by recrystallization from the same solvent systems had mp 150–152°; ν_{max}^{KBr} 3265 (NH), 1690 (amide I), 1665 (C=O), 1615 and 1590 (C=C), and 1530 cm^{-1} (amide II); $\lambda_{max}^{CH_3OH}$ 239 mμ (ε × 10^{-3} = 17.8), 278 (18.6), and 455 (3.7).

The 4-(3-*N*,*N*-diethylaminopropylamino)-3-acylamino-1,2-naphthoquinones listed in Table I were synthesized by an analogous procedure.

1-(3′-*N*,*N*-Diethylaminopropyl)-2-pentylnaphth[1,2-*d*]imidazole-4,5-dione (IVb).—A solution of 2.51 g, 6.1 mmol, of IIIb in 200 ml of AcOH was refluxed for 0.5 hr. It was concentrated by freeze-drying and the remaining residue was chromatographed on 400 g of Al_2O_3 using $CHCl_3$ as the eluent. A red band was collected. Removal of the $CHCl_3$ on a rotary evaporator followed by recrystallization of the remaining red crystals from EtOAc gave 1.69 g (72%) of IVb, mp 138–141°. The analytical sample prepared by recrystallization from EtOAc had mp 140–142°, ν_{max}^{KBr} 1670 cm^{-1} (C=O); λ_{max}^{MeOH} 261 mμ (ε × 10^{-3} 22.6), 269 (22.2), and 449 (1.4); $\lambda_s^{CH_3OH}$ 253 (20.2); $\lambda_{max}^{0.1\ N\ HCl}$ 254 (24.0); λ_{max}^{pH7} 261 (22.8) and 268 (21.8); λ_s^{pH7} 253 (19.6); $\lambda_{max}^{0.1\ N\ NaOH}$ 240 (17.9) and 260 (14.6); $\lambda_s^{0.1\ N\ NaOH}$ 267 (13.1).

The 1-(3′-*N*,*N*-diethylaminopropyl)-2-alkylnaphth[1,2-*d*]imidazole-4,5-diones listed in Table II were synthesized by an analogous procedure.

Acknowledgment.—We thank Dr. Monroe E. Wall, Director of this laboratory, for his kind encouragement and support of this work.

Analogs of Steroid Hormones. III. Benz[*e*]indene Derivatives[1,2]

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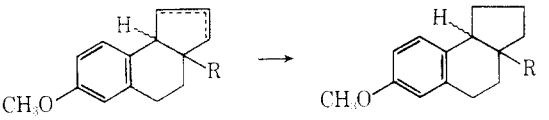
In view of the reported antiandrogenic activity of a 7-acetyl-2(3H)-phenanthrene derivative,[3] we became interested in preparing benz[*e*]indene analogs for purposes of comparison. We were also interested in developing methods for preparing compounds having angular carboalkoxy and carbinol groups. Starting with 3,4-dihydro-6-methoxy-1(2H)-naphthalenone (**2**), suitably substituted benz[*e*]inden-2-one derivatives were first prepared using Scheme I. Alkylation of the starting ketone with propargyl bromide followed by hydration of the product alkyne appeared to be the most convenient approach for the introduction of a propanone side chain. The method has been used by Islam,[4] Dauben,[5] and coworkers, but only on β-keto esters using alkoxide catalysts. We also wished to use the method on ketones such as **4**, which require more basic conditions for alkylation.

Catalytic hydrogenation of **9** and **10** produced mixtures from which both *cis* and *trans* isomers could be isolated and compared. All attempts to obtain both isomers of **11** from **8**, however, were unsuccessful, although five different methods involving catalytic and chemical were used, including one reduction in which the double bond was shifted to the *endo* position.[6]

These hydrogenation results are intermediate between those of simple hydrindenones and 16-keto steroid analogs. Augustine[7] found that the former formed only *cis* isomers even when an angular carbomethoxy group was present. Wilds[8] and ourselves[9] have found both *cis* and *trans* isomers formed from the hydrogenation of Δ^{14}-16-keto steroids, even when no angular group was present. Augustine[10] proposed a multistep process in which the catalyst–substrate complex is less hindered in the *cis* configuration. Wilds attributed some of his results to steric inhibition of adsorption on the catalyst by the angular group, thus resulting in the formation of *trans* isomers. This could explain the results from the hydrogenation of **9** and **10**, but the failure to obtain any *trans* isomer of **11** by any of the above methods could be explained by thermodynamic control of the reduction to give the more stable *cis* isomer with the hydrogenations occurring by some multistep process.

In an attempt to change the isomer ratios obtained, the hydroborations of **8** and **9** were studied. The boron residues were removed by acetolysis to produce mixtures of the alkenes, **14** and **15**. It proved impossible



14, R = H
15, R = CH$_3$

16, R = H
17, R = CH$_3$

to remove B without loss of the O functions. Analysis of **14** and **15** by glpc showed that all four possible isomers were present in substantial amounts in each case. Analysis showed that **16** contained about equal amounts of the *cis* and *trans* isomers, while **17** was 70% *trans*. Conversion of **11** into **16** produced a single isomer, corresponding to the faster moving isomer on glpc, and thus may be assigned the *cis* configuration.

The *cis* and *trans* isomers of **12** and **13** were distinguished by the following method. Since the *trans* isomers are more highly strained than the *cis*, the carbonyl stretch bands in the ir spectra should have the higher frequency.[11] The actual frequencies were 1747 and 1741 cm^{-1} for the presumed *trans* isomers and 1742 and 1737 cm^{-1} for the *cis* isomers, respectively. The half-height width of the angular methyl peak in the nmr spectrum of the presumed *trans* isomer of **12** was also greater than the *cis* by 0.2 cps.[12,13] The configura-

(1) Supported, in part, by Grant CA-05077, National Cancer Institute, National Institutes of Health.

(2) For the previous paper of this series, see R. E. Juday, L. Cubbage, J. Mazur, and B. Bukwa, *J. Med. Chem.*, **11**, 872 (1968).

(3) L. O. Randall and J. J. Selitto, *Endocrinology*, **62**, 689 (1958).

(4) A. M. Islam and R. A. Raphael, *J. Chem. Soc.*, 4086 (1952).

(5) W. G. Dauben, J. W. McFarland, and J. B. Rogan, *J. Org. Chem.*, **26**, 297 (1961).

(6) K. E. Fahrenholtz, A. Compaggi, M. Lurie, M. W. Goldberg, and R. W. Kierstead, *J. Med. Chem.*, **9**, 304 (1966). This technique, used on the phenanthrene analog of **8**, gave the *trans* isomer exclusively.

(7) R. L. Augustine and A. D. Broom, *J. Org. Chem.*, **25**, 802 (1960).

(8) A. L. Wilds, R. Zeitschel, R. Sutton, and J. Johnson, Jr., *ibid.*, **19**, 255 (1954).

(9) R. E. Juday and Bonnie Bukwa, unpublished results.

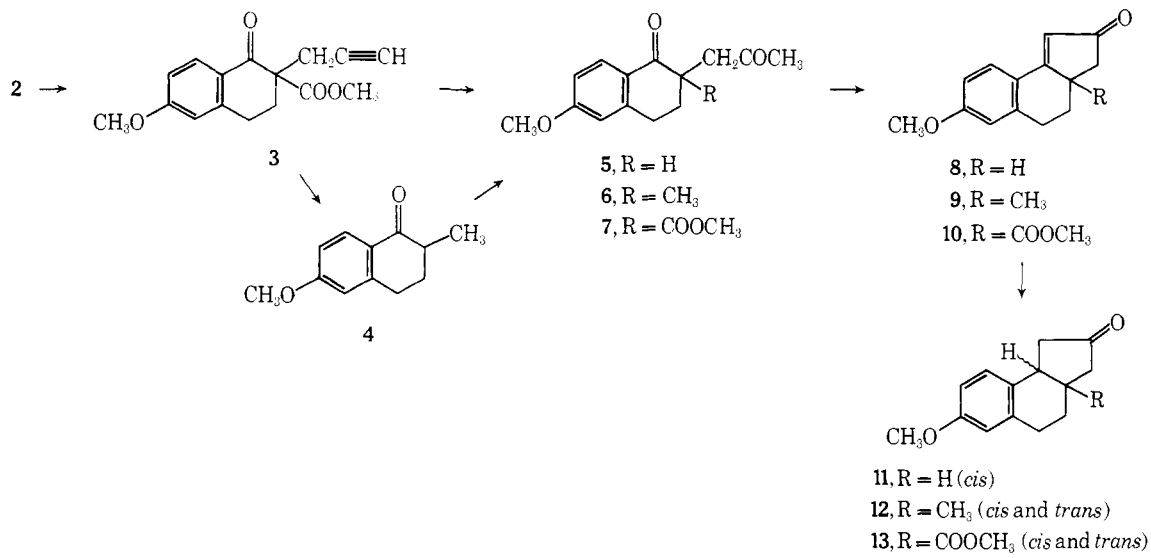
(10) For more complete discussion of the stereochemistry of the reduction of cyclic ketones, see: (a) R. L. Augustine, "Catalytic Hydrogenation," Marcel Dekker, Inc., New York, N. Y., 1965, pp 61–62; (b) R. L. Augustine and J. Van Peppen, *Ann. N. Y. Acad. Sci.*, **158**, 482 (1969); (c) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, Inc., New York, N. Y., 1965, pp 16–22.

(11) N. B. Colthup, L. H. Daly, and S. E. Wilberly, "Introduction to Infrared and Raman Spectroscopy," Academic Press, New York, N. Y., 1964, pp 239–241.

(12) M. Robinson, *Tetrahedron Lett.*, 1685 (1965).

(13) K. Williamson, T. Howell, and T. Spencer, *J. Amer. Chem. Soc.*, **88**, 325 (1966).

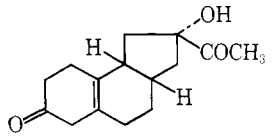
SCHEME I



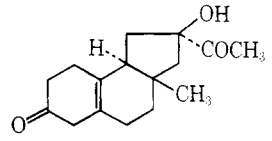
tion of the *trans* isomer of **13** was further confirmed by converting it into the *trans* isomer of **12** by an unambiguous method.

The steric results of the B_2H_6 reductions may be explained by the assumption that the reactions are kinetically controlled and that there is little difference in activation energy between the two possible modes of addition, even when an angular methyl group is present.

The compounds bioassayed, **22** and **23**, were prepared from **8** and **9** by conventional methods.



22



23

Single isomers of **22** and **23** were obtained. They would be expected to have the indicated configurations if addition of HC≡CMgBr occurred on the less hindered side of the molecules.

Neither **22** nor **23** showed significant antiandrogenic or antiuterotropic activity.[2]

Experimental Section[14]

Methyl 1,2,3,4-Tetrahydro-6-methoxy-1-oxo-2-(2-propynyl)-2-naphthalenecarboxylate (3).—A mixture of **2** (30.0 g), NaH[15] (4.6 g), and Me_2CO_3 (18.0 g) in DMAC (225 ml) was stirred at room temperature (Ar atm) until H_2 evolution had almost stopped. The reaction mixture was then cooled to 0° and a solution of propargyl bromide (30 g) in 15 ml of dioxane added keeping the temperature below 5°. The mixture was stirred 30 min at room temperature, cooled, and hydrolyzed. The precipitate was recrystallized (MeOH) to give 42.0 g (91%) of **3**, mp 111–113°. *Anal.* ($C_{16}H_{16}O_4$) C, H.

Methyl 2-Acetonyl-1,2,3,4-tetrahydro-6-methoxy-1-oxo-naphthalenecarboxylate (7).—Compound **3** (42 g) was dissolved in AcOH (150 ml), and cooled to room temperature. Formic acid (88%, 150 ml) and H_2O (10 ml) were added and the mixture was stirred at room temperature while a 5% solution of $Hg(OAc)_2$ was added dropwise until an exothermic reaction set in. The mixture was stirred 2 hr at room temperature, and diluted (H_2O). The precipitate was collected, dried, and recrystallized from MeOH to give 39.5 g (89%) of **7**, mp 110–111°. *Anal.* ($C_{16}H_{18}O_5$) C, H.

2-Acetonyl-3,4-dihydro-6-methoxy-1(2H)-naphthalenone (5).—Compound **7** (27.0 g) was added to a solution of KOH (22.0 g) in H_2O (30 ml) and EtOH (90 ml) and the mixture stirred at room temperature (Ar atm) until the solution remained clear when diluted with H_2O (about 30 min). The product was recrystallized from MeOH to give 18.5 g (86%) of **5**, mp 95–97° (**18**). *Anal.* ($C_{14}H_{16}O_3$) C, H.

3,4-Dihydro-6-methoxy-2-methyl-1(2H)-naphthalenone (4).—The methods used to prepare **3** and **5** were followed, using MeI instead of propargyl bromide in the alkylation step. Starting with **2** (20 g), a yield of 16 g of **4** was obtained, bp 105° (0.05 mm), lit.[16] 114° (0.1 mm).

3,4-Dihydro-6-methoxy-2-methyl-2-(2-propynyl)-1(2H)-naphthalenone (24).—A mixture of **4** (16.0 g), propargyl bromide (13.0 g), and NaH (2.3 g) suspended in diglyme (100 ml) was stirred at room temperature (Ar atm) for 12 hr. After work-up, the residue was distilled *in vacuo* to give 17.6 g (92%) of **24**, bp 127° (0.05 mm). *Anal.* ($C_{15}H_{16}O_2$) C, H.

2-Acetonyl-3,4-dihydro-6-methoxy-2-methyl-1(2H)-naphthalenone (6).—The procedure used to prepare **7** was followed. Starting with **30** (17.6 g), a yield of 18.2 g (96%) of **6** was obtained, bp 137° (0.05 mm). *Anal.* ($C_{15}H_{18}O_3$) C, H.

3,3a,4,5-Tetrahydro-7-methoxy-2H-benz[*e*]inden-2-one (8).—A mixture of **5** (15.5 g), NaH (1.9 g), and dry toluene (180 ml) was heated rapidly to boiling, with stirring, and was refluxed (Ar atm) for about 3 min, or until the evolution of H_2 slowed. The mixture was then cooled rapidly to 5° and hydrolyzed with ice and dilute AcOH. The crude product was vacuum distilled and recrystallized from MeOH to give 9.1 g (65%) of **8**, mp 136–138°. *Anal.* ($C_{14}H_{14}O_2$) C, H.

3,3a,4,5-Tetrahydro-7-methoxy-3a-methyl-2H-benz[*e*]inden-2-one (9).—The procedure used to prepare **8** was followed. Starting with 18.2 g of **6**, NaH (2.1 g), and toluene (150 ml) a yield of 12.0 g (60%) of **9** was obtained, mp 94–95°. *Anal.* ($C_{15}H_{16}O_2$) C, H.

Methyl 3,3a,4,5-Tetrahydro-7-methoxy-2-oxo-2H-benz[*e*]-inden-3a-carboxylate (10).—The procedure used to make **8** was followed, except that *N*-methylpyrrolidone or DMAC was added when the reaction mixture reached reflux temperature. Starting with **7** (5.0 g), NaH (0.5 g), and 50 ml of toluene, and adding 1.0 ml of *N*-methylpyrrolidone (or 1.5 ml DMAC) after the mixture started to reflux, a yield of 2.4 g (51%) of **10** was obtained, mp 177–179°. *Anal.* ($C_{16}H_{16}O_4$) C, H.

***cis*-1,3,3a,4,5,9b-Hexahydro-7-methoxy-2H-benz[*e*]inden-2-one (11). 1. Palladium–Charcoal[17] Hydrogenations. A. In Toluene.**—A mixture of 0.5 g of 5% Pd–C catalyst in 25 ml of toluene was boiled to remove H_2O, and then cooled. Compound

(14) All melting points are corrected. Ir spectra were obtained on a Beckman IR7 spectrophotometer. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. Nmr spectra were obtained on a Varian HA60 spectrophotometer. Spectral results agreed with the suggested structures routine.

(15) The NaH used throughout was a 53% suspension in mineral oil. Prior to use it was washed with cyclohexane. The amounts listed are on a dry weight basis.

(16) E. Buchta, M. Klisch, S. Maier, and H. Baxer, *Ann. Chem.*, **576**, 7 (1952).

(17) Catalyst from Englehard Industries.

8 (1.0 g) was added and the mixture hydrogenated at room temperature and at atmospheric pressure until the H_2 uptake stopped. Approximately 1 mol was absorbed. The product was recovered and recrystallized in MeOH to give 0.92 g of product, mp 68–69°. Glpc analysis of the product showed that a single isomer was present. *Anal.* ($C_{14}H_{16}O_2$) C, H.

B. In Alcohol.—When the hydrogenation was carried out in EtOH, H_2 uptake stopped after about 1.5 mol of H_2 had been absorbed. The product contained about equal amounts of alcohol and saturated ketone and had to be oxidized using the method outlined below.

2. Raney Ni[18] Hydrogenations.—To a solution of 15.0 g of **8** in 100 ml of dry dioxane was added 6.0 g of moist catalyst and the mixture was stirred, at room temperature and 1 atm of H_2, until gas uptake stopped after the absorption of about 2 mol. The carbinol was recovered and oxidized to **11** using the Sarett[19] reagent. The product (overall yield 80%) was identical with that obtained in part **1a**.

3. Li–NH_3 Reduction.—A solution of **8** (2.0 g) in THF (25 ml) was added to a solution of Li (0.3 g) in liquid NH_3 (100 ml) at −35°. After stirring at −35° for 10 min, H_2O was added, and the NH_3 evaporated. A yield of 1.8 g of **11**, identical with that obtained by hydrogenation, was obtained.

4. Li–NH_3 Reduction of the Ketal Derivative.—Compound **8** was converted into 2,2-ethylenedioxy-2,3,4,5-tetrahydro-7-methoxy-1*H*-benz[*e*]indene by the procedure used to prepare **25**. Starting with 10.5 g of **8**, and refluxing the reaction mixture 24 hr, a yield of 9.5 g (75%) of the ketal was obtained, mp 86–88°. *Anal.* ($C_{16}H_{18}O_3$) C, H. The ketal was reduced using the method outlined above in part 3, except that morpholine was used as solvent instead of THF. The crude reduction product was hydrolyzed with 88% formic acid to give a product identical with that obtained by hydrogenation of **8**.

1,3,4,5-Tetrahydro-7-methoxy-2H-benz[*e*]inden-2-one (28). A sample of **2** (0.4 g) was hydrolyzed by stirring in 88% formic acid for 30 min at room temperature. The product was recovered by dilution and solvent extraction to give 0.3 g (93%) of the product, mp 73–75°. The C=O in the ir spectra was at 1750 cm^{-1}, confirming that the double bond was in the *endo* position. *Anal.* ($C_{14}H_{14}O_2$) C, H.

***cis*- and *trans*-1,3,3a,4,5,9b-Hexahydro-7-methoxy-3a-methyl-2H-benz[*e*]inden-2-one (12).**—Compound **9** was hydrogenated using the procedure outlined for **8** in part 1A. The product was obtained in almost quantitative yield. Glpc of the crude product showed that it contained two isomers. The slower moving isomer was assigned the *trans* configuration on the basis of its ir and nmr spectra (*vide supra*). The *trans* isomer, when separated and recrystallized from MeOH, melted at 78–80°. *Anal.* ($C_{15}H_{18}O_2$) C, H.

The mother liquors from the separation of the *trans* isomer were evaporated and distilled at 145–150° (0.05 mm) to give the *cis* isomer (C=O, 1743 cm^{-1}). *Anal.* ($C_{15}H_{18}O_2$) C, H.

Methyl *cis*- and *trans*-1,3,3a,4,5,9b-Hexahydro-7-methoxy-2-oxo-2H-benz[*e*]inden-3a-carboxylate (13).—Compound **10** was hydrogenated using the procedure outlined for **8** in part 1A. Glpc analysis of the crude product showed it to contain 70% of the *trans* isomer. The *trans* isomer was separated by crystallization from MeOH, mp 79–81°; ketone C=O stretch 1741 cm^{-1}. *Anal.* ($C_{16}H_{18}O_4$) C, H.

The *cis* isomer was recovered from the mother liquors and was an oil distilling at 176–179° (0.05 mm); ketone C=O stretch 1737 cm^{-1}. *Anal.* ($C_{16}H_{18}O_4$) C, H.

Conversion of *trans*-13 to *trans*-12. A. Methyl 2,2-Ethylenedioxy-2,3,3a,4,5,9b-hexahydro-7-methoxy-1H-benz[*e*]inden-3a-carboxylate (25).—A solution of **13** (6.3 g), ethylene glycol (6.0 g), and *p*-toluenesulfonic acid (0.1 g) in 50 ml of C_6H_6 and 25 ml of diglyme was refluxed for 5 hr, using a Dean–Stark trap to remove H_2O formed. The solution was cooled and diluted (H_2O). The C_6H_6 layer was washed free of diglyme and evaporated and the residue recrystallized to give 3.8 g (82%) of **25**, mp 99–101°. *Anal.* ($C_{18}H_{22}O_5$) C, H.

B. 2,2-Ethylenedioxy-2,3,3a,4,5,9b-hexahydro-3a-hydroxymethyl-7-methoxy-1H-benz[*e*]indene (26).—Compound **25** was reduced (LAH, THF) at 0°. Starting with 3.5 g of **25**, a yield of 2.5 g (79%) of **26** was obtained, mp 149–150°. *Anal.* ($C_{17}H_{22}O_4$) C, H.

C. 2,2-Ethylenedioxy-2,3,3a,4,5,9b-hexahydro-3a-hydroxymethyl-7-methoxy-1H-benz[*e*]indene 2-Methanesulfonate (27).—A solution of **26** (2.3 g) and $MeSO_2Cl$ (1.8 g) in dry pyridine (30 ml) was stirred at room temperature for 4 hr. The crude product was recrystallized from C_6H_6–C_6H_{12} to give a 2.8 g (96%) of **27**, mp 146° dec. *Anal.* ($C_{18}H_{24}O_6S$) C, H.

D. *trans*-1,2,3a,4,5,9b-Hexahydro-7-methoxy-3a-methyl-2H-benz[*e*]inden-2-one (12).—A mixture of **27** (2.7 g), dried KI (6.0 g), powdered CaH_2 (0.8 g), and dry DMAC was stirred at reflux (Ar atm) for 2.5 hr. The mixture was cooled, and treated with ice and dilute AcOH. The product was isolated by C_6H_6 extraction and evaporation of the solvent, but was not sufficiently pure for analysis. The crude iodide was dissolved in a mixture of 20 ml of AcOH and 20 ml of 88% formic acid and stirred for 60 min at room temperature. The crude iodo ketone was dissolved in EtOH (50 ml) and hydrogenated over 0.5 g of Pd–C with $NaHCO_3$ (1.0 g) present to neutralize the acid formed. The product proved to be identical with that isolated from the hydrogenation of **9**.

Mixture of *cis*- and *trans*-3a,4,5,9b-Tetrahydro-7-methoxy-1H-benz[*e*]indene and *cis*- and *trans*-3a,4,5,9b-Tetrahydro-7-methoxy-3H-benz[*e*]indene (14).—An excess of diborane[20] was passed through a solution of **8** (5.0 g) in dioxane (30 ml) and THF (30 ml) at 10°. The solution was stirred 12 hr at room temperature, followed by evaporation of the solvent *in vacuo*. The residue was taken up in AcOH (25 ml) and the mixture heated at 250° for 60 min in an autoclave. The product, 2.2 g (44%), distilled at 110–115° (0.05 mm). Glpc analysis of the product showed that four components were present in about equal amounts. *Anal.* ($C_{14}H_{16}O$) C, H.

From 11.—Starting with **11** (4.7 g) the same reaction was carried out as outlined above. In this case this product contained only two components, corresponding to the faster migrating components of the above mixture. When **11** was first reduced to the carbinol with $NaBH_4$ and then hydroborated, the same mixture of alkenes was obtained. The carbinol was unaffected by acetolysis at 250°. This indicates that some borate ester of the carbinol is initially formed, which undergoes dehydration subsequently. Whether there is more than one boron atom present in the complex formed from **8** was not established.

Mixture of *cis*- and *trans*-3a,4,5,9b-Tetrahydro-7-methoxy-3a-methyl-1H-benz[*e*]indene and *cis*- and *trans*-3a,4,5,9b-Tetrahydro-7-methoxy-3a-methyl-3H-benz[*e*]indene (15).—Starting with **9** (5.0 g) and using the procedure outlined for **14**, a yield of 3.8 g (81%) of **15**, distilling at 110–115° (0.05 mm), was obtained. Glpc analysis of the product showed that four components were present. *Anal.* ($C_{15}H_{18}O$) C, H.

From 12.—Starting with crude **12** (2.9 g) the same reaction was carried out as outlined above. Glpc analysis of the product showed that the same four components were present in about the same proportions.

Mixture of *cis*- and *trans*-2,3,3a,4,5,9b-Hexahydro-7-methoxy-1H-benz[*e*]indene (16).—The samples of **14** obtained both from **8** and **11** were hydrogenated over Pd–C. Glpc analysis of the product obtained from **8** showed that two components were present in about equal amounts, thus showing that the original hydroboration was not stereoselective. The product from **11** contained only one component, corresponding to the faster moving component of the other sample. Since the *trans* isomer has a flatter molecule, one would expect it to migrate slower than the *cis* isomer. *Anal.* ($C_{14}H_{18}O$) C, H.

Mixture of *cis*- and *trans*-2,3,3a,4,5,9b-Hexahydro-7-methoxy-3a-methyl-1H-benz[*e*]indene (17).—The samples of **15** obtained from both **9** and **12** were hydrogenated over Pd–C. Glpc analysis of the products showed that both *cis* and *trans* isomers were present in about the same ratios, 60% *trans* to 40% *cis*, as that obtained by hydrogenation of **9**. *Anal.* ($C_{15}H_{20}O$) C, H.

2-Ethynyl-2,3,3a,4,5,9b-hexahydro-7-methoxy-1H-benz[*e*]-inden-2-ol (18). A solution of **11** (14.6 g) in THF was added to a 100% excess of HC≡CMgBr in THF made by the method of Jones.[21] The mixture was allowed to stir overnight at room temperature, and then hydrolyzed. The crude product was vacuum distilled and recrystallized from C_6H_6–C_6H_{12} to give **18** (13.8 g, 85%), mp 85–86°. Tlc analysis indicated that only a single isomer was present. *Anal.* ($C_{16}H_{18}O_2$) C, H.

(18) Raney Catalyst Co. catalyst.

(19) L. H. Sarett, *J. Amer. Chem. Soc.*, **70**, 1690 (1948).

(20) H. C. Brown and B. C. Subba Rao, *ibid.*, **81**, 6428 (1959).

(21) E. R. H. Jones, L. Skattebol, and M. C. Whiting, *J. Chem. Soc.*, 4765 (1956).

2-Ethynyl-2,3,3a,4,5,9b-hexahydro-7-methoxy-3a-methyl-1H-benz[*e*]inden-2-ol (19).—The procedure for preparing **18** was used. Starting with the *trans* isomer of **12** (8.0 g) a yield of 7.8 g (87%) of **19** was obtained, bp 134–137° (0.05 mm). *Anal.* ($C_{17}H_{20}O_2$) C, H.

2,3,3a,4,5,9b-Hexahydro-7-methoxy-2-(2-methyl-1,3-dioxolan-2-yl)-1H-benz[*e*]inden-2-ol (20).—The method of Nieuwland[22] was used to convert **18** into **20**. A solution of redistilled BF_3 etherate (2 ml) and HgO (0.5 g) in 15 ml of dry ethylene glycol was added to a solution of **18** (14.2 g) in 90 ml of dry ethylene glycol cooled to −10°. After the addition was complete, the mixture was allowed to warm to room temperature over a period of several hours, stirred overnight, and hydrolyzed. The crude product was recrystallized from C_6H_6–C_6H_{12} to give **20** (11.5 g, 64%), mp 106–108°. Tlc analysis indicated that only one isomer was present. *Anal.* ($C_{18}H_{24}O_4$) C, H.

2,3,3a,4,5,9b-Hexahydro-7-methoxy-3a-methyl-2-(2-methyl-1,3-dioxolan-2-yl)-1H-benz[*e*]inden-2-ol (21).—The procedure used to prepare **20** from **18** was followed. Starting with **19** (7.9 g) a yield of 8.1 g (91%) was obtained, mp 99–100°. Tlc analysis indicated that only a single isomer was present. *Anal.* ($C_{19}H_{26}O_4$) C, H.

2β-Acetyl-1,2,3,3aβ,4,5,6,8,9,9bβ-decahydro-2α-hydroxy-7H-benz[*e*]inden-7-one (22).—Compound **20** was converted into **22** using a procedure outlined previously[2] for similar compounds. Starting with **20** (6.0 g) a yield of 3.1 g (64%) of **22** was obtained, boiling range 149–152° (0.05 mm). *Anal.* ($C_{15}H_{20}O_3$) C, H.

2α-Acetyl-1,2,3,3a,4,5,6,8,9,9bα-decahydro-2β-hydroxy-3β-methyl-7H-benz[*e*]inden-7-one (23).—The procedure used to prepare **22** was used. Starting with **21** (6.0 g), a yield of 3.5 g (73%) of the product was obtained, after the initial product was purified by column chromatography using silica gel H as adsorbent, followed by redistillation, boiling range 148–150° (0.05 mm). *Anal.* ($C_{16}H_{22}O_3$) C, H.

(22) J. A. Nieuwland, R. R. Vogt, W. L. Foohey, *J. Amer. Chem. Soc.*, **52**, 1018 (1930).

Organic Disulfides and Related Substances. XXVIII. Analogs of *o*-(2-Protoaminoethyldithio)benzoate As Antiradiation Drugs[1a–c]

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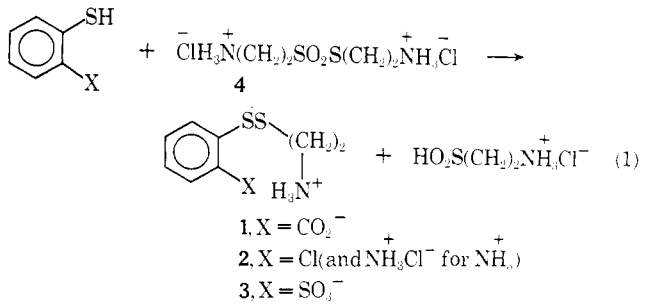
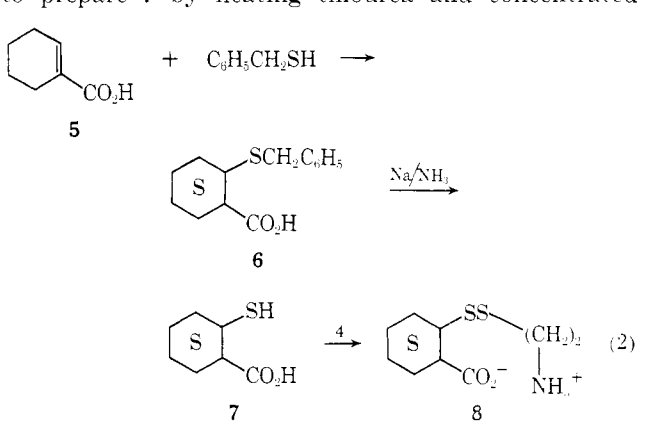
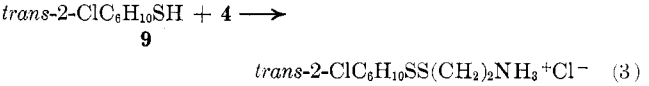
o-(2-Protoaminoethyldithio)benzoate (**1**)[2] has shown promise as an antiradiation drug,[3a] and two analogous compounds, *o*-(2-aminoethyldithio)chlorobenzene·HCl (**2**) and *o*-(2-protoaminoethyldithio)benzenesulfonate (**3**), also have shown activity.[3b] Although several other derivatives, isomers, and analogs have been inactive,[3] the saturated analogs of **1**–**3** were desired in order to establish whether the aromatic or the aliphatic system would provide the better basis for further extensions. Disulfides **1**–**3** were prepared by thioalkylation of the appropriate thiol with 2-aminoethyl 2-aminoethanethiolsulfonate·2HCl (**4**), as shown by eq 1,[3] and the same approach seemed feasible for the saturated compounds.



In order to prepare the cyclohexane analog of **1**, it was necessary to synthesize 2-mercapto-1-cyclohexanecarboxylic acid (**7**). This was accomplished by the addition of α-toluenethiol to cyclohexene-1-carboxylic acid (**5**) and reduction of the benzyl sulfide (**6**) to the thiol **7** (eq 2). Others have attempted to prepare **7** by heating thiourea and concentrated HBr with hexahydrosalicylic acid and then treating with NaOH. However, they were unable to obtain a pure product.[4] Thioalkylation of **7** with **4** gave 2-(2′-protoaminoethyldithio)-1-cyclohexanecarboxylate (**8**). Although the reaction of α-toluenethiol with **5** would seem more likely to give at the outset *trans* addition, and therefore **6** as the *cis* product, the presence of excess hot piperidine in turn would seem likely to have afforded ample opportunity for epimerization to the presumably more stable *trans* isomer of **6**. In any event, tlc of **7** in two systems showed only a single spot, and prolonged treatment with base failed to effect any apparent change. Only single spots also were seen for the mercury (II) mercaptide of **7** and for disulfide **8**. Thus it would seem that a single isomer of **6** resulted, probably the *trans*.



Thioalkylation of the known *trans*-2-chlorocyclohexanethiol (**9**) gave *trans*-2-aminoethyl 2-chlorocyclohexyl disulfide·HCl (**10**), the reduced analog of **2** (eq 3).



Attempts to prepare the saturated analog of **3** were thwarted by a series of unsuccessful attempts to prepare the requisite thiol, 2-mercaptocyclohexanesulfonic acid.

(1) (a) Paper XXVII: L. Field and R. B. Barbee, *J. Org. Chem.*, **34**, 1792 (1969). (b) This investigation was supported by the U. S. Army Medical Research and Development Command, Department of the Army, under Research Contracts No. DA-49-193-MD-2030 and DADA17-69-C-9128. Taken from part of the forthcoming Ph.D. dissertation of P. M. G., Vanderbilt University. (c) Reported in part at the Southeastern Regional Meeting of the American Chemical Society, Tallahassee, Fla., Dec 1968; Abstracts, p 98.

(2) Nomenclature suggested by Dr. F. Y. Wiselogle. See F. G. Bordwell, M. L. Peterson, and C. S. Rondestvedt, Jr., *J. Amer. Chem. Soc.*, **76**, 3945 (1954). Previously **1** was named *o*-(2-aminoethyldithio)benzoic acid;[3] although the dipolar ionic structure of **1** is merely inferred from its behavior, rather than rigorously proved, the "proto" nomenclature seems to be a justifiable simplication.

(3) (a) R. R. Crenshaw and L. Field, *J. Org. Chem.*, **30**, 175 (1965); (b) L. Field and H. K. Kim, *J. Med. Chem.*, **9**, 397 (1966).

(4) J. F. Burke, and M. W. Whitehouse, *Biochem. Pharmacol.*, **14**, 1039 (1965).