The Chemistry of Polycyclic Arene Imines. III. *N*-Alkylation of Phenanthrene 9,10-Imine [1]

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Phenanthrene 9,10-imine (**1**) was shown to undergo *N*-alkylation without aziridine ring cleavage by (a) metallation with sodium methylsulfinylmethide followed by addition of an alkyl halide at -20°; (b) reaction of **1**, sodium hydride and the halide in dimethylformamide at 40°; (c) treatment of a dichloromethane solution of **1**, the halide and triethylbenzylammonium chloride with aqueous sodium hydroxide under phase transfer conditions. The syntheses of *N*-isopropyl-, *N*-butyl-, *N*-pentyl-, *N*-allyl- and *N*-benzylphenanthrene 9,10-imine (**2-6**) are described.

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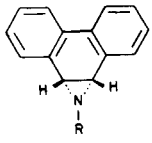
The observation that phenanthrene 9,10-imine (**1**) [2] and some other unsubstituted polycyclic aziridines [3-6] possess extremely high mutagenic potencies [7] urged us to investigate also the properties of the *N*-alkylated derivatives. In a previous paper we described the preparation of three *N*-alkylphenanthrene imines by cyclodehydration of the corresponding 10-akylamino-9,10-dihydrophenanthren-9-ols [8] and examined their biological activities [9]. However, this synthetic method gives low yields and requires tedious purifications.

In the framework of our present studies on the special chemical properties of arene imines [1] [10] we have now investigated the possibility of direct alkylation of the readily available unsaturated parent compound [4].

In comparison to simple ethylenimine derivatives [11], the polycyclic arene imines were shown to be less nucleophilic and more sensitive to ring rearrangement. Thus, most of the reported reactions of **1** with electrophiles (*e.g.* acyl an sulfonyl halides) resulted in cleavage of the three membered ring [10]. Only four cases, *viz*, the silylation by either *N,O*-bis(trimethylsilyl)acetamide or trimethylchlorosilane [10]; the phosphonylation by triethyl chlorophosphate [10]; *N*-chlorosuccinimide chlorination [11], and Michael addition of methyl vinyl ketone]12] were reported to take place with retention of the aziridine structure.

Attempts to alkylate **1** at the nitrogen atom with alkyl halides in the presence of various bases, including tertiary amines, sodium dispersions and even alkyl lithium and Grignard reagents gave negative results. Successful *N*-metallation of **1** and subsequent reaction of the imine anion with alkyl halides took place by using either sodium methylsulfinylmethide (Corey's reagent) or sodium hydride in dimethylformamide.



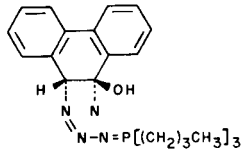
1 R = H
2 R = $CH(CH_3)_2$
3 R = $(CH_2)_3CH_3$
4 R = $(CH_2)_4CH_3$
5 R = $CH_2CH{=}CH_2$
6 R = $CH_2C_6H_5$

By this method we prepared in good yields the *N*-butyl, *N*-amyl- and *N*-benzylphenanthrene 9,10-imines (**3**, **4** and **6**, respectively).

Still better results were obtained when the alkylation was carried out under phase transfer conditions [13]. *N*-Benzylphenanthrene 9,10-imine (**6**) was obtained in 87-94% yield when a solution of **1**, triethylbenzylammonium chloride (TEBA) and excess benzyl bromide in dichloromethane (molar ratio 1:0.23:18) was stirred at room temperature with concentrated (50%) aqueous sodium hydroxide. In a similar manner reaction of **1** with 2-bromopropane, 1-iodobutane and allyl chloride (but not allyl bromide) afforded compounds **2**, **3** and **5**, respectively. When an alkyl iodide was used in the alkylation, excess phase transfer catalyst was needed owing to the "poisoning effect" of the lipophilic halide [14].

The nature of the phase transfer catalyst seems to play an important role in the alkylation process. Thus, while triethylbenzylammonium chloride and bromide gave equally good results, tetrabutyl- and tetraoctylammonium salts led either to very low yields or did not work at all.

In the course of this study we also improved the synthesis of the starting material **1**. On reacting *trans*-10-azidophenanthren-9-ol [15] with tri-*n*-butylphosphine in cold anhydrous ether, the insoluble intermediate **7** (Staudinger adduct) separated in nearly quantitative yield and in a very pure form. Heating **7** in dichloromethane smoothly gave the expected imine. In this two step procedure the process of separating **1** from excess phosphine and side products is avoided.



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The structure of **7** was established by elemental analysis, infrared spectrum (OH band at 3200 cm^{-1}; complete absence of free N_3 absorption), ^1H and ^{31}P nuclear magnetic resonance (See Experimental) and by fast atomic bombardment mass spectrometry (FAB) [16]. The latter method clearly indicates a molecular weight of 439 [distinguished $(M-1)^+$ ion peak] though the molecular ion is absent from both the 70 eV EI and the 150 eV CI mass spectra.

EXPERIMENTAL

trans-9,10-Dihydro-10[(tributylphospho)azido]phenanthren-9-ol (**7**).

A solution of 6.4 g (27 mmoles) of *trans*-10-azido-9,10-phenanthren-9-ol [15] and 7.6 ml (32 mmoles) of tri-*n*-butylphosphine in 100 ml of degassed anhydrous ether was stirred under nitrogen at room temperature for 5 minutes. The fluffy colorless precipitate that separated was filtered and washed with cold anhydrous ether to give 11.0 g (93%) of analytically pure **7**, mp 91-93° dec; ir (nujol); 3200 cm^{-1} (OH), no free N_3 band; 300 MHz pmr (deuteriochloroform): δ 0.873 (t, 9H, J = 7 Hz, C*H*$_3$), 1.339 (sextet, 6H, J = 7 Hz, C*H*$_2$CH$_3$), 1.468 (m, CH$_2$C*H*$_2$CH$_2$), 1.832 (m, 6H, PC*H*$_2$), 2.672 (br s, 1H, O*H*), 4.747 (d, 1H, J = 9 Hz, H10), 5.150 (br d, 1H, J = 9 Hz, H9), 7.186-7.360 (m 5H, H1, H2, H3, H6, H7), 7.654 (dd, 1H, $J_{6,8}$ = 2 Hz, $J_{7,8}$ = 7 Hz, H8), 7.736 (dd, 1H, J_a = 7 Hz, J_b = 1.5 Hz, H4 or H5), 7.762 (dd, J_a = 7 Hz, J_b = 1.5 Hz, H4 or H5); 120 MHz ^{31}P nmr (deuteriochloroform-phosphoric acid): 41.34 ppm; + FAB ms [16] (4-6 kV Ar); m/e (relative intensity) 438 [(M-H)$^+$, 5], 220 ($C_{14}H_{10}N_3^+$, 100); ms: (70 eV, 250°), m/e (relative intensity), 415 [(M-CH$_3$)$^+$, 1], 409 [(M-2CH$_3$)$^+$, 2], 393 [(M-CH$_3$-H$_2$O)$^+$, 3], 383 [(M-C$_4$H$_8$)$^+$, 24], 382 [(M-C$_4$H$_9$)$^+$, 14], 369 [(M-C$_5$H$_{10}$)$^+$, 7], 354 [(M-C$_6$H$_{13}$)$^+$, 5], 337 [(M-C$_6$H$_{12}$-H$_2$O)$^+$, 3], 326 [(M-C$_8$H$_{17}$)$^+$, 2], 237 ($C_{14}H_{11}N_3O^+$, 3), 218 ($C_{14}H_8N_3^+$, 7), 207 ($C_{14}H_{11}N_2^+$, 9), 202 ($C_{12}H_{27}P^+$, 5) 193 ($C_{14}H_{11}N^+$, 31), 178 ($C_{14}H_{10}^+$, 21), 165 ($C_{13}H_9^+$, 100), 152 ($C_{12}H_8^+$, 13).

Anal. Calcd. for $C_{26}H_{38}N_3OP$: C, 71.04; H, 8.71; N, 9.56; P, 7.05. Found: C, 70.83; H, 8.49; N, 9.81; P, 7.19.

When a suspension of **7** in dichloromethane was refluxed under nitrogen for 2 hours and the solvent was evaporated, the residue afforded after addition of hexane and recrystallization from cyclohexane pure **1**, mp 163-164° (lit [4] 163-164°).

Alkylation of **1** with the Aid of Corey's Reagent.

In a typical experiment a mixture of 125 mg (5.2 mmole) of sodium hydride (95%) and 3 ml of freshly dried dimethyl sulfoxide was stirred under argon at 70° for 30 minutes (until evolution of hydrogen ceased). The mixture was diluted with 10 ml of anhydrous tetrahydrofuran, cooled to -20° and 200 mg (1.04 mmoles) of **1** was added. After 30 minutes at this temperature 0.6 ml (5.2 mmoles) of benzyl chloride was added and vigorous stirring was continued for further 15 minutes. The reaction mixture was digested with cold water and the organic material was extracted with dichloromethane. The dichloromethane solution was washed with 20% aqueous ammonia (2×), water (2×), dried and evaporated to give an oil that upon trituration with cold ether yielded 92 mg of analytically pure 1-benzyl-1*a*,9*b*-dihydrophenanthro[9,10-*b*]azirine (**6**). Concentration of the ether solution followed by column chromatography on silica gel (ether-hexane 1:5 served as eluent) afforded a further 58.7 mg of pure **6**; total yield 52.5%; mp 126-128° (lit [8] 128°).

Alkylation of **1** with Alkyl Halide and Sodium Hydride in Dimethylformamide.

Typically a mixture of 125 mg (5.2 mmoles) of sodium hydride (95%), 200 mg (1.04 mmoles) of **1**, 0.68 ml (5.2 mmoles) of *n*-amyl iodide and 10 ml of anhydrous dimethylformamide was stirred under argon at 40°. After 24 hours the mixture was digested with cold water and the organic material was taken into dichloromethane. The solution was washed with 20% aqueous ammonia (2×) and with water (2×). Evaporation of the solvent gave a yellow oil which was purified by column chromatography on silica (a 1:25 mixture of ethyl acetate-hexane served as eluent) to yield 163.4 mg (63% of 1-pentyl-1*a*,9*b*-dihydrophenanthro[9,10-*b*]azirine (**4**) as colorless crystals, mp 62-64° (from ether-hexane); 300 MHz pmr (deuteriochloroform): δ 0.900 (t, 3H, J = 7 Hz, C*H*$_3$,), 1.349 (m, 4H, C*H*$_2$), 1.664 (quintet, 2H, J = 7.3 Hz, C*H*$_2$), 2.579 (t, 2H, J = 7.3 Hz, NC*H*$_2$), 3.037 (s, 2H, H1a, H9b), 7.323 (m, 4H, H3, H4, H7, H8), 7.517 (dd, 2H, $J_{2,3}$ = 7.0 Hz, $J_{2,4}$ = 1.5 Hz, H2, H9); 8.016 (dd, 2H, $J_{3,5}$ = 1.5 Hz, $J_{4,5}$ = 7.9 Hz, H5, H6); ms: (70 eV, 70°) m/e (relative intensity) 263 (M$^+$, 76), 248 [(M-CH$_3$)$^+$, 13], 220 [(M-C$_3$H$_7$)$^+$, 18], 207 [(M-C$_4$H$_8$)$^+$, 61], 206 [(M-C$_4$H$_9$)$^+$, 60], 194 ($C_{14}H_{12}N^+$, 29), 193 ($C_{14}H_{11}N^+$, 71), 192 ($C_{14}H_{10}N^+$, 51), 179 ($C_{14}H_{11}^+$, 100), 178 ($C_{14}H_{10}^+$, 82), 165 ($C_{13}H_9^+$, 93), 152 ($C_{12}H_8^+$, 17).

Anal. Calcd. for $C_{19}H_{21}N$: C, 86.65; H, 8.04; N, 5.32. Found: C, 86.61; H, 8.18; N, 5.52.

1-Butyl-1*a*,9*b*-dihydrophenanthro[9,10-*b*]azirine (**3**) and 1-Benzyl-1*a*,9*b*-dihydrophenanthro[9,10-*b*]azirine (**6**).

By the same method 1-butyl- and 1-benzyl-1*a*,9*b*-dihydrophenanthro-[9,10-*b*]azirine (**3** and **6**) were obtained in 61 and 65% yield, respectively. The mp of **3** was 89-90° (lit [8] 87°); 300 MHz pmr (deuteriochloroform): δ 0.901 (t, 3H, J = 7.4 Hz, C*H*$_3$), 1.369 (sextet, 2H, J = 7.4 Hz, C*H*$_2$CH$_3$), 1.610 (quintet, 2H, J = 7.4 Hz, CH$_2$C*H*$_2$CH$_2$), 2.521 (t, 2H, J = 7.4 Hz, NC*H*$_2$), 2.953 (s, 2H, H1a, H9b), 7.245 (ddd, 2H, $J_{1,4}$ = 1.6 Hz, $J_{3,4}$ = 7.2 Hz, $J_{4,5}$ = 9.0 Hz, H4, H7), 7.302 (ddd, 2H, $J_{2,3}$ = $J_{3,4}$ = 7.2 Hz, $J_{3,5}$ = 1.6 Hz, H3, H8), 7.456 (dd, 2H, $J_{2,3}$ = 7.2 Hz, $J_{2,4}$ = 1.6 Hz, H2, H9), 7.967 (dd, $J_{3,5}$ = 1.6 Hz, $J_{4,5}$ = 9.0 Hz, H5, H6). Compound **6** was identical in every respect with an authentic sample obtained by the previous method.

Alkylation of **1** by Phase-Transfer Technique.

A mixture of 250 mg (1.29 mmoles) of **1**, 70 mg (0.3 mmole) of TEBA, 4 g (33 mmoles) of 2-bromopropane, 15 ml of dichloromethane and 20 ml of 50% aqueous sodium hydroxide was refluxed with magnetic stirring for 48 hours. The cooled mixture was diluted with 25 ml of ether and 25 ml of water. The organic layer was dried, concentrated and flash chromatographed on neutral Woelem alumina for dry column chromatography (hexane, and hexane-ether mixtures served as eluents) to give 67 mg (22%) of pure 1-(2-propyl)-1*a*,9*b*-dihydrophenanthro[9,10-*b*]azirine (**2**). Attempts to purify the crude product on silica gel resulted in partial decomposition of the aziridine, mp 130°; uv (dichloromethane): λ max (log ϵ) 232.2 (4.04), 243.3 (3.94 sh), 272.5 (4.11), 276.6 (4.11), 281.5 (4.11), 294.3 (3.80 sh), 306.5 nm (3.63); 300 MHz pmr (deuteriochloroform): δ 1.229 (d, 6H, J = 6.3 Hz, C*H*$_3$), 1.873 [heptet, 1H, J = 6.3 Hz, (CH$_3$)C*H*], 3.062 (s, 2H, H1a, H9b), 7.289 (ddd, 2H, $J_{1,4}$ = 1.6 Hz, $J_{3,4}$ = 7.2 Hz, $J_{4,5}$ = 8.0 Hz, H4, H7), 7.344 (ddd, 2H, $J_{2,3}$ = $J_{3,4}$ = 7.2 Hz, $J_{3,5}$ = 1.6 Hz, H3, H8), 7.511 (dd, 2H, $J_{2,3}$ = 7.2 Hz, $J_{2,4}$ = 1.6 Hz, H2, H9), 8.005 (dd, 2H, $J_{3,5}$ = 1.6 Hz, $J_{4,5}$ = 8.0 Hz, H5, H6); ms: (70 eV, 50°) m/e (relative intensity) 235 (M$^+$, 44), 220 [(M-CH$_3$)$^+$, 9], 193 ($C_{14}H_{11}N^+$, 41), 192 ($C_{14}H_{10}N^+$, 100), 179 ($C_{14}H_{11}^+$, 9), 178 ($C_{14}H_{10}^+$, 29), 165 ($C_{13}H_9^+$, 70), 152 ($C_{12}H_8^+$, 8).

Anal. Calcd. for $C_{17}H_{17}N$: C, 86.77; H, 7.28; N, 5.95. Found: C, 86.57, H, 7.26; N, 5.87.

Compound **3** was obtained by this method in 72% yield (after 24 hours) from 1.55 mmoles of **1**, 8 mmoles of *n*-butyl iodide and 6 mmoles of TEBA. Similarly, the *N*-benzyl-derivative **6** was formed in 87-94% yield from 1.29 mmoles of **1** and 23 mmoles of benzyl bromide in the presence of 0.3 mmoles of TEBA. Ten hours were required for the completion of this reaction. Substitution of the benzyl bromide by the corresponding chloride reduced the rate of reaction and the yield of **6** was only 20% after 24 hours.

1-(2-propenyl)-1*a*,9*b*-phenanthro[9,10-*b*]azirine (**5**).

A well stirred mixture of 500 mg (2.59 mmoles) of **1**, 4.5 g (59 mmoles) of allyl chloride, 300 mg (1.32 mmoles) of TEBA [17], 30 ml of dichloromethane and 30 ml of 50% aqueous sodium hydroxide was refluxed for 48 hours. The cooled mixture was diluted with ether and water and the organic solution was washed successively with 10% aqueous ammonia

and water. Evaporation of the solvent afforded an oil which was purified by flash chromatography on silica gel (using hexane 3:17 and 3:7 ether-hexane mixtures as eluents) followed by sublimation at 70° (0.05 mm) and recrystallization from pentane to give 400 mg (66%) of **5**. When all **5** was removed from the column 60 mg of the starting material could be recovered by changing the eluent to pure ether, mp 98-99° (from pentane); uv (dichloromethane): λ max (log ε) 232.1 (4.02), 241.2 (3.91 sh), 270.6 (4.06 sh), 277.1 (4.07), 282 (4.06 sh), 295.7 (3.78 sh), 305.7 nm (3.52); 300 MHz pmr (deuteriochloroform): δ 3.033 (s, 2H, H1a, H9b), 3.169 (dd, 2H, J_1 = 5.1 Hz, J_2 = 1.5 Hz, $HCH_2CH=CH_2$), 5.124 (dd, 1H, J_1 = 10.7 Hz, J_2 = 1.5 Hz, CH-C$\langle^{H}_{H}$), 5.215 (dd, 1H, J_1 = 17.3 Hz, J_2 = 1.5 Hz, CH=C$\langle^{H}_{H}$), 5.945 (X_2YZ pattern, 1H, J_1 = 5.1 Hz, J_2 = 10.7 Hz, J_3 = 17.3 Hz, $CH=CH_2$), 7.259 (ddd, 2H, $J_{2,4}$ = 1.5 Hz, $J_{3,4}$ = 7.3 Hz, $J_{4,5}$ = 7.7 Hz, H4, H7), 7.321 (ddd, 2H, $J_{2,3}$ = $J_{3,4}$ = 7.3 Hz, $J_{3,5}$ = 1.5 Hz, H3, H8), 7.647 (dd, 2H, $J_{2,3}$ = 7.3 Hz, $J_{2,4}$ = 1.5 Hz, H2, H9), 7.984 (dd, 2H, $J_{3,5}$ = 1.5 Hz, $J_{4,5}$ = 7.7 Hz, H5, H6); ms: (70 eV, 90°) m/e (relative intensity) 233 ($M^{+\cdot}$, 58), 232 [$(M-1)^+$, 7], 219 ($C_{15}H_{12}N^+$, 4), 206 ($C_{15}H_{12}N^+$, 5), 205 ($C_{15}H_{11}N^{+\cdot}$, 5), 194 ($C_{14}H_{12}N^+$, 6), 193 ($C_{14}H_{11}N^{+\cdot}$, 54), 192 ($C_{14}H_{10}N^+$, 100), 191 ($C_{14}H_9N^{+\cdot}$, 14), 190 ($C_{14}H_8N^{+\cdot}$, 15), 178 ($C_{14}H_{10}^{+\cdot}$, 56), 176 ($C_{14}H_8^{+\cdot}$, 21), 166 ($C_{13}H_{10}^{+\cdot}$, 23), 165 ($C_{13}H_9^+$, 98), 152 ($C_{12}H_8^{+\cdot}$, 13).

Anal. Calcd. for $C_{17}H_{15}N$: C, 87.52; H, 6.48; N, 6.00. Found: C, 87.40; H, 6.23; N, 5.90.

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[17] While substitution of TEBA by triethylbenzylammonium bromide did not affect the yield, the application of tetrabutyl- and tetraoctyl-ammonium bromides and hydrogensulfates as phase transfer catalysts led to only 5-7% of **5** under similar experimental conditions.