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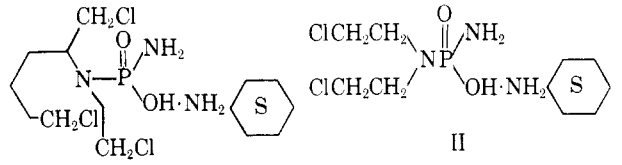
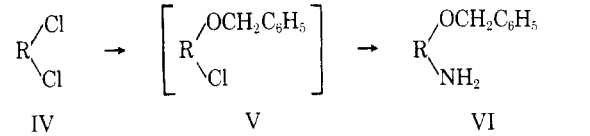
We report here the synthesis of a new phosphorodiamidic acid mustard (I) structurally analogous to the known potent antitumor agent, N,N-bis(2-chloroethyl)phosphorodiamidic acid cyclohexylamine[3] (II), in which the bis(2-chloroethyl)amine mustard moiety in II is replaced by the more cytoactive nitrogen-mustard,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



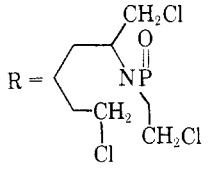
I



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 dichlorophosphoramidate[4] 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 dichlorophosphoramidate 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 $C_{21}H_{31}Cl_3N_3O_2P$: 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 pyridylurethan have been found to possess modest analgesic and sedative properties.[2] A variety of halogenated carbanilates have potent teriostatic activity.[3] The activity of these urethans w

(1) Supported by Research Corporation (Frederick Gardner 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).

tremely sensitive to the position of the halogen in the aromatic rings. Some dicarbamates and -urethans derived from 2,2-dialkyl-1,3-propanediols display sedative and antispasmodic properties.[4]

This paper reports the synthesis of the title urethans derived from 1,1-dimethylol-3-cyclopentene for screening as possible antispasmodics and anticonvulsants. N.m.r. evidence is presented which unequivocally establishes the position of the cyclopentene double bond.

### Experimental Section[5]

**1,1-Dimethylol-3-cyclopentenedi-N-phenylurethan.**—The diol (0.5 g., 0.004 mole) was dissolved in 10 ml. of dry benzene. Phenyl isocyanate (1.0 g., 0.008 mole) was then added, and the solution was boiled under reflux for 5 hr. During this time the clear solution began to deposit colorless needles. The solvent was removed by a stream of dry nitrogen. The residue was recrystallized from 95% ethanol affording 0.97 g. (68%) of pale yellow needles, m.p. 186–188°. A small sample was recrystallized from aqueous ethanol yielding an analytically pure product, m.p. 186.5–187°. The infrared spectrum (KBr disk) shows bands at 3230 (N–H) and 1690 cm.$^{-1}$ (C=O).

*Anal.* Calcd. for $C_{21}H_{22}N_2O_4$: C, 68.84; H, 6.05; N, 7.65. Found: C, 69.17; H, 6.09; N, 7.45.

Because of the lengthy period of heating in this reaction there was some concern about positional isomerization of the double bond in the cyclopentene ring. That this did not occur is shown by the n.m.r. spectrum of the product. It shows the following singlet absorptions given in parts per million relative to tetramethylsilane: 2.27, 4 protons (ring methylene hydrogens); 4.08, 4 protons ($-CH_2-O-$); 5.60, 2 protons (vinyl hydrogen); and 8.66, 2 protons (N–H). In addition a 10-proton multiplet is found centered at 7.24 (aromatic region). The specific proton assignments were made by consideration of chemical shifts and relative integrated areas and by comparison with the spectrum of the diol. The method used for distinguishing the two sets of methylene protons has previously been discussed.[6]

**1,1-Dimethylol-3-cyclopentenedi-N-(α-naphthyl)urethan.**—To 0.5 g. (0.004 mole) of the diol in 10 ml. of dry benzene was added 1.35 g. (0.008 mole) of α-naphthyl isocyanate. The solution was boiled under reflux for 10 hr. The solvent was removed by evaporation using dry nitrogen. The residual solid was recrystallized from ethanol and benzene affording 1.1 g. (61%) of fine white needles, m.p. 208–210°. A small amount was recrystallized again giving the pure product, m.p. 208.5–209.5°. The infrared spectrum (KBr disk) shows bands at 3200 (N–H) and 1680 cm.$^{-1}$ (C=O). The n.m.r. spectrum was obtained as a 1% solution in deuterioacetone containing tetramethylsilane as an internal standard. The chemical shifts for the various protons in the di-α-naphthylurethan listed in the same order as for the di-N-phenylurethan are 2.32, 4.18, 5.60, 8.56, and 7.26.

*Anal.* Calcd. for $C_{29}H_{26}N_2O_4$: C, 74.66; H, 5.62; N, 6.00. Found: C, 75.00; H, 5.67; N, 6.28.

(4) F. M. Berger, *J. Pharmacol. Exptl. Therap.*, **112**, 413 (1954); (b) J. Lincoln, British Patent 894,434 (April 18, 1962); (c) E. Rosenberg, British Patent 904,410 (Aug. 29, 1962).

(5) Melting points are corrected. Infrared spectra were determined on a Perkin-Elmer Infracord recording spectrophotometer. The n.m.r. spectra were determined on a Varian Model A-60 spectrometer. Spectra were obtained by Mr. Robert Steed. The analyses were performed by C. F. Geiger.

(6) E. J. Grubbs and D. J. Lee, *J. Org. Chem.*, **29**, 3105 (1964).

## Syntheses of 3-Cyano-3-methyl-4-thiochromanone and 3-Carbomethoxy-3-methyl-4-thiochromanone

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In an attempted synthesis of thia steroid analogs, the compounds were synthesized as intermediary models. The method of synthesis is analogous to the route used by Bachmann, *et al.*,[1] and Johnson, *et al.*,[2] for the preparation of equilenin.

### Experimental Section

**3-Hydroxymethylene-4-thiochromanone (I).**—To a suspension of 10.8 g. of sodium methoxide in 30 ml. of benzene was added a solution of 15.2 g. of ethyl formate in 70 ml. of benzene. To the ice-cooled mixture was added a solution of 16.4 g. of 4-thiochromanone[3] in 100 ml. of benzene with stirring. A pink precipitate gradually formed, and after 4 hr. at room temperature it was hydrolyzed with 70 ml. of water. The organic layer was extracted with water and with 10% NaOH solution. The aqueous portions were combined, washed with ether, and acidified with HCl with cooling. The separated oil was extracted with ether. The extract was washed with water, dried, and concentrated to give 18.0 g. (94%) of crude I which was satisfactory for the next step. Distillation of the crude product gave a light yellow oil, b.p. 157–158° (4 mm.), accompanying decomposition.

*Anal.* Calcd. for $C_{10}H_8O_2S$: C, 62.50; H, 4.20. Found: C, 62.83; H, 4.31.

When the condensation was carried out by using sodium ethoxide, the yield of I dropped to 85%.

**Reaction of I with Hydroxylamine.**—A solution of 8.0 g. of I in 80 ml. of acetic acid was stirred for 8 hr. at 85–90° with 6.0 g. of powdered hydroxylamine hydrochloride. Most of the acetic acid was removed under reduced pressure, and the residue was diluted with water and extracted with benzene and ether. The combined organic layer was washed with saturated $NaHCO_3$ solution and with water. Evaporation of the dried solution gave 8.0 g. (quantitative yield) of a dark reddish viscous condensation product (II) which was directly isomerized as described below.

**3-Cyano-4-thiochromanone (III).**—A solution of 13.0 g. of II in 100 ml. of benzene was added to a cooled solution of 2.5 g. of sodium in 30 ml. of methanol. After stirring for 1.5 hr. at room temperature, the mixture was treated with 80 ml. of water and extracted with 5% NaOH solution. Acidification of the combined aqueous solutions with HCl gave 8.8 g. (68%) of III as tan needles, m.p. 92–95°. Recrystallization from aqueous ethanol gave a pure sample of m.p. 101.5–102°.

*Anal.* Calcd. for $C_{10}H_7NOS$: C, 63.49; H, 3.73. Found: C, 63.68; H, 3.79.

**3-Cyano-3-methyl-4-thiochromanone. A. Directly from II.**—A solution of 16.0 g. of II in 150 ml. of benzene was added to a cold solution of 3.4 g. of sodium in 50 ml. of methanol. After stirring for 30 min. at room temperature, the mixture was refluxed for 10 min. and cooled. The mixture was treated with 10 ml. of methyl iodide and allowed to stir at room temperature for 30 min. An additional 6 ml. of methyl iodide was added, and after 30 min. at room temperature, the mixture was refluxed for 4 hr. The solvents were largely removed at reduced pressure; the residue was taken up in benzene, washed with dilute NaOH solution and with water, dried, and concentrated. Distillation of the residue gave 9.3 g. (53%) of the product, b.p. 154–156° (2 mm.), as light yellow viscous oil.

*Anal.* Calcd. for $C_{11}H_9NOS$: C, 65.02; H, 4.46. Found: C, 65.21; H, 4.74.

The 2,4-dinitrophenylhydrazone formed small orange crystals from ethyl acetate, m.p. 195–196°.

*Anal.* Calcd. for $C_{17}H_{13}N_5O_4S$: C, 53.26; H, 3.42. Found: C, 53.04; H, 3.12.

**B. From III.**—A solution of 6.5 g. of III in 60 ml. of warm benzene was added to a solution of 2.9 g. of sodium in 50 ml. of methanol. The mixture was then refluxed for 20 min. To the cooled mixture was added 4.0 ml. of methyl iodide and the resulting mixture was allowed to stir at room temperature for 45 min. An additional 4 ml. of methyl iodide was then added, and after 30 min. 2 ml. of methyl iodide was introduced and the mixture was refluxed for 2.5 hr. The product was isolated as described above; yield 2.4 g. (34%). Unchanged III (1.5 g.) was recovered from the alkaline washings.

(1) W. E. Bachmann, W. Cole, and A. L. Wilds, *J. Am. Chem. Soc.*, **62**, 824 (1940).

(2) W. S. Johnson, J. W. Petersen, and C. D. Gutsche, *ibid.*, **69**, 2942 (1947).

(3) F. Krollpfeiffer and H. Schultze, *Ber.*, **56**, 1821 (1923).