Synthesis of Two New Heterocyclic Ring Systems: Benzo[3,4]cyclohepta[1,2-*d*]-pyrimidines and Benzo[3,4]cyclohepta[2,1-*d*]pyrimidines (1,2)

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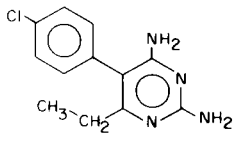
Three 2,4-diamino-10,11-dihydro-9*H*-benzo[3,4]cyclohepta[1,2-*d*]pyrimidines (**6a-6c**) representing the first examples of a new ring system were synthesized from 2-benzosuberones and cyanoguanidine. Similarly, 2,4-diamino-6,7-dihydro-5*H*-benzo[3,4]cyclohepta[2,1-*d*]pyrimidine (**24**) was prepared from 1-benzosuberone. The ultraviolet spectral properties of these compounds were examined with reference to those of the analogs in which the central ring is five- and six-membered.

In previous papers we described the synthesis of several types of condensed 2,4-diaminopyrimidine ring systems related in structure to the small-molecule folic acid antagonist and antimalarial agent pyrimethamine (**1**) (3). These included 2,4-diamino-9*H*-indeno[2,1-*d*]-pyrimidines (**2**) (4), 1,3-diamino-5*H*-[1]benzopyrano(and thiopyrano)[3,4-*d*]-pyrimidines (**3**) (5), 1,3-diamino-5,6-dihydrobenzo[*f*]-quinazolines (**4**) (6), and 1,3-diaminobenzo[*f*]quinazolines (**5**) (7). We would like to report the preparation of the heretofore unknown 2,4-diamino-10,11-dihydro-9*H*-benzo-[3,4]cyclohepta[1,2-*d*]pyrimidine ring system (**6**) *via* the routes shown in Scheme I. The availability of these new compounds provided a further opportunity to study the effect of small changes in molecular geometry upon the biological activity of tricyclic pyrimethamine analogs (8).



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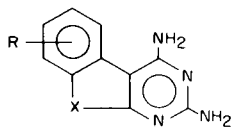


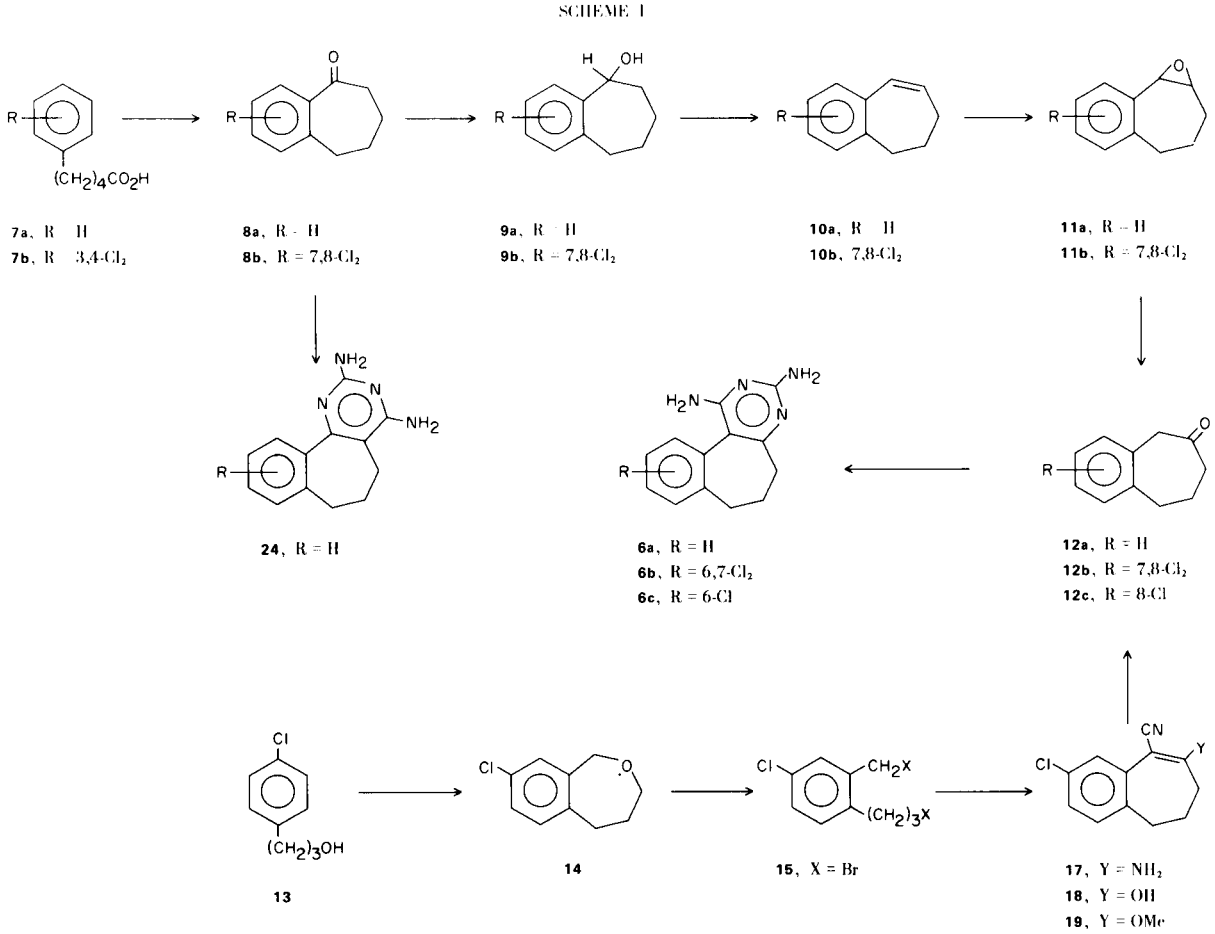
2, X = CH_2
3, X = OCH_2, SCH_2
4, X = CH_2CH_2
5, X = CH=CH
6, X = $CH_2CH_2CH_2$

5-Phenylpentanoic acid (**7a**) was converted into 1-benzosuberone (**8a**) in 80-90% yield on treatment with hot polyphosphoric acid (9), and 5-(3,4-dichlorophenyl)pentanoic acid (**7b**) was transformed into 7,8-dichloro-1-benzosuberone (**8b**) by reaction with thionyl chloride and cyclization of the resultant acid chloride with aluminum chloride (10). The deactivating influence of electron-withdrawing chloro substituents manifested itself noticeably in the latter reaction, which afforded yields not exceeding 55%. Reduction of **8a** and **9b** with lithium aluminum hydride and dehydration of the resultant alcohols **9a** and **9b** with potassium hydrogen sulfate at elevated temperature and reduced pressure, following the method of Huisgen and coworkers (11), led to olefins **10a** and **10b** in approximately 65% overall yield.

The nmr spectrum of olefin **10b** in deuteriochloroform showed the halogen-deshielded aromatic protons as two singlets at τ 2.76 and τ 2.81, the vinyl protons as two unsymmetrical doublets of triplets at τ 3.66 (poorly resolved) and τ 4.10, and the methylene protons as three complex multiplets in the τ 7.0-τ 8.2 region. A comparison spectrum of 1,2-dihydronaphthalene showed the aromatic protons at τ 2.95, the vinyl protons as two doublets of triplets (both sharply resolved) at τ 3.55 (J_{AB} = 10 Hz, J_{AC} = 1.5 Hz) and τ 4.03 (J_{AB} = 10 Hz, J_{BC} = 4 Hz), and the methylene protons as two complex arrays of signals in the τ 7.0-τ 8.0 region. The low degree of resolution observed for the $C_{(1)}$ vinyl proton signal in olefins **10a** and **10b** is consistent with the distorted chair geometry of the seven-membered ring.

Oxidation of **10a** and **10b** with *m*-chloroperbenzoic acid afforded epoxides **11a** and **11b** in up to 75% yield, and further treatment of these with magnesium bromide or boron trifluoride in ether effected rapid and complete isomerization to a mixture of carbonyl compounds (12), chief among which were the desired 2-benzosuberones **12a** and **12b**. Not unexpectedly, these proved to be rather unstable and difficult to purify. For this reason, condensation with cyanoguanidine, under the previously described fusion conditions (6b,13), had to be carried out without purification. The desired products **6a** and **6b** were formed

SCHEME I



in yields (25% and 14% respectively) that were only slightly lower than those of the corresponding 1,3-diamino-5,6-dihydrobenzo[*f*]quinazolines (**4**) from 2-tetralones.

The nmr spectrum of epoxide **11b** in deuteriochloroform showed the aromatic protons as singlets at τ 6.08 (J = 4 Hz), the $C_{(2)}$ epoxide proton as a quartet (with superimposed fine structure) at τ 6.63, and the methylene protons as complex absorption in the τ 7.0-τ 8.5 region. The low-field aromatic singlet at τ 2.39 was assigned to the $C_{(9)}$ proton on the basis of the expected anisotropic influence of the neighboring epoxide ring. Similar and even slightly greater deshielding was noted in the spectrum of ketone **8b**, in which the aromatic protons signals appeared at τ 2.12 and τ 2.62.

Condensation of 3-(*p*-chlorophenyl)-1-propanol (**13**) (14) with formaldehyde and aluminum-chloride-catalyzed cyclization of the resultant *O*-chloromethyl ether (15) afforded the hitherto undescribed 8-chloro-5,6-dihydro-1*H*, 3*H*-2-benzoxepin (**14**). As observed above in connection with the synthesis of **8b**, halogen-substitution in the phenyl ring tended to retard closure of the seven-membered ring, the yield of **14** being only about 40%. The isolated methylene group in **14** was discernible in the nmr spectrum as a singlet at τ 5.48.

Cleavage of the ether ring in **14** by heating with dry hydrogen bromide gas in the absence of solvent furnished dibromide **15** in over 80% yield, and reaction of the latter with sodium cyanide afforded dinitrile **16** with similar ease. Nmr spectra of **15** and **16** showed the isolated benzylic $-CH_2Br$ and $-CH_2CN$ protons as singlets at τ 5.50 and τ 6.28, respectively.

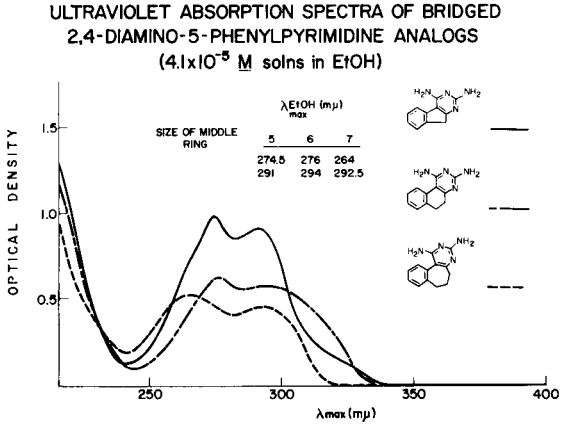


Figure 1

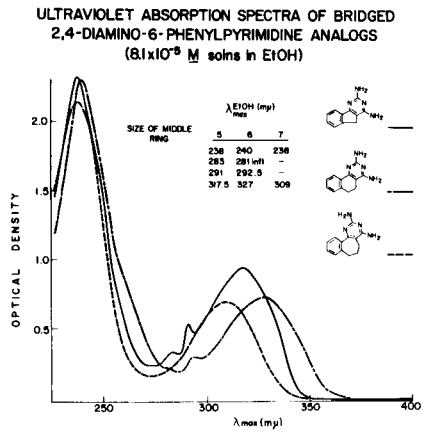
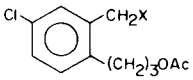
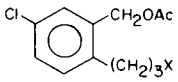


Figure 2

It is of interest to note that the use of glacial acetic acid as a solvent in the cleavage of **14** with hydrogen bromide resulted in extensive acetolysis to a bromo acetate, as evidenced by strong infrared absorption at 1755 cm^{-1} and the appearance in the nmr spectrum of a singlet at τ 8.05. The position of the bromo and acetoxy groups in this product could be assigned on the basis of further reaction with sodium cyanide, which gave a cyano acetate showing methylene absorption at τ 6.28. Inasmuch as this τ value was consistent with a phenylacetonitrile but too high for a benzyl acetate methylene group, the bromo acetate and cyano acetate were formulated as **20** and **21**, and alternative structures **22** and **23** had to be ruled out.



20, X = Br
21, X = CN



22, X = Br
23, X = CN

Thorpe cyclization of dinitrile **16** in the presence of sodium ethoxide led to amino nitrile **17**, but the yield was lower than had been observed earlier in the synthesis of the corresponding five-membered (4) and six-membered (6a) amino nitriles. The ultraviolet absorption spectrum of **17**, containing a maximum at 297 nm similar to that of the smaller-ring homologs, was indicative of the conjugated amino nitrile form. Likewise, the infrared spectrum, with a characteristic set of three peaks in the 3500-3300 cm^{-1} region and a nitrile stretching band at 2210 cm^{-1}, was consistent with the conjugated tautomer.

Selective hydrolysis of the amino group in **17** was achieved in 80% yield by the action of concentrated hydrochloric acid at room temperature. In contrast to the previous findings with smaller-ring homologs (4,6a), seven-membered nitrile **18** proved to be capable of existence as a keto-enol tautomer mixture in solution. The infrared spectrum, when taken in potassium chloride, contained strong OH absorption at 3280 cm^{-1}, a single conjugated nitrile peak at 2230 cm^{-1}, and no carbonyl absorption. In chloroform solution, on the other hand, the OH was reduced in intensity, a second, unconjugated nitrile peak was seen at 2275 cm^{-1}, and a moderately prominent carbonyl peak appeated at 1740 cm^{-1}. A plausible explanation for the incompletely enolic character of **18** is that the conformation of the seven-membered ring is one that does not provide an opportunity for very strong resonance stabilization of the enol form.

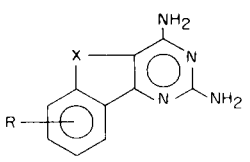
In accord with the foregoing results, attempted formation of enol ether **19** by treatment of **18** with diazomethane led to a mixture of products from which only a small amount of the desired compound could be recovered. Likewise unsuccessful was an attempt to bring about direct methanolysis of **17** with dilute methanolic sulfuric acid; in this instance, only a difficultly separable mixture of **18** and **19** was produced. Accordingly, vigorous hydrolysis with 30-35% methanolic sulfuric acid was carried out in order to effect simultaneous hydrolysis of the amino group and removal of the nitrile group. After separation of some minor byproducts of undetermined structure by column chromatography, a 35-45% yield of 8-chloro-2-benzosuberone (**12c**) was obtained. Like **12a** and **12b**, this compound was a low-melting and somewhat unstable material. The infrared spectrum contained a strong C=O peak at 1710 cm^{-1}, and the nmr spectrum showed the isolated $C_{(1)}$ methylene protons as a singlet at τ 6.43. As with **12a** and **12b**, condensation of this material with cyanoguanidine proceeded satisfactorily under the usual fusion conditions (6b,13), yielding **6c**.

The availability of 1-benzosuberone (**8a**) and 7,8-dichloro-1-benzosuberone (**8b**) during this work offered an opportunity to apply the cyanoguanidine condensation reaction to the synthesis of the hitherto unreported 2,4-diamino-6,7-dihydro-5*H*-benzo[3,4]cyclohepta[2,1-*d*]pyrimidine ring system (**24**), which differs from **6** only in that the ring nitrogens and amino groups are transposed. Unfortunately, however, in marked contrast to the ease of reaction of 1-tetralone (13a), condensation of **8a** with cyanoguanidine proceeded only with great difficulty, giving less than 5% of the desired product (**24**, R = H). Furthermore, repeated efforts to condense cyanoguanidine with **8b** met with complete failure, yielding mainly melamine and other high-melting byproducts of unknown structure. It is apparent from these and previous (13a) results, that yields in the reaction of cyanoguanidine with 1-benzocyclanones tend to vary as a function of ring size, the order ($6 > 5 >> 7$) being in good agreement with such measures of carbonyl group reactivity (16) as the dissociation con-

stant for the cyanohydrin and the rates of semicarbazone formation, perbenzoic acid oxidation, and sodium borohydride reduction, all of which have been explained by Brown and coworkers (17) in terms of the I-strain concept.

As part of our effort to correlate molecular geometry and biological properties in bridged pyrimethamine analogs, a comparative study of the ultraviolet absorption spectra of ring systems **2**, **4**, and **6** (all R = H) was carried out. As can be seen in Figure 1, an increase in the number of carbons in the X-bridge from one to two causes both the low and high wavelength maxima to undergo small red shifts, with a twofold decrease in intensity. This red shift has been said (6b) to come about because the phenyl and pyrimidine rings share a common axis in **4** but not in **2**; despite the greater coplanarity present in the latter ring system, the dominant effect here appears to be the ability of the two π orbitals to assume a coaxial relationship. When the length of the X-bridge is extended to three carbons in **6**, coaxiality is still possible, but the geometric requirements of the seven-membered ring lead to a further loss of coplanarity. This manifests itself in a blue shift, which is especially noticeable in the low wavelength maximum but involves very little decrease in optical density. Russell (19) has called attention to the fact that, of the two characteristic absorption bands in 2,4-diamino-5-phenylpyrimidines, it is the one at lower wavelength whose position is most sensitive to changes in dihedral angle. Our data with **4** and **6** support this view. Furthermore, our finding that there is little difference in optical density between these two ring systems is consistent with the conclusions of various workers (20) that extinction coefficients are determined by transition moments derived from electron distributions in the ground and excited states having no particular relationship to dihedral angle.

In conjunction with our ultraviolet spectral correlation of ring systems **2**, **4**, and **6**, it seemed of interest to also carry out a comparison of the spectra of **24** (R = H), 2,4-diamino-9*H*-indeno[1,2-*d*]pyrimidine (**25**) (13a), and 1,3-diamino-9,10-dihydrobenzo[*h*]quinazoline (**26**) (13a). The data for these compounds is shown in Figure 2. In this instance, it can be seen that the low wavelength maximum is the one that is essentially insensitive to changes in middle-ring size, whereas the high wavelength undergoes an appreciable red shift when the number of atoms in the bridge is increased from one to two, and a blue shift (with some loss of fine structure) when the number of atoms is increased to three. Just as in the isomeric series, the ultraviolet absorption features of these homologous compounds appear to reflect the ability of the phenyl and pyrimidine rings to assume both a coaxial and coplanar relationship.



24, X = $CH_2CH_2CH_2$
25, X = CH_2
26, X = CH_2CH_2

EXPERIMENTAL (21)

5-(3,4-Dichlorophenyl)pentanoic Acid (**7b**).

A. From *o*-Dichlorobenzene.

In a modification of the procedure of Papa and coworkers (22), 4-carbethoxybutyroyl chloride (89 g., 0.5 mole) was allowed to react with *o*-dichlorobenzene (400 ml.) in the presence of anhydrous aluminum chloride (133 g., 1.0 mole) at 80° for 18 hours. After slow addition of ice-water (1500 ml.) and concentrated sulfuric acid (100 ml.), the unreacted *o*-dichlorobenzene was removed by exhaustive steam distillation (23). Extraction with chloroform (750 ml.) afforded 53 g. (41%) of 5-(3,4-dichlorophenyl)-4-oxopentanoic acid as a tan solid, m.p. 137.5-140°. Analytically pure material was obtained after two recrystallizations from ether; m.p. 143-144°.

Anal. Calcd. for $C_{11}H_{10}Cl_2O_3$: C, 50.59; H, 3.86. Found: C, 50.36; H, 3.83.

The foregoing acid (52 g., 0.2 mole) was heated with potassium hydroxide (44 g., 0.78 mole) and 95% hydrazine (14 g., 0.43 mole) in ethylene glycol (450 ml.) under reflux for 1 hour. The condenser was removed until the temperature rose to 150° and refluxing was continued for another 3 hours (alternatively, the temperature could be raised to 190° for 45 minutes). Acidification with ice-water (1500 ml.) and 6 *N* hydrochloric acid (150 ml.) yielded 17 g. (81%) of crude **7b** as a gummy tan solid. Recrystallization from 1:5 carbon tetrachloride/petroleum ether (b.p. 37-52°) gave analytically pure product, m.p. 63-63.5°.

Anal. Calcd. for $C_{11}H_{12}Cl_2O_2$: C, 53.45; H, 4.89. Found: C, 53.38; H, 4.97.

B. From 3,4-Dichlorobenzaldehyde.

Condensation of 3,4-dichlorobenzaldehyde (68 g., 0.39 mole) with diethyl ethylidenemalonate (108 g., 0.58 mole) was carried out as described by Gardner and coworkers (22), except that 1) ice-cooling of the initially exothermic reaction was necessary and 2) the total reaction time could be shortened from 24-48 hours to 1-2 hours. Crystallization from 50% ethanol gave 3,4-dichlorocinnamylidenemalonic acid (66 g., 60%) as an intensely yellow powder, m.p. 194-195.5° (gas evolution); λ max (ethanol) (nm) 240 (ϵ 9330), 328 (ϵ 29,370).

Anal. Calcd. for $C_{12}H_8Cl_2O_4$: C, 50.20; H, 2.81; Cl, 24.70. Found: C, 50.22; H, 2.87; Cl, 24.66.

Catalytic hydrogenation of the foregoing diacid (10 g., 0.035 mole) in absolute ethanol (100 ml.) in the presence of platinum oxide (0.25 g.) was carried out in a Parr low-pressure apparatus until the theoretical uptake of hydrogen was achieved (*ca.* 64 hours), giving 3-(3,4-dichlorophenyl)propylmalonic acid as an oil. Unexpectedly, heating of this material in boiling pyridine (100 ml.) for 2 days failed to bring about complete decarboxylation. Examination of nmr spectra disclosed that this resulted from the fact that a significant amount of esterification had taken place during reduction. Accordingly, the crude mixture recovered after pyridine treatment was subjected to the action of 50% sulfuric acid (100

ml.) under reflux for 2 hours, whereupon hydrolysis and decarboxylation proceeded to completion. Purification by reprecipitation from alkali afforded 6.5 g. (77%) of **7b** as a light-tan solid, m.p. 63-65°. The infrared spectrum was identical with that of the product obtained from *o*-dichlorobenzene *via* Procedure A.

7,8-Dichloro-1-benzosuberone (**8b**).

A mixture of **7b** (17 g., 0.069 mole) and thionyl chloride (30 g., 0.25 mole) was refluxed for 30 minutes on the steam bath. After evaporation of the unreacted thionyl chloride under reduced pressure, with repeated addition of dry benzene to assist in the removal of the last traces of the reagent, the crude acid chloride was dissolved in carbon disulfide (400 ml.) and the solution was added very slowly (4 hours) to a rapidly stirred suspension of aluminum chloride (11 g., 0.083 mole) in carbon disulfide (400 ml.). After another 17 hours at room temperature, hydrolysis with ice-water (300 ml.) and concentrated hydrochloric acid (10 ml.) and extraction with chloroform (3 x 100 ml.) gave a light-amber oil which solidified on trituration with petroleum ether (b.p. 30-60°); yield 8.5 g. (54%). Analytically pure material was obtained by recrystallization from ligroin (b.p. 60-90°); m.p. 70-71°; ν max (potassium chloride) 3000, 1670 (C=O) cm^{-1}.

Anal. Calcd. for $C_{11}H_{10}Cl_2O$: C, 57.66; H, 4.41; Cl, 30.95. Found: C, 57.60; H, 4.41; Cl, 30.67.

2,3-Dichloro-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-9-ol (**9b**).

A solution of **8b** (11.5 g., 0.05 mole) in ether was added dropwise (30 minutes) to a slurry of lithium aluminum hydride (0.48 g., 0.012 mole) in ether (50 ml.). After 3 hours of refluxing and overnight stirring at room temperature, hydrolysis and evaporation of the ether layer left 12 g. of crude **9b**, m.p. 111-117°. One recrystallization from *n*-hexane (charcoal) yielded 8.9 g. (77%) of analytically pure material; m.p. 120-123°; ν max (potassium chloride) 3400 (OH), 3000, 2990 cm^{-1}.

Anal. Calcd. for $C_{11}H_{12}Cl_2O$: C, 57.16; H, 5.23; Cl, 30.68. Found: C, 57.18; H, 5.12; Cl, 30.58.

2,3-Dichloro-6,7-dihydro-5*H*-benzocycloheptene (**10b**).

A mixture of **9b** (7.4 g., 0.03 mole) and powdered potassium bisulfate (15 g., 0.1 mole) was heated under reduced pressure at 175-185° (bath temp) in a microdistillation apparatus to give 5 g. (83%) of colorless liquid, b.p. 130-136°/0.3-0.4 mm; ν max (potassium chloride) 3000, 2900, 1620 cm^{-1}.

Anal. Calcd. for $C_{11}H_{10}Cl_2$: C, 61.99; H, 4.73; Cl, 33.27. Found: C, 61.82; H, 4.71; Cl, 33.57.

2,3-Dichloro-8,9-epoxy-6,7,8,9-tetrahydro-5*H*-benzocycloheptene (**11b**).

Epoxidation of **10b** (6.4 g., 0.03 mole) with *m*-chloroperbenzoic acid (5.7 g., 0.033 mole) in chloroform (100 ml.) at 0° for 5 days afforded 5.1 g. (74%) of colorless solid, m.p. 53.5-55°, after recrystallization from petroleum ether (b.p. 30-60°).

Anal. Calcd. for $C_{11}H_{10}Cl_2O$: C, 57.66; H, 4.39; Cl, 30.95. Found: C, 57.63; H, 4.42; Cl, 31.24.

7,8-Dichloro-2-benzosuberone (**12b**).

The foregoing epoxide (5.1 g., 0.022 mole) in ether (200 ml.) was treated with boron trifluoride etherate (3.2 ml.) at room temperature for 30 minutes. After removal of a white precipitate, the filtrate was washed with water (4 x 50 ml.), dried, and evaporated to a colorless oil; yield 4.9 g. (96%). The analytical sample was prepared by chromatography on silica gel, with benzene as the eluting solvent.

Anal. Calcd. for $C_{11}H_{10}Cl_2O$: C, 57.66; H, 4.39. Found: C, 58.12; H, 4.56.

8-Chloro-5,6-dihydro-1*H*,3*H*-2-benzoxepin (**14**).

Dry hydrogen chloride gas was bubbled through a rapidly stirred mixture of 3-(*p*-chlorophenyl)-1-propanol (**13**) (14) (157 g., 0.92 mole) and paraformaldehyde (30 g., 1.0 mole) at < 25° for 3.5 hours. The crude product was taken up in carbon disulfide (600 ml.) and dried by treatment with a generous amount of powdered anhydrous calcium chloride. One-half of this dried solution was added dropwise to a stirred suspension of anhydrous aluminum chloride (61 g., 0.46 mole) in carbon disulfide (600 ml.) cooled by means of a Dry Ice-acetone bath. Addition was effected at such a rate as to maintain the internal temperature between -4° and -2°. The cooling bath was removed when the addition was complete, and stirring was continued for 15 minutes, during which the temperature rose to a maximum of 14°. The mixture was then poured into crushed ice, and the organic phase was separated, diluted with dichloromethane to reduce emulsification, washed with 5% sodium bicarbonate and water, dried, and evaporated under reduced pressure. Vacuum distillation of the combined products from 4 identical cyclization runs through a Vigreux column gave the following fractions: 1) 3 g., b.p. 40-48°/0.005 mm; 2) 127 g. (41% yield), b.p. 75-80°/0.05-0.005 mm; 3) 6.5 g., b.p. 87-110°/0.02 mm. A redistilled center cut, b.p. 81°/0.1 mm, was microanalyzed.

Anal. Calcd. for $C_{10}H_{11}ClO$: C, 65.75; H, 6.07. Found: C, 65.44; H, 6.19.

2-(3-Bromopropyl)-5-chlorobenzyl Bromide (**15**).

Anhydrous hydrogen bromide gas was bubbled through **14** (49 g., 0.27 mole) at 150° for 6 hours. The cooled mixture was taken up in ether (500 ml.), and the latter solution was washed with saturated sodium chloride (6 x 100 ml.), decolorized with charcoal, dried, and evaporated to an amber oil which solidified on standing. Recrystallization from petroleum ether (b.p. 30-60°) gave analytically pure material, m.p. 52-54°.

Anal. Calcd. for $C_{10}H_{11}Br_2Cl$: C, 36.79; H, 3.39. Found: C, 36.73; H, 3.40.

2-(3-Cyanopropyl)-5-chlorophenylacetonitrile (**16**).

A solution of **15** (71 g., 0.22 mole) in DMSO (220 ml.) was added slowly under a nitrogen atmosphere to a stirred suspension of sodium cyanide (26 g., 0.53 mole) in DMSO (280 ml.). The reaction was exothermic, cooling by means of an ice-bath being necessary to maintain the temperature at 40-50°. After 4 days at room temperature, the mixture was poured into water (2.5 l.) and the product was extracted with dichloromethane (1.8 l.). Solvent evaporation left 46 g. (97%) of brown oil which solidified on standing. Three recrystallizations from carbon tetrachloride (charcoal) gave analytically pure material, m.p. 58-59.5°; ν max (potassium chloride) 2980, 2900, 2270 (C≡N cm^{-1}.

Anal. Calcd. for $C_{12}H_{11}ClN_2$: C, 65.90; H, 5.07; N, 12.80. Found: C, 66.08; H, 5.01; N, 12.83.

8-Amino-2-chloro-9-cyano-6,7-dihydro-5*H*-benzocycloheptene (**17**).

A solution of metallic sodium (3.6 g., 0.16 g.-atom) in absolute ethanol (290 ml.) was added dropwise under a nitrogen atmosphere to a rapidly stirred solution of **16** (34 g., 0.16 mole) in boiling ethanol (250 ml.). Stirring was continued under reflux for 2 hours and at room temperature overnight. Dilution with water (1 l.), acidification to *p*H 5 with concentrated hydrochloric acid, and extraction with chloroform (400 ml.) yielded an amber-colored gum which solidified on trituration with cold benzene; yield 6.1 g. (18%); m.p. 159-162°. Recrystallization from carbon tetrachloride (charcoal) gave colorless flakes, m.p. 159-161°; ν max (potassium chloride) 3510, 3450, 2980, 2900, 2190 (conjugated (C≡N), 1660 cm^{-1}.

Anal. Calcd. for $C_{12}H_{11}ClN_2$: C, 65.90; H, 5.07; N, 12.80. Found: C, 66.01; H, 5.04; N, 12.68.

2-Chloro-9-cyano-6,7-dihydro-5*H*-benzocyclohepten-9-ol (**18**).

A mixture of **17** (2.3 g., 0.011 mole) and concentrated hydrochloric acid (20 ml.) was stirred at room temperature for 64.5 hours, then poured into ice and basified to *p*H 8 with 20% sodium hydroxide (60 ml.). The sodium salt which precipitated out was collected, re-suspended in water, and neutralized (to *p*H 6) with 0.1 *N* hydrochloric acid (40 ml.). Recrystallization of the resultant **18** (1.8 g., 78%) from ether-petroleum ether (b.p. 30-60°) (charcoal) afforded analytically pure shiny white plates, m.p. 152-153°; ν max (potassium chloride) 3280, 3000, 2220 (enolic C≡N), 1630 cm^{-1}; ν max (chloroform) 3600, 3280, 3000, 2920, 2270 (unconjugated C≡N), 2220 (enolic C≡N), 1740 (C≡N), 1740 (C=O), 1600 cm^{-1}.

Anal. Calcd. for $C_{12}H_{10}ClNO$: C, 65.61; H, 4.58; N, 6.37. Found: C, 65.77; H, 4.49; N, 6.38.

8-Chloro-2-benzosuberone (**12c**).

Concentrated sulfuric acid (30 ml.) was added dropwise with stirring to a cold solution of **17** (6.0 g., 0.027 mole) in methanol (120 ml.), and the mixture was heated under reflux for 6 hours, another 18 ml. of acid being added in 1-2 ml. portion every 30 minutes. Overnight stirring at room temperature, dilution with water (850 ml.), extraction with ether (750 ml.), drying, and solvent evaporation left an oil (5.4 g.). Purification was accomplished by chromatography on a silica gel column, which was eluted successively with 1:4 benzene-petroleum ether (b.p. 30-60°) (5 x 50 ml.), 1:1 benzene-petroleum ether (5 x 50 ml.), and pure benzene (9 x 50 ml.). Evaporation of fractions 12-17 left an oil (2.5 g.) which solidified on standing; m.p. 47.5-51°; ν max (carbon tetrachloride) 2980, 2900, 1720 (C=O) cm^{-1}.

Anal. Calcd. for $C_{11}H_{11}ClO$: C, 67.87; H, 5.69; Cl, 18.21. Found: C, 67.69; H, 5.66; Cl, 18.03.

2,4-Diamino-10,11-dihydro-9*H*-benzo[3,4]cyclohepta[1,2-*d*]pyrimidine (**6a**).

A mixture of **12a** (11,12) (4.5 g., 0.028 mole) and cyanoguanidine (2.6 g., 0.031 mole) was heated in an open pear-shaped flask at 180-210° (internal temperature) for 30 minutes. The cooled solid was pulverized in a mortar, washed with ether and recrystallized from 95% ethanol (charcoal); yield 1.2 g. (19%); m.p. 241-246°. Further recrystallization yielded almost colorless microcrystals; m.p. 253-254.5°; ν max (potassium chloride) 3400, 3300, 3180, 2900, 1640, 1565 cm^{-1}; λ max (ethanol) (nm) 265 (ϵ 14,070), 294 (ϵ 12,190); λ max (*p*H 1) (nm) 252 (ϵ 16,570), 275 infl (ϵ 8320).

Anal. Calcd. for $C_{13}H_{14}N_4$: C, 69.00; H, 6.23; N, 24.76. Found: C, 69.02; H, 6.23; N, 24.74.

2,4-Diamino-6,7-dichloro-10,11-dihydro-9*H*-benzo[3,4]cyclohepta[1,2-*d*]pyrimidine (**6b**).

Condensation of **12b** (1.9 g., 0.0083 mole) with cyanoguanidine (0.76 g., 0.0091 mole) as described in the preceding experiment gave 0.35 g. (14%); m.p. 307-310° dec. Two recrystallizations from absolute ethanol yielded analytically pure material, m.p. 319-321° dec; ν max (potassium chloride) 3510, 3280, 3030, 1635, 1585 cm^{-1}; λ max (ethanol), (nm) 272 (ϵ 14,040), 300 (ϵ 12,680); λ max (*p*H 1) (nm) 259 (ϵ 16,220), 282 infl (ϵ 9680), 292 infl (ϵ 8050).

Anal. Calcd. for $C_{13}H_{12}Cl_2N_4$: C, 52.89; H, 4.09; N, 18.98. Found: C, 52.83; H, 4.32; N, 18.97.

2,4-Diamino-6-chloro-10,11-dihydro-9*H*-benzo[3,4]cyclohepta-[1,2-*d*]pyrimidine (**6c**).

Condensation of **12c** (2.8 g., 0.014 mole) with cyanoguanidine (1.3 g., 0.016 mole) as described for the synthesis of **6a** yielded 1.1 g. (28%); m.p. 278-284°. Additional recrystallization from absolute ethanol (charcoal) gave the analytical specimen, m.p. 281-283.5°; ν max (potassium chloride) 3570, 3450, 3230, 3030, 1625, 1575 cm^{-1}; λ max (ethanol) (nm) 272 (ϵ 12,730), 296.5 (ϵ 13,350); λ max (*p*H 1) (nm) 254 (ϵ 15,010), 282.5 (ϵ 8710).

Anal. Calcd. for $C_{13}H_{13}ClN_4$: C, 59.88; H, 5.02; Cl, 13.59; N, 21.48. Found: C, 59.87; H, 3.00; Cl, 13.44; N, 21.41.

2,4-Diamino-6,7-dihydro-5*H*-benzo[3,4]cyclohepta[2,1-*d*]pyrimidine (**24**).

A mixture of **8a** (10 g., 0.062 mole) and cyanoguanidine (7.9 g., 0.094 mole) was heated at 180-220° (internal temperature) for 1 hour as described for the synthesis of **6a**. The cooled melt was pulverized and extracted overnight with 2-propanol (1 l.) in a Soxhlet apparatus. The insoluble residue (5.1 g.) contained melamine and other high-melting byproducts. Evaporation of the 2-propanol under reduced pressure gave 3.3 g. of solid, m.p. 215-217°, consisting of some **24**, unreacted cyanoguanidine, and melamine. Trituration of this mixture with cold ethanol (300 ml.) left the melamine (0.9 g.) undissolved, leaving on evaporation 2.3 g. of **24** and a large amount of cyanoguanidine. A third trituration with cold 2-propanol (250 ml.), removal of the insoluble residue (0.3 g.), and evaporation left 1.7 g. of **24** still contaminated with a substantial amount of cyanoguanidine. This material was heated for 10 minutes with dilute ammonium hydroxide (100 ml.) in order to dissolve the cyanoguanidine. Filtration of the insoluble portion (1.1 g. after drying) and recrystallization from ethanol (charcoal) yielded 0.5 g. (3.5%) of product, m.p. 210.5-213°. Analytically pure **24** was obtained by vacuum sublimation at 0.005 mm pressure, with very slow heating (25) of the sample from room temperature to 150°; m.p. 226.5-228°; ν max (potassium chloride) 3510, 3320, 3180, 2940, 1640, 1615, 1545 cm^{-1}; λ max (ethanol) (nm) 237 (ϵ 21,350), 307 (ϵ 6970); λ max (*p*H 1) (nm) 235 (ϵ 14,740), 297 (ϵ 10,611).

Anal. Calcd. for $C_{13}H_{14}N_4$: C, 69.00; H, 6.23; N, 24.76. Found: C, 68.94; H, 6.30; N, 24.85.

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(2) Presented in part before the Division of Medicinal Chemistry at the 2nd Northeast Regional Meeting of the American Chemical Society, Providence, R. I., October 20, 1970, and the 161st National Meeting of the American Chemical Society, Los Angeles, Calif., March 31, 1971.

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