A New Synthesis of 6-Substituted Benzo[a]pyrenes[1]

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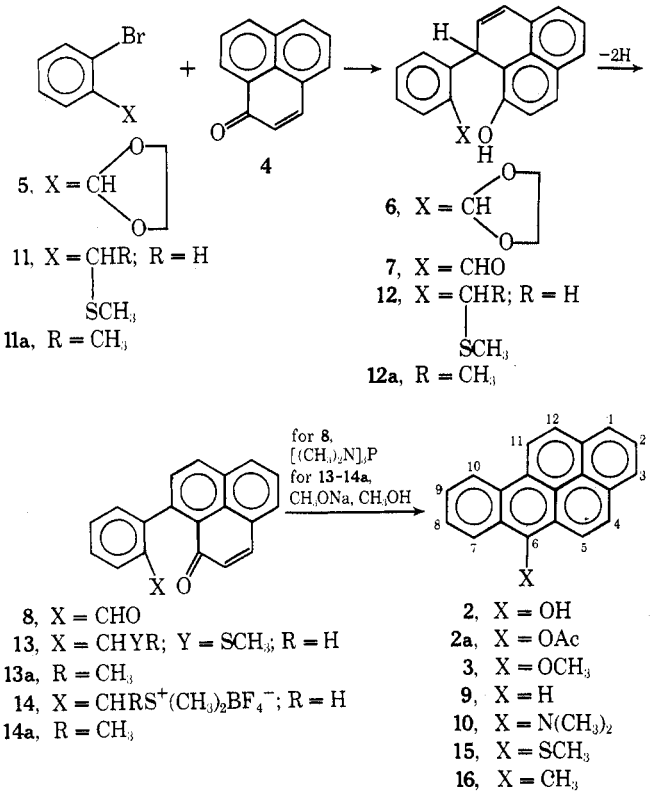
The synthesis of o-(9-phenalenonyl)benzaldehyde (8) from 2-o-bromophenyl-1,3-dioxolane (5) and phenalenone (4) is described. Treatment of 8 with tris(dimethylamino)phosphine yields small amounts of benzo[a]pyrene and 6-dimethylaminobenzo[a]pyrene (10). Treatment of 4 with lithio derivatives prepared from o-bromobenzyl methyl sulfide (11), and o-bromo-(1-methylthioethyl)benzene (11a) afforded (after oxidation of intermediate dihydro compounds) 9-[o-(methylthiomethyl)phenyl]phenalenone (13) and 9-[o-(1-methylthioethyl)phenyl]phenalenone (13a), respectively, both of which, by treatment with methyl iodide and the product with silver tetrafluoroborate, were converted into dimethyl[o-(9-phenalenonyl)benzyl]sulfonium tetrafluoroborate (14) and dimethyl[α-methyl-o-(9-phenalenonyl)benzyl]sulfonium tetrafluoroborate (14a), respectively. The reaction of 14 with sodium methoxide in methanol afforded mainly 6-acetoxybenzo[a]pyrene (2a) (on acetylation of the reaction mixture), together with smaller amounts of 6-methoxybenzo[a]pyrene (3) and 6-methylthiobenzo[a]pyrene (15).

In a preliminary communication[3] our efforts to prepare 5a,6-epoxy-5a,6-dihydrobenzo[a]pyrene (1) were outlined. Although 1 was not isolated, the formation of 6-hydroxybenzo[a]pyrene (2) and 6-methoxybenzo[a]pyrene (3) presumably involved 1 which was unstable under the reaction conditions. In this paper these and other efforts are described in more detail.

The desirability of preparing arene oxides and the methods which have been developed for their synthesis have been reviewed.[4] The importance of these epoxides in possible metabolic pathways of carcinogenic and noncarcinogenic aromatic hydrocarbons formed the subject of a symposium.[5] However, no analog of 1 has yet been isolated.

Our first attempt at synthesis of 1 is outlined in Scheme I. The details are given in the Experimental Section.

Scheme I



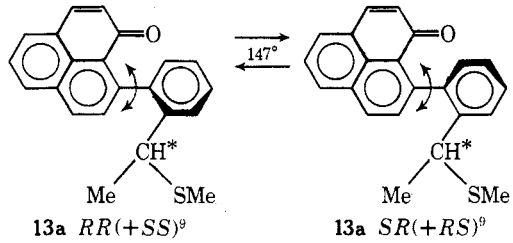
When 8 was treated with tris(dimethylamino)phosphine (TDP) in an attempt to extend the synthesis of epoxides previously developed here,[6] a small yield (32%) of benzo[a]pyrene 9 was obtained. Under slightly different conditions a small yield of 6-dimethylaminobenzo[a]pyrene 10 was obtained. No effort was made to improve either of these yields.

The next attempt to prepare 1 is outlined in Scheme I. The final ring closure was an attempt to apply a previous intermolecular epoxide synthesis[7] to an intramolecular situation.

In the reactions of the lithium derivative formed from 11 both dihydro product, 12, and oxidized product, 13, are produced. By an oxidative work-up (heating with quinone) all 12 can be converted into 13. As described previously,[3] when 14 was treated with methanolic sodium methoxide and the reaction product acetylated by treatment with acetic anhydride there were isolated 66% of 2a, 10% of 3, and 10% of 15. A rationalization for the formation of 2 and 3 involving the formation of the epoxide 1 has been presented.[3] When lithium methoxide was used in acetonitrile–methanol, 68% of 2a and 14% of 15 were isolated.

In the hope that an epoxide of type 1 might be more stable if the hydrogen in the 6 position were replaced by a methyl group, we prepared the series of compounds, 11a–14a, by starting from 11a. Interestingly, yields of 12a (17%) and 13a (52%) were obtained when reaction of the lithio derivative of 11a with 4 was carried out at −60 to −50°. However, when the reaction was run at 0° neither 12a nor 13a could be isolated from the mixture of products formed. A small yield of 6-methylbenzo[a]pyrene[8] (16) was the only crystalline product obtained.

In attempting to purify 13a by crystallization it was noted that a form, mp 146–147°, could be isolated. On melting and resolidification of this material the melting point fell to 131–135°. The higher melting point form showed only one doublet at δ 1.37 for a C-methyl group in the NMR, whereas the lower melting form showed two C-methyl doublets. We interpret these facts by assuming that the 146–147° form represents one of the two diastereomeric racemates possible, since there are two sources of chirality in the molecule: one due to the asymmetric carbon, and one due to biphenyl-type isomerism, as shown below. At the



13a *RR*(+*SS*)[9] 13a *SR*(+*RS*)[9]

melting point, rotation about the biphenyl bond results in the formation of a mixture of the two racemates.[10] We thank Dr. K. Mislow for providing the references cited.[10]

The 147° isomer of **13a** was readily converted into **14a** but all efforts to cyclize this to a derivative of benzo[a]pyrene gave such mixtures of products that work in this area was abandoned.

Experimental Section[11]

2-*o*-Bromophenyl-1,3-dioxolane (5). A mixture of 86 g of *o*-bromobenzaldehyde and 1 g of toluenesulfonic acid in 80 g of ethylene glycol and 200 ml of benzene was refluxed for 18 hr, water being removed as formed, to yield 74 g (81%) of **5**, bp 102–106° (0.5 mm) [lit.[12] bp 126–127° (5 mm)].

2-[(*o*-1*H*,9-Hydroxyphenalen-1-yl)phenyl]-1,3-dioxolane (6).* A Grignard reagent was prepared from 2.9 g of mg, 7.6 g of ethylene dibromide, and 19 g of **5** in 150 ml of THF. This Grignard reagent was cooled to −30° under N_2 and treated with a solution of 9.0 g (0.05 mol) of **4** in 50 ml of THF during 5 min. The mixture was held at −30 to −10° for 1 hr and then treated with excess saturated aqueous NH_4Cl. After a conventional work-up, crystallization from benzene–hexane afforded 11.5 g (70%) of **6**, mp 173–175°, suitable for further use. Additional recrystallization from benzene–hexane yielded the analytical sample: mp 176–177°; ir (KBr) 3280 cm^{-1}; NMR (DMSO-d_6) δ 4.05 (s, 4, $-CH_2-$), 5.52 (br, 1, CHCH=CH), 6.06 (d of d, 1, J = 10 and 5 Hz, CHCH=CH), 6.47 (s, 1, OCHO), 6.50–7.58 (m, 10, ArH and CHCH=CH), 9.60 (s, 1, OH). When a similar reaction was carried out in THF at reflux a mixture of many products was obtained from which only an 8% yield of benzo[a]pyrene (**9**), mp 176–177°, was isolated. The uv spectrum agreed with that given previously.[13]

In a reaction involving 3.4 g of **5** and 0.85 g of **4** in THF at −30 to −10° as above, hydrolysis with dilute HCl instead of NH_4Cl yielded 0.75 g (55%) of *o*-(1*H*,9-hydroxyphenalen-1-yl)benzaldehyde (**7**),* mp 171–174°, suitable for further work. The analytical sample, mp 173–174°, was obtained by recrystallization from benzene–hexane: ir (KBr) 3340 (OH), 1670 cm^{-1} (CO); NMR (DMSO-d_6) δ 5.97–6.49 (m, 2, CHCH=CH), 6.70 (d of d, 1, J = 10 and 1 Hz, CHCH=CH), 9.77 (s, 1, OH), 10.67 (s, 1, CHO).

o*-(9-Phenalenonyl)benzaldehyde (8). In a typical experiment, a mixture of 200 mg of **7**, 400 mg of benzoquinone,[14] and 10 ml of benzene was held at reflux for 30 min. After the usual work-up, which included washing with saturated $Na_2S_2O_4$ and with 10% NaOH, there was obtained 180 mg (90%) of yellow **8**, mp 125–126°. Recrystallization from benzene–EtOH yielded the analytical sample: mp 125.5–126.5°; ir (KBr) 1680, 1630 (CO), 1618 cm^{-1} (C=C), 5.95 μ; NMR ($CDCl_3$) δ 6.45 (d, 1, J = 10 Hz, CH=CHCO), 7.10–8.18 (m, 10, ArH, CH=CHCO), 9.79 (s, 1, CHO).

Benzo[a]pyrene (9) and 6-Dimethylaminobenzo[a]pyrene (10).* A mixture of 50 mg of **8**, 200 mg of tris(dimethylamino)phosphine (TDP), and 5 ml of benzene was refluxed for 1 hr and worked up as usual. The only crystalline product isolated by chromatography over alumina was **9** (3 mg, 6%), mp 176–178°, not depressed by mixing with authentic **9**. When a similar mixture was refluxed in *o*-dichlorobenzene for 24 hr a 32% yield of **9** was obtained. When 1.5 mmol each of **8** and TDP in *o*-dichlorobenzene were stirred for 7 days and refluxed for 24 hr, chromatography on alumina using benzene yielded a first fraction (R_f 0.75 on silica gel plate) as a yellow oil which afforded a brown picrate (14%), mp 170–172°. The picrate was chromatographed on alumina to yield a yellow solid which was unstable to heat in the presence of air. On the basis of elemental and mass spectral[15] analyses (exact mass, 295.1365, calcd for $C_{22}H_{17}N$, 295.1361) the structure **10** was assigned to this compound but no further attempts were made to improve the yield or derivatize.

1-(*o*-Methylthiomethyl)phenyl-1*H*-phenalen-9-ol (12) and 9-[*o*-(Methylthiomethyl)phenyl]phenalenone (13). To the solution of *o*-(methylthiomethyl)phenyllithium prepared from 117 ml of 2.2 *M* *n*-BuLi in hexane and 57 g of *o*-bromobenzyl methyl sulfide (**11**) as described[16] was added at 0° 10.0 g of **4** in portions under N_2. After 2 hr at 0° and 4 hr at room temperature the mixture was refluxed overnight. The mixture was treated with dilute HCl and worked up as usual. A benzene solution of the residue yielded crystals which were recrystallized from dimethylformamide (DMF) to yield 2.5 g (25%) of an orange solid, mp 250–251° dec, which elementary* and mass spectral analyses indicated to be a dimer of phenalenone (exact mass, 358.0998, calcd for $C_{26}H_{14}O_2$, 358.0994). The remaining product from the mother liquors was chromatographed on 1 kg of silica gel. Fraction 2 [benzene–petroleum ether (bp 30–60°) (1:4)] gave a mixture of a solid and an oil. Recrystallization from benzene–petroleum ether (bp 60–100°) yielded 3.0 g (17%) of **12:*** mp 147.0–148.5°; ir (KBr) 3200 cm^{-1}; NMR ($CDCl_3$) δ 2.09 (s, 3, SCH_3), 3.74 and 4.02 (AB q, 2, J = 16.7 Hz, CH_2), 5.51 (d of d, 1, J = 4 and 2 Hz, CHCH=CH), 5.93 (d of d, 1, J = 10 and 4 Hz, CHCH=CH), 6.55 (d of d, 1, J = 10 and 2 Hz, CHCH=CH), 6.50 (s, 1, OH), 6.90–8.20 (m, 9, ArH). Fraction 4 [benzene–petroleum ether (bp 30–60°) (4:1)] yielded 2.6 g (16%) of orange prisms of **13:*** mp 149–150°; ir (KBr) 1630 and 1618 cm^{-1}; NMR ($CDCl_3$) δ 1.90 (s, 3, SCH_3), 3.41 and 3.52 (AB q, 2, J = 16 Hz, CH_2), 6.60 (d, 1, J = 10 Hz, COCH=CH), 7.02–8.25 (m, 10, COCH=CH, ArH).

A solution of 1.97 g of **12** and 4 g of benzoquinone in 40 ml of benzene was held at reflux for 20 min; the solution was washed with saturated sodium dithionate and 18% NaOH and worked up as usual. Recrystallization from benzene yielded 86% of **13**. In general it was better to chromatograph reaction mixtures obtained by reaction of *o*-(methylthiomethyl)phenyllithium with **4** *before* any attempt to oxidize the **12** present with quinone because chromatographic separation of **13** and **4** is difficult.

Dimethyl[*o*-(9-phenalenonyl)benzyl]sulfonium Tetrafluoroborate (14). After a solution of 1.00 g of **13** and 6.6 g of methyl iodide in 20 ml of acetonitrile was stirred at 20–25° for 30 min, 0.56 g of $AgBF_4$ was added and stirring was continued for 3 hr. The mixture was filtered and AgI was washed with solvent. After removal of about ⅔ of the solvent by rotary evaporation, addition of EtOH afforded 1.15 g (90%) of yellow **14:** mp 197–199° dec; ir (KBr) 1630 and 1618 cm^{-1}; NMR (DMSO-d_6) δ 2.71 and 2.80 [two s, 6, $(CH_3)_2S^+$], 4.46 and 4.62 (AB q, 2, J = 14 Hz, CH_2), 6.60 (d, 1, J = 10 Hz, COCH=CH), 7.05–8.60 (m, 10, COCH=CH, ArH). As **14** is unstable on heating it is best not to recrystallize before proceeding to the next step.

6-Acetoxybenzo[a]pyrene (2a), 6-Methoxybenzo[a]pyrene (3), and 6-Methylthiobenzo[a]pyrene (15). To the CH_3ONa solution prepared from 1.0 g of Na and 20 ml of MeOH was added a solution of 0.60 g of **14** in 10 ml of CH_3CN and 10 ml of benzene. The mixture was stirred under N_2 for 3 hr, when a TLC analysis on silica gel pretreated with triethylamine using benzene–EtOAc (1:9) showed a major spot (R_f 0.33), which corresponded to known 6-hydroxybenzo[a]pyrene (**2**). Since **2** is known to be somewhat unstable toward chromatography,[17] the crude mixture was treated with 10 ml of Ac_2O and the product was isolated as usual and chromatographed over 70 g of silica gel. Fraction 1 [ether–petroleum ether (bp 30–60°) (1:99)] on crystallization from petroleum ether (bp 60–100°) yielded 40 mg of **15,*** mp 168.5–169.0° (lit.[18] mp 169–170.5°). The second fraction, obtained with the same eluent, was rechromatographed over silica gel as above to yield an additional 8 mg of **15** (total yield 10%) followed by a fraction which yielded 45 mg (10%) of **3**, mp 173–174° (lit.[19] mp 174–175°). From the third fraction [ether–petroleum ether (bp 30–60°) (1:4)] was isolated 268 mg of pure **2a**, mp 208–209°, not depressed by mixing with an authentic sample.[8] When 0.62 g of **14** in 25 ml of CH_3CN and 40 ml of benzene was treated for 2 hr at 15–20° with MeOLi prepared by treating 0.5 g of Li with 40 ml of MeOH, a work-up similar to that described above yielded 14% of **15** and 67% of **2a**. The use of Me_2SO or CH_3CN in treatment of **14** with bases gave smaller yields of the same products.

o*-Bromo(1-methylthioethyl)benzene (11a).** A mixture of 96.5 g of *o*-bromoethylbenzene,[20] bp 68–70° (8 mm), 93 g of *N*-bromosuccinimide, 1 g of benzoyl peroxide, and 250 ml of CCl_4 was held at reflux for 2 hr. After a conventional work-up the residue was added to a solution made by treating 29 g of CH_3SH with the MeONa prepared by treating 12 g of Na with 250 ml of MeOH. After refluxing for 30 min and the usual work-up there was obtained 103 g (86%) of **11a, bp 84–85°, on fractionation through a 30-in. Widmer column topped with a total-reflux partial take-off head.

1-[*o*-(1-Methylthioethyl)phenyl]-1*H*-phenalen-9-ol (12a) and 9-[*o*-(1-Methylthioethyl)phenyl]phenalenone (13a). A solution of 13.0 g of **11a** in 30 ml of dry ether was added during 10 min to 23 ml of 2.2 *M* *n*-BuLi in hexane and 0°. After stirring at 0° for 30 min the solution was cooled to −60° and treated with 8.0 g of **4** in portions and the mixture was held at −60 to −50° for 40 min and poured into dilute HCl. After standing at 15–20° overnight, 3.3 g of a yellow solid, mp 170–178°, had separated and was collected. Crystallization from benzene–petroleum ether (bp 30–60°) yielded 2.5 g (17%) of light yellow **12a:** mp 177–179°; ir (KBr) 3300 cm^{-1} (OH); NMR (DMSO-d_6) δ 1.64 (d, 3, J = 7 Hz, $CHCH_3$), 1.93 (s, 3, SCH_3), 4.81 (q, 1, J = 7 Hz, $CHCH_3$), 5.59 (br,

1, CHCH=CH), 6.06 (d of d, 1, J = 10 and 5 Hz, CHCH=CH), 6.66 (d of d, 1, J = 10 and 2 Hz, CHCH=CH), and 6.85–6.70 (m, 9, ArH).

The filtrate from the above yellow solid and the mother liquors from recrystallization were combined and worked up as usual. The organic product was chromatographed over 400 g of alumina. From the second fraction eluted with benzene–ether (4:1) was obtained 7.6 g (52%) of orange solid, mp 121–128°. On recrystallization from benzene–petroleum ether (bp 60–100°) and four times from benzene–ethanol a portion of **13a**, mp 146.0–147.5°, ir (KBr) 1630, 1610 cm^{-1}, was obtained. However, after the melting point had been taken the remelting point was 131–135°. The NMR of the 147° form in $CDCl_3$ showed the following: δ 1.37 (d, 3, J = 6 Hz, $CHCH_3$), 1.83 (s, 3, SCH_3), 3.32 (q, 1, J = 6 Hz, $CHCH_3$), 6.60 (d, 1, J = 10 Hz, CH=CHCO), and 7.10–8.25 (m, 10, ArH, CH=CHCO). The lower melting samples of **13a** showed two doublets ($CHCH_3$) at δ 1.37 and 1.47, the remaining NMR spectrum being similar to that of the high-melting **13a**. When the lithio derivative of **11a** was treated with **4** at 0° only 45% of **16**[8] was isolated.

Dimethyl[α-methyl-*o*-(9-phenalenonyl)benzyl]sulfonium Tetrafluoroborate (14a). In a reaction of **13a** (820 mg) with CH_3I, etc., entirely similar to that for the conversion of **13** to **14**, except that the reaction with CH_3I was run for 2 hr, there was obtained 850 mg (80%) of **14a**,* mp 218–220° dec, having the expected ir and NMR spectra. All attempts to obtain benzo[*a*]pyrene derivatives by treatment of **14a** with CH_3ONa in MeOH failed to yield appreciable amounts of any pure substance.

Registry No.—**4**, 548-39-0; **5**, 34824-58-3; **6**, 55669-59-5; **7**, 55669-60-8; **8**, 55669-61-9; **9**, 50-32-8; **10**, 55669-62-0; **10** picrate, 55669-63-1; **11**, 19614-11-0; **11a**, 55669-64-2; **12**, 55669-65-3; **12a**, 55669-66-4; **13**, 52288-10-5; **13a** isomer 1, 55669-67-5; **13a** isomer 2, 55721-20-5; **14**, 52288-12-7; **14a**, 55669-69-7; ethylene dibromide, 106-93-4; tris(dimethylamino)phosphine, 1608-26-0; *o*-(methylthiomethyl)phenyllithium, 52288-09-2; phenalenone dimer, 55669-48-2; $AgBF_4$, 14104-20-2; *o*-bromoethylbenzene, 1973-22-4.

References and Notes

(1) This work was supported by grants from the National Science Foundation (GP 12445) and the U.S. Public Health Service (07394).

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Alkaline Hydrolysis of Cationic Di- and Trimethylthiopurines

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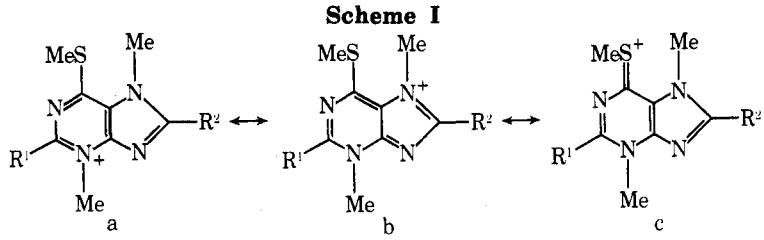
Di- and trimethylthiopurines, which bear two *N*-methyl substituents, exist as resonating cations in which the charge spreads over both rings. Alkali hydrolyzes the methylthio groups in a fixed order, which for 3,7-dimethyl-2,6,8-trimethylthiopurinium cation is 2, 6, 8. Hydrolysis of dimethylthiopurinium cations follows the same order.

In a previous study on di- and trimethylthiopurines it was found that those derivatives, which can form anions, are not attacked by alkali. On the other hand, the *N*-methyl homologs exist above pH 7 only as neutral molecules and thus can be hydrolyzed, the sequence of the reaction being determined by the position of the *N*-alkyl group.[1] It was assumed that the polarized form of the latter creates a positive center which directs the hydroxyl ion to the nearest SMe-substituted carbon atom.

Di- and trimethylthiopurines bearing two *N*-alkyl substituents are resonating cations (Scheme I), their structure being independent of pH in the range 0–14. Consider, for

Scheme I



1, R^1 = SMe; R^2 = H
2, R^1 = R^2 = SMe
3, R^1 = H; R^2 = SMe