Mono-, and Dibenzacridine Imines. Synthesis of 1a,11b-Dihydrobenz[*c*]azirino[*a*]acridine, 4b,5a-Dihydrodibenz[*c,h*]-azirino[*a*]acridine and 1a,13b-Dihydrodibenz[*c,j*]azirino[*a*]acridine

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The syntheses of the K-imine derivatives of benz[*c*]acridine, dibenz[*c,h*]acridine and dibenz[*a,h*]acridine are described. The parent hydrocarbons **1, 6** and **11** were oxidized with sodium hypochlorite under phase transfer conditions to the corresponding K-oxides **4, 9** and **14**, which in turn were reacted with sodium azide. The resulting azido alcohols were then cyclized with tributylphosphine to the title compounds **5, 10** and **15**.

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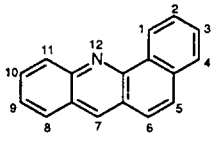
Although a vast amount of research has been published on the activation of carbocyclic carcinogenic polyarenes [1], only limited studies have been done on the primary metabolic transformations of the analogous nitrogen-containing pollutants [2,3]. Even less research has been performed on arenimines which are possible secondary metabolites of the carcinogenic heterocycles. The only paper published so far in this area describes the syntheses of aziridine derivatives of the tricyclic nitrogen-heteroarenes benzo[*f*]quinoline, benzo[*h*]quinoline and 1,10-phenanthroline [4,5].

In this paper we report the syntheses of the first arenimine derivatives of tetra- and pentacyclic benz- and dibenzacridines.



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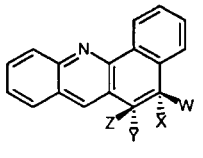
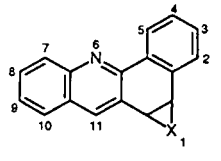
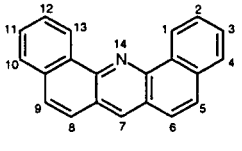


2, W=OH X=Z=H Y=N3
3, W=Y=H X=N_3 Z=OH



4, X=O
5, X=NH



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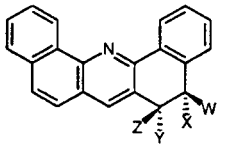
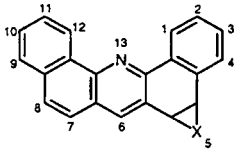
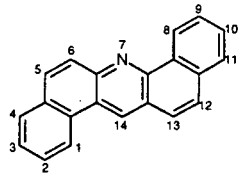


7, W=OH X=Z=H Y=N_3
8, W=Y=H X=N_3 Z=OH



9, X=O
10, X=NH



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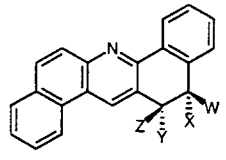
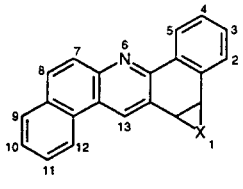
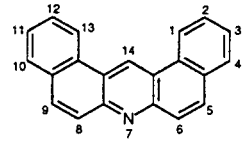


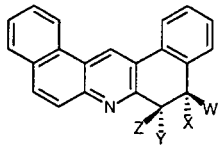
12, W=OH X=Z=H Y=N_3
13, W=Y=H X=N_3 Z=OH



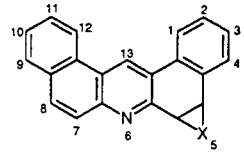
14, X=O
15, X=NH



16



17, W=OH X=Z=H Y=N_3
18, W=Y=H X=N_3 Z=OH



19, X=O
20, X=NH

The synthesis of 1a,11b-dihydrobenz[*c*]azirino[*a*]acridine (benz[*c*]acridine 5,6-imine (**5**)) was accomplished by treatment of the corresponding epoxide **4** (obtained by hypochlorite oxidation of benz[*c*]acridine (**1**) [6]) with sodium azide followed by tributylphosphine-assisted cyclization [7] of the two *trans*-azido alcohols **2** and **3**, so formed. Attempts to use other methods for the conversion of the azido alcohols into the aziridine [8-12] led to negative results. Likewise, compounds **10** and **15**, which are the K-imines of dibenz[*c,h*]acridine (**6**) and dibenz[*a,h*]acridine (**11**), respectively, were obtained by azide-mediated

epoxide-ring opening in **9** and **14** followed by treatment with tributylphosphine. For the preparation of 4b,5a-dihydrodibenz[*c,h*]oxireno[*a*]acridine (dibenz[*c,h*]acridine 5,6-oxide (**14**)) and 1a,13b-dihydrodibenz[*c,j*]oxireno[*a*]acridine (dibenz[*a,h*]acridine 5,6-oxide (**15**)) we employed the simple hypochlorite method rather than the osmium tetroxide-sodium periodate stepwise oxidation [3] which could not be reproduced successfully in our laboratory. Also, 4b,5a-dihydrodibenz[*a,j*]oxireno[*c*]acridine (dibenz[*a,j*]acridine 5,6-oxide (**1a**)) was best prepared from the parent compound **16** and sodium hypochlorite. The oxide reacted smoothly with azide ion to give a mixture of azido alcohols **17** and **18**, however the latter compounds could not be cyclized to 4b,5a-dihydrodibenz[*a,j*]azirino-[*c*]acridine (**20**) by any of the known methods [7-12].

EXPERIMENTAL

Reaction of 1a,11b-Dihydrobenz[*c*]oxireno[*a*]acridine (**4**) with Sodium Azide.

A mixture of 300 mg (1.22 mmoles) of **4** [6], 4 g (62.5 mmoles) of sodium azide, 100 ml of acetone and 50 ml of water was stirred under exclusion of air at room temperature for 72 hours. The acetone was removed under reduced pressure and the resulting precipitate was extracted with dichloromethane. The dried organic solution was concentrated and chromatographed on alumina deactivated with 15% of water, using hexane containing from 2 to 25% ethyl acetate as eluent. There was obtained 210 mg (60%) of a mixture of *trans*-6-azido-5,6-dihydro-5-benz[*c*]acridinol (**2**) and *trans*-5-azido-5,6-dihydro-6-benz[*c*]acridinol (**3**) as colorless crystals; mp 143-145°; ir (nujol): 3300 (OH), 2150 cm^{-1} (N_3); ^1H nmr (deuteriochloroform): 200 MHz δ 4.80 (d, 0.4 H, $J_{5,6}$ = 8 Hz, H5 of **3**), 4.92 (d, 1.2 H, $J_{5,6}$ = 8 Hz, H5, H6 of **2**), 5.01 (dd, 0.4 H, $J_{5,6}$ = 8 Hz, $J_{6,OH}$ = 2 Hz, H6 of **3**), 7.51-7.86 (m, 6H, Ar*H*), 8.15 (d, 1H, J = 8 Hz, H8 or H11 of both isomers), 8.23 (s, 0.6 H, H7 of **2**), 8.33 (s, 0.4 H, H7 of **3**), 8.56 (dd, 0.6 H, $J_{1,2}$ = 11 Hz, $J_{1,3}$ = 2 Hz, of **2**), 8.60 (dd, 0.4 H, $J_{1,2}$ = 12 Hz, $J_{1,3}$ = 2.5 Hz, H1 of **3**).

Anal. Calcd. for $C_{17}H_{12}N_4O$: C, 70.83; H, 4.17; N, 19.44. Found: C, 71.11; H, 3.94; N, 19.42.

1a,11b-Dihydrobenz[*c*]azirino[*a*]acridine (**5**).

To a mixture of 70 mg (0.24 mmole) of **2** and **3** dissolved in 45 ml of dichloromethane was added at 0° under exclusion of air, 60.5 µl (0.24 mmole) of tributylphosphine. The mixture was first stirred for 30 minutes at 0° and then for 30 minutes at 25°. Finally, the solution was refluxed for 5 hours. The solvent was evaporated and the residue chromatographed on silica gel deactivated with 20% water, using hexane containing from 2 to 20% ethyl acetate as eluent. There was obtained 27 mg (46%) of **5** as pale yellow crystals, mp 130° dec (from ether-hexane); ir (nujol): 3350 cm^{-1} (NH); ^1H nmr (deuteriochloroform): 200 MHz δ 3.66 (d, 1H, $J_{1a,11b}$ = 5 Hz, H1a or H11b), 3.79 (d, 1H, $J_{1a,11b}$ = 5 Hz, H1a or H11b), 7.46-7.83 (m, 6H, Ar*H*), 8.15 (d, 1H, J = 8 Hz, H7 or H10), 8.33 (s, 1H, H11), 8.96 (dd, 1H, $J_{3,5}$ = 2 Hz, $J_{4,5}$ = 8 Hz, H5); lc-ms: (70 eV, particle beam 65°) m/z (relative intensity) 244 ($M^{+\cdot}$, 53), 299 ($C_{17}H_{11}N^{+\cdot}$, 100), 228 ($C_{17}H_{10}N^+$, 28), 217 ($C_{16}H_{11}N^{+\cdot}$, 15), 216 ($C_{16}H_{10}N^+$, 11).

Anal. Calcd. for $C_{17}H_{12}N_2$: C, 83.61; H, 4.92; N, 11.48. Found: C, 83.31; H, 4.95; N, 11.15.

4b,5a-Dihydrodibenz[*c,h*]oxireno[*a*]acridine (**9**).

To 44 ml of commercial 10% aqueous sodium hypochlorite, buffered to *p*H-8.5 with 0.8 *M* aqueous sodium hydrogen phosphate, was added 305 mg (0.9 mmole) of tetrabutylammonium hydrogen sulfate and 307 mg (1.1 mmoles) of **6** [13] in 45 ml of chloroform. The mixture was stirred vigorously at room temperature for 5 hours. The organic phase was separated, washed (x3) with water and dried on sodium sulfate. Removal of the solvent at room temperature under reduced pressure afforded 233 mg (72%) of **9**, mp 178-179° (lit [3] 179-180°); ^1H nmr (deuteriochloroform): 200 MHz δ 4.60 (d, 1H, $J_{4b,5a}$ = 5 Hz, H4b or H5a), 4.72 (d, 1H, $J_{4b,5a}$ = 5 Hz, H4b or H5a), 7.45-8.30 (m, 9H, Ar*H*), 8.46 (dd, 1H, $J_{1,2}$ = 8 Hz, $J_{1,3}$ = 2 Hz, H1), 8.77 (dd, 1H, $J_{10,12}$ = 2 Hz, $J_{11,12}$ = 8, H12).

trans-6-Azido-5,6-dihydro-5-dibenz[*c,h*]acridinol (**7**) and *trans*-5-Azido-5,6-dihydro-6-dibenz[*c,h*]acridinol (**8**).

As for the preparation of **2** and **3**, 307 mg (1 mmole) of **6** was reacted for 5 days at room temperature with excess of sodium azide in aqueous acetone. Chromatography on alumina deactivated with 15% of water, using a 3:1 mixture of hexane-ethyl acetate as eluent, afforded 240 mg (71%) of a 3:2 mixture of the two azido alcohols **7** and **8**, respectively; mp 185° dec; ir (nujol) 3300 (OH), 2120 cm^{-1} (N_3); ^1H nmr (deuteriochloroform): 200 MHz δ 4.80 (m, 1.1 H, H5, H6 of **7**). 4.92 (d, 0.45 H, $J_{5,6}$ = 5 Hz, H5 or H6 of **8**), 4.98 (d, 0.45 H, $J_{5,6}$ = 5 Hz, H5 or H6 of **8**), 7.44-7.90 (m, 8H, Ar*H*), 7.99 (d, 1H, J = 7 Hz), 8.02 (d, 1H, J = 6 Hz), 8.46 (s, 0.55 H, H7 of **7**), 8.49 (s, 0.45 H, H7 of **8**); gc-ms: (70 eV, 150°) m/z (relative intensity) 338 ($M^{+\cdot}$, 17), 310 ($C_{21}H_{14}N_2O^{+\cdot}$, 28), 309 ($C_{21}H_{13}N_2O^+$, 29), 296 ($C_{21}H_{14}NO^+$, 23), 295 ($C_{21}H_{13}NO^{+\cdot}$, 27), 282 ($C_{20}H_{12}NO^+$, 35), 281 ($C_{20}H_{11}NO^{+\cdot}$ or $C_{20}H_{13}N_2^+$, 78), 280 ($C_{20}H_{12}N_2^{+\cdot}$, 34), 279 ($C_{21}H_{13}N^{+\cdot}$, 100), 266 ($C_{20}H_{12}N^+$, 22).

Anal. Calcd. for $C_{21}H_{14}N_4O$: C, 74.56; H, 4.14; N, 16.57. Found: C, 74.38; H, 4.17; N, 16.11.

4b,5a-Dihydrodibenz[*c,h*]azirino[*a*]acridine (**10**).

In the manner described for the preparation of **5**, 40 mg (0.12 mmole) of the above mixture of **7** and **8** was reacted with 29.4 µl (0.12 mmole) of tributylphosphine. After 7 hours of vigorous reflux, the resulting product was chromatographed on silica gel deactivated with 20% water (3:1 hexane-ethyl acetate as eluent). There was obtained 14.7 mg (42%) of **10** as pale yellow crystals, mp 176°; ir (nujol) 3320 cm^{-1} (NH); ^1H nmr (deuteriochloroform): 200 MHz δ 3.70 (d, 1H, $J_{4b,5a}$ = 5 Hz, H4b or H5a), 3.86 (d, 1H, $J_{4b,5a}$ = 5 Hz, H4b or H5a), 7.36-7.65 (m, 8H, H2, H3, H4, H7, H8, H9, H10, H11), 7.91 (dd, H1, $J_{1,2}$ = 6 Hz, $J_{1,3}$ = 2 Hz, H1), 8.09 (dd, 1H, $J_{10,11}$ = 1.5 Hz, $J_{11,12}$ = 6 Hz, H12), 8.70 (s, 1H, H6); lc-ms: (70 eV, particle beam 65°) m/z (relative intensity) 294 ($M^{+\cdot}$, 51), 279 ($C_{21}H_{13}N^{+\cdot}$, 14), 278 ($C_{21}H_{12}N^+$, 25), 267 ($C_{20}H_{13}N^{+\cdot}$, 14), 266 ($C_{20}H_{12}N^+$, 15).

Anal. Calcd. for $C_{21}H_{14}N_2$: C, 85.71; H, 4.76; N, 9.52. Found: C, 85.31; H, 5.01; N, 9.93.

1a,13b-Dihydrodibenz[*c,j*]oxireno[*a*]acridine (**14**).

By the procedure described for **9**, **14** was obtained from **11** [14] in 70% yield, mp 163° (lit [3] 164-165°); ^1H nmr (deuteriochloroform): 200 MHz δ 4.51 (d, 1H, $J_{1a,13b}$ = 4 Hz, H1a or H13b), 4.60 (d, 1H, $J_{1a,13b}$ = 4 Hz, H1a or H13b), 7.39-7.71 (m, 8H, H2, H3, H4, H7, H8, H9, H10, H11), 8.01 (dd, 1H, $J_{3,5}$ = 2 Hz, $J_{4,5}$ = 7 Hz, H5), 8.40 (s, 1H, H13), 8.87 (dd, 1H, $J_{10,12}$ = 2 Hz, $J_{11,12}$ = 8 Hz, H12).

Reaction of **14** with Sodium Azide.

In the manner described for **4**, **14** was converted into a mixture of *trans*-13-azido-12,13-dihydro-12-dibenz[*a,h*]acridinol (**12**) and *trans*-12-azido-12,13-dihydro-13-dibenz[*a,h*]acridinol (**13**) in 69% yield, mp 174° dec; ir (nujol): 3305 (OH), 2100 cm^{-1} (N_3); ^1H nmr (deuteriochloroform): 200 MHz δ 4.79 (d, 0.75 H, $J_{12,13}$ = 9 Hz, H12 or H13 of **12**), 4.83 (d, 0.25 H, $J_{12,13}$ = 9 Hz, H12 or H13 of **13**), 4.96 (d, 0.75 H, $J_{12,13}$ = 9 Hz, H12 or H13 of **12**), 5.00 (d, 0.25 H, $J_{12,13}$ = 9 Hz, H12 or H13 of **13**), 7.41-7.96 (m, 9, Ar*H*), 8.42 (s, 0.25 H, H14 of **13**), 8.43 (s, 0.75 H, H14 of **12**), 8.48 (two overlapping dd, 1 H, $J_{1,2}$ = 7 Hz, $J_{1,3}$ = 2.5 Hz, H1 of **12** and **13**); gc-mc: (70 eV, 140°) m/z (relative intensity) 338 ($M^{+\cdot}$, 14), 310 ($C_{21}H_{14}N_2O^{+\cdot}$, 16), 309 ($C_{21}H_{12}NO^+$, 20), 296 ($C_{21}H_{14}NO^+$, 28), 295 ($C_{21}H_{13}NO^{+\cdot}$, 100), 282 ($C_{20}H_{13}N_2O^+$, 81), 281 ($C_{20}H_{11}NO^{+\cdot}$ or $C_{20}H_{13}N_2^+$, 75), 280 ($C_{20}H_{12}N_2^{+\cdot}$, 41), 279 ($C_{21}H_{13}N^{+\cdot}$, 58), 266 ($C_{20}H_{12}N^+$, 33).

Anal. Calcd for $C_{21}H_{14}N_4O$: C, 74.56; H, 4.14; N, 16.57. Found: C, 74.12; H, 4.52; N, 16.30.

1a,13b-Dihydrodibenz[*c,f*]azirino[*a*]acridine (**15**).

Treatment of the mixture of **12** and **13** with tributylphosphine gave 39% of pure **15** as pale yellow crystals; mp 162° dec (from hexane-ether); ir (nujol): 3330 cm^{-1} (NH); ^1H nmr (deuteriochloroform): 200 MHz δ 3.65 (d, 1H, $J_{1a,13b}$ = 5 Hz, H1a or H13b), 3.90 (d, 1H, $J_{1a,13b}$ = 5 Hz, H1a or H13b), 7.34-7.60 (m, 8H, H2, H3, H4, H7, H8, H9, H10, H11), 8.01 (dd, 1H, $J_{3,5}$ = 2 Hz, $J_{4,5}$ = 7 Hz, H5), 8.40 (s, 1H, H13), 8.78 (dd, 1H, $J_{10,12}$ = 2 Hz, $J_{11,12}$ = 7 Hz, H12); lc-ms: (70 eV, particle beam 65°) m/z (relative intensity) 294 ($M^{+\cdot}$, 54), 279 ($C_{21}H_{13}N^{+\cdot}$, 100), 278 ($C_{21}H_{12}N^+$, 18), 267 ($C_{20}H_{13}N^{+\cdot}$, 20), 266 ($C_{20}H_{12}N^+$, 14).

Anal. Calcd. for $C_{21}H_{11}N_2$: C, 85.71; H, 4.76; N, 9.52. Found: C, 85.43; H, 4.48; N, 9.80.

4b,5a-Dihydrodibenz[*a,j*]oxireno[*c*]acridine (**19**).

Hypochlorite oxidation of dibenz[*a,j*]acridine (**16**) [14] by the method described above, yielded 68% of **19**, mp 249-252° (lit [3] 252-254°); ^1H nmr (deuteriochloroform): 200 MHz δ 4.58 (d, 1H, J = 6 Hz, H4b or H5a), 4.69 (d, 1H, J = 6 Hz, H4b or H5a), 7.37-8.32 (m, 9H), 8.50 (dd, 1H, $J_{1,2}$ = 7.5 Hz, $J_{1,3}$ = 2 Hz, H1), 8.80 (dd, 1H, $J_{10,12}$ = 2 Hz, $J_{11,12}$ = 8 Hz, H12).

trans-6-Azido-5,6-dihydro-5-dibenz[*a,j*]acridinol (**17**) and *trans*-5-Azido-5,6-dihydro-6-dibenz[*a,j*]acridinol (**18**).

The reaction of **19** with excess of sodium azide in aqueous acetone yielded 69% of a 1:2 mixture of **17** and **18**, respectively, mp 193° dec; ^1H nmr (deuteriochloroform): 200 MHz δ 4.83 (m, 1.33 H, H5, H6 of **18**), 4.93 (d, 0.33 H, $J_{5,6}$ = 5 Hz, H5 or H6 of **17**), 4.99 (d, 0.33 H, $J_{5,6}$ = 5 Hz, H5 or H6 of **17**), 7.43-7.89 (m, 8 H, Ar*H*), 7.99 (d, 0.6 6 H, $J_{12,13}$ = 8 Hz, H13 of **18**), 8.12 (d, 0.33 H, $J_{12,13}$ = 8 Hz, H13 of **17**), 8.47 (s, 0.66 H, H14 of **18**), 8.50 (s, 0.33 H, H14 of **17**); lc-ms: (70 eV, particle beam 65°) m/z (relative intensity) 338 ($M^{+\cdot}$, 12), 310 ($C_{21}H_{14}N_2O^{+\cdot}$, 25), 309 ($C_{21}H_{13}N_2O^+$, 31), 296 ($C_{21}H_{14}NO^+$, 27), 295 ($C_{21}H_{13}NO^{+\cdot}$, 23), 282 ($C_{20}H_{12}NO^+$, 40), 281 ($C_{20}H_{13}N_2^+$, 82), 280 ($C_{20}H_{12}N_2^{+\cdot}$, 32), 279 ($C_{21}H_{13}N^{+\cdot}$, 100), 266 ($C_{20}H_{12}N^+$, 18).

Anal. Calcd. for $C_{21}H_{14}N_4O$: C, 74.56; H, 4.14; N, 16.57. Found: C, 74.68; H, 4.25; N, 16.05.

Acknowledgement.

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[5] Biological studies revealed that while the mutagenicity of the K-region imines derived from carbocyclic polyarenes is always substantially higher than that of the corresponding K-region oxides, the activities of the imines and oxides derived from 1,10-phenanthroline and benzo[*h*]quinoline (but not of benzo[*f*]quinoline) [3] are of the same order of magnitude. The biological activity of the arene imines was shown to depend strongly on the position of the nitrogen atom in the skeleton of the parent heterocyclic arene. A full report on the biological tests of these compounds will be published in a separate paper.

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