracted with three 50-ml. portions of ether. The combined ether extracts were dried over magnesium sulfate, filtered and concentrated by distillation to an oily residue which partly crystallized. Filtration afforded 15 g. of solid (a) and an oil (b). The solid (a) was triturated with boiling benzene and filtered leaving 1,4-diphenylcyclo-hexanediol-1,4, m.p. 223° after one crystallization from chloroform-ethanol; reported<sup>6</sup> m.p. 225°. Concentration and cooling of the benzene solution afforded 8.5 g. of II. The mother liquor was combined with the oil and distilled at 0.05 mm. in a bath of 200-220°. After a forerun of I, 22 g. of distillate, which solidified on standing, was crystallized from benzene yielding 15.5 g. of II. The combined product (24.0 g., 48.5%) melted at 127-128° after recrystallization from a small amount of methanol.

Anal. Calcd. for C<sub>12</sub>H<sub>14</sub>O<sub>2</sub>: C, 75.8; H, 7.4. Found: C, 75.7; H, 7.6.

The semicarbazone prepared in the usual way was crystallized from absolute ethanol, m.p. 191-192°.

Anal. Calcd. for  $C_{13}H_{17}N_{9}O_{2}$ : C, 63.1; H, 6.9; N, 17.0. Found: C, 63.1; H, 6.7; N, 17.3.

(25) J. R. Vincent, A. F. Thompson, Jr., and L. I. Smith, J. Org. Chem., 3, 603 (1939).

1-Hydroxy-5-phenyl-8-oxabicyclo [3.2.1] octane (III). II (7.7 g.), anhydrous potassium carbonate (0.8 g.) and dry methanol (80 ml.) were placed in a 200-ml., round bottom, three necked flask equipped with a mercury-sealed stirrer, equilibrating addition funnel, and a calcium chloride tube. The flask was cooled in an ice bath and ethyl N-nitroso-N-methyl carbamate (6.3 g.) was added dropwise over a period of 1 hr. After being stirred and cooled for 1-3 hr., the mixture was allowed to stand at room temperature overnight. Filtration and distillation *in vacuo* left a residue which was molecularly distilled at 140° (0.2 mm.) to give 8.2 g. of III as a viscous, colorless oil. On scratching and warming to 50°, it completely solidified.

Anal. Calcd. for  $C_{18}H_{16}O_2$ : C, 76.4; H, 7.9. Found: C, 76.2; H, 7.9.

Purification was effected by conversion in 81-100% of the theoretical yield to the *semicarbazone*; m.p. 146-147° after crystallization from a methanol-ethyl acetate mixture.

Anal. Calcd. for  $C_{14}H_{19}N_{9}O_{2}$ : C, 64.3; H, 7.3; N, 16.1. Found: C, 64.1; H, 7.1; N, 16.0.

The semicarbazone was hydrolyzed in essentially quantitative yield by refluxing for 0.5-1 hr. with 10% phosphoric acid. The residual oil solidified on standing and was crystallized from *n*-hexane-benzene; m.p.  $80-81^{\circ}$ . The infrared spectrum showed the complete absence of absorption in the carbonyl region.

4-Phenylcycloheptanone (IV). Crude III (2.04 g.) was dissolved in benzene (50 ml.) and ether (20 ml.) and cooled in an ice bath. Dry hydrogen chloride was passed into the solution for a period of 5 hr. Removal of solvents *in vacuo* gave a residue which was hydrogenated in benzene at atmospheric pressure and room temperature using 10% palladium-on-carbon as catalyst. Filtration, distillation *in vacuo* and evaporative distillation<sup>26</sup> at 130° (1.5 mm.) afforded a viscous oil which was purified through the semicarbazone and could then be crystallized from hexane; m.p. 52-53° (the m.p. 23-25° reported by Bergmann and Yaroslavsky<sup>13</sup> must refer to quite impure material; consequently their reported yield is of questionable significance). *Anal.* Calcd. for C<sub>13</sub>H<sub>16</sub>O: C, 82.9; H, 8.6. Found: C, 83.0; H, 8.6.

4-Phenylcycloheptanone semicarbazone was crystallized from methanol, m.p. 176-177°.

Anal. Calcd. for  $C_{14}H_{19}N_{3}O$ : C, 68.5; H, 7.8; N, 17.1. Found: C, 68.8; H, 8.0; N, 17.1.

 $\beta$ -Phenyltropolone (V) and  $\gamma$ -Phenyltropolone (VI). To a refluxing solution of IV (4 g.) in absolute ethanol (5 ml.) freshly dried selenium dioxide (2.32 g.) in absolute ethanol (15 ml.) was added over a period of 1 hr.; refluxing was continued for an additional 5 hr. and the mixture was allowed to stand at room temperature overnight. Filtration of the solution and removal of the solvent left a residue which on evaporative distillation at 120° (0.1 mm.) afforded 3.2 g. of yellow oil.

Anal. Caled. for  $C_{18}H_{18}O_8$ : C, 73.1; H, 7.4; caled. for  $C_{18}H_{14}O_2$ : C, 77.2; H, 7.0. Found: C, 74.1, 74.6; H, 7.4, 7.3.

This material (2.4 g.) was dissolved in glacial acetic acid (2.2 ml.), cooled in an ice bath and treated dropwise with bromine (1.26 g.) in glacial acetic acid (1.1 ml.) over a period of 0.5 hr. The deep red solution was heated on the steam bath for 0.5 hr. and steam distilled. The residue from the steam distillation was thoroughly extracted with ether. Shaking the ether solution with 2 ml. of 6N sodium hydroxide precipitated the sodium salts which were filtered, washed with cold acetone, suspended in water, acidified with dilute hydrochloric acid, and extracted with ether. The dried (sodium sulfate) ether layer was concentrated to a residue which was sublimed at 150° (0.1 mm.). The resulting light yellow oil (0.708 g.) was converted to its copper salt (0.75 g., 25%) following the procedure of Doering and Knox.<sup>2</sup>  $\beta$ -Phenyltropolone (V), m.p. 96–97°,

(26) R. B. Woodward and W. von E. Doering J. Am. Chem. Soc., 67, 860 (1945), footnote 51.

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<sup>(23)</sup> R. S. Coffey and A. W. Johnson, J. Chem. Soc., 1741 (1958).

<sup>(24)</sup> Analyses were done by Schwartzkopf Microanalytical Laboratory, 56-19 37th Avenue, Woodside 77, N. Y. Melting points are corrected; boiling points are not corrected. The infrared spectra were obtained with the Perkin-Elmer Model 21 infrared spectrophotometer with sodium chloride optics.

reported<sup>2</sup> m.p. 97°, and  $\gamma$ -phenyltropolone (VI), m.p. 125.5-127°, reported<sup>2</sup> m.p. 125-126°, were isolated in 9 and 5% yields respectively. Infrared analysis of the crude mixture shows it to consist of approximately 61%  $\beta$ -phenyltropolone (IV) and 39%  $\gamma$ -phenyltropolone (VI). The infrared bands used for the analysis follow:  $\beta$ -isomer: 1387 cm.<sup>-1</sup> (d = 0.22) and 828 cm.<sup>-1</sup> (d = 0.20);  $\gamma$ -isomer: 1364 cm.<sup>-1</sup> (d = 0.32) and 862 cm.<sup>-1</sup> (d = 0.43) at 0.2 molar concentration in chloroform in a 0.104-mm. cell.

4-Hydroxycyclohexanone. Hydroquinone was catalytically reduced to cyclohexanediol-1,4<sup>37</sup> which was then converted to 4-hydroxycyclohexanone according to the method of Jones and Sondheimer.<sup>28</sup>

4-Hydroxycycloheptanone (1-hydroxy-8-oxabicyclo[3.2.1]octane) (VII). In a 200-ml., three necked, round bottom flask equipped with a mercury-sealed stirrer, an equilibrating addition funnel and a calcium chloride tube were placed 11.4 g. of 4-hydroxycyclohexanone, 100 ml. of absolute methanol and 2 g. of anhydrous powdered potassium carbonate. Ethyl N-nitroso-N-methylcarbamate (14.5 g.) was added dropwise over a period of 1.5 hr. at 0°. The mixture was stirred for 0.5 hr. and allowed to stand at room temperature overnight. Filtration and distillation left a residue which was distilled *in vacuo*. The fraction distilling at 94° (2 mm.; bath temperature 145-152°) weighed 11.6 g. (90%).

Anal. Calcd. for C<sub>7</sub>H<sub>12</sub>O<sub>2</sub>: C, 65.6; H, 9.4. Found: C, 65.6; H, 9.7.

The 2,4-dinitrophenylhydrazone derivative melted at  $154-155^{\circ}$  after crystallization from 95% ethanol; the melting point of a mixture with the 2,4-dinitrophenyl-hydrazone of the starting material (m.p.  $155-156^{\circ}$ ) was depressed, m.p.  $130-150^{\circ}$ .

Anal. Caled. for C<sub>18</sub>H<sub>16</sub>N<sub>4</sub>O<sub>5</sub>: C, 50.6; H, 5.2; N, 18.2. Found: C, 50.9; H, 5.5; N, 18.2. 1,4-Cycloheptanedione. To 2.6 g. of VII in 10 ml. of

1,4-Cycloheptanedione. To 2.6 g. of VII in 10 ml. of glacial acetic acid, a solution of 2 g. of chromic anhydride

(27) L. N. Owen and P. A. Robins, J. Chem. Soc., 320 (1949).

(28) E. R. H. Jones and F. Sondheimer, J. Chem. Soc., 615 (1949).

in 2 ml. of water and 8 ml. of glacial acetic acid, was added in portions with ice-cooling over a period of 5 min. The resulting solution was allowed to stand in an ice bath for 1 hr. and at room temperature overnight and was then poured over ice and extracted thoroughly with chloroform. The chloroform extracts were washed with aqueous sodium bicarbonate, dried and concentrated by distillation through a Vigreux column. The residue was evaporatively distilled at 90° (0.8 mm.); 1.3 g. (50%);  $n_D^{21}$  1.4842. The bis-2,4dinitrophenylhydrazone melted at 237° dec.; reported<sup>23</sup> m.p. 242° dec.

z-Bromo-4-hydrozycyclohepta-2,4,6-trienone. To 1 g. of 1,4cycloheptanedione in 1 ml. of glacial acetic acid, a solution of 2.56 g. of bromine in 1 ml. of acetic acid was added with cooling and swirling over a period of 20 min. The solution was allowed to stand in an ice bath for 0.5 hr. and then at room temperature overnight. The reaction mixture was steam distilled and the residue extracted thoroughly with ether. On partial distillation of the ether, a powdery yellow solid precipitated, which was crystallized from absolute ethanol; 155 mg., m.p. 195-196°.

Anal. Calcd. for C<sub>7</sub>H<sub>5</sub>BrO<sub>2</sub>: C, 41.8; H, 2.6; Br, 39.7; O, 15.9. Found: C, 42.0; H, 2.8; Br, 40.1; O, 15.9.

The yield of material was not reproducible, 0.10 g. being obtained in one instance and as little as 0.02 g. in others. It was insoluble in chloroform, carbon tetrachloride, carbon disulfide, and soluble in sodium bicarbonate solution. The bromoisotropolone reacted with ethereal diazomethane to give a liquid methyl ether.

Acknowledgment. We are indebted to Melvin J. Goldstein for assistance in the preparatory aspects of this work. We wish to acknowledge the generous support of the Damon Runyon Memorial Fund for Cancer Research in the form of Grant DRIR-148 and of the National Cancer Institute, of the National Institutes of Health, Public Health Service, in the form of Grant C-1130.

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# The Friedel-Crafts Reaction of o-Xylylene Bromide

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#### Received July 15, 1960

The Friedel-Crafts reaction of o-xylylene bromide with benzene in the presence of aluminum chloride was found to afford a mixture of anthracene and diphenylmethane. Similar reaction with toluene gave a sutsetic mixture of 2,6- and 2,7-dimethylanthracenes besides 3,4'-dimethyldiphenylmethane, while o-xylene afforded 3,4-dimethyl- and 3,3',4,4'-tetramethyldiphenylmethanes. No anthracene derivative was isolated in the last mentioned reaction. The condensation of o-xylylene bromide with benzene by means of titanium tetrachloride resulted in the formation of o-dibenzylbenzene, neither anthracene nor diphenylmethane being isolated. The use of ferric chloride catalyst gave a mixture of o-dibenzylbenzene and diphenylmethane, while the latter hydrocarbon was a sole product in the reaction with stannic chloride. Boron trifluoride was found to be inactive in this reaction.

There are many examples which indicate the Friedel-Crafts reaction of dihaloalkanes with benzenoid compounds affords cycli-alkylated products whenever possible.<sup>1</sup> The condensation of oxylylene bromide with benzene would therefore, be expected to give 9,10-dihydroanthracene (I) which should then readily be dehydrogenated to anthracene (II) in the presence of aluminum chloride.<sup>2</sup> Such an expectation could be realized to only a limited extent. When a solution of o-xylylene bromide in benzene was treated with anhydrous

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