Synthesis and Properties of 6-Substituted Benzo[*a*]pyrene Derivatives

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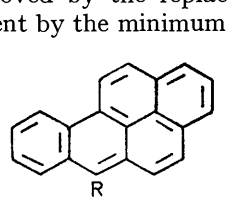
An improved route to benzo[*a*]pyrene-6-carbaldehyde is described, the nature of an impurity in this substance is discussed, the synthesis of a number of 6-substituted benzo[*a*]pyrene derivatives from the carbaldehyde is described, and the use of *N*-halogenosuccinimides for preparing 6-halogeno-derivatives of benzo[*a*]pyrene is examined. The fluorescence spectra and t.l.c. behaviour of the derivatives are described.

FIESER and HERSHBERG [1] prepared orange-yellow benzo[*a*]pyrene-6-carbaldehyde (1) in high yield, *via* a Vilsmeier–Haack reaction, by warming together benzo[*a*]pyrene, *N*-methylformanilide, and phosphoryl chloride in *o*-dichlorobenzene, removing the solvent by steam distillation, and recrystallising the product. They [2] converted this aldehyde into the methyl derivative, *via* a Wolff–Kishner reduction, and into the nitrile, by dehydration of the unstable oxime. By chromatography of the orange-yellow aldehyde we have shown that it consists mainly of a yellow substance, giving the analytical figures expected for a monoaldehyde and of a red-orange material whose C and H figures were near those anticipated for a 1 : 1 molecular complex of a monoaldehyde of benzo[*a*]pyrene and the parent hydrocarbon. The purity of the aldehyde produced was improved by the replacement of *o*-dichlorobenzene as solvent by the minimum volume of dimethylformamide.



(1) R = CHO
(2) R = Me
(3) R = CN
(4) R = CH_2·OH
(5) R = CO_2H
(6) R = CO·NH_2
(7) R = CH_2·NH_2
(8) R = Cl

The synthesis of the 6-methyl derivative (2) was improved by the use of the Huang-Minlon modification,[3] which reduced the reaction time, increased the yield, cut the process down to a single stage, and avoided the need to isolate the unstable hydrazone. A little of the 6-carbonitrile (3) was found to be produced as a by-product during this reaction, probably by loss of ammonia from the hydrazone. A molecular complex formed between the 6-methyl derivative and the nitrile, but the pure 6-methyl derivative could be removed by chromatography. 6-Hydroxymethylbenzo[*a*]pyrene (4) was prepared in high yield by Meerwein–Pondorff–Verley reduction of the 6-carbaldehyde.

Fieser and Hershberg [2] had found that benzo[*a*]pyrene-6-carbaldehyde could not be oxidised directly to the 6-carboxylic acid (5), so we attempted to prepare the latter by hydrolysis of the 6-carbonitrile. Alkaline hydrolysis gave benzo[*a*]pyrene-6-carboxamide (6) in high yield but no further hydrolysis took place. These observations were reminiscent of the experience of Fieser and Gates.[4] Windaus and Rennhak [5] prepared benzo[*a*]pyrene-1-carboxylic acid from 1-acetylbenzo[*a*]pyrene so that although an attempt to convert 6-(α-hydroxyethyl)benzo[*a*]pyrene directly into the 6-carboxylic acid had failed,[2] it seemed worth converting the alcohol into the 6-acetyl derivative and trying to oxidise that. Oppenauer oxidation of the alcohol with acetone failed, but use of *p*-benzoquinone gave the 6-acetyl derivative, although the yield was not good. The product was not oxidised when a haloform reaction was attempted. The difficulty experienced in the preparation of the 6-carboxylic acid is probably associated with steric hindrance coupled with the capacity of the large conjugated polycyclic system to maintain a high electron density at that position.

In an attempt to prepare 6-aminomethylbenzo[*a*]pyrene (7), catalytic hydrogenation of the 6-carbonitrile was investigated. Spectroscopy showed the

[1] L. F. Fieser and E. B. Hershberg, *J. Amer. Chem. Soc.*, 1938, **60**, 2542.
[2] L. F. Fieser and E. B. Hershberg, *J. Amer. Chem. Soc.*, 1939, **61**, 1565.
[3] Huang-Minlon, *J. Amer. Chem. Soc.*, 1946, **68**, 2487.
[4] L. F. Fieser and M. D. Gates, *J. Amer. Chem. Soc.*, 1940, **62**, 2335.
[5] A. Windaus and S. Rennhak, *Z. physiol. Chem.*, 1937, **249**, 256.

product still contained a nitrile grouping and that the aromatic system had been reduced. Lithium aluminium hydride reduction of the nitrile gave a 10% yield of a product with an i.r. spectrum consistent with the presence of an amino-group; reduction of the 6-carboxamide by this reagent gave an 80% yield of a similar product for which satisfactory analytical figures were not obtained. Attempts to purify the aminoride yl derivative failed.

Finally, in the light of previous experience with *N*-halogenosuccinimides as halogenating agents,[6] the monohalogenation of benzo[*a*]pyrene with these agents was examined. Use of *N*-chlorosuccimimide in propylene carbonate gave 6-chlorobenzo[*a*]pyrene (8), identified by comparison with an authentic sample,[7] in higher yield than that achieved by the older method.[7] Use of *N*-bromosuccinimide gave rise to a monobromobenzo[*a*]pyrene in high yield both in polar and in non-polar solvents. In the light of previous experience with these reagents, this was probably the 6-bromo-derivative. *N*-Iodosuccinimide did not iodinate benzo[*a*]pyrene cleanly; intractable tars were formed.

The compounds derived from the aldehyde must all be 6-substituted, as Fieser and Hershberg [2] proved the orientation of the parent compound. It was particularly important from the point of view of subsequent biological studies that the benzo[*a*]pyrene derivatives should be free of the parent hydrocarbon and also of the precursors from which they were synthesised. In all cases no sign of contaminants could be detected and the amount of benzo[*a*]pyrene, or derivatives, contaminating the products described in the Table was less than 0·01%. *p*-Nitrobenzenediazonium chloride in acetic acid couples with benzo[*a*]pyrene with production of an intense purple colour. We confirm Fieser and Campbell's [8] claim that this will detect 1·2 p.p.m. of benzo[*a*]pyrene. The yellow sample of aldehyde showed no trace of benzo[*a*]pyrene when this test was applied. Benzo[*a*]pyrene could be detected on a thin-layer plate either by its reaction with *p*-nitrobenzene diazonium chloride or by its fluorescence. The latter method was the more sensitive: the hydrocarbon could be detected when 100 μl of a solution containing 0·1 p.p.m. of benzo[*a*]pyrene was applied to the plates.

EXPERIMENTAL

I.r. spectra were measured for potassium bromide discs with a Perkin-Elmer 337 spectrophotometer. U.v. spectra were measured with a Unicam SP 800 spectrophotometer. Fluoresence spectra were measured for solutions in ethanol with an Aminco–Bowman spectrophotofluorimeter; excitation spectra were obtained by use of an emission wavelength of 435 nm, and an excitation wavelength of 365 nm was used for emission spectra. Ascending thin-layer chromatograms were run on aluminium oxide G (Merck) with benzene as eluant. Chromatography columns were protected from light by wrapping in aluminium foil.

Benzo[*a*]pyrene was either purchased from Koch–Light Ltd. or prepared from pyrene by the method of Bachmann, Carmack, and Safir [9] as modified by Norman and Waters.[10] In either case the product was further purified by extraction with benzene, chromatography on alumina, and crystallisation from benzene, then from benzene–methanol, and finally from aqueous acetic acid (m.p. 178—179°).

T.l.c. and fluorescence characteristics of benzo[*a*]pyrene derivatives

Compound	R_F Value	Colour in u.v. light (366 nm)	Fluorescence emission spectra ($\lambda_{max.}$/nm)	Fluorescence excitation spectra ($\lambda_{max.}$/nm)
Benzo[*a*]-pyrene	0·95	Violet	410, 432, 456, 490	231, 249, 262, 280, 290, 303, 320, 348, 364, 382, 404
Benzo[*a*]pyr-ene-6-carb-aldehyde	0·86	Yellow	412, 436, 460	231, 266, 289, 356, 370, 381, 407
6-Methylbenzo-[*a*]pyrene	0·93	Violet	415, 439, 466, 495	233, 249, 262, 284, 294, 306, 340, 358, 377, 395, 410
Benzo[*a*]pyrene-6-carbonitrile	0·90	Orange-yellow	434, 456	232, 250, 264, 270, 285, 296, 309, 376, 394, 416
6-Hydroxy-methylbenzo-[*a*]pyrene	0·10	Violet	414, 435, 462	254, 262, 285, 296, 307, 340, 356, 364, 382, 397, 406
Benzo[*a*]pyrene-6-carbox-amide	0·01	Green-yellow	412, 434, 460	248, 262, 282, 294, 307, 338, 362, 379, 396, 405
6-Bromobenzo-[*a*]pyrene	0·97	Orange	416, 436, 461	231, 251, 266, 280, 287, 298, 308, 358, 370, 389, 409

Benzo[a]*pyrene-6-carbaldehyde* (1).—The orange-yellow product of Fieser and Hershberg [1] (0·5 g) was dissolved in benzene and passed slowly down a column (2·5 × 30 cm) of neutral grade alumina. Benzo[*a*]pyrene-6-carbaldehyde formed a broad yellow band incompletely separated from an orange band. The first 30 ml of yellow eluate was collected separately from the remainder and gave yellow *needles*, m.p. 202—203° (Found: C, 89·85; H, 4·4. $C_{21}H_{12}O$ requires C, 90·0; H, 4·3%); the second fraction gave an orange-yellow product, m.p. 198—199°. The two fractions had identical i.r. spectra, with a characteristic strong aryl aldehyde absorption at 1600 cm^{-1}. The latter was purified by repeated chromatography from benzene on alumina; only the upper, redder part of the zone was collected each time, to give *red-orange plates*, m.p. 159—160° (Found: C, 92·2; H, 5·35. $C_{41}H_{24}O$ requires C, 92·15; H, 4·5%). A red-orange product with similar m.p. and spectral properties was prepared by evaporating to dryness a solution containing equimolar amounts of benzo[*a*]pyrene and yellow benzo[*a*]pyrene-6-carbaldehyde in chloroform. The spectrum of the complex was not a simple summation of the spectra of the parent compounds.

[6] F. Dewhurst and P. K. J. Shah, *J. Chem. Soc.* (*C*), **1969**, 1503; 1970, 1737.
[7] A. Windaus and K. Raichle, *Annalen*, 1938, **537**, 157.
[8] L. F. Fieser and J. A. Campbell, *J. Amer. Chem. Soc.*, 1938, **60**, 1142.
[9] W. E. Bachmann, M. Carmack, and S. R. Safir, *J. Amer. Chem. Soc.*, 1941, **63**, 1682.
[10] R. O. C. Norman and W. A. Waters, *J. Chem. Soc.*, 1956, 2379.

Heating a mixture of benzo[*a*]pyrene (1 g), phosphoryl chloride (6 g), and *N*-methylformanilide (5 g) in the minimum volume of dimethylformamide on a steam-bath for 4 h followed by cooling gave a yellow product. Recrystallisation twice from chloroform and then chromatography from benzene on alumina gave the aldehyde (1) (90%), m.p. 202—203° (lit.,[1] 200·5—203·5) (Found: C, 89·9; H, 4·4%). [illegible] m.p. 2[illegible]

6-*Hydroxymethylbenzo*[a]*pyrene* (4).—The aldehyde (1) (1 g) and anhydrous aluminium isopropoxide (5 g) in anhydrous propan-2-ol (100 ml) were heated to not more than 80° and 50 ml of distillate was slowly collected. More propan-2-ol (50 ml) was added and heating was continued until the distillate was acetone-free. The mixture was then slowly poured, with vigorous stirring, into ice-cold 5% hydrochloric acid and the product recrystallised twice from benzene to give a 90% yield of pale yellow 6-*hydroxymethylbenzo*[a]*pyrene*, m.p. 270—271° (decomp.) (Found: C, 89·35; H, 5·0. $C_{21}H_{14}O$ requires C, 89·35; H, 4·95%).

Benzo[a]*pyrene*-6-*carbonitrile* (3).—Prepared by the method of Fieser and Hershberg,[2] this was purified by chromatography from benzene on alumina and had the properties reported. Refluxing with a mixture of glacial acetic acid and sulphuric acid for 24 h did not lead to hydrolysis.

6-*Methylbenzo*[a]*pyrene* (2).—A mixture of the aldehyde (1) (1·6 g) and 100% hydrazine hydrate (1·5 ml) was added to potassium hydroxide (1 g) in digol (diethylene glycol) (75 ml); the solution was heated at 100° for 30 min, then water and excess of hydrazine hydrate were distilled off. The mixture was heated at 140—150° for 2 h, water was added, and the product was chromatographed in benzene on activated alumina. Three fractions were obtained. The first gave pale yellow 6-methylbenzo[*a*]pyrene (84%), m.p. 218—219° (lit.,[2] 216—217°) (Found: C, 94·7; H, 5·45. Calc. for $C_{21}H_{14}$: C, 94·75; H, 5·25%). A second, blue fluorescent zone, eluted with benzene, gave a few dark yellow crystals on evaporation; a final yellow zone was eluted with acetone to give yellow crystals (50 mg), m.p. 234—235°, identified by their i.r. spectrum as benzo[*a*]-pyrene-6-carbonitrile. T.l.c. indicated the presence of both the methyl and cyano-derivatives in the dark yellow material from the second zone.

6-(α-*Hydroxyethyl*)*benzo*[a]*pyrene*.—This was prepared by the method of Fieser and Hershberg,[2] chromatographed from benzene on alumina, and used without further purification.

6-*Acetylbenzo*[a]*pyrene*.— 6-(α-Hydroxyethyl)benzo[*a*]-pyrene (0·3 g), *p*-benzoquinone (0·5 g), and anhydrous aluminium isopropoxide (2 g) were refluxed gently in dry benzene for 2 h. The solvent was distilled off and the mixture was hydrolysed with dilute sulphuric acid and extracted exhaustively with ether. The ether solution was washed with acid, 5% sodium hydroxide solution, and water and then dried ($MgSO_4$). The ether was distilled off and the residue was chromatographed in benzene on alumina and finally recrystallised from acetone to give the 6-*acetyl derivative*, m.p. 212—213° (decomp.) (Found: C, 89·2; H, 4·45. $C_{22}H_{14}O$ requires C, 89·8; H, 4·75%). The i.r. spectrum showed the presence of a carbonyl group and the absence of a hydroxy-group.

Benzo[a]*pyrene*-6-*carboxamide*.—The nitrile (3) (1 g) in digol (20 ml) was heated at 100° for 6 h with potassium hydroxide (2 g) dissolved in the minimum volume of water. The product obtained by cooling and addition of water was dissolved in benzene and passed down an alumina column. The column was washed with benzene until no more fluorescent material was eluted, then the yellow product was removed with acetone and recrystallised from benzene to give *benzo*[a]*pyrene*-6-*carboxamide* (85%), m.p. 276—277° (Found: C, 85·4; H, 2·25; N, 4·95. $C_{21}H_{13}NO$ requires C, 85·45; H, 4·4; N, 4·75%). This product was unchanged after refluxing with a mixture of concentrated hydrochloric acid and acetic acid for 36 h.

Attempted Synthesis of 6-*Aminoethylbenzo*[a]*pyrene* (7).—A mixture of the nitrile (3) (200 mg) and 10% palladium–charcoal (250 mg) in acetic anhydride (50 ml) was maintained at 100° for 48 h with vigorous stirring under hydrogen. On filtering and diluting with water a yellow product was obtained whose i.r. spectrum showed that a nitrile group was still present but that the aromatic ring system had been reduced. This product was not examined further.

A suspension of the nitrile (3) (100 mg) containing excess of lithium aluminium hydride (500 mg) in ether was refluxed with vigorous stirring for 2 h. After destruction of excess of hydride, yellow material (10 mg) with an i.r. spectrum characteristic of an amine was obtained from the ethereal layer. In an attempt to obtain a higher yield, a solution of the amide (6) (100 mg) in dry dioxan (20 ml) was added to a suspension of lithium aluminium hydride (500 mg) in dry ether (20 ml) and the mixture was maintained at 40° for 2 h with constant stirring. After destruction of excess of hydride a crude product (75 mg), m.p. 138—140°, was obtained (Found: C, 89·65; H, 6·65; N, 1·4. Calc. for $C_{21}H_{15}N$: C, 89·7; H, 5·35; N, 5·0%). The i.r. spectrum showed the presence of an amino-group but the analytical figures were not as expected for the 6-aminomethyl derivative. Attempts at purification led to decomposition and the material was not examined further.

6-*Bromobenzo*[a]*pyrene*.—*N*-Bromosuccinimide (700 mg) was added to benzo[*a*]pyrene (1 g) in propylene carbonate (20 ml); the mixture was maintained at 100° for 30 min and an equal volume of water was added. The product was dissolved in benzene and chromatographed on alumina, giving two yellow zones, the first of which contained a little benzo[*a*]pyrene. The second contained yellow 6-*bromobenzo*[a]*pyrene*, which was obtained in 75% yield, m.p. 223—224°, after recrystallisation twice from acetone (Found: C, 72·4; H, 3·6; Br, 24·05. $C_{20}H_{11}Br$ requires C, 72·55; H, 3·3; Br, 24·15%). An identical product (mixed m.p. and i.r. spectra) was obtained (70% yield) by refluxing a solution of benzo[*a*]pyrene (250 mg) and *N*-bromosuccinimide (180 mg) in carbon tetrachloride (25 ml.) gently for 3 h, cooling in ice, and purifying the product as before.

6-*Chlorobenzo*[a]*pyrene* (8).—*N*-Chlorosuccinimide (130 mg) was added to benzo[*a*]pyrene (250 mg) in propylene carbonate (10 ml); the mixture was maintained at 100° for 2 h and water was added. The product was dissolved in benzene, chromatographed on alumina, and recrystallised twice from benzene–methanol to give 6-*chlorobenzo*[a]*pyrene* (72%), m.p. 209—210° (Found: C, 83·9; H, 3·45; Cl, 12·2. $C_{20}H_{11}Cl$ requires C, 83·8; H, 3·85; Cl 12·35%). The method of Windaus and Raichle[7] (benzo[*a*]pyrene–sulphuryl chloride–carbon tetrachloride) gave an identical (mixed m.p. and i.r. spectra) product in 60% yield (lit.,[7] m.p. 210°).

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