50 mL of water and 100 mL of ethanol, and the solution was refluxed for 24 h. Each anilino ketone **27** precipitated when the solution was cooled. Purification of each anilino ketone was effected by crystallization from 95% ethanol.

Each anilino ketone **27** exhibited sharp peaks at about 3350 cm^{-1} (NH) and at about 3350 cm^{-1} (carbonyl) in its IR spectrum. Additional data are provided in Table VI.

Isolation of Ketoamides 26. The same procedure was followed as in the preparation of **27**, except that the period of reflux after the addition of water and ethanol was limited to 2 h. When the solution was cooled, each ketoamide **26** precipitated. Each was purified by crystallization from 95% ethanol.

The IR spectrum of each ketoamide exhibited two sharp carbonyl peaks at about 1690 and 1645 cm^{-1}. Additional data are provided in Table IV.

Rearrangement of 2 (R = Benzyl). A solution of 0.04 mol of **2** (R = benzyl) in 100–200 mL of THF was treated with 2 equiv of sodium hydride. The initially deep red solution was refluxed for 12 h and the solution was concentrated to dryness in vacuo. The yellow residue was dissolved in 50 mL of concentrated hydrochloric acid and 100 mL of ethanol, and the solution was refluxed for 24 h. Each desoxybenzoin crystallized when the solution was cooled and was recrystallized from 95% ethanol. Each desoxybenzoin was identified by comparison (melting point, mixture melting point, IR spectrum, and NMR spectrum) with an authentic sample of the desoxybenzoin.

Registry No. **1a**, 4553-59-7; **1b**, 15190-65-5; **1c**, 32323-74-3; **1d**, 32153-18-7; **1f**, 32377-36-9; **1g**, 72867-29-9; **1h**, 72881-52-8; **1i**, 54840-97-0; **1j**, 72867-30-2; **1k**, 72867-31-3; **1l**, 72867-32-4; **1m**, 72867-33-5; **1o**, 39640-73-8; **1p**, 32377-38-1; **1q**, 4686-05-9; **1r**, 72867-34-6; **2a**, 14062-91-0; **2b**, 72867-35-7; **2c**, 72867-36-8; **2d**, 5367-12-4; **2e**, 30057-98-8; **2f**, 72867-37-9; **2g**, 72867-38-0; **2h**, 72867-39-1; **2i**, 72867-40-4; **2j**, 72867-41-5; **2k**, 72867-42-6; **2l**, 72867-43-7; **2m**, 72867-44-8; **2n**, 72867-45-9; **2o**, 72867-46-0; **2p**, 72867-47-1; **2q**, 72867-44-8; **2r**, 72867-48-2; **2s**, 14101-08-7; **2t**, 72867-49-3; **2u**, 72867-50-6; **3a**, 72867-52-8; **3b**, 72867-54-0; **3c**, 72867-56-2; **3d**, 72867-58-4; **8a**, 30082-50-9; **8b**, 72867-59-5; **8c**, 72867-60-8; **9**, 30082-52-1; **14**, 72867-61-9; **22a**, 72867-62-0; **22b**, 72867-63-1; **22c**, 72867-64-2; **22d**, 72867-65-3; **22e**, 72867-66-4; **22f**, 72867-67-5; **22g**, 72867-68-6; **22h**, 72867-69-7; **22i**, 72867-70-0; **22j**, 72867-71-1; **23a**, 451-40-1; **23b**, 1889-71-0; **23c**, 62482-45-5; **23d**, 72867-72-2; **23e**, 3141-93-3; **23f**, 62381-24-2; **23g**, 33470-10-9; **23h**, 1009-14-9; **23j**, 16216-08-3; **26a**, 7714-86-5; **26b**, 72867-73-3; **26d**, 72881-53-9; **27a**, 5722-91-8; **27b**, 72867-74-4; **27c**, 6910-79-8; **27d**, 72867-75-5; $C_6H_5NH_2$, 62-53-3; *m*-$ClC_6H_4NH_2$, 108-42-9; *p*-$MeOC_6H_4NH_2$, 104-94-9; $C_6H_5CH_2NH_2$, 100-46-9; *p*-$ClC_6H_4CH_2NH_2$, 104-86-9; *n*-$C_5H_{11}NH_2$, 110-58-7; c-$C_6H_{11}NH_2$, 108-91-8; *m*-$MeOC_6H_4NH_2$, 536-90-3; *p*-$ClC_6H_4NH_2$, 106-47-8; 2,4,6-$(Me)_3C_6H_2NH_2$, 88-05-1; C_6H_5CHO, 100-52-7; HCHO, 50-00-0; *p*-ClC_6H_4CHO, 104-88-1; *m*-ClC_6H_4CHO, 587-04-2; *o*-ClC_6H_4CHO, 89-98-5; 3,4-$(MeO)_2C_6H_3CHO$, 120-14-9; *m*-$MeOC_6H_4CHO$, 591-31-1; *o*-$MeOC_6H_4CHO$, 135-02-4; *n*-C_4H_9CHO, 110-62-3; $C_6H_5CH(OH)CN$, 532-28-5; $HOCH_2CN$, 107-16-4; *p*-$ClC_6H_4CH(OH)CN$, 13312-83-9; *m*-$ClC_6H_4CH(OH)CN$, 53313-92-1; *o*-$ClC_6H_4CH(OH)CN$, 13312-84-0; 3,4-$(MeO)_2C_6H_3CH(OH)CN$, 6309-18-8; *m*-$MeOC_6H_4CH(OH)CN$, 53313-94-3; *o*-$MeOC_6H_4CH(OH)CN$, 53313-93-2; *n*-$C_4H_9CH(OH)CN$, 64350-07-8; C_6H_5COCl, 98-88-4; CH_3COCl, 75-36-5; *p*-$MeOC_6H_4CHO$, 123-11-5; dimethyl acetylenedicarboxylate, 762-42-5; ethyl acrylate, 140-88-5; methyl propargylate, 922-67-8; methyl acrylate, 96-33-3.

Notes

Reductive Methylation of Polycyclic Aromatic Quinones

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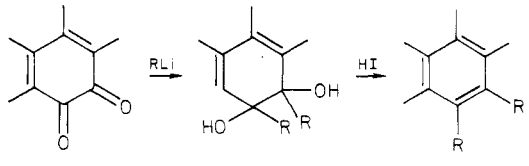
Introduction of methyl groups into appropriate molecular regions of polycyclic aromatic hydrocarbons can profoundly influence their carcinogenic activity.[1-3] In connection with studies directed toward determining the effects of methyl substitution on metabolic activation of carcinogenic hydrocarbons, we required a series of *o*- and *p*-dimethyl-substituted hydrocarbons. For this purpose, we developed a convenient synthetic approach involving reaction of the related quinones with methyllithium followed by reduction of the resulting dimethyl dihydro diols with HI in acetic acid:[4]



Results are summarized in Table I. Reactions with methyllithium were carried out in ether at room temperature. The NMR spectra of the crude dimethyl dihydro diols, which were employed directly in the subsequent step, were consistent with proposed structures. The overall yields of the dimethylarenes were generally high.

The only difficulty experienced was the tendency of certain dimethylarenes to undergo further hydrogenation of the dimethyl-substituted ring to furnish the related dihydro derivatives. In the case of chrysene-5,6-dione, the optimum yield of 5,6-dimethylchrysene (**4**) was obtained with short reaction time (5 min). Reactions conducted for longer periods or in the presence of phosphorus[4] afforded substantial amounts of 5,6-dimethyl-5,6-dihydrochrysene. In contrast, the analogous dimethyl derivatives of phenanthrene (**1**), benzo[*a*]pyrene (**2**), 7-methylbenzo[*a*]pyrene (**3**), and dibenz[*a*,*c*]anthracene (**5**) proved relatively insensitive to conditions; reductions carried out overnight (20 h) or in the presence of phosphorus gave no evidence of the formation of the corresponding dimethyldihydroarenes. In the case of benz[*a*]anthracene-7,12-dione, a precipitate which formed initially on combination of the reactants was identified as 7-iodomethyl-12-methylbenz[*a*]anthracene (**6a**). The latter dissolved rapidly on warming, with efficient conversion to 7,12-dimethylbenz[*a*]anthracene (**6b**). Like **4**, **6b** exhibited a propensity to

(1) Arcos, A. C.; Argus, M. F. "Chemical Induction of Cancer"; Academic Press: New York, 1974; Vol. IIA.

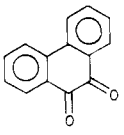
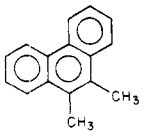
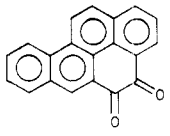
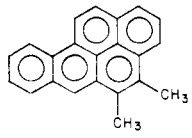
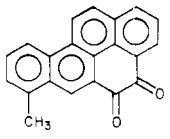
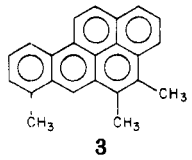
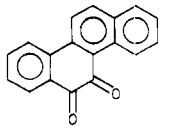
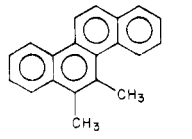
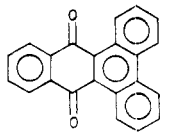
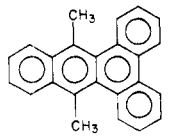
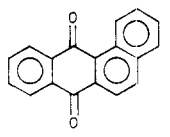
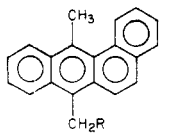
(2) Huggins, C. B.; Pataki, J.; Harvey, R. G. *Proc. Natl. Acad. Sci. U.S.A.* **1967**, *58*, 2253. Pataki, J.; Huggins, C. B. *Cancer Res.* **1969**, *29*, 506. Pataki, J.; Duguid, C.; Rabideau, P.; Huisman, H.; Harvey, R. G. *J. Med. Chem.* **1971**, *14*, 940. Harvey, R. G.; Dunne, F. B. *Nature (London)* **1978**, *273*, 566. Hecht, S. S.; Bondinell, W. E.; Hoffmann, D. *J. Natl. Cancer Inst.* **1974**, *53*, 1121.

(3) Harvey, R. G. In "Safe Handling of Chemical Carcinogens, Mutagens, and Teratogens: The Chemist's Viewpoint"; Walters, D. B., Ed.; Ann Arbor Science Publishers: Ann Arbor, MI, in press.

(4) Efficient reduction of polycyclic quinones to fully aromatic hydrocarbons with HI in acetic acid has also recently been described. Phosphorus has been shown in these studies to promote hydrogenation of polyarenes: Konieczny, M.; Harvey, R. G. *J. Org. Chem.* **1979**, *44*, 4813.

0022-3263/80/1945-1308$01.00/0

Table I. Reductive Methylation of Polycyclic Quinones

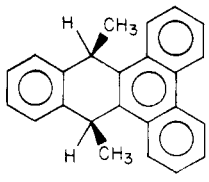
quinone	dimethylarene	yield, %	mp, °C	ref
	 **1**	92	142-143	13
	 **2**	99	190-191	14
	 **3**	98	205-206	*a*
	 **4**	83	128-129	15
	 **5**	98	184.5-185	*a*
	 **6a**, R = I **b**, R = H **c**, R = Cl	95	122-123	5

[a] Satisfactory analytical data were submitted for review.

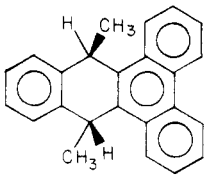
further reduction with longer reaction times, providing 7,12-dihydro-**6b**.

The iodo compound **6a** was previously obtained[5] from reaction of benz[*a*]anthracene-7,12-dione with methylmagnesium bromide followed by treatment of the resulting dimethyl dihydro diol with HI in methanol at 0 °C. Reduction of **6a** with stannous chloride and HCl furnished **6b** in 77% overall yield.[5] The analogous chloro compound (**6c**) was reported as the product of reaction of the same dimethyl dihydro diol with anhydrous hydrogen chloride.[6] Similar iodomethyl intermediates were not detected in any of the other examples cited in Table I, and it is unlikely that they are formed.

The unusually facile reduction of **4** and **6b** to the dihydroarene stage is evidently a consequence of the strong steric interaction between methyl and hydrogen in the bay regions of these two molecules. X-ray crystallographic analysis confirms substantial distortion of **6b** from planarity as a consequence of steric crowding in the bay region.[7] Substantial relief of steric strain is provided by hydrogenation in the meso regions of these compounds, thereby allowing the hindered methyl group to adopt the favored pseudoaxial position in the resulting flattened boat conformation.[8,9] It is less obvious why **5** does not undergo equally facile reduction. The likely explanation is that while formation of the cis stereoisomer **7a** would relieve strain in both bay regions, formation of the trans isomer **7b** would provide only partial relief.



7a, cis



7b, trans

In order to provide some evidence on the stereoselectivity of reduction, the isomeric identity of 7,12-dihydro-**6b** obtained from reduction of **6b** with HI was investigated. With short reaction time (15 min), the principal product detected by NMR analysis was *trans*-7,12-dihydro-**6b**, identical with an authentic sample of the latter obtained from reduction of **6b** with lithium in ammonia.[10] With slightly longer reaction periods (60 min), *cis*-7,12-dihydro-**6b** was the only dihydro isomer detected.[11] Epimerization of the trans stereoisomer to the thermodynamically favored cis stereoisomer evidently occurs rapidly under the conditions of reaction. This was verified experimentally with authentic *trans*-7,12-dihydro-**6b**. The latter on heating with HI in acetic acid under the standard conditions of reduction of the dimethyl dihydro diols afforded only *cis*-7,12-dihydro-**6b**. It appears, therefore, that reductions of dimethylarenes, such as **5** and **6b**, are trans stereospecific and favored only when the resulting trans-dihydro product is free to adopt a relatively sterically unhindered conformation.

In view of the stereospecific character of these reactions, it is unlikely that radical intermediates are involved. Product structure is consistent with a mechanism involving transfer of hydride from HI to one of the meso positions of **6b** followed by protonation of the resulting monoanion from the axial direction; similar stereospecific axial protonation of the same monoanion was proposed earlier to account for the trans stereospecific reduction of **6b** with lithium in ammonia.[10]

In summary, the two-step synthesis of dimethylarenes described herein provides a convenient synthetic approach to compounds of this type. In comparison with the relatively complex multistep syntheses of **1**, **2**, **4**, and **6** reported previously,[5,6,13-15] the present method offers the advantages of fewer steps and higher yields. It would appear, therefore, that this method is the preferred choice for those cases for which it is applicable. The facile epimerization of *trans*-7,12-dihydro-**6b** in HI and acetic acid also suggests the potential utility of the reagent for the

(5) Sandin, R. B.; Fieser, L. F. *J. Am. Chem. Soc.* **1940**, *62*, 3098.
(6) Newman, M. S.; Sankaran, V. *Tetrahedron Lett.* **1977**, 2067.
(7) Iball, J. A. *Nature (London)* **1964**, *201*, 916.
(8) Mono- and dialkyldihydroanthracenes have been shown to exist preferentially in flattened boat conformations with bulky substituents oriented pseudoaxially.[9]
(9) (a) Rabideau, P. W. *Acc. Chem. Res.* **1978**, *11*, 141. (b) Brinkmann, A. W.; Gordon, M.; Harvey, R. G.; Rabideau, P. W.; Stothers, J. B.; Ternay, A. L. *J. Am. Chem. Soc.* **1970**, *92*, 5912. (c) Fu, P. P.; Harvey, R. G.; Paschal, J. W.; Rabideau, P. W. *J. Am. Chem. Soc.* **1975**, *97*, 1145.
(10) Harvey, R. G.; Arzadon, L.; Grant, J.; Urberg, K. *J. Am. Chem. Soc.* **1969**, *91*, 4535.
(11) *cis*- and *trans*-7,12-dihydro-**6b** are readily distinguished by their NMR spectra.[10,12]
(12) Harvey, R. G.; Arzadon, L. *Tetrahedron* **1969**, *25*, 4887.
(13) (a) Bradsher, C. K.; Jackson, Jr., W. J. *J. Am. Chem. Soc.* **1954**, *76*, 4140. (b) Rabideau, P. W.; Harvey, R. G. *J. Org. Chem.* **1970**, *35*, 25.
(14) Comp, J. L.; Daub, G. H. *J. Am. Chem. Soc.* **1958**, *80*, 6049.
(15) Newman, M. S. *J. Am. Chem. Soc.* **1940**, *62*, 870.

epimerization of dialkyldihydroaromatic ring systems generally, previously accomplished with *n*-butyllithium–*N,N,N',N'*-tetramethylethylenediamine.[9c]

Experimental Section

Physical Data. Proton NMR spectra were obtained on a Varian T-60 spectrometer in $CDCl_3$ with tetramethylsilane as internal standard. The integrated NMR spectra were consistent in all cases with the structural assignments and essentially identical with the spectra of authentic standard compounds, where available. All melting points are uncorrected.

Materials. Phenanthrene-9,10-dione, chrysene-5,6-dione, and benz[*a*]anthracene-7,12-dione were commercial samples recrystallized from benzene before use. Benzo[*a*]pyrene-4,5-dione[16] and dibenz[*a,c*]anthracene-9,14-dione[17] were synthesized by the methods reported earlier. 7-Methylbenzo[*a*]pyrene-4,5-dione was prepared by adaptation of the method utilized for preparation of benzo[*a*]pyrene-4,5-dione.[16] *trans*-7,12-Dimethyl-7,12-dihydrobenz[*a*]anthracene was synthesized by the method described.[10] Benzene was purified by distillation from CaH_2 and stored over molecular sieves, type 4A. Diethyl ether was dried over sodium. The HI employed was a 57% aqueous solution (Fisher) preserved with ~1% hypophosphorous acid.

Reactions of Polycyclic Quinones with Methyllithium. A partial solution of the quinone (10 mmol) in benzene (100 mL) or an equal volume of benzene–ether (1:1) was treated with a solution of methyllithium (27 mmol, 15 mL of a 1.8 M solution) in ether under N_2 at room temperature. The resulting solution was stirred for 24 h and then worked up conventionally to provide the crude dimethyl dihydro diol (confirmed by NMR) which was reduced directly with HI in acetic acid.

Reduction of Dimethyl Dihydro Diols with HI. 1. General Procedure. A solution of the dimethyl dihydro diol (3.4 mmol) and 57% HI (2 mL, 15 mmol) in acetic acid (50 mL) was heated at reflux for 15 h and then poured into a 1% aqueous sodium bisulfite solution (100 mL). The precipitate was collected by filtration, washed with water, and dried. Purification by chromatography on silica gel with benzene–hexane (1:1) as eluant afforded the pure dimethylarenes (Table I).

2. 5,6-Dimethylchrysene (4). Reactants were heated together in refluxing acetic acid for only 5 min and then immediately poured into 1% bisulfite solution and stirred overnight. During this time the original slightly sticky precipitate became crystalline. Workup by the general procedure gave pure **4** (Table I).

3. 7,12-Dimethylbenz[*a*]anthracene (6b). Upon combination of the reactants in the proportions specified in the general procedure, **6a** precipitated out. The temperature was gradually increased until **6a** dissolved and then the reaction mixture was poured into 1% bisulfite solution and worked up in the usual manner to afford pure **6b** (Table I). The identity of **6a** was confirmed by NMR: (Me_2SO-d_6) δ 3.20 (s, 3, CH_3), 5.40 (s, 2, CH_2I), and 7.50–8.45 (m, 9, aromatic). As previously reported,[5] this compound decomposed on attempted crystallization or melting.

Reduction of 6b. These reactions were conducted on a 1-g scale according to the general procedure for the reduction of the dihydro diols. Product ratios were determined by high-resolution NMR analysis (270 MHz) in comparison with authentic samples of *cis*- and *trans*-7,12-dihydro-**6b** whose NMR spectra showed the following: trans δ 1.51 (d, 3, 7-CH_3, J = 7.31 Hz), 1.91 (d, 3, 12-CH_3, J_{12} = 6.93 Hz), 4.19 (q, 1, H_7), and 4.96 (q, 1, H_{12}); cis δ 1.60 (d, 3, 7-CH_3, J_7 = 7.30 Hz), 1.64 (d, 3, 12-CH_3, J_{12} = 7.34 Hz), 4.22 (q, 1, H_7), and 4.85 (q, 1, H_{12}). These data are in essential agreement with those reported earlier[10,12] for the less well-resolved 60-MHz spectra except that $\delta_{12\text{-}CH_3}$ of the trans isomer was found at somewhat lower field than reported (δ 1.72).[10]

Reaction for 15 min gave **6b** (25%), *trans*-7,12-dihydro-**6b** (50%), and *cis*-7,12-dihydro-**6b** (25%). After 60 min, reduction of **6b** was 85% complete, and *cis*-7,12-dihydro-**6b** was the sole dihydro isomer detectable. Recrystallization of the crude product from ethanol gave pure *cis*-7,12-dihydro-**6b**, mp 108.5–109 °C (lit.[12] mp 106–107 °C).

Epimerization of *trans*-7,12-Dihydro-6b. *trans*-7,12-Dihydro-**6b** (1 g) on treatment with HI in refluxing acetic acid by the general procedure employed for the reduction of the dihydro diols underwent essentially quantitative conversion after 1 h to the cis isomer (by NMR).

Acknowledgment. This research was supported by grants (CA 11968 and CA 09183) and a research contract (CP 033385) from the National Cancer Institute, DHEW. The HX 270 Bruker NMR spectrometer was funded through University of Chicago Cancer Research Center Grant CA 14599.

Registry No. **1**, 604-83-1; **2**, 16757-89-4; **3**, 72496-73-2; **4**, 3697-27-6; **5**, 632-53-1; **6a**, 27018-50-4; **6b**, 57-97-6; *cis*-7,12-dihydro-**6b**, 24316-23-2; *trans*-7,12-dihydro-**6b**, 23660-33-5; **6c**, 13345-62-5; phenanthrene-9,10-dione, 84-11-7; benzo[*a*]pyrene-4,5-dione, 42286-46-4; 7-methylbenzo[*a*]pyrene-4,5-dione, 72496-74-3; chrysene-5,6-dione, 2051-10-7; dibenz[*a,c*]anthracene-9,14-dione, 3228-74-8; benz[*a*]anthracene-7,12-dione, 2498-66-0.

(16) Harvey, R. G.; Goh, S. H.; Cortez, C. *J. Am. Chem. Soc.* **1975**, *97*, 3468.
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Dibenzoazasemibullvalenes

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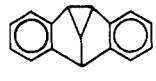
Dibenzosemibullvalene (1) has been known for many years.[1,2] However, dibenzoazasemibullvalene (2) has



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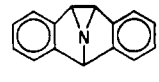
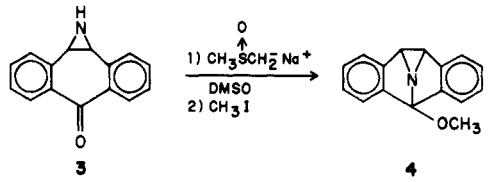


2

eluded all reported synthetic efforts to date.[3] The "aza" derivative of **1** is of interest because the high degree of strain associated with the semibullvalene structure should force the nitrogen and its nonbonded electrons away from the rest of the molecule, making the system more prone to form metal–ligand complexes. Also, since many 5,10-bridged dibenzocycloheptenes are known to exhibit biological activity,[4] dibenzoazasemibullvalene is of pharmaceutical interest.

I wish to report the first successful synthesis of the alkoxydibenzoazasemibullvalene **4** from the novel aziridinyl ketone **3**. The yield is high, 90–95%, and the product is



3 4

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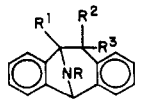
(4) French Patent 2 170 862 claims 5,10-iminodibenzocycloheptenes to be antidepressants, anticonvulsants, and sedatives.



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