The Syntheses of 4b,5a-Dihydro-5*H*-benzo[3,4]-phenanthro[1,2-*b*]azirine and 1a,11b-Dihydro-6,11-dimethyl-1*H*-benz[3,4]anthra[1,2-*b*]azirine

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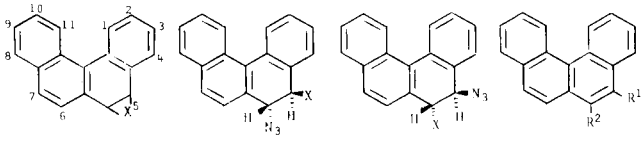
Received August 18, 1988

The syntheses of the K-imine derivatives of carcinogenic benzo[*c*]phenanthrene and 7,12-dimethylbenz-[*a*]anthracene are described. Treatment of *trans*-5-azido-5,6-dihydrobenzo[*c*]phenanthren-6-ol (**3**) and *trans*-6-azido-5,6-dihydrobenzo[*c*]phenanthren-5-ol (**5**) with thionyl chloride yielded the corresponding β-chloro azides, which in turn, were reacted with lithium aluminium hydride to give 4b,5a-dihydro-5*H*-benzo[3,4]-phenanthro[1,2-*b*]azirine (**2**). In a similar manner *trans*-5-azido-5,6-dihydro-7,12-dimethylbenz[*a*]anthracen-6-ol (**11**) and *trans*-6-azido-5,6-dihydro-7,12-dimethylbenz[*a*]anthracen-5-ol (**13**) were transformed to the respective chloro azides and, converted into 1a,11b-dihydro-6,11-dimethyl-1*H*-benz[3,4]anthra[1,2-*b*]azirine (**10**).

J. Heterocyclic Chem., **26**, 377 (1989).

The mutagenic potencies of the various polycyclic arene imines prepared in our laboratory [1-3] were found (a) to be exceptionally high, and (b) to correlate with the activities of the corresponding, less potent, arene oxides [4]. Thus, we assume that the imines are secondary metabolites of polycyclic hydrocarbons, and may take part in the carcinogenic process. Verification of this theory requires,



1, X=O; 3, X=OH; 5, X=OH; 7, R¹=N₃, R²=H

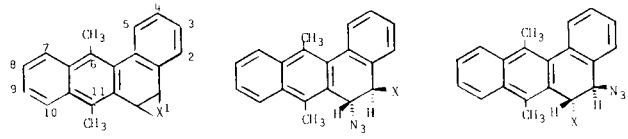
2, X=NH; 4, X=Cl; 6, X=Cl; 8, R¹=H, R²=N₃

however, further testing of a critical number of imine derivatives of the major carcinogenic compounds. Unfortunately, this could not be done so far, since our previous arene imine syntheses, that involve the treatment of β-azido alcohols with tertiary phosphines [5] or phosphites [6] [7] could not be applied successfully to many polycyclic aromatic systems [8].

In this paper we report the syntheses of the title compounds, which are K-region imines of the well known carcinogens benzo[*c*]phenanthrene and 7,12-dimethylbenz-[*a*]anthracene.

The synthesis of benzo[*c*]phenanthrene 5,6-imine (4b,5a-dihydro-5*H*-benzo[3,4]phenanthro[1,2-*b*]azirine, **2**) was accomplished by reacting of the 1:1 mixture of the two *trans*-azido alcohols **3** and **5** (prepared as previously described from oxide **1** [1]) with thionyl chloride, followed by lithium aluminium hydride reduction of the resulting mixture of *trans*-chloro azides **4** and **6**. 1-Phenylnaphthalene-2,2'-dicarboxaldehyde, required for the preparation of **1**, was obtained by ozonolysis of benzo[*c*]phenanthrene. The yield was only 42% as compared to 50% obtained by the osmium tetroxide-sodium metaperiodate method [1], but avoided the application of the expensive osmium reagent.

Since the reaction of secondary carbinols with thionyl chloride follows usually the S_Ni mechanism, we expected smooth transformation of **3** and **5** to **4** and **6**, respectively. In practice, only 27% of the chloro azides could be isolated. The main products (65%), 5- and 6-azidobenzo-[*c*]phenanthrene **7** and **8**, respectively are assumed to result from dehydrohalogenation of the labile *cis* isomers of **4** and **6** that could have been formed during the substitution of the hydroxyl groups of **3** and **5**. Attempts to increase the yield of the chloro azides on account of **7** and **8** by employing of oxalyl chloride as chlorinating agent, and by decreasing the reaction temperature were unsuccessful.



9, X=O; 11, X=OH; 13, X=OH

10, X=NH; 12, X=Cl; 14, X=Cl

7,12-Dimethylbenz[*a*]anthracene 5,6-imine (1a,11b-dihydro-6,11-dimethyl-1*H*-benz[3,4]anthra[1,2-*b*]azirine, **10**) was obtained from oxide **9** by the same sequence of reactions as **2** from **1**. In this synthesis, however, the azido alcohols **11** and **13** and thionyl chloride formed exclusively *trans*-chloro azides free of any azidodimethylbenzanthracene. The nucleophilic oxirane ring opening of **9** by sodium azide has already been shown to give **11** and **13** as the major and minor products, respectively [1]. The 200 MHz pmr analysis which included lanthanide-induced shift measurements with $Eu(fod)_3$ [tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato-*O,O'*)europium] provided now refined data for the ratio of **11**:**13** which proved to be 4:1. This ratio is identical with that of the isomeric hydroxy-*t*-butylthio-5,6-dihydro-7,12-dimethylbenz[*a*]-anthracenes observed by Beland and Harvey for the reaction of **9** and sodium *t*-butyl mercaptide [9], and is in

perfect agreement with our molecular orbital calculations [10] [11].

In contrast to the reaction of **3** and **5** with lithium aluminium hydride the reductive cyclization of **12** and **14** could not be performed in the usual manner. Quenching of the reaction mixture with water or alcohol resulted in the formation of a fully aromatized fluorescent amino-7,12-dimethylbenz[*a*]anthracene in addition to the expected imine. The amine was characterized by its two CH_3-proton signals at 2.781 and 2.929 ppm, the downfield peaks at 8.264 and 8.360 ppm (typical for the parent dimethylbenz[*a*]anthracene), and the lack of the aziridine proton resonances at 3.581 and 3.928 ppm.

Successful isolation of pure imine **10** was, however, accomplished, when the reacted lithium aluminum hydride slurry was extracted with dry benzene without decomposition of the excessive reducing agent.

EXPERIMENTAL

Ozonolysis of Benzo[*c*]phenanthrene.

A stream of ozone was passed through a solution of 4.0 g (17.5 mmoles) of benzo[*c*]phenanthrene in 150 ml of dichloromethane at -78°. After 90 minutes, when the analysis indicated complete consumption of the starting hydrocarbon, the reaction mixture was treated with 50 g of potassium iodide and 120 ml of acetic acid, and stirred at room temperature for 4 hours. The liberated iodine was reduced with aqueous sodium bisulfite. The organic layer was washed with 15% aqueous sodium hydroxide and water, and dried over magnesium sulfate. The solvent was evaporated and the residue chromatographed on silica gel, using hexane-ether mixtures (from 30 to 70% ether) as eluent. There was obtained 1.9 g (42%) of 1-phenylnaphthalene-2,2'-carboxaldehyde as a pale yellow oil that was identical with an authentic sample prepared by the osmium tetroxide-metaperiodate method [1].

Reaction of *trans*-5-Azido-5,6-dihydrobenzo[*c*]phenanthrene-6-ol (**3**) and *trans*-6-Azido-5,6-dihydrobenzo[*c*]phenanthren-5-ol (**5**) with Thionyl Chloride.

A solution of 1.25 g (4.2 mmoles) of a 1:1 mixture of the hemihydrates of **3** and **5** [1] and 6 ml (84 mmoles) of thionyl chloride in 40 ml of dry benzene was stirred under argon at room temperature. After 48 hours the mixture was diluted with 20 ml of ether and poured on ice. The organic layer was washed with 5% aqueous sodium bicarbonate, dried and concentrated. The resulting yellow oil was flash chromatographed on silica gel, using hexane with 0-20% ether as eluent. The first fraction consisted of 730 mg (65%) of the aromatic azides **7** and **8**, pale yellow crystals, mp 130° dec; ir (nujol): 2100 cm^{-1} (N_3); 200 MHz pmr (deuteriochloroform): δ 7.213-8.009 (m, 8H), 8.120 and 8.165 [two s ratio 3:2, 1H, H6 (**7**), H5 (**8**)], 8.991 (m, 2H, H1, H12).

Anal. Calcd. for $C_{16}H_{11}N_3$: C, 80.28; H, 4.08. Found: C, 79.90; H, 4.35.

The second fraction consisted of 351 mg (27%) of a mixture of **4** and **6** in ratio 3:2, pale yellow viscous oil; ir (nujol): 2090 cm^{-1} (N_3); 200 MHz pmr (deuteriochloroform): δ 4.752 (d, 0.6H, J = 3.2 Hz), 4.780 (d, 0.4H, J = 3.1 Hz), 5.171 (d, 0.6H, J = 3.2 Hz), 5.181 (d, 0.4H, J = 3.1 Hz), 7.349-8.102 (m, 9H), 8.565 (d, 1H, J = 5.3 Hz).

Anal. Calcd. for $C_{16}H_{12}ClN_3$: C, 70.71; H, 3.96; Cl, 11.59; N, 13.74. Found: C, 71.01; H, 4.20; Cl, 11.76; N, 13.63.

4b,5a-Dihydro-5*H*-benzo[3,4]phenanthro[1,2-*b*]azirine (**2**).

To a suspension of 0.6 g (15 mmoles) of lithium aluminium hydride in 20 ml of dry ether was added dropwise under nitrogen atmosphere at 5°, a solution of 0.40 g (1.3 mmoles) of the above mixture of **4** and **6** in 5 ml of the same solvent. The mixture was stirred at room temperature for 3 hours, and then successively treated with 1 ml of water, 1 ml of 10% aqueous sodium hydroxide and once again with 1 ml of water. The solids were filtered off and washed with 50 ml of benzene. The organic solution was washed with water and dried on magnesium sulfate. Upon concentration of the solution and addition of cold ether and hexane 212 mg (48%) of pale yellow **2** separated; mp 105° (from cyclohexane); ir (nujol): 3400 cm^{-1} (NH); uv (dichloromethane): λ max (log ϵ) 229 (4.13), 252 (4.22), 262 (4.33), 272 (4.36), 2.95 (3.78), 306 (3.82), 335 (2.85), 347 (2.77), 3.98 nm (3.82); 200 MHz pmr (deuteriochloroform): δ 3.596 (d, 1H, J = 6 Hz, H4b), 3.806 (d, 1H, J = 6 Hz, H5a), 7.107-8.630 (m, 10H, Ar*H*); ms: (70 eV, 90°) m/e (relative intensity) 243 ($M^{+\cdot}$, 100), 228 ($C_{16}H_{12}^{+\cdot}$, 17), 215 ($C_{17}H_{11}^{+}$, 29), 213 ($C_{17}H_9^{+}$, 6), 107 ($C_7H_9N^{+\cdot}$, 10).

Anal. Calcd. for $C_{16}H_{13}N$: C, 88.86; H, 5.39; N, 5.75. Found: C, 88.60; H, 5.49; N, 5.48.

trans-5-Azido-5,6-dihydro-7,12-dimethylbenz[*a*]anthracen-6-ol (**11**) and *trans*-6-Azido-5,6-dihydro-7,12-dimethylbenz[*a*]anthracen-5-ol (**13**).

Under the conditions described previously [1] **9** gave a mixture of **11** and **13** as hemihydrates in 87% yield, mp (**11** + **13**) 57-60° dec; 200 MHz pmr (deuteriochloroform): δ 1.862 (br s, 2H, H_2O, O*H*), 2.790 [s, 0.6H, CH_3 (**13**)], 2.801 [s, 2.4H, CH_3 (**11**)], 2.906 [s, 0.6H, CH_3 (**13**)], 2.936 [s, 2.4H, CH_3 (**11**)], 4.717 [d, 0.2H, J = 3.2 Hz, H6 (**13**), affected by deuterium oxide], 4.788 [d, 0.8H, J = 3.3 Hz, H5 (**11**), affected by deuterium oxide], 5.106 [d, 0.8H, J = 3.3 Hz, H6 (**11**)], 5.175 [d, 0.2H, J = 3.2 Hz, H5 (**13**)], 7.315-7.669 (m, 6H, Ar*H*), 8.099-8.178 (m, 2H, Ar*H*); 200 MHz pmr (3.8 x 10^{-5} mole of **11** + **13** and 3.8 x 10^{-5} mole of Eu(fod)$_3$ in 0.5 ml of deuteriochloroform after 4 hours): δ 4.042 [s, 2.4H, CH_3 (**11**)], 4.066 [s, 3H, CH_3 (**11** and CH_3 (**13**)], 5.030 [s, 0.6H, CH_3 (**13**)], 7.840 (two overlapping dd, 2H, H9, H10 (**11**) and H9, H10 (**13**)], 8.138 (dd, 0.8H, $J_{1,2}$ = 7.5 Hz, $J_{2,3}$ = 7.9 Hz, H2 (**11**)], 8.487 [t, 0.8H, $J_{2,3,4}$ = 7.9 Hz, H3 (**11**), 8.715 (two overlapping d, 2H, H8, H11 (**11**) and H8, H11 (**13**)], 9.173 [d, 0.8H, $J_{3,4}$ = 7.9 Hz, H4 (**11**)], 9.550 [d, 0.2H, $J_{1,2}$ = 7.5 Hz, H1 (**13**)], 9.675 [d, 0.8H, $J_{1,2}$ = 7.5 Hz, H1 (**11**)], 11.020 [br s, 0.2H, H5 (**13**)], 11.369 [br s, 0.8H, H6 (**11**)], 12.715 [br s, 0.8H, H5 (**11**)], 15.510 [br s, 0.2H, H6 (**13**)], data for H2, H3, H4 of **13** could not be accurately determined.

Anal. Calcd. for $C_{20}H_{17}N_3O.0.5H_2O$: C, 74.06; H, 5.59; N, 12.95. Found: C, 73.83; H, 5.66; N, 12.71.

Reaction of Azido Alcohols **11** and **13** with Thionyl Chloride.

In the manner described above 0.40 g (1.2 mmoles) of the mixture of **11** and **13** was treated with 4 ml of thionyl chloride and 30 ml of benzene for 6 hours at room temperature. Addition of ice and ether followed by the usual workup and chromatography on silica gel (hexane with 10% ether served as eluent) afforded 315 mg (78%) of a 4:1 mixture of *trans*-5-azido-6-chloro- and *trans*-6-azido-5-chloro-5,6-dihydro-7,12-dimethylbenz[*a*]anthracene **12** and **14**, respectively free of fully aromatized azide; mp of the mixture of chloro azides 115-116°; ir (nujol): 2083 cm^{-1} (N_3); 300

MHz pmr (deuteriochloroform): δ 2.802 [s, 3.4H, C*H*$_3$ (**12**)], 2.848 [s, 0.6H, C*H*$_3$ (**14**), 2.942 [s, 0.6H, C*H*$_3$ (**14**)], 2.952 [s, 2.4H, C*H*$_3$ (**12**)], 4.844 [d, 0.2H, J = 3.0 Hz, H6 (**14**)], 5.189 [d, 0.8H, J = 2.9 Hz, H5 (**12**) or H6 (**12**)], 5.196 [d, 0.8H, J = 2.9 Hz, H5 (**12**) or H6 (**12**)], 5.555 [d, 0.2H, J = 3 Hz, H5 (**14**)], 7.335-7.685 (m, 6H, Ar*H*), 8.110-8.193 (m, 2H, Ar*H*); ms: (70 eV, 90°) m/e (relative intensity) 335, 333 ($M^{+\cdot}$, 5, 16), 293 ($C_{18}H_{10}{}^{37}Cl^+$, 3), 291 ($C_{18}H_{16}{}^{35}Cl^+$, 10), 270 ($C_{20}H_{16}N^+$, 13), 258 ($C_{20}H_{18}H^{+\cdot}$, 93), 256 ($C_{20}H_{16}{}^{+\cdot}$, 100), 178 ($C_{14}H_{10}{}^{+\cdot}$, 20), 177 ($C_{14}H_9{}^+$, 43), 176 ($C_{14}H_8{}^{+\cdot}$, 56), 128 ($C_{10}H_8{}^{+\cdot}$, 13).

Anal. Calcd. for $C_{20}H_{16}ClN_3$: C, 71.96; H, 4.83; Cl, 10.62; N, 12.59. Found: C, 71.53; H, 5.04; Cl, 11.04; N, 12.67.

1a,11b-Dihydro-6,11-dimethyl-1*H*-benz[3,4]anthra[1,2-*b*]azirine (**10**).

A solution of 150 mg (0.45 mmole) of a mixture of **12** and **14** in 5 ml of dry ether was added dropwise, under nitrogen, at 5° to a stirred suspension of 300 mg (7.9 mmoles) of lithium aluminium hydride in 4 ml of the same solvent. After 45 minutes, when all the starting material was consumed, the mixture was diluted with 30 ml of benzene, and filtered under nitrogen. The solid was washed repeatedly with benzene. The combined benzene solutions were concentrated under reduced pressure at room temperature, filtered once again and the solvent evaporated to dryness. There was obtained 77 mg (63%) of pure **10** as pale yellow crystals, mp 120°; uv (dichloromethane): λ max (log ε) 226 (4.23), 266 (4.49), 296 (4.07), 305 (4.05), 355 (2.89), 372 nm (2.48); 200 MHz pmr (deuteriochloroform): δ 2.841 (s, 3H, C*H*$_3$), 2.990 (s, 3H, C*H*$_3$), 3.582 (d, 1H, J = 5.4 Hz, H5a), 3.928 (d, 1H, J = 5.4 Hz, H4b), 7.208-7.746 (m, 6H, Ar*H*), 8.032-8.118 (m, 2H, Ar*H*); ms: (70 eV, 250°) m/e (relative intensity) 271 ($M^{+\cdot}$, 100), 256 ($C_{20}H_{16}{}^{+\cdot}$, 68), 243 ($C_{19}H_{15}{}^+$, 11), 241 ($C_{19}H_{13}{}^+$, 22), 239 ($C_{19}H_{11}{}^+$, 25), 226 ($C_{18}H_{10}{}^{+\cdot}$, 10), 128 ($C_{10}H_8{}^{+\cdot}$, 36), 127 ($C_{10}H_7{}^+$, 26).

Anal. Calcd. for $C_{20}H_{17}N$: C, 88.52; H, 6.31; N, 5.16. Found: C, 88.28; H, 6.46; N, 4.85.

Acknowledgement.

We thank the Basic Research Foundation (administrated by the Israel Academy of Sciences and Humanities) for financial support of this study.

REFERENCES AND NOTES

[1] J. Blum, I. Yona, S. Tsaroom and Y. Sasson, *J. Org. Chem.*, **44**, 4178 (1979).

[2] I. Yona and J. Blum, *Org. Prep. Proced. Int.*, **13**, 109 (1981).

[3] J. Blum and S. Ben-Shoshan, *J. Heterocyclic Chem.*, **20**, 1461 (1983).

[4] H. Glatt, G. Ludewig, K. L. Platt, F. Waechter, I. Yona, S. Ben-Shoshan, P. Jerushalmy, J. Blum and F. Oesch, *Cancer Res.*, **45**, 2600 (1985).

[5] Y. Ittah, Y. Sasson, I. Shahak, S. Tsaroom and J. Blum, *J. Org. Chem.*, **43**, 4271 (1978).

[6] M. Weitzberg, Z. Aizenshtat, P. Jerushalmy and J. Blum, *J. Org. Chem.*, **45**, 4252 (1980).

[7] M. Weitzberg, D. Avnir, Z. Aizenshtat and J. Blum, *J. Heterocyclic Chem.*, **20**, 1019 (1983).

[8] In reference [1] *e.g.*, we showed that it is not possible to prepare phosphorus-free **2** and **10** by the azido alcohol-phosphine method.

[9] F. A. Beland and R. G. Harvey, *J. Am. Chem. Soc.*, **98**, 4963 (1976).

[10] S. Shtelzer, A. Y. Meyer, T. Sheradsky and J. Blum, *J. Org. Chem.*, **53**, 161 (1988).

[11] The energy differences between the precursors of **11** and **13** were calculated to be 0.0333 β in favor of **11**. A full account on the molecular orbital calculations will be reported in a separate paper.