Arene Imine Derivatives of Nitrogen Heterocycles: 1a,9b-Dihydrobenz[*h*]-azirino[*f*]quinoline, 1a,9b-Dihydrobenz[*f*]azirino[*h*]quinoline and 1a,9b-Dihydroazirino[*f*][1,10]phenanthroline

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Received July 25, 1989

The syntheses of the K-imine derivatives of benzo[*h*]quinoline (**1**), benzo[*f*]quinoline (**2**) and 1,10-phenanthroline (**3**) are described. The parent nitrogen heterocycles were oxidized with sodium hypochlorite to the corresponding K-oxides, **4**, **6** and **8**, which in turn were reacted with sodium azide. The resulting azido alcohols were then cyclized with triethyl phosphite to the title compounds **5**, **7** and **9**. The oxirane ring cleavage in benzo[*h*]quinoline 5,6-oxide (**4**) and in benzo[*f*]quinoline 5,6-oxide (**6**) by sodium azide proceeded by the predicted regioselectivity: **4** gave *trans*-5-azido-5,6-dihydro-6-benzo[*h*]quinolinol (**11**) and *trans*-6-azido-5,6-dihydro-5-benzo[*h*]quinolinol (**10**) as the major and minor products respectively, and **6** yielded solely *trans*-6-azido-5,6-dihydro-5-benzo[*f*]quinolinol (**12**). The latter compound proved by X-ray analysis to crystallize as a hydrogen bonded dimer.

J. Heterocyclic Chem., **27**, 1197 (1990).

The exceptionally high mutagenic potencies of polycyclic arene imines [1-3], the observed correlation between their biological activities and those of the corresponding arene oxides [1], and the refractory behavior of the aziridines towards naturally occurring epoxide hydrolases [1], led us to assume that arene imines are secondary metabolites of polycyclic aromatic hydrocarbons, and are involved in the carcinogenic process. In order to examine the validity of this assumption, we found it imperative to prepare a wide variety of polycyclic arene imines and test their biological properties [4]. The imines synthesized so far were, with the exception of one sulfur containing compound [5], all derived from aromatic carbocyclic structures.

In this paper we report the syntheses of the first polycyclic arene imines of the nitrogen containing heterocycles benzo[*h*]quinoline (**1**), benzo[*f*]quinoline (**2**), and 1,10-phenanthroline (**3**).

The syntheses of 1a,9b-dihydrobenz[*h*]azirino[*f*]quinoline (benzo[*h*]quinoline 5,6-imine, **5**), 1a,9b-dihydrobenz[*f*]-azirino[*h*]quinoline (benzo[*f*]quinoline 5,6-imine, **7**), and 1a,9b-dihydroazirino[*f*][1,10]phenanthroline (1,10-penanthroline 5,6-imine, **9**) were accomplished by initial hypochloride-oxidation of **1**, **2** and **3** under phase transfer conditions [6]. The oxidation process proved to be extremely sensitive to the *p*H. Positive results were obtained only when the *p*H was carefully regulated during the reactions between 8 and 9. The stereochemistry of the oxiranes has not been determined, but on account of the observed structure of **12** (*vide infra*) we can conclude that at least **6** (which serves as its precursor) is a *down* epoxide. The epoxides were then treated with sodium azide to give the respective azido alcohols **10-13**, which in turn were cyclized to the respective imines **5**, **7** and **9** with the aid of triethyl phosphite [5]. Attempts to apply tributylphosphine [7] in the cyclization of **13** gave, however, negative results.

The interaction of unsymmetrical epoxides such as **4** and **6** with sodium azide can theoretically give two kinds of *trans*-azido alcohols - one in which the azide group is remote from, and one in which it is close to the heterocyclic ring. In fact, we found that **4** forms a mixture of **10** (29%) and **11** (71%), but **6** proved to give only one azido alcohol (**12**) in which the N_3 moiety is at the 6 position.

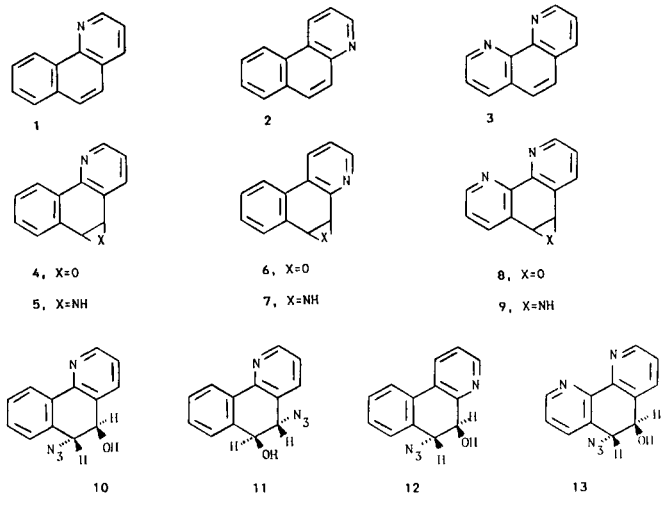

Table 1
Crystallographic Data of Compound **12**

Formula: $C_{13}H_{10}N_4O$	ρCalcd = 1.40 g cm^{-3}
Molecular weight = 238.3	μ(Mo K$_\alpha$) = 0.56 cm^{-1}
Space group Pbca	number of unique reflections: 1447
a = 15.306(4) Å	number of reflections with I ≥ 2σ$_I$ 1027
b = 10.079(3) Å	R = 0.067
c = 14.631(5) Å	R_W = 0.037
V = 2257.1 (8) Å^3	$W^{-1} = \sigma^2$
Z = 8	

These results are in perfect agreement with our theoretical predictions based on MO calculations [8]. The calculated index for the nucleophilic ring opening in **4** was found to have a moderate value of 0.012 β in favor of the production of **11**. The index for **6** was high (0.045 β) and in favor of N_3 substitution at the remote 6 position [9], and as shown previously, suggests the formation of a single product [8].

The structure of the azido alcohol derived from **6** was unequivocally proven by X-ray diffraction analysis. The crystal data, the positional parameters, and the bond lengths and angles are listed in Tables 1-3 [10]. The ORTEP and stereoscopic drawings that are presented as Figures 1 and 2, respectively, show that the N_3 and OH groups are *trans* to each other. Figure 2 indicates that **12** exists as a symmetrical dimer (with a significantly high ρ value of 1.40 g cm^{-1}) formed by two intermolecular hydrogen bonds between the hydroxyl oxygen and the ring nitrogen atoms. Each distance between the connecting heteroatoms was found to be 2.854(5) Å.

Table 2
Final Positional Parameters and Equivalent Thermal Parameters for **12** with Estimated Standard Deviations in Parentheses

Atom	X	Y	Z	Ueq
O	.4351(2)	1.1127(3)	.4205(2)	.052(2)
N(1)	.5355(3)	.9134(5)	.2397(3)	.054(3)
N(2)	.5488(3)	.9177(4)	.1563(4)	.056(3)
N(3)	.5636(4)	.9107(5)	.0811(4)	.089(5)
N(4)	.4237(3)	.8082(4)	.4644(3)	.042(3)
C(1)	.2854(3)	.7547(5)	.3463(3)	.048(1)
C(2)	.3002(3)	.6767(6)	.4218(3)	.052(1)
C(3)	.3679(3)	.7059(5)	.4798(4)	.047(1)
C(4a)	.4094(3)	.8836(4)	.3897(3)	.036(1)
C(5)	.4709(3)	.9993(5)	.3766(3)	.039(1)
C(6)	.4827(3)	1.0287(5)	.2755(3)	.043(1)
C(6a)	.3974(3)	1.0379(5)	.2248(3)	.037(1)
C(7)	.3870(3)	1.1244(5)	.1517(3)	.048(1)
C(8)	.3107(3)	1.1283(6)	.1024(4)	.054(2)
C(9)	.2432(4)	1.0445(5)	.1268(3)	.055(1)
C(10)	.2517(4)	.9588(5)	.1997(3)	.050(1)
C(10a)	.3295(3)	.9537(5)	.2499(3)	.037(1)
C(10b)	.3403(3)	.8619(5)	.3284(3)	.037(1)

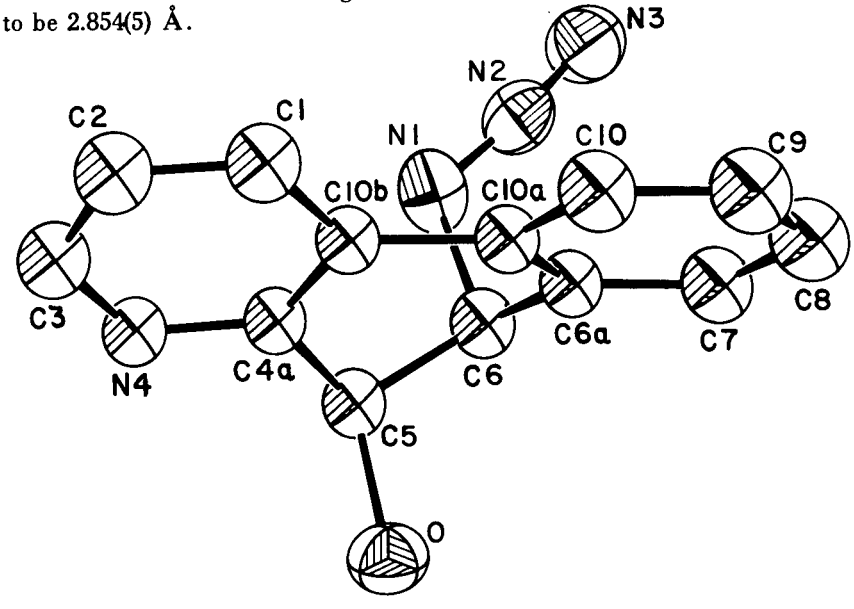

Figure 1. ORTEP drawing of **12**.

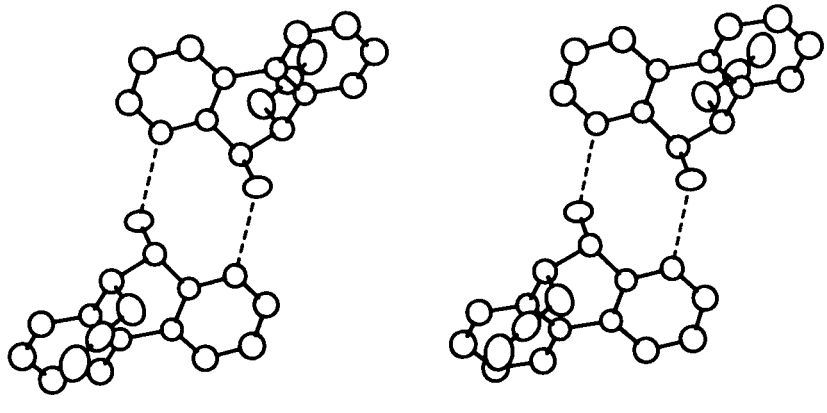

Figure 2. Stereoscopic view of the dimer of **12**.

Table 3
Selected Bond Lengths Å and Angles (°) with Estemated Standard Deviations in Parentheses

Bond Lengths

O-C(5)	1.421(6)	C(4a)-C(10b)	1.404(6)
N(1)-N(2)	1.237(8)	C(5)-C(6)	1.520(6)
N(1)-C(6)	1.510(7)	C(6)-C(6a)	1.504(7)
N(2)-N(3)	1.126(8)	C(6a)-C(7)	1.395(7)
N(4)-C(3)	1.357(6)	C(6a)-C(10a)	1.385(6)
N(4)-C(4a)	1.350(6)	C(7)-C(8)	1.371(7)
C(1)-C(2)	1.374(7)	C(8)-C(9)	1.382(8)
C(1)-C(10b)	1.394(7)	C(9)-C(10)	1.379(7)
C(2)-C(3)	1.371(7)	C(10)-C(10a)	1.400(7)
C(4a)-C(5)	1.510(7)	C(10a)-C(10b)	1.484(7)

Bond Angles

N(2)-N(1)-C(6)	113.8(4)	C(5)-C(6)-C(6a)	112.8(4)
N(1)-N(2)-N(3)	174.0(6)	C(6)-C(6a)-C(7)	120.8(4)
C(3)-N(4)-C(4a)	117.4(4)	C(6)-C(6a)-C(10a)	119.1(4)
C(2)-C(1)-C(10b)	119.7(5)	C(7)-C(6a)-C(10a)	120.0(4)
C(1)-C(2)-C(3)	119.9(5)	C(6a)-C(7)-C(8)	121.2(5)
N(4)-C(3)-C(2)	122.4(5)	C(7)-C(8)-C(9)	118.9(5)
N(4)-C(4a)-C(5)	115.9(4)	C(8)-C(9)-C(10)	120.8(5)
N(4)-C(4a)-C(10b)	123.5(4)	C(9)-C(10)-C(10a)	120.6(5)
C(5)-C(4a)-C(10b)	120.6(4)	C(6a)-C(10a)-C(10)	118.5(4)
O-C(5)-C(4a)	108.9(4)	C(6a)-C(10a)-C(10b)	120.0(4)
O-C(5)-C(6)	109.2(4)	C(10)-C(10a)-C(10b)	121.6(4)
C(4a)-C(5)-C(6)	110.4(4)	C(1)-C(10b)-C(4a)	117.0(4)
N(1)-C(6)-C(5)	104.5(4)	C(1)-C(10b)-C(10a)	124.2(4)
N(1)-C(6)-C(6a)	109.7(4)	C(4a)-C(10b)-C(10a)	118.7(4)

The tendency of the OH group of the β-azido alcohols to form hydrogen bonds can be deduced also from the ir bands at ≈ 3340 cm^{-1}. Furthermore, compound **13** (as some other polycyclic azido alcohols studied previously [11]), crystallizes as a hemihydrate from which the removal of water of crystallization, without decomposition of the molecule, has proved difficult.

EXPERIMENTAL

Oxidation of Benzo[*h*]quinoline (**1**), Benzo[*f*]quinoline (**2**) and 1,10-Phenanthroline (**3**).

Racemic benz[*h*]oxireno[*f*]quinoline (**4**), benz[*f*]oxireno[*h*]-quinoline (**6**) and oxireno[*f*][1,10]phenanthroline (**8**) were prepared from **1**, **2** and **3**, respectively, by the method of Krishnan *et al.* [6]. The corresponding yields of isolated **4**, **6** and **8** were 65, 70 and 86% provided the *p*H was carefully adjusted to 8-9 during the entire reaction period.

E-6-Azido-5,6-dihydro-5-benzo[*h*]quinolinol (**10**) and *E*-5-Azido-5,6-dihydro-6-benzo[*h*]quinolinol (**11**).

To a solution of 20 g (0.31 mole) of sodium azide in 150 ml of water was added 650 mg (3.33 mmoles) of **4** in 300 ml of acetone. The mixture was stirred under nitrogen at room temperature for 72 hours. Most of the acetone was removed under reduced pressure and the residue extracted with 50 ml of dichloromethane. The organic solution was dried over magnesium sulfate and the solvent was evaporated. The residual solid was purified by column chromatography on silica gel (mixtures of ether-hexane served as eluent) to give 445 mg (56%) of a colorless mixture of **10** and **11**. The ratio of the isomers was found to be 2:5, mp, **10** + **11**, 118-119° dec; ir (nujol): 3340 (OH), 2090 cm^{-1} (N_3); 200 MHz pmr (deuteriochloroform): δ 4.691 [d, 0.7H, J = 7.5 Hz, H5 (**11**)], 4.732 (d, 0.3 H, J = 7.3 Hz, H6 (**10**)], 4.825 (d, 0.7 H, J = 7.5 Hz, H6 (**11**), affected by deuterium oxide], 4.892 (d, 0.3H, J = 7.3 Hz, H5 (**10**), affected by deuterium oxide], 7.190-7.606 (m, 4H, H3, H4, H8, H9), 7.762 [dd, 0.3H, $J_{7,8}$ = 8.0 Hz, $J_{7,9}$ = 2.5 Hz, H7 (**10**)], 7.890 (dd, 0.7H, $J_{7,8}$ = 8.4 Hz, $J_{7,9}$ = 2.5 Hz, H7 (**11**)], 8.220 (dd, 0.3H, $J_{8,10}$ = 2.5 Hz, $J_{9,10}$ = 7.5 Hz, H6 (**10**)], 8.294 [dd, 0.7H, $J_{8,10}$ = 2.2 Hz, $J_{9,10}$ = 7.2 Hz, H4 (**11**)], 8.522-8.573 [two overlapping dd, 1H, $J_{2,4}$ = 2.5 Hz, $J_{2,3}$ = 8.4 Hz, H2 (**10** + **11**)]; ms: (70 eV, 80°) m/e (relative intensity) 238 ($M^{+\cdot}$, 30), 210 ($C_{13}H_{10}N_2O^{+\cdot}$, 33), 209 ($C_{13}H_9N_2O^+$, 59), 196 ($C_{13}H_{10}NO^+$, 16), 181 ($C_{12}H_7NO^{+\cdot}$, 100), 179 ($C_{13}H_9N^{+\cdot}$, 21), 166 ($C_{12}H_8N^+$, 12), 126 ($C_{10}H_6^{+\cdot}$, 31).

Anal. Calcd. for $C_{13}H_{10}N_4O$: C, 65.56; H, 4.20; N, 23.52. Found: C, 65.84; H, 4.20; N, 23.24.

1a,9b-Dihydrobenz[*h*]azirino[*f*]quinoline (**5**).

A solution of 300 mg (1.26 mmoles) of the previous mixture of **10** and **11** and 0.22 ml (1.26 mmoles) of triethyl phosphite in 5 ml of dichloromethane was refluxed under nitrogen for 20 hours. The solvent was removed under reduced pressure. Upon addition of a mixture of 10 ml of ether and 10 ml of hexane the crystalline imine precipitated. Recrystallization from a mixture of benzene and hexane afforded 210 mg (86%) of colorless **5**, mp 106°; ir (nujol): 3450 cm^{-1} (NH); 300 MHz pmr (deuteriochloroform): δ 3.549 (d, 1H, $J_{1a,9b}$ = 5.1 Hz, H1a or H9b), 3.597 (d, 1H, $J_{1a,9b}$ = 5.1 Hz, H1a or H9b), 7.179-7.470 (m, 3H, H3, H7, H8), 7.561 (dd, 1H, $J_{7,9}$ = 2.1 Hz, $J_{8,9}$ = 6.7 Hz, H9), 7.810 (dd, 1H, $J_{2,3}$ = 8.4 Hz, $J_{2,4}$ = 1.8 Hz, H2), 8.592 (dd, 1H, $J_{6,7}$ = 7.1 Hz, $J_{6,8}$ = 2.5 Hz, H6), 8.665 (dd, 1H, $J_{2,4}$ = 1.8 Hz, $J_{3,4}$ = 6.5 Hz, H4); ms: (70 eV, 70°) m/e (relative intensity) 194 ($M^{+\cdot}$, 100), 193 ($C_{13}H_9N_2^+$, 52), 179 ($C_{13}H_9N^{+\cdot}$, 23), 167 ($C_{12}H_9N^{+\cdot}$, 35), 166 ($C_{12}H_8N^+$, 35).

Anal. Calcd. for $C_{13}H_{10}N_2$: C, 80.45; H, 5.15; N, 14.41. Found: C, 80.10; H, 5.08; N, 14.46.

E-6-Azido-5,6-dihydro-5-benzo[*f*]quinolinol (**12**).

In the manner described above for the formation of **10** and **11**, 352 mg (1.8 mmoles) of **6** were reacted with sodium azide to give **12** as the only azido alcohol. Column chromatography on silica gel (using mixtures of ether-hexane, gradient from 50 to 100% ether, as eluent) followed by recrystallization from ethyl acetate afforded 295 mg (69%) of colorless prisms, mp 157-159° dec; ir (nujol) 3340 (OH), 2085 cm^{-1} (N_3); 300 MHz pmr (deuteriochloroform): δ 4.707 (d, 1H, $J_{5,6}$ = 11.2 Hz, H6); 4.881 (d, 1H, $J_{5,6}$ = 11.2 Hz, H5, affected by deuterium oxide), 7.373-7.447 (m, 3H, Ar*H*), 7.659-7.720 (m, 2H, Ar*H*), 8.021 (dd, 1H, $J_{1,2}$ = 7.8 Hz, $J_{1,3}$ = 1.4 Hz, H1 or H10), 8.510 (d, 1H, $J_{2,3}$ = 4.5 Hz, H3); ms: (70 eV 80°) m/e (relative intensity) 238 ($M^{+\cdot}$, 29), 210 ($C_{13}H_{10}N_2O^{+\cdot}$, 6), 208 ($C_{13}H_8N_2O^{+\cdot}$, 11), 179 ($C_{13}H_9N^{+\cdot}$, 100), 165 ($C_{12}H_7N^{+\cdot}$, 8), 152 ($C_{12}H_8^{+\cdot}$, 21).

Anal. Calcd. for $C_{13}H_{10}N_4O$: C, 65.56; H, 4.20; N, 23.52. Found: C, 65.42; H, 4.21; N, 23.62.

X-Ray Crystal Structure of **12**.

A suitable crystal was obtained by slow concentration (4 days) of an ethyl acetate solution of **12**.

Data were measured on a PW1100/20 Philips Four-circle Computer-Controlled Diffractometer. MoKα (λ = 0.71069 Å) radiation with a graphite crystal monochromator in the incident beam was used. The unit cell dimensions were obtained by a least-squares fit of 24 centered reflections in the range of $10 \leq \theta \leq$

14°. Intensity data were collected using the $\omega - 2\theta$ technique to a maximum 2θ of 45°. The scan width, $\triangle\omega$, for each reflection was 1.00 + 0.35•tan θ with a scan speed of 3.00 deg/minute. Background measurements were made for a total of 20 seconds at both limits of each scan. Three standard reflections were monitored every 60 minutes. No systematic variations in intensities were found.

Intensities were corrected for Lorentz and polarization effects. All non-hydrogen atoms were found by using the results of the SHELXS-86 direct method analysis [12]. After several cycles of refinements [13] the positions of the hydrogen atoms were found, and added with a constant isotropic temperature factor of 0.05 Å^2 to the refinement process. Refinement proceeded to convergence by minimizing the function $\Sigma w(| F_o | - | F_c |)^2$. A final difference Fourier synthesis map showed several peaks less than 0.3 e/Å^3 scattered about the unit cell without a significant feature.

The discrepancy indices, $R = \Sigma \| F_o | - | F_c \| / \Sigma | F_o |$ and $R_w = \Sigma w(| F_o | - | F_c |)^2 / [\Sigma | F_o |^2]^{1/2}$ are presented with other pertinent crytallographic data in Table 1. Selected positional parameters, bond lengths and angles are given in Table 2 and Table 3.

1a,9b-Dihydrobenz[*f*]azirino[*h*]quinoline (**7**).

In the manner described for the preparation of **5**, the previous azido alcohol was reacted with triethyl phosphite. The crude oily aziridine was triturated with ether and hexane to give a colorless powder that was washed with hexane and recrystallized from a mixture of benzene and hexane, yield 85%, mp 150-151° dec; ir (nujol): 3410 cm^{-1} (NH); 200 MHz pmr (deuteriochloroform): δ 3.716 (d, 1H, $J_{1a,9b}$ = 5.1 Hz, H9b), 3.872 (d, 1H, $J_{1a,9b}$ = 5.1 Hz, H1a), 7.329-7.434 (m, 3H, H4, H7, H8), 7.636 (dd, 1H, $J_{7,9}$ = 2.8 Hz, $J_{8,9}$ = 6.8 Hz, H9), 7.980 (dd, 1H, $J_{6,7}$ = 8.9 Hz, $J_{6,8}$ = 2.8 Hz, H6); 8.292 (d, 1H, $J_{4,5}$ = 8.1 Hz, H5); 8.535 (dd, 1H, $J_{3,4}$ = 5.9 Hz, $J_{3,5}$ = 1.2 Hz, H3); ms: (68 eV, 70) m/e (relative intensity) 194 ($M^{+\cdot}$, 100), 193 ($C_{13}H_9N_2^+$, 64), 179 ($C_{13}H_9N^{+\cdot}$, 10), 167 ($C_{12}H_9N^+$, 35), 166 ($C_{12}H_8N^{+\cdot}$, 25).

Anal. Calcd. for $C_{13}H_{10}N_2$: C, 80.45; H, 5.15; N, 14.41. Found: C, 80.09; H, 4.92; N, 14.03.

trans-6-Azido-5,6-dihydro[1,10]phenanthrolin-5-ol (**13**).

As described for the preparation of **10** and **11**, 500 mg (2.55 mmoles) of **8** in 150 ml of acetone was reacted at room temperature for 24 hours with 10 g (0.156 moles) of sodium azide in 75 ml of water. Concentration of the solution under reduced pressure to a volume of 50 ml, followed by cooling of the residue at 0° for 60 minutes, afforded colorless crystals of the azido alcohol. Drying of the crystals at 1 mm for 24 hours gave 460 mg (73%) of **13** as hemihydrate, mp 99-100° dec; ir (nujol) 3420 (OH), 2104 cm^{-1} (N_3); 300 MHz pmr (hexadeuteriodimethyl sulfoxide): δ 4.848 (d, 1H, $J_{5,6}$ = 8.9 Hz, H5, affected by deuterium oxide), 5.047 (d, 1H, $J_{5,6}$ = 8.9 Hz, H6), 6.499 (br s, 2H, O*H*, H_2O), 7.485 (m, 2H, H3, H8), 7.980 (dd, 2H, $J_{2,4} = J_{7,9}$ = 1.5 Hz, $J_{3,4} = J_{7,8}$ = 9.0 Hz, H4, H7), 8.685 (dd, 2H, $J_{2,4} = J_{7,9}$ = 1.5 Hz, $J_{2,3} = J_{8,9}$ = 5.8 Hz, H2, H9); ms: (70 eV, 140°) m/e (relative intensity) 211 [$(M\text{-}N_2)^{+\cdot}$, 1], 197 ($C_{12}H_9N_2O^+$, 4), 194 ($C_{12}H_8N_3^+$, 26), 193 ($C_{12}H_7N_3^{+\cdot}$, 100), 184 ($C_{11}H_8N_2O^{+\cdot}$, 7), 166 ($C_{11}H_6N_2^{+\cdot}$, 23), 139 ($C_{10}H_5N^{+\cdot}$, 27).

Anal. Calcd. for $C_{12}H_9N_5O•½H_2O$: C, 58.08; H, 4.03; N, 28.22. Found: C, 58.00; H, 3.78; N, 27.80.

1a,9b-Dihydroazirino[*f*][1,10]phenanthroline (**9**).

Treatment of 254 mg (1.02 mmoles) of the previous azido alcohol with 185 mg (1.06 mmoles) of triethylphosphite in 10 ml of boiling dichloromethane afforded after 10 hours crude **9** as a semisolid. Trituration with ether and recrystallization from a mixture of dichloromethane and hexane gave 170 mg (78%) of the imine as monohydrate (even after prolonged drying at 1 mm at 65°), mp 190-192° dec (darkens >170°); ir (nujol): 3410 cm^{-1} (NH); 200 MHz pmr (deuteriochloroform): δ 1.6 (br s, 2H, H_2O); 3.619 (d, 2H, $J_{1,1a} = J_{1,9b}$ = 7.2 Hz, H1a, H9b turns into s in the presence of deuterium oxide), 7.356 (dd, 2H, $J_{2,3} = J_{8,9}$ = 7.7 Hz, $J_{3,4} = J_{7,8}$ = 4.4 Hz, H3, H8), 7.930 (dd, 2H, $J_{2,3} = J_{8,9}$ = 7.7 Hz, $J_{2,4} = J_{7,9}$ = 1.5 Hz, H2, H9), 8.815 (d, 2H, $J_{3,4} = J_{7,8}$ = 4.4 Hz, H4, H7); ms: (70 eV, 70°) m/e (relative intensity) 195 ($C_{12}H_9N_3^{+\cdot}$, 100), 194 ($C_{12}H_8N_3^+$, 34), 180 ($C_{12}H_8N_2^{+\cdot}$, 23), 168 ($C_{11}H_8N_2^{+\cdot}$, 69), 140 ($C_{10}H_6N^+$, 15).

Anal. Calcd. for $C_{12}H_9N_3•H_2O$: C, 67.59; H, 5.20; N, 19.71. Found: C, 67.50; H, 4.89; N, 19.47.

Acknowledgements.

We thank Dr. Shmuel Cohen for his help in X-ray analysis and the Basic Research Foundation (administrated by the Israel Academy of Sciences and Humanities) for financial support of this study.

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