Reductions of a Model Barbiturate System with Sodium Borohydride[1,2]

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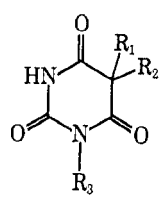
The model barbiturate system of 5,5-dibenzyl-1,3-dimethylbarbituric acid (**4**) underwent facile reduction with sodium borohydride in absolute methanol (1 hr, 25°), giving 5,5-dibenzyl-6-hydroxy-1,3-dimethylhydrouracil (**7**) and 5,5-dibenzyltetrahydro-*trans*-4,6-dihydroxy-1,3-dimethyl-2(1H)-pyrimidinone (**8**). The *trans*-4,6-dihydroxy-2(1H)-pyrimidinone **8** was formed largely in preference to its *cis* isomer **9**, apparently through an efficient stereoregulated reduction of **7**. *trans*-**8** was isomerized by either dilute mineral acid or alkali to 5,5-dibenzyltetrahydro-*cis*-4,6-dihydroxy-1,3-dimethyl-2(1H)-pyrimidinone (**9**). Exhaustive sodium borohydride reduction of **4** (conducted in aqueous ethanol, 24 hr, 25°) gave 2-benzyl-3-phenyl-1-propanol (**6a**); the formation of **6a** was unexpected in light of the recent work of Kondo and Witkop, in which the exhaustive reduction products from related barbiturate drugs were 1,3-glycols.

Witkop, Cerutti, and coworkers[3a-c] reported recently on a number of sodium borohydride reductions and reductive cleavages (with and without photoinduction) occurring at the "imide-carbonyl" of some biologically and medicinally important heterocyclic compounds.[3] In their examples of hydrogenolytic fission of the barbiturate system,[3a] it was shown that the malonyl part of barbital (**1**), hexobarbital (**2**), and mephobarbital (**3**) underwent reductive cleavage to a 2,2-disubstituted 1,3-glycol during prolonged exposure (68–75 hr) to aqueous (or aqueous ethanolic) borohydride solution.

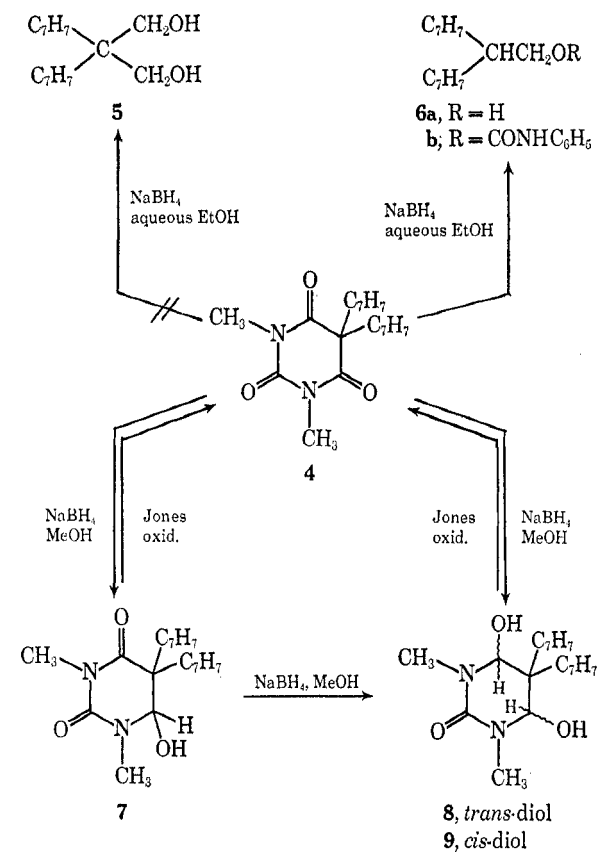


1, $R_1 = R_2 = C_2H_5$; $R_3 = H$
2, $R_1 = R_3 = CH_3$; R_2 = 1-cyclohexenyl
3, $R_1 = C_2H_5$; $R_2 = C_6H_5$; $R_3 = CH_3$

We now report related sodium borohydride reductions and a unique hydrogenolysis of the barbiturate system. The model system 5,5-dibenzyl-1,3-dimethylbarbituric acid (**4**) was chosen for this study, since it was anticipated that structural assignments of reduction products would be aided by the symmetry of **4** and its constituents, *e.g.*, 5,5-dibenzyl groups.[4]

Exhaustive sodium borohydride reduction of **4** (aqueous ethanol, 24 hr) led predominantly (46% yield) to formation of the unusual hydrogenolytic product, 2-benzyl-3-phenyl-1-propanol (**6a**). Minor products in this reaction were dihydrobarbiturate **7** and *cis*-tetrahydrobarbiturate **9**, isolated in yields of 24 and 5%, respectively. The 1,3-glycol **5**, if formed, was not identified.

SCHEME I



Reduction of **4** by methanolic sodium borohydride (1 hr, 25°) gave two principal products, the dihydrobarbiturate **7** (average yield 30%) and the *trans*-tetrahydrobarbiturate **8** (average yield 6%). A *cis*-tetrahydrobarbiturate **9** was formed also in very low yield (average yield 0.3%; ratio of *trans*-**8**/*cis*-**9** at least 10:1 in all experiments). Direct reduction ($NaBH_4$, MeOH, 25°) of dihydrobarbiturate **7** to largely the *trans*-tetrahydrobarbiturate **8** established the reaction sequence: **4** → **7** → **8**. *trans*-Tetrahydrobarbiturate **8**

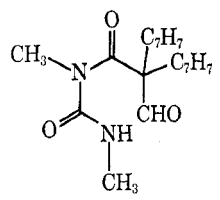
(1) This investigation was supported by Public Health Service Research Grant GM 13606 (Thomas C. Butler, Principal Investigator) from the National Institute of General Medical Sciences.

(2) Following a suggestion by Dr. K. L. Loening (Chemical Abstracts Service), the terms, dihydrobarbiturate and tetrahydrobarbiturate, have been used for brevity to connote derivatives of the hydrouracil and 2(1H)-pyrimidinone systems, respectively.

(3) (a) Y. Kondo and B. Witkop, *J. Org. Chem.*, **33**, 206 (1968); (b) Y. Kondo and B. Witkop, *J. Amer. Chem. Soc.*, **90**, 764 (1968); (c) P. Cerutti, Y. Kondo, W. R. Landis, and B. Witkop, *ibid.*, **90**, 771 (1968), and references therein. (d) Related sodium borohydride reductions of hydantoin systems have appeared recently: J. E. Scott and G. Henderson, *Biochem. J.*, **109**, 209 (1968); K. H. Dudley and P. Hemmerich, *J. Org. Chem.*, **32**, 3049 (1967). (e) Hydroborations of some barbiturates have been reported: E. E. Smissman, A. J. Matuszak, and C. N. Corder, *J. Pharm. Sci.*, **53**, 1541 (1964).

(4) R. K. Hill and T. H. Chan, *Tetrahedron*, **21**, 2015 (1965). Appearing during review of our manuscript was an account on the conformational requirement for observable magnetic nonequivalence of benzylic methylene protons: R. E. Lyle and J. J. Thomas, *Tetrahedron Lett.*, 897 (1969). Due to the conformational uncertainties of, a difference of substituents at the chiral center in, and the questionable rotamer dispositions of seemingly hindered 5,5-dibenzyl groups in the barbiturate reduction products here, no conclusions have been drawn regarding the magnetic nonequivalence, or lack of it, of benzylic methylene protons in spectra of chiral compounds, *e.g.*, **7**, **8**, and **12**.

was found to be stable at the pH of the reaction mixture (*i.e.*, "spent" borohydride solution), but it underwent isomerization to the more stable *cis*-tetrahydrobarbiturate **9** in the presence of either strong base (NaOME, MeOH) or dilute mineral acid (H^+, aqueous THF). The *cis*-tetrahydrobarbiturate **9** was stable in "spent" borohydride solution, as expected. Each of compounds **7**, **8**, and **9** was reconverted into **4** by Jones oxidation. Ring-opened, isomeric structures, *e.g.*, **10** for **7**, and **11** for **8** or **9**, were precluded on the basis of nmr data.



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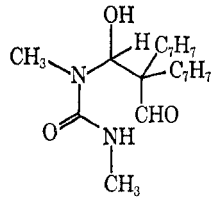

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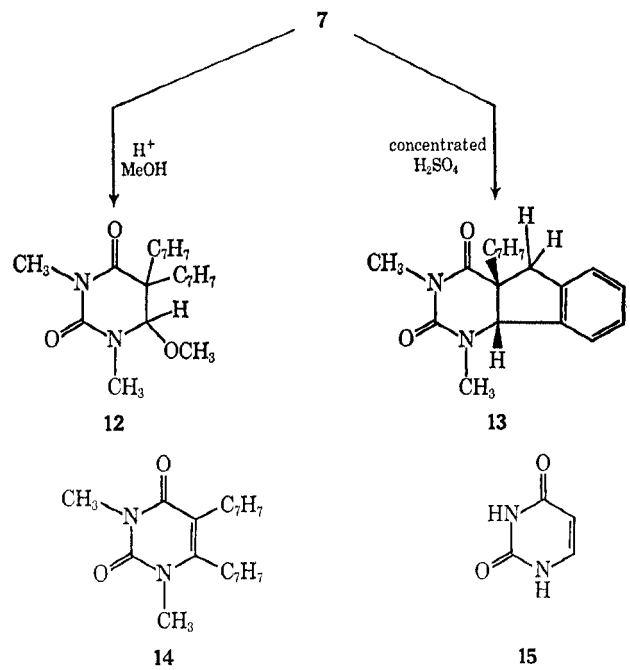
Dihydrobarbiturate 7.—The ir spectrum of **7** (KBr disk) contained sharp bands at 3430 (ν_{OH}), 1707 ($\nu_{4\text{-}CO}$), and 1665 cm^{-1} ($\nu_{2\text{-}CO}$); an absence of absorption in the amide II–amide III band region (*i.e.*, 1665–1500 cm^{-1}) was in accord with ring-closed formula **7**.[5,6] The nmr spectrum of **7** ($CDCl_3$, 10% solution) more firmly established its ring-closed structure. An AB quartet, the doublets of which were centered at δ 3.78 and 4.40 (J = 5 Hz, each doublet integrating at one proton), was assigned to the secondary >CHOH group, since deuterium exchange caused disappearance of the δ 4.40 doublet as well as collapse of the δ 3.78 doublet to a sharp singlet. The chemical nonequivalence indicated for the pair of N-methyl groups (*e.g.*, two sharp three-proton singlets at δ 2.76 and 2.96) was viewed as supportive evidence that reduction occurred at the 4-oxo group and not at the less hindered 2-oxo group.

Regarding resonances for the two sets of benzylic methylene protons, one set was observed as a two-proton singlet (δ 3.28), the other set as an AB spin–spin system (doublets centered at δ 3.00 and 2.58, J = 14 Hz). This disparity in multiplicities for the benzylic methylene proton resonances might be attributed to an effect of molecular dissymmetry,[4,7] which, in this event, would be indicated as a stereodependent (conformational) effect.[4] What would remain questionable, however, would be the contribution of rotamer populations of each seemingly hindered benzyl group[8] to the overall resonance picture, or a solute–solvent complexation effect[9] which might affect rotamer populations. It is noteworthy here that a second AB spin–spin system (corresponding to the δ 3.28 singlet in $CDCl_3$) was observed in the pyridine-d_5 spectrum of **7**; this splitting was probably "solvent-induced," but, in lieu of other solvent and temperature data, could have been more positively accepted as a molecular dissymmetry effect.

Additional evidence for formula **7** was gained from two derivatives. In methanolic solution containing a trace of mineral acid, dihydrobarbiturate **7** readily formed the O-methyl derivative **12** whose structure was based upon a similar interpretation of its ir and nmr data, as in the argument for structure **7**. In concentrated sulfuric acid, dihydrobarbiturate **7** underwent cyclodehydration to the 1H-indeno[1,2-*d*]pyrimidine-2,4(3H,4aH)-dione **13**.[10] Formation of **14**, which was considered likely in view of the "neopentyl-like" skeleton of **7** and the known strong acid lability of a 5-benzyl group in a 5,5-disubstituted barbituric acid,[11] was ruled out on the basis of the uv and nmr data. The uv spectrum of **13** remained similar to that of **7** and did not exhibit a longer wavelength absorption (250–270 mμ) characteristic of uracil (**15**) and its derivatives.[12] The nmr spectrum ($CDCl_3$) contained a one-proton singlet at δ 4.48 (methine proton), two sharp resonances at 2.94 and 3.10 (two N-methyl groups), and an aromatic multiplet integrating for a sum of nine protons.



12 13 14 15

Tetrahydrobarbiturates 8 and 9.—Elemental analyses and high resolution mass spectrometry confirmed identical compositions for the tetrahydrobarbiturates **8** and **9**. The *trans*- and *cis*-4,6-diol assignments to these isomeric tetrahydrobarbiturates were based exclusively upon nmr spectral data, *i.e.*, the equivalency, or lack of it, of the chemical shifts of resonances for the two sets of benzylic methylene protons in **8** and **9**. Ir spectral measurements of **8** and **9** in a nonpolar medium, *e.g.*, carbon tetrachloride, might have afforded further supportive evidence for the assignments but were precluded by insufficient solubilities. The following ir data (KBr disks) were obtained, however. The

(5) A. R. Katritzky and A. P. Ambler in "Physical Methods in Heterocyclic Chemistry," Vol. II, A. R. Katritzky, Ed., Academic Press Inc., New York, N. Y., 1963, p 193.

(6) L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," John Wiley & Sons, Inc., New York, N. Y., 1962, p 217.

(7) (a) F. A. Bovey, *Chem. Eng. News*, **43**, 119 (Aug 30, 1965); (b) M. van Gorkom and G. E. Hall, *Quart. Rev.* (London), **22**, 14 (1968).

(8) C. A. Cupas, J. M. Bollinger, and M. Haslanger, *J. Amer. Chem. Soc.*, **90**, 5502 (1968).

(9) (a) N. S. Bhacca and D. H. Williams, "Applications of Nmr Spectroscopy in Organic Chemistry," Holden-Day Inc., San Francisco, Calif., 1964, p 159; (b) P. V. Demarco, E. Farkas, D. Doddrell, B. L. Mylari, and E. Wenkert, *J. Amer. Chem. Soc.*, **90**, 5480 (1968); (c) T. Ledaal, *Tetrahedron Lett.*, 1683 (1968).

(10) A *cis*-ring fusion is proposed for **13**, since construction of a *trans* system using CPK atomic models appeared impractical.

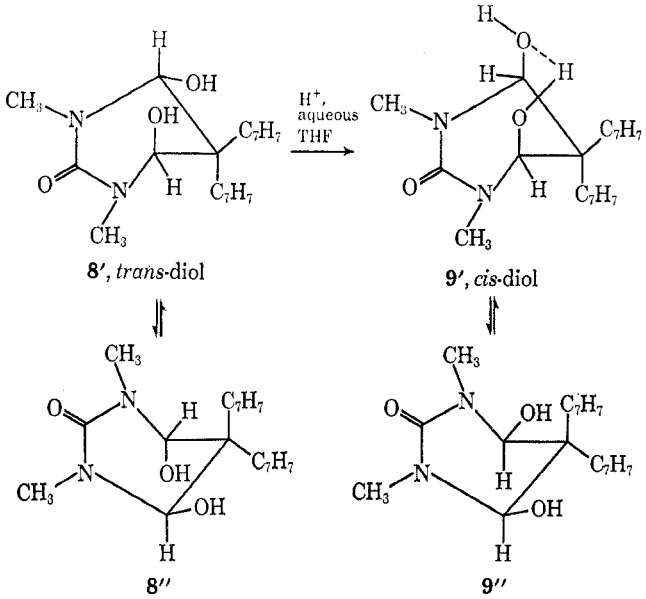
(11) E. W. Maynert and E. Washburn, *J. Amer. Chem. Soc.*, **75**, 700 (1953).

(12) J. J. Fox and I. Wempen, *Advan. Carbohydrate Chem.*, **14**, 283 (1959).

trans-tetrahydrobarbiturate **8** exhibited bands at 3360 (ν_{OH}) and 1625 cm^{-1} ($\nu_{2\text{-}CO}$). The occurrences of additional bands at 1595 and 1535 cm^{-1} were unexplainable in terms of **8** but were accepted in light of the nmr data. As a rule, a cyclic lactam shows no absorption in this region.[6] The spectrum of *cis*-tetrahydrobarbiturate **9** contained bands at 3480 and 3190 (ν_{OH}) and 1615 cm^{-1} ($\nu_{2\text{-}CO}$); the assignments of hydroxyl stretching frequencies to the 3480- and 3190-cm^{-1} absorptions were supported in this case by lack of secondary amide bands in the 1615–1515-cm^{-1} region.[13]

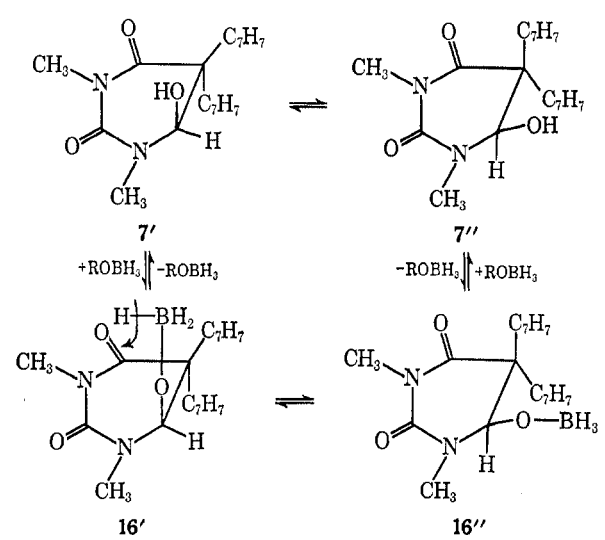
Assignments of ring-closed formulas having 4,6-diol groups were consistent with nmr data measured of each tetrahydrobarbiturate in three solvent systems; $CDCl_3$,[14] DMSO-d_6, and pyridine-d_5. Spectra of **8** and **9** were similar in the respects that resonances for the two secondary alcohol functions (>CHOH) of each isomer were traced as one sharp four-proton AB spin–spin system and that resonances for the two N-methyl groups were traced as one sharp six-proton singlet, but different in the respect that the chemical shifts of the resonances for the two sets of benzylic methylene protons of one isomer were equivalent (sharp four-proton singlet) and of the other isomer nonequivalent (two sharp two-proton singlets).

Conformers **8′** and **8″** of the *trans*-4,6-diol system are merely conformational enantiomers and, assuming the rate of ring inversion at ambient temperature would be fast relative to the nmr time scale,[15,16] that spectrum indicating chemical equivalencies for the two sets of secondary alcohol functions, chemical equivalencies for the two N-methyl groups, and chemical equivalencies for the two sets of benzylic methylene protons would represent the *trans*-tetrahydrobarbiturate **8**. On the other hand, the *cis*-4,6-diol system **9** has "chemically distinguishable" conformers, *e.g.*, **9′** and **9″**. For either of the two conformers, or for the situation where the two conformers have a low barrier to ring inversion at ambient temperature, one would expect the nmr spectrum to indicate chemically equivalent N-methyl groups, as well as chemically equivalent secondary alcohol functions, but *chemically nonequivalent* benzylic methylene groups. That spectrum showing these characteristics was attributed accordingly to *cis*-tetrahydrobarbiturate **9**.



Mechanism.—Inspection of the dihydrobarbiturate system **7** (CPK atomic models) indicates that four atoms of the ring system and their attached substituents [*i.e.*, $-N(CH_3)\cdot CO\cdot N(CH_3)\cdot CO-$] lie in a common plane, and suggests that the molecule could exist in either of two conformations shown by **7′** and **7″**. Steric approach analysis[17,18] of the reduction of **7** to *trans*-4,6-diol **8** would implicate that a conformational equilibrium favoring **7′** was involved and as well that 1,3-diaxial interactions (*i.e.*, electrostatic repulsion and/or steric interference of borohydride with *axial*-hydroxyl) were of marginal importance. It would seem that if such 1,3-diaxial interactions were relevant, the mechanism would involve conformer **7″**; however, the more favorable route for approach of borohydride to **7″** would lead one to predict predominant formation of *cis*-4,6-diol **9**.

It is of interest to note that intramolecularly assisted hydride transfer[19] would provide a directive effect consistent with formation of lesser stable *trans* isomer **8**. The proposal here would withstand criticism[20] directed at similar proposals in instances where product ratios favored the more stable isomer. Intramolecular hydride transfer would require conformer **7′** (and/or **16′**) whose existence, if not favored,



(13) L. P. Kuhn, *J. Amer. Chem. Soc.*, **74**, 2491 (1952). In a study of the infrared properties of the three cyclohexanediol systems, the author observed a hydroxyl frequency (KBr spectrum) as low as 3220 cm^{-1}.

(14) *trans*-Tetrahydrobarbiturate **8** (chromatographically uniform, tlc) was sparingly but sufficiently soluble in $CDCl_3$ to permit tracing its spectrum (HA 100) using a high recorder output. This spectrum, taken of **8** in $CDCl_3$ (whose label indicated no stabilizer present), was identical (except for the δ value of the OH resonance) with that of **9** measured in $CDCl_3$. We presumed that traces of deuterium chloride present in the nonstabilized solvent were responsible for a ready isomerization of **8** into **9**, since it was possible to demonstrate by tlc that the supernatant from a suspension of **8** in reagent grade chloroform (containing stabilizer) contained a detectable amount of **9** (in addition to **8**) after ~3 hr at ambient temperature (*i.e.*, the time given in the nmr experiment for saturation (25°) of $CDCl_3$ by **8**).

(15) F. G. Riddell, *Quart. Rev.* (London), **21**, 364 (1967), a review of heterocyclic conformational analysis.

(16) H. Finegold and H. Kwart, *J. Org. Chem.*, **27**, 2361 (1962), use of the nmr method for determination of structures of isomeric cyclohexane-1,3-diols.

(17) E. Toromanoff in "Topics in Stereochemistry," Vol. 2, N. L. Allinger and E. L. Eliel, Ed., John Wiley & Sons, Inc., New York, N. Y., 1967, p 157.

(18) D. N. Kirk, *Tetrahedron Lett.*, 1727 (1969), and references therein.

(19) E. C. Pesterfield and D. M. S. Wheeler, *J. Org. Chem.*, **30**, 1513 (1965), and references therein.

(20) H. O. House, H. Babad, R. B. Toothill, and A. W. Noltes, *ibid.*, **27**, 4141 (1962).

would at least seem probable on grounds that (1) **7′** (or **16′**) would be void of an N-methyl equatorial hydroxyl (alkoxyborohydride) confrontation present in **7″** (or **16″**), and (2) **7′** (or **16′**) would appear favored by the "anomeric effect," *i.e.*, the preference of OR for an axial position owing to repulsion of parallel-oriented electron pairs.[21] By analogy, hydride release in **16′** would be presumably fast (comparatively to borohydride itself),[19] and the relative kinetic factor for the intramolecular reaction (k_I) *vs.* the bimolecular reaction (k_{II}) would be theoretically large (*i.e.*, $k_I/k_{II} >> k_{II}$, the "propinquity effect").[22]

Experimental Section[23]

5,5-Dibenzyl-1,3-dimethylbarbituric Acid (4).—1,3-Dimethylbarbituric acid was prepared by the method of either Clark-Lewis and Thompson[24] or Pfleiderer and Schündehütte.[25] Alkylation of 1,3-dimethylbarbituric acid with benzyl chloride was carried out as described by Cope, *et al.*,[26] to give **4**, mp 134–136°. The following spectral data of **4** were measured: ir (KBr disk) 1750 (w) and 1680 cm^{-1} (s); nmr ($CDCl_3$) δ 2.92 (s, 6, two NCH_3), 3.42 (s, 4, two benzylic CH_2), 6.90–7.20 (m, 10, arom ring **H**); uv 230 mμ (ϵ 5700).

General.—Product mixtures were separated by preparative thick layer chromatography on 20 × 40 cm plates coated with Brinkmann silica gel HF_{254} (adsorbent thickness, 1.25 mm); plates were activated at 75–80° for 18 hr prior to use. The particular solvent systems employed for elution permitted clean separations of as much as 0.5 g of crop A or crop B (note below) on a single plate. Generally, the recovery of **8** from crop A, and **4** from crop B, was not worthy of the time spent in the working of their respective silica zones.

A known mixture of **7**, **8**, and **9** was separated on a thick layer plate (solvent system B) to test whether **8** or **9** underwent isomerization to the other, and to estimate material recoveries. A mixture consisting of **7** (100 mg), **8** (56.1 mg), and **9** (53.7 mg) was thus handled as described below and gave recoveries of 68.8, 76.3, and 69.0%, respectively. Recoveries were based on weights of chromatographically uniform solids obtained after the chloroform treatment.[14]

Reduction of 1,3-Dimethyl-5,5-dibenzylbarbituric Acid (4) to 5,5-Dibenzyl-6-hydroxy-1,3-dimethylhydrouracil (7) and 5,5-Dibenzyltetrahydro-*trans*-4,6-dihydroxy-1,3-dimethyl-2(1H)-pyrimidinone (8).—To a magnetically stirred, supersaturated (25°) solution of **4** (2.0 g, 5.9 mmol) in absolute methanol (60 ml) was added during 20 min (in four portions) sodium borohydride (904 mg, 23.8 mmol). After the last addition of borohydride, the solution was stirred for an additional 40 min, after which tlc indicated the presence of **4**, **7**, and **8**. In solvent system A, compounds **4**, **7**, **8**, and **9** had R_f values of about 0.85, 0.15, 0.00, and 0.00, respectively. In solvent system B, compounds **7**, **8**, and **9** had R_f values of 0.60, 0.10, and 0.25, respectively.

The reaction solution was gradually diluted with 40 ml of water, and the precipitate (crop A) which separated during 20 min was filtered off and was washed with 12 ml of 50% aqueous methanol. Crop A (878.5 mg) contained (by tlc) predominantly **4** and **7**, in addition to a small quantity of **8**.

The pooled filtrate and washings from crop A were further diluted with 40 ml of water and kept at 25° for 20 hr. The precipitate (crop B) was filtered off and was washed with water. Tlc showed crop B (653.7 mg) to contain predominantly **7** and **8**, in addition to a small quantity of **4**.

Crop A (878.5 mg) was divided into two equal portions, each of which was dissolved in 4 ml of chloroform and streaked onto a thick layer plate; the plates were eluted in 10% ethyl acetate–chloroform, and those silica zones containing identical compounds were collected and combined. The following procedure for the recovery of **7** (from two plates used for separation of crop A) was used for recovery of all compounds (those of crop B as well) from the silica adsorbent. The pooled silica zone of **7** (from two plates) was leached successively with 12 25-ml protions of absolute methanol; the combined, filtered methanol extract was stripped under reduced pressure, and the residue was freed from silica by rubbing under aliquots of chloroform; filtration and stripping of the pooled chloroform extract gave a residue of **7** which crystallized readily under a few drops of ethyl acetate. The bulk of the recovered starting material **4** and a small quantity of **8** were obtained in crystalline form in a similar manner. In the handling of **8** in chloroform, the contact time was kept at a minimum.[15]

Crop B (653.7 mg) was halved; each portion was dissolved in 5 ml of absolute methanol and streaked onto a 20 × 40 cm plate (plate must be free of methanol before elution); the plates were eluted in 1:1 ethyl acetate–chloroform. Identities and purities of zones were established by tlc; zones containing identical compounds were combined, and the compounds were recovered from the adsorbent as described above for **7**. Crop B usually afforded a goodly amount of **7**, the bulk of **8**, a small amount of **4**, and, in some instances, a very small amount of **9** (6–9 mg). Identical compounds from crops A and B were combined.

The recovery of crude, chromatographically uniform **4**, confirmed by tlc and ir, was 90.2 mg.

Dihydrobarbiturate 7.—The yield of crude, chromatographically pure **7** was 616.4 mg; the sample was recrystallized from the minimum volume of absolute ethanol, first at 25° then at −12°, giving **7** (557.4 mg): melting point sharp collapse and melting at 181–183° with a few crystals resisting fusion until 192°; ir (KBr disk) 3430 (s), 1707 (s), 1665 (s), 1607 (vw), 1495 (s), 1421 (s), 1131 (s), and 1062 cm^{-1} (s); nmr in $CDCl_3$ (10%), see text [a spectrum of a 3% solution showed the doublet (J = 5 Hz), assignable to >CHOH, in the δ 3.00–3.10 region (assignment established by deuterium exchange)]; DMSO-d_6 (3%), δ 6.68 (d, 1, J = 5 Hz, >CHOH), 4.32 (d, 1, 5 Hz, >CHOH), 2.70 (s, NCH_3), 2.64 (s, 3, NCH_3), 3.02 (s, 2, CH_2) (the apparent AB quartet assigned to the other CH_2 group could not be evaluated owing to interference by the 2.70 N-methyl and DMSO peaks; the spectrum was temperature independent in the range of ambient to 100°); pyridine-d_5 (3%), δ 8.50 (d, 1, 5 Hz, >CHOH), 4.76 (d, 1, 5 Hz, >CHOH), 2.90 (s, 3, NCH_3), 3.00 (s, 3, NCH_3); AB quartet, doublets centered at 3.15 and 2.88 (1 each, J = 14 Hz, CH_2) [an AB quartet with doublets centered at 3.70 and 3.50 (1 each, J = 14 Hz, CH_2) was temperature dependent, the 100° spectrum showing almost complete coalescence to a singlet]; mass spectrum (70 eV) *m/e* (rel intensity) 338 (0.5), 247 (100), 169 (10), 159 (19), 92 (11), 91 (46) (Calcd for $C_{20}H_{22}N_2O_3$: 338.1630. Found: 338.1640.); uv 230 mμ (ϵ 2980).

Anal. Calcd for $C_{20}H_{22}N_2O_3$ (338.2): C, 70.98; H, 6.55; N, 8.28. Found: C, 71.06; H, 6.61; N, 8.13.

***trans*-Tetrahydrobarbiturate 8.**—The yield of crude, chromatographically pure **8** was 150.6 mg; the sample was recrystallized by solution of **8** in warm ethanol, and adding water to the solution (25°) until precipitation of **8** was complete: yield, 132.8 mg, mp 171–177° (best sample of **8** prepared had mp 183–187°

(21) E. L. Eliel and C. A. Giza, *J. Org. Chem.*, **33**, 3754 (1968).

(22) For a discussion of this point, see T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms," Vol. 1, W. A. Benjamin Inc., New York, N. Y., 1966, p 119.

(23) Thin layer chromatography: Thin layer chromatograms were prepared by coating microscope slides with silica gel H. Solvent systems employed were: solvent system A, benzene–ethyl acetate–acetic acid (90:10:1); solvent system B, ethyl acetate–chloroform (1:1); and solvent system C, ethyl acetate–chloroform (1:9). Zones were visualized by spraying the eluted chromatograms with 5% phosphomolybdic acid in ethanol (PMA) and, then, baking the slide on the surface of a hot plate (zones were developed within minutes). The reagent (PMA) permitted detection of **7**, **8**, or **9** at concentrations of 0.5 mg/ml (5-μl sample applied) and 0.3 mg/ml (10-μl sample applied).

Micromelting points were taken on a Kofler hot stage microscope and are uncorrected; where accumulation of moisture was observed before actual collapse of crystals, and where the observation proved characteristic, the melting point range connotes the points of significant moisture and complete fusion.

Ultraviolet spectra were recorded on a Cary Model 15 spectrophotometer; absolute ethanol was used as solvent. Nmr spectra were recorded on a Varian HA-100 instrument (North Carolina State University), except for compounds **6a** and **6b** whose solubility permitted use of the Varian A-60 instrument (Research Triangle Institute). Solutions for nmr spectra contained tetramethylsilane as an internal standard. Infrared spectra were measured with a Perkin-Elmer Model 257 instrument; samples were prepared in the form of pressed KBr disks.

Mass spectra (70 eV) were measured on a AEI-MS-902 spectrometer at the Research Triangle Institute Center for Mass Spectrometry. High resolution mass spectrographic measurements (peak matchings) were conducted by Mr. F. Williams (Research Triangle Institute Laboratory).

Micro analyses were carried out by Micro-Tech Laboratories, Skokie, Ill.

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with moisture first seen at 181°). Traces of **9** in a sample of **8** sometimes appeared *after recrystallization* (detectable by tlc, but not ir). Formation of **9** in such cases probably occurred after extraction of **8** from its silica zone, *i.e.*, when special care was not exercised during chloroform treatment;[14] though contamination of **8** by **9** was not apparent (by tlc) prior to recrystallization, *cis*-**9** (owing to its less solubility in polar solvents) was probably further concentrated in the sample by the recrystallization process. In a separate experiment, *trans*-**8** in aqueous ethanol showed no tendency for isomerization to *cis*-**9** (as evidenced by tlc during 12 hr). The following data were measured from a sample of **8** free of **9** (by tlc): ir (KBr disk) 3380–3340 (s), 1625 (s), 1595 (vs), 1530 (s), and 1500 cm^{-1} (m), the ratio of the 1625, 1595, and 1530 bands being about 7:11:8; nmr in $CDCl_3$[14] [saturated solution; a sample of **8** (10 mg) was suspended in $CDCl_3$ (0.45 ml) and was kept at 25° for 3 hr; insoluble **8** was filtered off and the spectrum was traced using a high recorder output], δ 4.40 (d, 2, J = 6 Hz, >CHOH), 4.16 (d, 2, J = 6 Hz, >CHOH), 3.10 (s, 2, CH_2), 2.80 (s, 6, two NCH_3), 2.56 (s, 2, CH_2) (deuterium exchange caused disappearance of the δ 4.40 doublet and collapse of the 4.16 doublet to a singlet); DMSO-d_6 (3%), δ 6.06 (d, 2, J = 6 Hz, >CHOH), 4.30 (d, 2, J = 6 Hz, >CHOH), 2.70 (s, 4, two CH_2) (the two NCH_3 resonances were seen as one sharp singlet at δ 2.40 protruding from the DMSO multiplet; deuterium exchange caused disappearance of the δ 6.06 doublet and collapse of the 4.30 doublet to a two-proton singlet); pyridine-d_5 (3%), sharp AB quartet, δ 7.75 (d, 2, J = 6 Hz, two >CHOH) and 5.00 (d, 2, J = 6.0 Hz, two >CHOH), 3.32 (s, 4, two benzylic CH_2), 2.92 (s, 6, two NCH_3) (deuterium exchange caused disappearance of δ 7.75 doublet and collapse of the 5.00 doublet to a sharp two-proton singlet); mass spectrum (70 eV) m/e (rel intensity) 340 (4), 322 (11), 263 (29), 236 (54), 231 (64), 224 (18), 206 (25), 172 (36), 146 (21), 133 (54), 115 (25), 92 (18), 91 (100), 42 (35) (Calcd for $C_{20}H_{24}N_2O_3$: 340.1787. Found: 340.1791.); uv 230 mμ (ϵ 330).

Anal. Calcd for $C_{20}H_{24}N_2O_3$ (340.2): C, 70.55; H, 7.10; N, 8.23. Found: C, 70.72; H, 7.12; N, 8.19.

cis-**Tetrahydrobarbiturate 9.**—The yield of crude, chromatographically pure **9** was 8.7 mg, the identity of which was established by comparison (tlc and ir) with material prepared from the acid-catalyzed rearrangement of **8**.

In the final three experiments conducted by I. J. D. (2.0-g runs of **4**), the overall, combined yield of crude, chromatographically pure products (*i.e.*, **4**, **7**, **8**, and **9**) ranged from 798 to 865 mg; yields of individual products in these experiments ranged as follows: **4** (90–154 mg), **7** (545–616 mg), **8** (91–150 mg), and **9** (5–9 mg).

Isomerization of 5,5-Dibenzyltetrahydro-*trans*-4,6-dihydroxy-1,3-dimethyl-2(1H)-pyrimidinone (8) to 5,5-Dibenzyltetrahydro-*cis*-4,6-dihydroxy-1,3-dimethyl-2(1H)-pyrimidinone (9).—To a stirred solution of **8** (73.8 mg, mp 176–184°, tlc indicating a trace of **9**) in tetrahydrofuran (5.0 ml) was added successively 3 drops of 6 *N* hydrochloric acid and 2.0 ml of water; after 2 min, tlc (solvent system B) indicated the conversion of **8** into **9** was complete. The solution was diluted with 10 ml of water and, while stirring was continued, nitrogen was bubbled through the solution (2 hr) to sweep out most of the THF. The precipitate (55.5 mg, chromatographically uniform) was filtered off, washed with water, and recrystallized from absolute ethanol, giving 54.7 mg of **9**: mp 191–193° with a trace of fusion first seen at 187°; ir (KBr disk) 3480 (m, sharp), 3190 (m, broad), 1615 (s), 1515 (s), 1500 (m), 1420 (m), 1070 (s), 1030 (s), and 1010 cm^{-1} (s); nmr in $CDCl_3$ (3%), δ 4.76 (d, 2, J = 7 Hz, >CHOH), 4.16 (d, 2, J = 7 Hz, >CHOH), 3.10 (s, 2, CH_2), 2.78 (s, 6, two NCH_3), 2.54 (s, 2, CH_2) (deuterium exchange caused the disappearance of the δ 4.76 doublet and collapse of the 4.16 doublet to a two-proton singlet); DMSO-d_6 (3%), δ 5.96 (d, 2, J = 7 Hz, >CHOH), 4.08 (d, 2, J = 7 Hz, >CHOH), 2.66 (s, 6, two NCH_3) [the other CH_2 (benzylic methylene) group was apparently obscured by the DMSO multiplet (or the water peak); deuterium exchange caused the disappearance of the δ 5.96 doublet and the collapse of the 4.08 doublet to a two-proton singlet]; pyridine-d_5 (3%), sharp AB quartet, δ 7.78 (d, 2, J = 6 Hz, two CHOH) and 4.50 (d, 2, J = 6 Hz, CHOH), 3.40 (s, 2, benzylic CH_2), 2.74 (s, 2, benzylic methylene), 3.01 (s, 6, two NCH_3). Deuterium exchange caused disappearance of δ 7.78 doublet and collapse of 4.50 doublet to a sharp two-proton singlet: mass spectrum (70 eV) m/e (rel intensity) 340 (5), 322 (10), 263 (19), 248 (13), 236 (40), 231 (60), 224 (18), 206 (20), 172 (26), 146 (15), 133 (50), 117 (14), 116 (11), 115 (23), 91 (100), 69 (23), 60 (17), 58 (18), 42 (38) (Calcd for $C_{20}H_{24}N_2O_3$: 340.1787. Found: 340.1791.); uv 230 mμ (ϵ 290).

Anal. Calcd for $C_{20}H_{24}N_2O_3$ (340.4): C, 70.56; H, 7.11; N, 8.23. Found: C, 70.74; H, 7.08; N, 8.21.

A conversion of **8** into **9** in alkaline solution could also be followed by tlc. Thus a solution of *trans*-tetrahydrobarbiturate **8** (50 mg) in methanol (1 ml) was treated with sodium methylate (25 mg) and the solution was let stand at 25° for 3 hr, during which tlc (solvent system B) indicated a conversion of **8** into **9**, in addition to a production of **7** (presumably autoxidation) and a new zone (unidentified, but giving a transient magenta color with PMA[27]) moving with the solvent front. Dilution of the solution with water (~5 ml) gave a white precipitate (20.2 mg, multiple zones on tlc) which furnished pure **9** (5 mg), mp 190–192°, upon recrystallization (absolute ethanol, 1 ml, −12°).

Reduction of 1,3-Dimethyl-6-hydroxy-1,3-dimethylhydrouracil (7) to 5,5-Dibenzyltetrahydro-*trans*-4,6-dihydroxy-1,3-dimethyl-2(1H)-pyrimidinone (8).—A total of 89.3 mg (2.36 mmol) of sodium borohydride was added in four portions during 20 min to a stirred solution of 200 mg (0.59 mmol) of **7** in 6.0 ml of absolute methanol; after the borohydride addition, the solution was stirred for an additional 40 min, whereupon tlc (solvent system B) indicated two reaction components, **7** and **8**. The solution was diluted with 10 ml of water, and the precipitate which separated during 3 hr (25°) was filtered off and washed with water: yield (vacuum dried) 163.6 mg, comprised solely of **7** and **8** (tlc). The sample (163.6 mg) was chromatographed on a thick layer plate (20 × 40 cm, 1.25-mm layer of silica gel HF_{254}, activated 18 hr at 75–80°, solvent system B), and the usual work-up gave crude **8** (62.2 mg, chromatographically uniform, mp 168.5–175°), confirmed by ir spectra and tlc. The recovery of crude **7** was 68.5 mg (chromatographically uniform), confirmed by tlc and ir spectra.

Hydrogenolysis of 1,3-Dimethyl-5,5-dibenzylbarbituric Acid (4) to 2-Benzyl-3-phenylpropan-1-ol (6a).—To a stirred solution of 1.0 g (2.97 mmol) of **4** in 50 ml of absolute ethanol (25°) was added a solution of 450 mg (11.9 mmol) of sodium borohydride in 15 ml of water at such a rate (~20 min) to avoid precipitation. The reduction was monitored by tlc, showing during 24 hr the production of **6a** (solvent system A), and **7**, **8**, and **9** (solvent system B). After 24 hr the solution was diluted with 75 ml of water and was extracted with three 50-ml portions of ether. The pooled ether extract was dried (Na_2SO_4) and evaporated to an oil, all of which was dissolved in a minimum volume of warm ethyl acetate (to which then was added just enough drops of methanol so that solution was maintained at room temperature). Preparative thick layer chromatography of this solution (one 20 × 40 cm plate coated with 1.25 mm of silica gel HF_{254}, activated 18 hr, solvent system C) gave a good separation of the four components: **6a**, **7**, **8**, and **9**. The compounds were isolated from the silica zones in the usual manner.

2-Benzyl-3-phenylpropan-1-ol (**6a**) was obtained as a chromatographically uniform oil (312 mg) which failed to crystallize in the cold (−12°) or from various solvent pairs: ir (CCl_4, 20%) 3640 (w), 3460 (broad, s), 1605 (m), and 1497 cm^{-1} (s); nmr ($CDCl_3$, 21%) δ 1.78 (s, 1, CH_2OH), 1.83–2.35 (m, 1, CH), 2.64 (d, 4, J = 7 Hz, two benzylic CH_2), 3.40 (d, 2, J = 5 Hz, CH_2OH), 7.20 (s, 10, aromatic ring **H**); mass spectrum (70 eV) m/e (rel intensity) 226 (20), 208 (8), 117 (80), 92 (76), 91 (100). No ions were observed above m/e 227 (P + 1).

Oil **6a** (312 mg, 1.38 mmol) and phenyl isocyanate (357 mg, 3.00 mmol) were each dissolved in carbon tetrachloride, and the solutions were mixed (total volume of the final solution was 2.0 ml) and let stand at room temperature for 20 hr. The solution was concentrated to one-half its volume and cooled; when crystallization was complete (~2 hr) the mixture was diluted with petroleum ether. The chromatographically uniform solid (410 mg, solvent system A) was filtered off and was recrystallized from absolute methanol (minimum volume, first at 25°, then −12°) to give **6b** (301 mg) as white needles, mp 101–104.5°. The analytical sample (three recrystallizations) had mp 105.5–106.5°; ir (KBr disk) 3282 (m), 1705 (s), 1605 (s), and 1555 cm^{-1} (s); nmr ($CDCl_3$) δ 2.10–2.80 (multiplet with protruding doublet at 2.67, J = 5 Hz, integrating to 5, two benzylic CH_2 and >CH), 4.05 (d, 2, J = 5 Hz, CH_2OCO), 6.70 (s, 1, NH), 7.00–7.50 (m, 15, aromatic ring **H**); mass spectrum (70 eV) m/e (rel intensity)

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345 (10), 208 (30), 117 (100), 91 (47) (Calcd for $C_{23}H_{23}NO_2$: 345.1729. Found: 345.1737.).

Anal. Calcd for $C_{23}H_{23}NO_2$ (345.4): C, 79.97; H, 6.71; N, 4.06. Found: C, 79.82; H, 6.77; N, 4.07.

Dihydrobarbiturate 7 (236 mg, chromatographically uniform, solvent system B) was obtained in crystalline form by the usual work-up and was confirmed by melting point and ir spectrum.

***cis*-Tetrahydrobarbiturate 9** (the apparent thermodynamic product) was obtained in crystalline form (47.7 mg) and was confirmed by its melting point and ir spectrum. A small quantity (estimated less than 15 mg) of a yellow gum having the thin layer properties of *trans*-tetrahydrobarbiturate **8** was also isolated, but not further investigated.

1,3-Dimethyl-6-methoxy-1,3-dimethylhydrouracil (12).—A solution of **7** (118 mg) in absolute methanol (5 ml) was treated with 2 drops of 6 *N* hydrochloric acid and was kept at 25° for 2.5 hr; tlc (solvent system A) showed a new major zone and only a faint zone of **7**. The solution was diluted with 15 ml of water, and the precipitate (112 mg, chromatographically uniform) which separated during 30 min was filtered off. The solid was recrystallized from absolute methanol (0.5–1.0 ml, first at 25°, then −12°), giving **12** (93.8 mg): mp 141.5–142.5°; ir (KBr disk) 1710 (s) and 1672 cm^{-1} (s); nmr ($CDCl_3$, 3%) δ 3.84 (s, 1, >CHOCH$_3$), 3.24 [s, 3, O(N)CH$_3$], 2.92 [s, 3, O(N)CH$_3$], 2.78 [s, 3, O(N)CH$_3$], 3.14 (s, 2, benzylic >CH$_2$), AB quartet 2.94 (d, 1, J = 14 Hz), and 2.54 (d, 1, J = 14 Hz) assigned to other benzylic >CH$_2$; mass spectrum (70 eV) *m/e* (rel intensity) 352 (18), 321 (24), 261 (89), 229 (29), and 91 (100); uv 230 mμ (ϵ 3130).

Anal. Calcd for $C_{21}H_{24}N_2O_3$ (352.4): C, 71.56; H, 6.86; N, 7.95. Found: C, 71.56; H, 6.85; N, 7.95.

4aβ-Benzyl-5,9bβ-dihydro-1,3-dimethyl-1H-indeno[1,2-*d*]pyrimidine-2,4(3H,4aH)-dione (13).—A solution of **7** (200 mg) in concentrated sulfuric acid (1 ml, sp gr 1.84) was effected at 25°, giving a deep yellow solution which was let stand for 30 min. Tlc (solvent system A) at the 30-min interval indicated a complete reaction (tlc of the reaction was conducted by adding 1 drop of the reaction solution to 1 ml of water, partitioning with ether, and spotting of the organic layer). The reaction solution was poured onto ice, and the precipitate (128 mg) was filtered off, washed with water, and recrystallized from absolute methanol (1–2 ml), giving **13** (100.2 mg): mp 153.0–154.5°; ir (KBr disk) 1710 (s) and 1680 cm^{-1} (s); nmr ($CDCl_3$, 5%) see text. Parts of the benzylic methylene resonances were obscured by the NCH$_3$; there were seen, however, a signal centered at δ 3.64 (d, 1, J = 16 Hz), one centered at 3.32 (d, 0.7, J = 12 Hz), and a signal protruding at 2.80. Integration of the aromatic multiplet (δ 7.0–7.4, which included a weak solvent peak) gave a sum of 8.9 protons. Its mass spectrum (70 eV) was comprised of *m/e* (rel intensity) 320 (6), 230 (15), 229 (100), 228 (6), 143 (12); uv 230 mμ (ϵ 3780).

Anal. Calcd for $C_{20}H_{20}N_2O_2$ (320.4): C, 74.97; H, 6.29; N, 8.75. Found: C, 74.83; H, 6.36; N, 8.67.

Jones Oxidations of Dihydrobarbiturate 7, *trans*-Tetrahydrobarbiturate 8, and *cis*-Tetrahydrobarbiturate 9. Dihydrobarbiturate 7.—A solution of **7** (50.0 mg) in acetone (10 ml, distilled from permanganate) was stirred at 0–5° and 0.1 ml of Jones reagent[28] was added. The oxidation was indicated complete after 40 min (tlc, solvent system A), and the solution was diluted with 60 ml of water. The white precipitate (43.6 mg, chromatographically uniform, and identical with **4** as judged by comparison by tlc and ir spectra) was filtered off and was recrystallized from absolute ethanol to give **4** (28.1 mg), mmp 132–134.5°.

***cis*-Tetrahydrobarbiturate 9.**—A sample of **9** (31.65 mg) was oxidized with 0.1 ml of Jones reagent in the same manner to give crude **4** (21.7 mg, chromatographically pure, and identical with authentic **4** as judged by tlc and its ir spectrum), which was recrystallized from absolute ethanol to give 9.0 mg of pure **4**, mmp 132.5–136°.

***trans*-Tetrahydrobarbiturate 8.**—A sample of **8** (12.0 mg) in 2.0 ml of acetone (0–5°) was oxidized with Jones reagent (3 drops) to give 8.87 mg of crude **4** (mp 127–132.5°, chromatographically pure), which was identified by comparative tlc and its ir spectrum.

Stabilities of 8 and 9 in "Spent" Methanolic Borohydride Solution.—A solution of sodium borohydride (225 mg) in absolute methanol (15 ml) (strong hydrogen evolution for 15–20 min) was loosely stoppered and was kept at 25° for 16 hr prior to use.

Samples (10 mg) of *trans*-**8** and *cis*-**9** were each dissolved in 0.3 ml of the "spent" borohydride solution, and each solution was checked by tlc (solvent system B) on the hour for 6 hr and then after 24 hr.

cis-**9** was stable, its tlc showing only one zone during 24 hr; at the 24 hr mark, its methanolic solution was diluted with water to precipitate pure **9** (6.1 mg, identified by tlc and ir).

trans-**8** showed no evidence for isomerization to *cis*-**9** during 4 hr, but did show a new zone moving at the solvent front (magenta color with PMA,[23] presumably the degradation product noted above with sodium methylate, MeOH); at the 5-hr mark, a trace of *cis*-**9** could be detected; after 24 hr, the zone of *cis*-**9** remained faint, but was more definite (the three-component mixture was largely *trans*-**8**). Dilution of the methanolic solution with water precipitated pure crystalline **8** (5.3 mg, identified by tlc and ir).

Infrared Spectral Data.—Some solid state (KBr, Nujol) and solution (dioxane) spectral values for related, well-characterized compounds have been reported elsewhere.[3a-c,27]

Saturated solutions of **8** and **9** in carbon tetrachloride (spectrograde) were prepared by suspending finely divided samples (2.0 mg/ml) of each compound in solvent at 25°; suspensions were agitated (25°) for 30–90 min prior to filtration and the spectral measurement. Measurements were made on a Perkin-Elmer 221 spectrophotometer, operating at the maximal ordinate expansion (20×) of the absorbance scale; sodium chloride windows having a 3.0-mm thickness were used. *trans*-**8** was too insoluble for a measurement. *cis*-**9** gave a spectrum in some trials, but no significance was attached to the data (3612, 3525, and 1715 cm^{-1}); we were unable to reproduce this spectrum at will (numerous trials), and it was indicated in other trials that the compound was undergoing changes during the measurement (loss of 3612 and 1715 cm^{-1} absorption).

Of the spectra measured from the solid state (*i.e.*, KBr spectra of **4**, **7**, **8**, **9**, **15**, and **16**), only that of **8** showed bands (*e.g.*, 1595 and 1535 cm^{-1}) in the amide II–amide III band region These bands would seemingly indicate ring-opened structure **11** for **8**. However, the 1625-cm^{-1} band ($\nu_{2\text{-CO}}$) was considered "too low" for assignment to a formyl group of **11** and, in addition, the spectrum was void of absorption at 2700–2800 cm^{-1}, a region commonly inspected for confirmation of a formyl group. None of the ring-closed compounds showed significant absorption in the amide II–amide III region when spectra were measured from solution ($CHCl_3$ and/or CCl_4, Table I).

TABLE I

INFRARED SPECTRA DATA OF DIHYDROURACIL AND 2(1H)-PYRIMIDINONE DERIVATIVES IN CHLOROFORM AND/OR CARBON TETRACHLORIDE SOLUTION

Compound	Phase (concentration)	ν_{OH}	$\nu_{4\text{-CO}}$	$\nu_{2\text{-CO}}$
7	$CHCl_3$ (0.1 *M*)[a]	3600 3480	1720	1673
7	CCl_4 (0.0005 *M*)[b]	3608 3540 (sh)	1715	1675
15	$CHCl_3$ (0.1 *M*)[a]		1720	1675
16	$CHCl_3$ (0.1 *M*)[a]		1711	1672
4	$CHCl_3$ (0.1 *M*)[a]		1755	1682

[a] Perkin-Elmer Model 257 infrared spectrophotometer; sodium chloride windows having a 0.05-mm thickness were used for solution spectra. [b] Perkin-Elmer Model 221 infrared spectrophotometer; sodium chloride windows having a 3.0-mm thickness were used for carbon tetrachloride spectra. Good visualization of the ν_{OH} bands of **7** (in CCl_4) required a 20× ordinate expansion; the ν_{CO} region required either 10× or 5× expansion; programming for ordinate expansions was made according to recommendations in the instrument manual. Spectral values were also measured from 1×10^{-3} *M* and saturated solutions, and were identical with values noted in Table I.

Registry No.—Sodium borohydride, 1303-74-8; **4**, 21991-30-0; **6a**, 21991-31-1; **7**, 21991-32-2; **8**, 21996-

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78-1; **9**, 22037-96-3; **12**, 21991-33-3; **13**, 21996-79-2; **15**, 66-22-8; **16**, 22027-12-9.

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Syntheses and Reactions of Phosphates from Dibromoanthrone, Anthraquinone Anil, and 1,8-Dichloroanthraquinone

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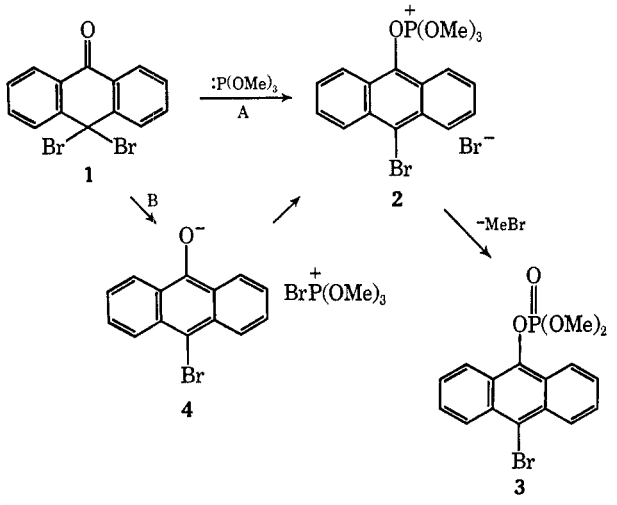
10,10-Dibromoanthrone and trimethyl phosphite gave dimethyl (10-bromo-9-anthryl) phosphate, which in turn gave Diels–Alder adducts from maleic anhydride and acrylic acid. The acrylic acid adduct had the carboxylic acid group vicinal to the bridgehead bromine atom, which was verified by cleavage in hydriodic acid to the corresponding bridgehead alcohol. Dimethyl (10-anilino-9-anthryl) phosphate was formed from anthraquinone anil and methyl phosphite; no attack of trimethyl phosphite at the imino center was observed. This phosphate easily formed an adduct with maleic anhydride which was opened with hydriodic acid to yield (10-keto-9,10-dihydro-9-anthryl)succinic acid. 1,8-Dichloroanthraquinone and trimethyl phosphite in glacial acetic acid gave 1,8-dichloro-10-dimethylphosphato-9-anthrone. This reaction appears to be general, and dimethyl (4-hydroxytetrachlorophenyl) phosphate was similarly formed from chloranil and trimethyl phosphite in acetic acid.

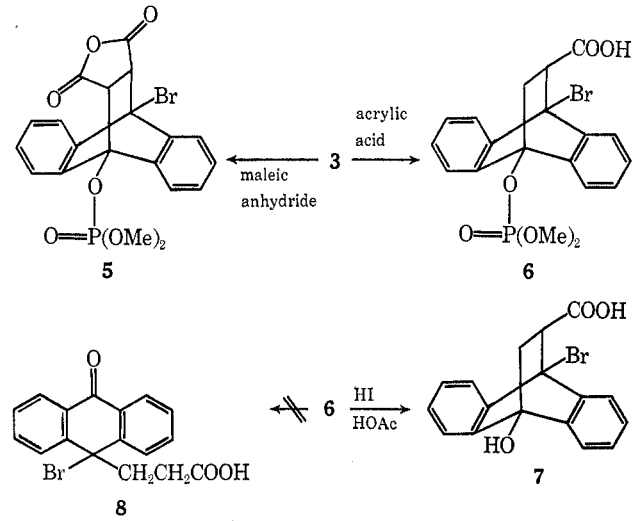
4-Bromo-2,5-cyclohexadienones have been reported to react with trialkyl phosphites to give dialkyl aryl phosphates.[2a,3a,b] Analogous reactions are known between α-haloaldehydes, such as chloroacetaldehyde, and trialkyl phosphites, which give vinyl phosphates.[2b,4,5] This suggests that the unstudied 10-halo-9-anthrones should react with trimethyl phosphite to give dimethyl 9-anthryl phosphates, which would provide a route to new 9,10-disubstituted anthracenes suitable for the continuation of our orientation studies in the Diels–Alder reaction.

10,10-Dibromoanthrone (**1**) was found to react rapidly and exothermically with trimethyl phosphite to give dimethyl (10-bromo-9-anthryl) phosphate (**3**) in high yield. Two mechanisms have been proposed for this type of reaction. One (path A) involves nucleophilic attack of trimethyl phosphite at the carbonyl center to form quaternary phosphonium salt **2**, which gives the product by intermolecular demethylation. The other (path B) involves attack of trimethyl phosphite on bromine to form ion pair **4** which then leads to the product *via* the same intermediate as path A.

There has been considerable discussion of these two mechanisms.[2c,3a,6–8] Certain α-cyclohexanones are considered to react with triethyl phosphite without initial attack of phosphorus on halogen,[8] while Miller has presented evidence that 4-bromo-2,5-cyclohexadienones go by path B.[3b] Compound **1** can be considered to be analogous to a 4-bromo-2,5-cyclohexadienone.

Phosphate **3** formed adduct **5** with maleic anhydride easily, but the acrylic acid adduct, **6**, was formed in





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