Benzo[*a*][3,6]phenanthrolines

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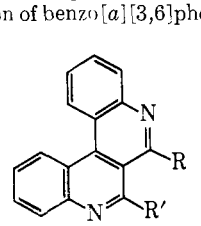
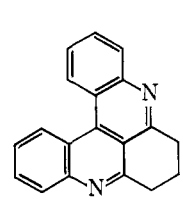
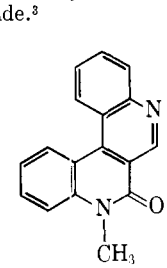
During the course of synthetic studies on polyazapolycyclic compounds related to the potent carcinogen tricycloquinazoline,[2] a number of benzo[*a*][3,6]phenanthrolines were prepared. Compounds Ia–c and II resulted from a double Friedländer condensation of 2,2′-diaminobenzophenone with the appropriate β-diketone. Derivatives of Ia were prepared *via* Id and of Ib by exploiting the active 7-methyl group. Attempts to effect a Bischler–Napieralski cyclization of 6-anilino-7-hydroxybenzo[*a*][3,6]phenanthroline (Ii) to a triazanaphtho[1,2,3-*fg*]naphthacene related to isotricycloquinazoline[2] failed, as did attempts to dehydrogenate II. Compound III was obtained by alkaline ferricyanide oxidation of benzo[*a*][3,6]phenanthroline methiodide.[3]



Ia, R = R′ = OH
b, R = OH; R′ = CH_3
c, R = R′ = C_6H_5
d, R = Cl; R′ = OH
e, R = OH; R′ = styryl
f, R = OH; R′ = COOH
g, R = OH; R′ = H
h, R = H; R′ = H
i, R = NHC_6H_5; R′ = OH



II



III

Experimental Section[4]

6-Hydroxy-7-methylbenzo[*a*][3,6]phenanthroline (Ib).—2,2′-Diaminobenzophenone[3] (2.1 g.), piperidine (0.1 ml.), and ethyl acetoacetate (8 ml.) were heated together under reflux for 1 hr. 6-Hydroxy-7-methylbenzo[*a*][3,6]phenanthroline (1.2 g.), m.p. 328–332° dec., separated; it was collected and washed with hot ethanol (25 ml.). Evaporation of the mother liquors to 3–4 ml. followed by dilution with ethanol (25 ml.) gave 0.7 g. more of Ib; total yield, 1.9 g., 72%. Sublimation at 260–280° (2 mm.) yielded pale yellow needles: m.p. 333–336° dec.; $\lambda_{max}^{CH_3COOH}$ 265, 319, 362, 384 mμ (ε 32,890, 5105, 5975, 6592).

Anal. Calcd. for $C_{17}H_{12}N_2O$: C, 78.8; H, 4.8; N, 10.6. Found: C, 78.5; H, 4.7; N, 10.8.

The **hydrochloride** separated as yellow needles, m.p. 324–326°, from a solution of the base in 2 *N* HCl.

Anal. Calcd. for $C_{17}H_{13}ClN_2O$: N, 9.45. Found: N, 9.5.

The **picrate** was prepared in ethanol solution and recrystallized from acetic acid as yellow needles, m.p. 262–264° dec.

Anal. Calcd. for $C_{23}H_{15}N_5O_8$: C, 56.4; H, 2.8; N, 14.0. Found: C, 56.4; H, 3.1; N, 14.3.

6-Hydroxy-7-styrylbenzo[*a*][3,6]phenanthroline (Ie).—6-Hydroxy-7-methylbenzo[*a*][3,6]phenanthroline (2.6 g.) in benzaldehyde (20 ml.) and acetic anhydride (20 ml.) was heated under reflux for 3 hr. The styryl derivative (2.3 g., 67%) deposited as yellow needles during the reaction. It was recrystallized from aqueous dimethylformamide; m.p. 298–300°; $\lambda_{max}^{CHCl_3}$ 266, 318 mμ (ε 24,040, 25,120).

Anal. Calcd. for $C_{24}H_{16}N_2O$: C, 82.4; H, 4.4; N, 8.0. Found: C, 82.7; H, 4.6; N, 8.0.

7-Carboxy-6-hydroxybenzo[*a*][3,6]phenanthroline (If).—Ie (0.92 g.) and potassium permanganate (3.0 g.) were heated in boiling acetone (200 ml.) for 2 hr. Sodium hydroxide (2 *N*, 20 ml.) was added to the mixture and heating was continued for a further 10 min. The suspension was left for 12 hr. and filtered. The filtrate was acidified to congo red with 5 *N* HCl and decolorized with sodium dithionite (1 g.). Removal of the acetone *in vacuo* gave If (0.44 g., 62%). It crystallized from aqueous dimethylformamide as olive green needles: m.p. 356–360° dec.; $\lambda_{max}^{CH_3COOH}$ 263, 325, 360, 375 mμ (ε 39,260, 5321, 6855, 6823).

Anal. Calcd. for $C_{17}H_{10}N_2O_3$: C, 70.3; H, 3.5; N, 9.7. Found: C, 69.9; H, 3.7; N, 9.9.

6-Hydroxybenzo[*a*][3,6]phenanthroline (Ig).—When If (0.29 g.) was heated gradually to redness at atmospheric pressure, Ig (0.19 g., 76%) sublimed. It was recrystallized from 1-butanol to give pale yellow needles. It had no melting point but sublimed above 320°; $\lambda_{max}^{CH_3COOH}$ 262, 325, 360, 372 mμ (ε 37,330, 5188, 7031, 6902).

Anal. Calcd. for $C_{16}H_{10}N_2O$: C, 78.1; H, 3.7; N, 11.1. Found: C, 78.0; H, 4.1; N, 11.4.

Benzo[*a*][3,6]phenanthroline[3] (Ih). **A.**—Ig (0.12 g.) was intimately mixed with zinc dust (0.5 g.) and heated to redness. The parent heterocycle distilled and crystallized. Recrystallization from ligroin (b.p. 80–100°) gave pale yellow prisms (31 mg., 25%), m.p. and m.m.p. 165–167°. The ultraviolet absorption spectrum was identical with that of an authentic sample.[3]

B.—Zinc dust distillation of 6,7-dihydroxybenzo[*a*][3,6]-phenanthroline (Ia) as described above afforded 23% of Ih.

6,7-Dihydroxybenzo[*a*][3,6]phenanthroline (Ia).—2,2′-Diaminobenzophenone (2.1 g.), piperidine (0.1 ml.), and diethyl malonate (8 ml.) were heated together under reflux for 1.5 hr. A pale yellow solid separated. The suspension was cooled and diluted with methanol (10 ml.); Ia (1.75 g.) was collected. A further 0.16 g. was obtained by evaporation of the mother liquors to 3–4 ml.; total yield 1.9 g. (74%). The product was purified either by recrystallization from dimethylformamide or by sublimation at 310–320° (4 mm.) to give yellow needles: m.p. 359–362° dec.; $\lambda_{max}^{CH_3COOH}$ 269, 324, 356, 378, 397 mμ (ε 15,810, 7413 6561, 9162, 8630).

Anal. Calcd. for $C_{16}H_{10}N_2O_2$: C, 72.9; H, 4.2; N, 10.7. Found: C, 73.3; H, 3.8; N, 10.7.

6-Chloro-7-hydroxybenzo[*a*][3,6]phenanthroline (Id).—Ia (5.2 g.) and phosphoryl chloride (40 ml.) were heated together under reflux (bath temperature 120–140°) until a homogeneous solution was obtained (about 1.5 hr.). The cooled solution was poured onto crushed ice (600 g.). The solid was collected, washed well with water, and dried *in vacuo* over phosphorus pentoxide. Crystallization from dimethylformamide furnished 6-chloro-7-hydroxybenzo[*a*][3,6]phenanthroline (5.7 g., 97%) as brown needles, m.p. 315–319°.

Anal. Calcd. for $C_{16}H_9ClN_2O$: C, 68.4; H, 3.2; N, 10.0. Found: C, 68.2; H, 3.5; N, 9.7.

The chloro compound (Id) was unaffected by boiling water for 30 min. but was readily hydrolyzed to Ia in hot 4 *N* HCl.

6-Anilino-7-hydroxybenzo[*a*][3,6]phenanthroline (Ii).—A solution of Id (1 g.) in aniline (10 ml.) was heated under reflux for 30 min. Ethanol (10 ml.) was added to the cooled solution and Ii (0.96 g., 80%) precipitated. It crystallized as yellow needles from dimethylformamide; m.p. 328–331° dec.; $\lambda_{max}^{CHCl_3}$ 260, 292, 295, 320, 430 mμ (ε 33,880, 22,700, 22,440, 28,250, 4581).

Anal. Calcd. for $C_{22}H_{15}N_3O$: C, 78.3; H, 4.5; N, 12.5. Found: C, 78.6; H, 4.65; N, 12.6.

The **hydrochloride** crystallized from 5 *N* HCl as yellow needles, m.p. 322–326°.

Anal. Calcd. for $C_{22}H_{16}ClN_3O$: N, 11.2. Found: N, 10.9.

Treatment of Ii (1 g.) with boiling 20% KOH in ethylene glycol (20 ml.) for 6 hr. gave Ia (0.62 g., 82%).

6,7-Diphenylbenzo[*a*][3,6]phenanthroline (Ic).—A mixture of 2,2′-diaminobenzophenone (1.06 g.), dibenzoylmethane (1.1 g.), and acetic acid (0.5 ml.) were heated together in an aniline vapor bath for 1 hr. A further 0.5 ml. of acetic acid was added after 30 min. Crystallization of the product from ethanol gave Ic (1.4 g., 75%) as pale yellow needles: m.p. 227–228°; $\lambda_{max}^{C_2H_5OH}$ 238, 283, 385 mμ (ε 34,400, 34,750, 1687).

Anal. Calcd. for $C_{28}H_{18}N_2$: C, 87.9; H, 4.7; N, 7.3. Found: C, 87.6; H, 4.5; N, 7.2.

The **picrate** was prepared in ethanol and recrystallized from 1-butanol as yellow plates, m.p. 274–276° dec.

Anal. Calcd. for $C_{34}H_{21}N_5O_7$: N, 11.45. Found: N, 11.1.

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[1] National Institutes of Health, Bethesda, Md.

[2] T. Parfitt, M. W. Partridge, and H. J. Vipond, *J. Chem. Soc.*, 3062 (1962).

[3] M. Partridge and H. J. Vipond, *ibid.*, 632 (1962).

[4] Melting points were determined in a standard capillary melting point apparatus and are uncorrected.

2,8-Dihydro-6H-dibenzo[*a*][3,6]phenanthroline (II).—A solution of 2,2′-diaminobenzophenone (2.1 g.) and 1,3-cyclohexanedione (1.1 g.) in acetic acid (20 ml.) was heated under reflux for 30 min. A crystalline solid separated which possessed the properties of a ketone but not those of an aromatic primary amine.[5]

The acetic acid mother liquors were diluted with water (100 ml.), boiled, and cooled to yield II (2.2 g., 81%). It recrystallized from aqueous ethanol as colorless needles: m.p. 180–181°; $\lambda_{max}^{C_2H_5OH}$ 269, 336, 354, 372 mμ (ε 41,509, 35,810, 4819, 5808).

Anal. Calcd. for $C_{19}H_{14}N_2$: C, 84.4; H, 5.2; N, 10.4. Found: C, 84.2; H, 5.0; N, 10.6.

The **picrate** was prepared in ethanol solution and recrystallized as green needles from aqueous acetic acid; m.p. 205–207°.

Anal. Calcd. for $C_{25}H_{17}N_5O_7$: N, 14.0. Found: N, 13.8.

5,6-Dihydro-5-methyl-6-oxobenzo[*a*][3,6]phenanthroline (III).—A mixture of benzo[*a*][3,6]phenanthroline methiodide[1] (0.8 g.), potassium ferricyanide (5.0 g.), and NaOH (2 *N*, 50 ml.) was heated under reflux for 5 hr. The suspended solid was collected, dried, and crystallized from ethanol as yellow needles; yield of III, 0.39 g. (71%); m.p. 217–218°; $\lambda_{max}^{CHCl_3}$ 259, 316, 329, 372 mμ (ε 41,210, 5129, 5395, 8222).

Anal. Calcd. for $C_{17}H_{12}N_2O$: C, 78.4; H, 4.65; N, 10.8. Found: C, 78.3; H, 4.7; N, 10.9.

(5) A possible structure for this compound is 2,2′-di(3-oxocyclohexylimino)benzophenone (0.38 g., 9%). It recrystallized from aqueous formic acid as pale green plates, m.p. 336–340°. *Anal.* Calcd. for $C_{25}H_{24}N_2O_3$: N, 7.0. Found: N, 6.9. The di(hydrogen sulfate) separated from a solution of base in 1:1 ethanol and 2 *N* H_2SO_4 as green prisms, m.p. above 400°. *Anal.* Calcd. for $C_{25}H_{28}N_2O_{11}S_2$: N, 4.7. Found: N, 4.9.

Cyclohexylammonium Hydrogen N-2-Chloroethyl-N-5-chloro(1-chloromethyl)pentyl Phosphorodiamidate[1]

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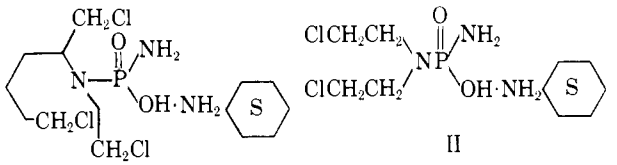
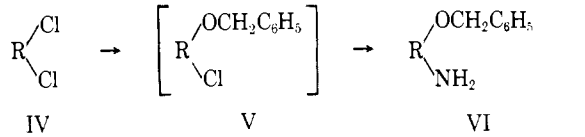
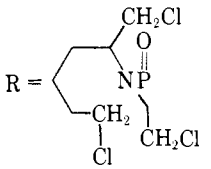
We report here the synthesis of a new phosphorodiamidic acid mustard (I) structurally analogous to the known potent antitumor agent, N,N-bis(2-chloroethyl)phosphorodiamidic acid cyclohexylamine[3] (II), in which the bis(2-chloroethyl)amine mustard moiety in II is replaced by the more cytoactive nitrogen-mustard, N-2-chloroethyl-N-5-chloro(1-chloromethyl)pentylamine (III).[4]



I II



IV V VI



(1) Supported by a research grant (CA-02130) from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service.

(2) To whom inquiries should be addressed.

(3) O. M. Friedman, E. Boger, H. Sommer, and V. Grubliauskas, *J. Med. Chem.*, **6**, 50 (1963).

The new phosphordiamidic acid mustard I was prepared by a procedure paralleling that used for the synthesis of the simpler analog II. The known dichlorophosphoramidic[1] IV was condensed with sodium benzylate to give the benzyl chloro derivative V which, without isolation, was treated with ammonia, affording the benzyl amide VI as a solid crystalline product. Hydrogenolysis of the benzyl ester (VII) gave the phosphorodiamidic acid I isolated as a crystalline cyclohexylammonium salt.

When tested against the KB cell line in tissue culture, the cyclizable mustard phosphoramidic acid I interestingly showed about the same toxicity, ED_{50} = 30 μg./ml., as the simpler analog II, ED_{50} = 35 μg./ml.[5] The compound will be submitted for animal testing.

Experimental Section

Benzyl N-2-Chloroethyl-N-5-chloro-1-(chloromethyl)pentyl Phosphorodiamidate (V).—To a stirred suspension of 0.45 g. of sodium hydride in 10 ml. of sodium-dried benzene cooled in ice was added a solution of 1.03 ml. of benzyl alcohol, over a period of 10 min.; the mixture was stirred in the cold overnight. The resulting suspension of sodium benzylate was added over a period of 10 min. to a stirred solution of 3.55 g. of the dichlorophosphoramidic III[4] in 25 ml. of dry benzene in the cold, and the stirring was continued for an additional 2 hr. in the cold. The resulting V, without isolation, was treated with ammonia by bubbling the gas through the cooled solution for 2 hr. until the precipitation of NH_4Cl was complete. After the suspended NaCl and NH_4Cl were filtered, the filtrate was treated with a mixture of 1 g. of Norit A and 1 g. of Nuchar $C_{190}N$. The resulting clear solution, on evaporation, left a residue of 3.1 g. (77%) of light yellow oil, $n^{26}D$ 1.5286.

Anal. Calcd. for $C_{15}H_{24}Cl_3N_2O_2P$: C, 44.85; H, 6.02; Cl, 26.48; P, 7.71. Found: C, 44.88; H, 6.10; Cl, 26.43; P, 7.57.

Cyclohexylammonium Hydrogen N-2-Chloroethyl-N-5-chloro-(1-chloromethyl)pentyl Phosphorodiamidate (I).—Hydrogenolysis of 1.5 g. of V over 0.4 g. of 10% palladium–charcoal in 50 ml. of absolute ethanol, cooled in ice, at a slight overpressure of hydrogen, was complete in 10 min. After filtration to remove the catalyst, 0.4 ml. of cyclohexylamine was added immediately, and the solution evaporated to dryness. The resulting clear oil was shaken with acetone and allowed to stand in the cold for 2 days when crystallization occurred. The product was filtered, washed with acetone, and thoroughly dried under vacuum to give 0.3 g. (20%) of crystalline product, m.p. 101–103°.

Anal. Calcd. for $C_{21}H_{41}Cl_3N_3O_2P$: C, 40.90; H, 7.62; Cl, 25.91; N, 10.22; P, 7.54. Found: C, 40.81; H, 7.48; Cl, 25.69; N, 10.05; P, 7.75.

(4) O. M. Friedman, H. Sommer, and E. Boger, *J. Am. Chem. Soc.*, **82**, 5202 (1960).

(5) By Dr. G. E. Foley, Children's Cancer Research Foundation, Inc., Boston, Mass. We are indebted to Dr. Sidney Farber, Director of the Foundation, for kind permission to report these preliminary results.

Synthesis of the Di-N-phenyl- and Di-N-(α-naphthyl)urethans of 1,1-Dimethylol-3-cyclopentene[1]

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Recent interest in the biological activity of certain carbamates and urethans has sharply increased. Several pyridylurethar have been found to possess modest analgesic and sedative pro ties.[2] A variety of halogenated carbanilates have potent teriostatic activity.[3] The activity of these urethans w

(1) Supported by Research Corporation (Frederick Gardn Grant) and the National Science Foundation (Grant GP4417)

(2) N. P. Buu-Hoi, R. Rips, and C. Derappe, *J. Med. Chem.*,

(3) D. J. Beaver, D. P. Roman, and P. J. Stoffel, *J. Am. C* 1236 (1957); *J. Med. Chem.*, **6**, 501 (1963).