The Synthesis of Some New Azabenzo[a]pyrenes and Monomethylazabenzo[a]pyrenes[1a]

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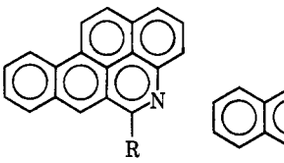
4-Azabenzo[a]pyrene (**1a**), 5-methyl-4-azabenzo[a]pyrene (**1b**), 12-azabenzo[a]pyrene (**3a**), 11-methyl-12-azabenzo[a]pyrene (**3b**), 5-azabenzo[a]pyrene (**2a**), and 4-methyl-5-azabenzo[a]pyrene (**2b**) were obtained in good yields by the Bischler–Napieralski cyclodehydration of the appropriate amides with polyphosphoric acid. The ultraviolet absorption and nuclear magnetic resonance spectra of all six compounds were consistent with their assigned structures. These compounds are being submitted for both carcinogenic and carcinostatic testing.

Benzo[a]pyrene and many of its derivatives have been shown to be powerful carcinogens, and a study of the carcinogenic activity of some methylated benzo[a]pyrenes prepared in this laboratory has been reported recently.[2] In addition, benzo[a]pyrene has been shown to exhibit antitumor action.[3-5] Several years ago we initiated a program to synthesize a number of azabenzo[a]pyrenes for use in carcinogenic and carcinostatic studies in the hope that such compounds would exhibit a lower carcinogenic activity and possibly a higher carcinostatic activity than the parent hydrocarbon. The substitution of methyl groups in the 1, 2, 3, 4, 5, 6, 11, and 12 positions gives monomethylbenzo[a]pyrenes which are highly carcinogenic. It was felt that a study should be made of compounds with nitrogen heteroatoms in these positions. The 1-, 3-, and 6-aza derivatives should be of particular interest since these positions are attacked in metabolism in rats whereby the animal oxidizes the carcinogen.[6]

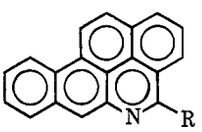
The syntheses of only three of the possible 12 azabenzo[a]pyrenes have been reported; namely, 10-azabenzo[a]pyrene,[7,8] 8-azabenzo[a]pyrene,[8] and 7-azabenzo[a]pyrene.[8] We are reporting herewith the synthesis of three new azabenzo[a]pyrenes, namely the 4-, 5-, and 12-aza derivatives (**1a**, **2a**, and **3a**, respectively) as well as the 5-methyl-4-, 4-methyl-5-, and 11-methyl-12-azabenzo[a]pyrenes (**1b**, **2b**, and **3b**, respectively).

Of particular interest are the 4- and 5-azabenzo[a]pyrenes and their methyl derivatives, since they are the first azabenzo[a]pyrenes to be prepared in which the annular nitrogen atom is located in the K region of the benzo[a]pyrene skeleton.

4-Keto-1,2,3,4-tetrahydrochrysene (**4**) and 1-keto-1,2,3,4-tetrahydrobenz[a]anthracene (**5**) were prepared according to previously described procedures to be converted, respectively, to 4-formamido-1,2,3,4-tetrahydrochrysene (**6**) and 1-formamido-1,2,3,4-tetrahydrobenz[a]anthracene (**7**) *via* the Leuckart reaction.[9] Indeed, 4-keto-1,2,3,4-tetrahydrochrysene (**4**) afforded the formamide **6** in 85% yield *via* the Leuckart reaction with formamide and formic acid. All attempts to cyclize the formamide **6** to 1,2,3,3a-tetrahydro-4-azabenzo[a]pyrene failed with the usual Bischler–Napieralski reagents.



1a, R = H; **b**, R = CH_3



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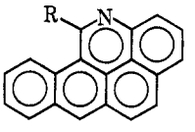
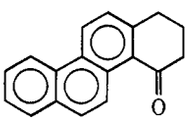


3a, R = H; **b**, R = CH_3



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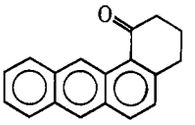

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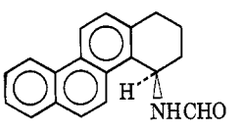

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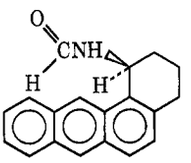

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Examination of molecular models of the amide **6** indicated that the formamido group was not in a conformation suitable for facile attack at the aromatic ring carbon. It has been reported by Cook and Thomson[10] that the cyclization of 4-formamidophenanthrene (**8**) with phosphorus pentoxide in refluxing xylene gave 4-azapyrene (**9**) in 33% yield. Studies in this laboratory of the Bischler–Napieralski cyclization of 4-formamido-1,2,3,4-tetrahydrophenanthrene (**10**) to 1,2,3,3a-tetrahydro-4-azapyrene (**11**) showed this amide to be equally as inert towards cyclodehydration as the amide **6**.[11] We, therefore, abandoned the approach *via* the tetrahydroamides **6** and **7**, and turned our attention to aromatized amides similar to 4-formamidophenanthrene.

The ketones **4** and **5** were converted to their respective azines **12a** and **12b** in nearly quantitative yields by heating with 95% hydrazine in alcohol containing hydrochloric acid.[12] Dehydrogenation of the

(1) (a) From the dissertation presented by Richard E. Phillips, Jr., to the graduate faculty of the University of New Mexico in partial fulfillment of the requirements for the degree of Doctor of Philosophy. This investigation was supported in part by a Research Grant (C-4714) from the National Cancer Institute of the National Institutes of Health, U. S. Public Health Service. (b) National Science Foundation Trainee, 1965–1969. (c) Author to whom inquiries should be directed. (d) Graduate Research Assistant, Feb 1960 to June 1962.

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(10) J. W. Cook and W. H. S. Thomson, *J. Chem. Soc.*, 395 (1945).

(11) G. H. Daub and R. L. Taber, unpublished work.

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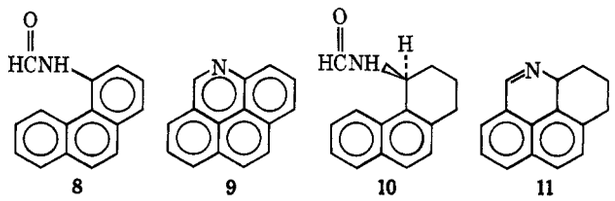

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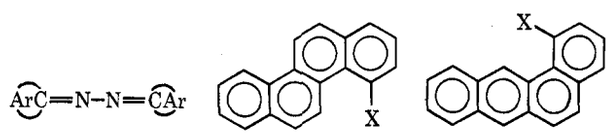
azines **12a** and **12b** with 10% palladium on charcoal in refluxing triethylbenzene afforded the amines **13b** and **14b**, isolated as their hydrochlorides, **13a** and **14a**, in 59 and 48% yields, respectively.



12a, azine from **4**
b, azine from **5**

13 14

a, X = NH_3Cl
b, X = NH_2
c, X = NH(C=O)H
d, X = $NH(C{=}O)CH_3$

Liberation of the free amines from the hydrochloride salts with aqueous ammonia followed by acylation with formic acid or acetyl chloride afforded 4-formamidochrysene (**13c**), 4-acetamidochrysene (**13d**), 1-formamidobenz[*a*]anthracene (**14c**), and 1-acetamidobenz[*a*]anthracene (**14d**) in 76, 72, 68, and 44% yields, respectively (see Table I).

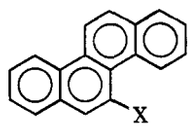
TABLE I

PHYSICAL PROPERTIES AND YIELDS FOR THE FORMAMIDES AND ACETAMIDES[c]

$ArNH_2$	ArNHCOR	Yield, %	Mp, °C
Ar = 4-Chrysenyl (**13b**)	**13c**,[a] R = H	76	246.5–247.5
	13d,[a] R = CH_3	72	245–246
Ar = 1-Benz[*a*]-anthracenyl (**14b**)	**14c**,[a] R = H	68	268–268.5
	14d,[a] R = CH_3	44	265–266
Ar = 5-Chrysenyl (**15d**)	**15e**,[b] R = H	77	253–253.5
	15f,[b] R = CH_3	71	250–251

[a] Sublimed at reduced pressure and crystallized from ethyl acetate. [b] Crystallized from ethyl acetate. [c] Satisfactory analytical data (±0.4% for C and H) were reported for all new compounds listed in the table.

The amides **15e** and **15f** were prepared *via* chrysene-5-carboxylic acid (**15a**), which was readily available using the method of Fieser and Joshel.[13] The Schmidt reaction of chrysene-5-carboxylic acid (**15a**) with sodium azide in a mixture of trifluoracetic acid, trifluoroacetic anhydride, and chloroform was carried out in a manner similar to that described by Rutherford and Newman.[14] The expected chrysene-5-isocyanate (**15b**) and 5-trifluoroacetamidochrysene (**15c**) were obtained, the latter product probably resulting from reaction of the isocyanate **15b** with trifluoroacetic acid. The crude mixture of **15b** and **15c** upon hydrolysis with alcoholic potassium hydroxide afforded 5-aminochrysene (**15d**) in 92% overall yield from **15a**. Formylation and acetylation of the amine **15d** afforded 5-formamidochrysene (**15e**) and 5-acetamidochrysene (**15f**) in 77 and 71% yields, respectively (see Table I).



15a, X = COOH
b, X = N=C=O
c, X = $NH(C{=}O)CF_3$
d, X = NH_2
e, X = NH(C=O)H
f, X = $NH(C{=}O)CH_3$

A study of the Bischler–Napieralski cyclodehydration of the formamide **8** to 1-azapyrene (**9**) using a variety of reagents (*e.g.*, phosphorus pentoxide in refluxing xylene, anhydrous hydrofluoric acid, polyphosphate ester, phosphorus oxychloride, aluminum chloride in methylene chloride, and polyphosphoric acid) showed polyphosphoric acid to be the most effective. Cannon and Webster[15] also showed polyphosphoric acid to be a more effective Bischler–Napieralski catalyst than the more classical condensing agents in a study of the cyclization of some *N*-acylphenylethylamines to the corresponding 3,4-dihydroisoquinolines.

Thus, cyclization of the amides **13c**, **13d**, **14c**, **14d**, **15e**, and **15f** to the corresponding azabenzo[*a*]pyrenes **1a**, **1b**, **3a**, **3b**, **2a**, and **2b** was accomplished by heating with polyphosphoric acid, the crude products being obtained in excellent yields (see Table II).

TABLE II

THE BISCHLER–NAPIERALSKI CYCLODEHYDRATION OF THE AMIDES TO THE AZABENZO[a]PYRENES WITH POLYPHOSPHORIC ACID[e]

Amide	Azabenzo[*a*]-pyrene	Reaction time, hr	Reaction temp, °C	Yield,[a] %	Mp, °C
13c	**1a**[b,c]	2.0	150	66	173.5–174
13d	**1b**[b,d]	2.0	150	59	160.5–161.5
14c	**3a**[c]	1.5	130	80	230–231
14d	**3b**[c]	1.5	130	53	184–185.5
15e	**2a**[c]	1.5	130	75	225–226.5
15f	**2b**[c]	1.5	130	80	190.5–191.5

[a] Yield of purified material. In all cases the crude yields were in the range of 96% of material with melting points not more than 10° below that of pure material. [b] Chromatographed on Woelm alumina (basic); column eluted with 7.5:1 benzene–ethyl acetate. [c] Recrystallized from ethyl acetate. [d] Recrystallized from benzene. [e] Satisfactory analytical data (±0.4% for C, H, and N) were reported for all new compounds listed in the table.

The similarity of the ultraviolet absorption spectra of these new azabenzo[*a*]pyrenes to that of benzo[*a*]pyrene[16] strongly supports their structures. The ultraviolet absorption spectra of these new compounds were in no way similar to those of chrysene and benz[*a*]anthracene.

The nuclear magnetic resonance spectra of these compounds also substantiates their assigned structures. Each of the unsubstituted azabenzo[*a*]pyrenes (**1a**, **2a**, and **3a**) has a one-proton singlet absorption with a δ value of between 10.24 and 10.46 ppm appear-

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(14) K. G. Rutherford and M. S. Newman, *ibid.*, **79**, 213 (1957).
(15) J. G. Cannon and G. L. Webster, *J. Amer. Pharm. Ass.*, **47**, 353 (1958).
(16) "U. V. Atlas of Organic Compounds," Vol. IV, Plenum Press, New York, N. Y., 1968, E6/20.

ing downfield from the other aromatic protons. These other aromatic protons appear as multiplets with δ values between 7.69 and 8.94 ppm. These singlet protons have been assigned to the position adjacent to the nitrogen atom in each of the three unsubstituted compounds, owing to the fact that this absorption peak disappears in the spectrum of each of the three monomethyl derivatives (**1b**, **2b**, and **3b**), and is replaced by a sharp three-proton singlet between δ values of 2.99 and 3.58 ppm. This sharp singlet is, of course, assigned to the methyl group in each case. The remaining aromatic protons of the monomethyl derivatives appear as a multiplet between δ values of 7.60 and 8.80 ppm.

Experimental Section[17]

4-Formamido-1,2,3,4-tetrahydrochrysene (**6**).—A mixture of 9.84 g (0.04 mol) of 4-keto-1,2,3,4-tetrahydrochrysene (**4**), mp 119–122°,[18–20] 80 ml of formamide, and 1.0 ml of 90% formic acid was heated at 175° in a 200-ml round-bottomed flask equipped with a stirrer, thermometer, and take-off condenser as described in "Organic Reactions,"[9] an additional 1.0 ml of formic acid being added every 2 hr over a period of 8 hr until a total of 5.0 ml of formic acid had been added. The reaction mixture was heated at 175° for a total of 13 hr, after which time it was cooled and the solid which separated was collected, washed with water, and air dried, affording 9.46 g (85.5% yield) of light tan crystals, mp 206–210°. Crystallization from benzene gave a first crop of 7.83 g of 4-formamido-1,2,3,4-tetrahydrochrysene (**6**) as a colorless solid, mp 211.5–212.5°. An analytical sample, mp 211.5–212.5°, was obtained by further recrystallization from benzene.

Anal. Calcd for $C_{19}H_{17}NO$: C, 82.88; H, 6.22. Found: C, 83.13; H, 6.22.

4-Keto-1,2,3,4-tetrahydrochrysene Azine (**12a**) and **1-Keto-1,2,3,4-tetrahydrobenz[*a*]anthracene Azine** (**12b**).—To a mixture of 3.2 g (0.013 mol) of 4-keto-1,2,3,4-tetrahydrochrysene (**4**) and 20 ml of 95% ethanol was added 0.35 ml (0.01 mol) of 95% hydrazine and 20 drops of concentrated hydrochloric acid.[12,21] The mixture was refluxed for 24 hr, after which time the precipitate was collected, triturated with hot ethanol, and dried to give 3.17 g (99.8% yield) of 4-keto-1,2,3,4-tetrahydrochrysene azine (**12a**) as a yellow solid, mp 309–310° (evacuated tube).

Anal. Calcd for $C_{36}H_{28}N_2$: C, 88.49; H, 5.78. Found: C, 88.44; H, 5.86.

Similar treatment of 1-keto-1,2,3,4-tetrahydrobenz[*a*]anthracene (**5**)[22] afforded a quantitative yield of orange 1-keto-1,2,3,4-tetrahydrobenz[*a*]anthracene azine (**12b**), mp 328.5–329° (evacuated tube).

Anal. Calcd for $C_{36}H_{28}N_2$: C, 88.49; H, 5.78. Found: C, 88.04; H, 5.76.

4-Aminochrysene Hydrochloride (**13a**) and **1-Aminobenz[*a*]anthracene Hydrochloride** (**14a**).—To a refluxing solution of 2.0 g (4.1 mmol) of 4-keto-1,2,3,4-tetrahydrochrysene azine (**12a**) in 150 ml of triethylbenzene (redistilled technical grade) was slowly added 0.6 g of 10% palladium on charcoal catalyst (Matheson Coleman and Bell, #5865).[12,21] The mixture was refluxed for 1 hr, after which time the hot mixture was filtered and the residue was washed with hot benzene. The combined filtrate and washings were allowed to cool and the small amount of yellow fluorescent precipitate which appeared was collected, washed with benzene, and discarded. The filtrate was saturated with dry hydrogen chloride and the precipitate which formed was collected, washed with ether, and dried. The dark green 4-aminochrysene hydrochloride (**13a**) thus obtained amounted to 1.35 g (59% yield). Attempts to obtain the pure amine from the hydrochloride were met with difficulty and therefore it was isolated and analyzed as its formyl and acetyl derivatives as described below.

Similar treatment of 1-keto-1,2,3,4-tetrahydrobenz[*a*]anthracene azine (**12b**) (reflux 1.5 hr) afforded a 48% yield of 1-aminobenz[*a*]anthracene hydrochloride (**14a**), which was directly converted to its acetyl and formyl derivatives as described below.

5-Aminochrysene (**15d**).—To a cold swirling solution (4°) of 1.0 g (3.7 mmol) of chrysene-5-carboxylic acid (**15a**),[13,23] mp 222.5–223.5°, 8.2 ml of trifluoroacetic acid, 8.2 ml of trifluoroacetic anhydride, and 25 ml of chloroform was slowly added 0.48 g (7.4 mmol) of sodium azide.[15] This mixture was stirred in the cold for 35 min, during which time a gray precipitate appeared. The mixture was filtered and the gray precipitate thus collected was washed with water, a portion of the precipitate being water soluble. The gray material which remained was dried and weighed 0.5 g, mp 160–161°. A small portion of this material was crystallized from ethyl acetate to give chrysene-5-isocyanate (**15b**) as a white, flocculent solid, mp 160–161°.

Anal. Calcd for $C_{19}H_{11}NO$: C, 84.74; H, 4.12. Found: C, 85.01; H, 4.27.

The organic solvents were removed from the filtrate above under reduced pressure, leaving 0.5 g of a brown solid, mp 230–250°. A small portion of this material was crystallized from ethyl acetate to give a solid, mp 247–247.5°. This compound was shown to contain fluorine by elemental analysis, and has been identified as 5-trifluoroacetamidochrysene (**15c**).

Anal. Calcd for $C_{20}H_{12}NOF_3$: C, 70.80; H, 3.54. Found: C, 71.20; H, 3.17.

The crude isocyanate **15b** and crude trifluoroacetamide **15c** were combined and mixed with 50 ml of 70% ethanol and 0.7 g of potassium hydroxide.[15] This mixture was refluxed for 4 hr, after which time it was poured over ice and allowed to stand overnight. The yellow precipitate which appeared was collected, washed with water, and dried to afford 0.74 g (92% yield) of crude 5-aminochrysene (**15d**), mp 141–148°. This material was crystallized from cyclohexane, yielding 0.64 g of yellow needles, mp 148.5–149.5°.

Anal. Calcd for $C_{18}H_{13}N$: C, 88.86; H, 5.39. Found: C, 88.88; H, 5.59.

General Procedure for the Preparation of the Formamides and Acetamides.—The appropriate amine hydrochloride (**13a** or **14a**) was decomposed with excess dilute ammonia or sodium carbonate solution and the liberated amine was extracted into ether. The ether solution was dried ($MgSO_4$) and the ether was removed. The crude amine (**13b** or **14b**) thus prepared or 5-aminochrysene (**15d**), mp 144–148°, was heated with an excess (5:1) of 97% formic acid on a steam bath until the excess formic acid had evaporated. The crude formamide (**13c**, **14c**, or **15e**) was triturated with water or 5% sodium carbonate solution, filtered, washed with water, dried, and purified as indicated in Table I.

The crude amine **13b**, **14b**, or **15d** was allowed to react with an excess (2:1) of acetyl chloride in pyridine solution (stirring) in an ice bath for 10–45 min, after which time the reaction mixture was allowed to warm to room temperature. The mixture was poured over ice, and the precipitate was collected, washed with dilute hydrochloric acid and water, and dried. The crude acetamide thus obtained was purified as indicated in Table I.

General Procedure for the Preparation of the Azabenzo[*a*]pyrenes and Their Methyl Derivatives.—The amides **13c**, **13d**, **14c**, **14d**, **15e**, and **15f** were cyclized with polyphosphoric acid (prepared according to Gilmore and Horton[24] from 24.8 g of phosphorus pentoxide and 16 ml of 85% phosphoric acid) by stirring a mixture of 1 g of amide with the acid for 1.5–2 hr at 125–130 for amides **13c**, **13d**, **14c**, and **14d** and 145–150° for amides **15e** and **15f**. The viscous reaction mixture was poured into ice water, stirred, and made basic with concentrated ammonia, and the precipitated azabenzo[*a*]pyrene was collected, washed with water, and dried. The crude products thus obtained were purified as shown in Table II.

(17) All melting points were taken in Pyrex capillary tubes in a Hoover-Thomas melting point apparatus and are uncorrected. Ultraviolet spectra were taken in 95% ethanol solution and were run on a Cary Model 14 spectrophotometer. Nmr spectra were run on a Varian Associates Model A-60A spectrometer in deuteriochloroform.

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(19) D. Phillips, *ibid.*, **75**, 3223 (1953).

(20) W. E. Bachmann and W. S. Struve, *J. Org. Chem.*, **4**, 456 (1939).

(21) E. C. Horning and M. G. Horning, *J. Amer. Chem. Soc.*, **69**, 1907 (1947).

(22) J. W. Cook and A. M. Robinson, *J. Chem. Soc.*, 505 (1938). Using 2 mol of aluminum chloride per mole of succinic anhydride in the Friedel–Crafts reaction with anthracene almost doubled the yield reported by these workers, who used these reagents in a 1:1 ratio.

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(24) R. C. Gilmore and J. W. Horton, *J. Amer. Chem. Soc.*, **73**, 1411 (1951).

Registry No.—**1a**, 24499-89-6; **1b**, 34440-84-1; **2a**, 24496-61-5; **2b**, 34440-86-3; **3a**, 24496-65-9; **3b**, 34440-88-5; **6**, 34440-89-6; **12a**, 34440-90-9; **12b**, 34440-91-0; **13c**, 34440-94-3; **13d**, 34440-92-1; **14c**, 34440-93-2; **14d**, 34440-95-4; **15b**, 34440-96-5; **15c**, 34440-97-6; **15d**, 34440-98-7; **15e**, 34440-99-8; **15f**, 34441-00-4.

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Notes

Cycloalkanones. I. The Stereochemistry of α,α'-Dibenzylcycloalkanones

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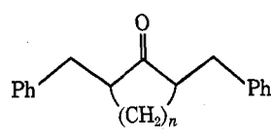
In the course of investigation of cycloalkanones for possible drug uses,[2] it became necessary to establish the stereochemistry of the series of α,α'-dibenzylcycloalkanones **1**–**4**. The *cis*- (**2a**) and *trans*- (**2b**) cyclo-



1, $n = 2$ **3**, $n = 4$
2, $n = 3$ **4**, $n = 5$

hexanones are known in the literature.[3,4] Both *cis*- (**1a**) and *trans*- (**1b**) cyclopentanone have been reported,[5] but the sterochemistry has not been established. A liquid dibenzylcycloheptanone has been reported[6] as well as its oxime.[7] The cis (**3a**) and trans (**3b**) isomers have not been isolated previously. Neither *cis*- (**4a**) nor *trans*- (**4b**) dibenzylcyclooctanone is known. In the present work, all four pairs of isomers were isolated and their configurations established.

The configurations of the isomeric ketones were established by lithium aluminum hydride reduction. Analysis for the number of alcohols obtained in each case was by vpc. The results are given in Table I. The assignment of the cyclohexanone isomers was consistent with the literature.[3] As a further check on the analysis, samples of the alcohols from both isomers of the cyclohexanone and cyclooctanone compounds were isolated by preparative vpc and used for mass spectral analysis. All showed the correct molecular ion peak. The molecular ion peak was small in all cases, but each had a large P − 18 peak, confirming that the compounds seen by vpc were the alcohols.

TABLE I
NUMBERS OF ALCOHOLS PRODUCED ON $LiAlH_4$ REDUCTION OF α,α'-DIBENZYLCYCLOALKANONES

Compd	Mp, °C	No. of alcohols[a]	Assigned configuration
1a	39–40	2	cis
1b	54–55	1	trans
2a	119–122	2	cis
2b	55	1	trans
3a	*b*	2	cis
3b	*c*	1	trans
4a	84–85	2	cis
4b	82–83	1	trans

[a] From $LiAlH_4$ reduction. [b] First ketone isolated during column chromatography. [c] Second ketone isolated during column chromatography.

As it was necessary for biological correlation to know which isomer predominated in an equilibrating system, one isomer of each pair of ketones was equilibrated in 0.1 *M* NaOEt, in ethanol. Samples were taken at 24-hr intervals until no change was seen. The cyclohexanones and cyclooctanones were separable as the ketones, but the cycloheptanones had to be reduced to the alcohols with $NaBH_4$. The equilibrium concentration of the cyclopentanones was not obtained owing to the inability to separate either the ketones or the alcohols on a variety of columns. The two alcohols from the cis ketone could be separated, but one of them overlapped the alcohol from the trans ketone. The equilibrium concentrations are given in Table II.

TABLE II
EQUILIBRIUM CONCENTRATIONS OF α,α'-DIBENZYLCYCLOALKANONES IN 0.1 *M* NaOEt IN ETHANOL

Compd	cis, %	trans, %
2	88	12
3	35	65
4	40	60

Experimental Section

All melting points are uncorrected and were obtained on a Mel-Temp apparatus. Analytical vpc utilized a Packard model 800 and preparative vpc utilized a Varian Aerograph Model 202. The α,α'-dibenzylidenecycloalkanones were prepared by base-catalyzed condensations of benzaldehyde with the appropriate

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