Communications TO THE EDITOR

Pentacyclo[5.3.0.0^{2,6}.0^{3,9}.0^{4,8}]decane

Sir:

We would like to report the synthesis of the title compound, I. Treatment of dodecachloropentacyclo[5.3.0.0^{2,6}.0^{3,9}.0^{4,8}]decane,[1] II, with lithium and *t*-butyl alcohol in tetrahydrofuran[2] afforded I, m.p. 125–127°, in approximately 35% yield, as well as *endo*-dicyclopentadiene, III.

The structural assignment of I was based on the following information. *Anal.* Calcd. for $C_{10}H_{12}$: C, 90.85; H, 9.15; mol. wt., 132. Found: C, 90.40; H, 9.51; mol. wt., 129 (cryoscopy, benzene); 132 (mass spectrometry). The infrared spectrum showed absorption maxima (CCl_4) at 3.45 (s), 3.58 (s), 6.97 (m), 7.67 (s), 7.90 (s), 8.10 (m), 8.22 (m), 9.91 (m), 10.13 (w), 10.56 (m), 11.16 (m), and 11.63 (w) μ. The ultraviolet spectrum showed no significant absorption above 200 mμ; the only semblance of a peak was observed at 213 mμ, with an extinction coefficient of 80. The NMR spectrum (Fig. 1) showed the absence of vinyl hydrogen atoms. Hence, unsaturation would have to arise from a tetrasubstituted double bond. However, in contrast to I, four different tetrasubstituted symmetrical ethylenic systems—2,3-dimethyl-2-butene, 1,2-dimethylcyclopentene, 1,2-dimethylcyclohexene, and $\Delta^{9,10}$-octalin—were shown to have "apparent" absorption maxima[3] in the ultraviolet between 213 and 217 mμ, with coefficients between 1300 and 1600.[4] No reaction took place between I and bromine or ozone. These results indicate that I is saturated. The NMR spectrum[5] revealed three distinct peaks at −2.82 (A), −2.49 (B), and −1.36 (C) p.p.m. relative to tetramethylsilane as an internal reference, with area ratios of A:B:C = 1.03:1.00:1.04.[6] This agrees with the postulate of three sets of four equivalent hydrogen atoms, as in I. The unsymmetrical structure IV, which has been considered as an alternative carbon skeleton for this series of compounds,[7] should reveal a more complicated NMR spectrum, since it contains at least five nonequivalent hydrogen atoms.

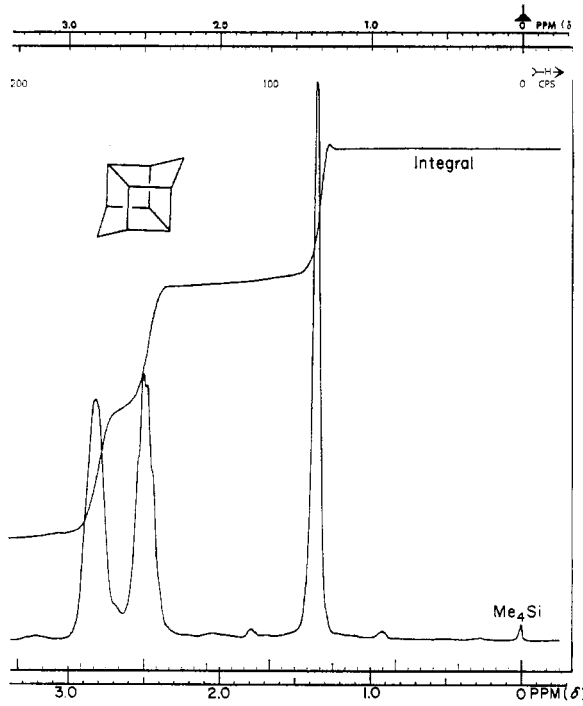
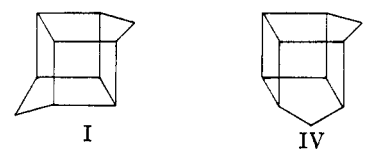


Fig. 1.—Pentacyclo[5.3.0.0^{2,6}.0^{3,9}.0^{4,8}]decane in carbon tetrachloride (0.5 g. per ml.).



The powder X-ray diffraction pattern of I showed peaks at 5.37 (s), 4.65 (m), and 2.69 (w) Å. (interplanar spacings). The pattern, consistent with a cubic crystal structure, indicated a unit cell length of 9.3 Å. X-ray diffraction results of II, also consistent with a cubic structure,[1c] indicated a unit cell length of 12.1 Å.

The identity of III was proved by its conversion to the phenylazide adduct,[8] m.p. 125–127°, mixed m.p. 124.5–127°, and by comparison of the infrared spectra of III and its derivative with authentic compounds. Interconversion of I and III was shown not to occur under the reaction conditions

(1) (a) H. J. Prins, *Rec. trav. chim.*, **65**, 455 (1946). (b) J. S Newcomer and E. T. McBee, *J. Am. Chem. Soc.*, **71**, 952 (1949). (c) E. T. McBee, C. W. Roberts, J. D. Idol, Jr., and R. H. Earle, Jr., *ibid.*, **78**, 1511 (1956). (d) D. H. Zijp and H. Gerding, *Rec. trav. chim.*, **77**, 682 (1958).

(2) P. Bruck, D. Thompson, and S. Winstein, *Chem. Ind.* (London), 405 (1960).

(3) O. H. Wheeler and J. L. Mateos, *J. Org. Chem.*, **21**, 1110 (1956), report, and cite references to, the appearance of "false energy" maxima at 200–215 mμ when ultraviolet absorption is measured with standard photoelectric spectrometers.

(4) The ultraviolet spectra were obtained with a Bausch and Lomb Spectronic 505 spectrophotometer, using commercial absolute ethanol as solvent.

(5) NMR spectral analyses were obtained with Varian V-4311 and Varian A-60 spectrometers.

(6) The splitting pattern was not reproducible. A appeared as a singlet with both instruments, whereas, B and C appeared sometimes as singlets and sometimes as a multiplet or triplet, respectively.

(7) P. Eaton, E. Carlson, P. Lombardo, and P. Yates, *J. Org. Chem.*, **25**, 1225 (1960).

(8) P. D. Bartlett and I. S. Goldstein, *J. Am. Chem. Soc.*, **69**, 2553 (1947).

used for their preparation. At present, no explanation is offered for the formation of III.

During the course of this work, several partially dechlorinated derivatives of II were obtained. They are under investigation and will be discussed, along with the chemistry of I, at a later date.

The authors are grateful to the National Science Foundation and the Hooker Chemical Corporation for grants in support of this research. The nuclear magnetic resonance spectrum was determined by Mr. W. E. Baitinger, the mass spectrum by Mr. L. J. Brand, the infrared and ultraviolet spectra by Mrs. W. L. Dilling, the X-ray diffraction pattern by Dr. J. L. White, and the microanalysis by Dr. C. S. Yeh, all of Purdue University.

DEPARTMENT OF CHEMISTRY
PURDUE UNIVERSITY
WEST LAFAYETTE, INDIANA

E. T. McBEE
WENDELL L. DILLING
H. P. BRAENDLIN

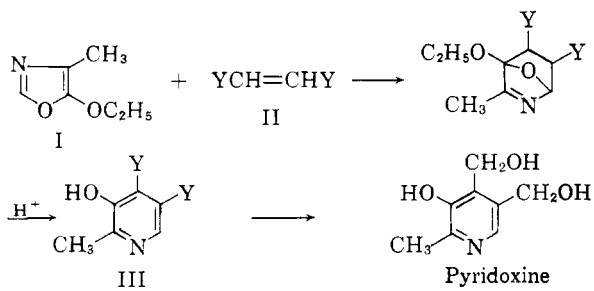
RECEIVED JANUARY 4, 1962

A New Synthesis of Pyridoxine (Vitamin B_6)

Sir:

Alkyl-substituted oxazoles have been found to react with maleic acid or its anhydride in a diene synthesis to yield, after cleavage of the oxygen bridge of the adduct, substituted pyridine-3,4-dicarboxylic acids (cinchomeronic acids).[1] The application of this condensation to the synthesis of 5-hydroxy-cinchomeronic acids from 5-alkoxyoxazoles suggested to us and to others[2] a route to products of pyridoxine-like structure.

We wish to report work employing several variants of this type of condensation which has now led to effective syntheses of pyridoxine.



a. $Y = COOC_2H_5$
b. $Y = CN$
c. $Y-Y = CH_2OCH_2$

Ethyl *d,l*-alaninate hydrochloride on treatment with formic-acetic anhydride yielded ethyl N-formyl-*d,l*-alaninate (78%), b.p.$_1$ 100°. *Anal.* Calcd. for $C_6H_{11}NO_3$: C, 49.6; H, 7.6; N, 9.7. Found: C, 49.9; H, 7.6; N, 9.8. This compound was refluxed in chloroform with phosphorous pentoxide for five hours,[3] quenched with aqueous potassium hydroxide, and the organic layer distilled to give 4-methyl-5-ethoxyoxazole (I) (60%), b.p.$_{50}$ 78–80°, $\lambda_{max.}$ 229 mμ, ϵ 4440 (methanol). *Anal.* Calcd. for $C_6H_9NO_2$: C, 56.7; H, 7.1; N, 11.0. Found: C, 56.8; H, 7.0; N, 10.9. The above oxazole condensed readily with a number of appropriate dienophiles to form 2-methyl-3-hydroxy-4,5-disubstituted-pyridines containing substituents (IIIa,b,c) which could be converted to pyridoxine as follows:

A. A mixture of the oxazole (I) with two moles of diethyl maleate (IIa) was heated at 110° for two hours and the adduct cleaved with ethanolic hydrogen chloride to give the diethyl ester of 2-methyl-3-hydroxypyridine-4,5-dicarboxylic acid hydrochloride (IIIa) (85%), m.p. 140–144° (lit., 144–145°[4]). This diester was reduced with lithium aluminum hydride to pyridoxine,[4] isolated as its hydrochloride and characterized by the identity of its melting point, mixed melting point, and ultraviolet and infrared spectra with those of an authentic sample.

B. A mixture of the oxazole (I) with one mole of fumaronitrile (IIb) was refluxed in methanol for five hours and the adduct cleaved with concentrated hydrochloric acid to give crystalline 2-methyl-3-hydroxy-4,5-dicyanopyridine (IIIb) (75%) as a monohydrate. Azeotropic dehydration in benzene gave bright yellow anhydrous material, m.p. 189–191°,[5] $\lambda_{max.}$ 235, 360 mμ, ϵ 12,900, 9300 (pH 7 phosphate buffer). *Anal.* Calcd. for $C_8H_5N_3O$: C, 60.4; H, 3.2; N, 26.4. Found: C, 60.4; H, 2.9; N, 26.5. Hydrogenation of IIIb in methanolic hydrogen chloride over 5% palladium on charcoal gave 2-methyl-3-hydroxy-4,5-diaminomethylpyridine trihydrochloride (III, Y = CH_2NH_2) (70%), m.p. 290° dec. (lit., 296° dec.[4]). Diazotization[4] in water at 85° yielded pyridoxine hydrochloride (79%), identified by melting point and spectra.

C. A solution of the oxazole (I) in a 20-mole excess of 2,5-dihydrofuran (IIc) containing 1% of trichloroacetic acid was heated in a bomb at 175° for three hours. Cooling overnight gave crystalline 2-methyl-3-hydroxy-4,5-epoxydimethylpyridine (IIIc) of 95% purity (ultraviolet) (58%). Recrystallization from ethanolic hydrogen chloride gave the hydrochloride, m.p. 239–240°, identical with an authentic sample[6] by mixed melting point and spectral comparisons. The cyclic ether (IIIc) was cleaved with 48% hydrobromic acid to the

(1) G. Ya. Kondrat'yeva, *Khim. Nauk i Prom.* **2**, 666 (1957); *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 484 (1959).

(2) G. Ya. Kondrat'yeva, and C. Huang, *Dokl. Akad. Nauk SSSR*, **141**, 628, 861 (1961).

(3) Method of P. Karrer, E. Myamichi, H. C. Storm, and R. Widmer, *Helv. Chim. Acta*, **8**, 205 (1925).

(4) A. Cohen and E. G. Hughes, Brit. Patent 625,997 (1949); A. Cohen, J. W. Haworth, and E. G. Hughes, *J. Chem. Soc.*, 4374 (1952).

(5) K. Makino, S. Morii, F. S. Chang, and Y. Tagami, *Bull. Chem. Soc. Japan*, **19**, 1 (1944) report a melting point of "*ca.* 60°" for material prepared by a different route; they give no analytical data.

(6) S. A. Harris and K. Folkers, *J. Am. Chem. Soc.*, **61**, 3307 (1939).

dibromide hydrobromide (III, Y = CH_2Br) and hydrolyzed to pyridoxine.[6,7]

MERCK & CO., INC.
RAHWAY, NEW JERSEY

E. E. HARRIS
R. A. FIRESTONE
K. PFISTER, 3RD
R. R. BOETTCHER
F. J. CROSS
R. B. CURRIE
M. MONACO
E. R. PETERSON
W. REUTER

RECEIVED APRIL 18, 1962

(7) S. A. Harris and K. Folkers, *J. Am. Chem. Soc.*, **61**, 1245 (1939).

Isomerization of Epoxides by Dicobalt Octacarbonyl

Sir:

It has been reported[1] that propylene oxide reacts with methanol and carbon monoxide under catalysis by dicobalt octacarbonyl to give methyl β-hydroxybutyrate. We have now isolated the major by-product of this reaction and identified it as acetone by means of gas-liquid chromatography, infrared spectra, and the preparation of suitable derivatives. Apparently the dicobalt octacarbonyl caused isomerization as well as carbonylation of the propylene oxide. Because isomerizations of α-alkylene oxides usually yield aldehydes[2,3] and not ketones, we have further examined this isomerization reaction and found that α-olefin oxides are readily rearranged to ketones in alcoholic solutions of dicobalt octacarbonyl.

In a 100-ml. three-necked flask equipped with thermometer, condenser, nitrogen inlet, and magnetic stirrer, 3.5 g. of dicobalt octacarbonyl[4] was dissolved in 45 ml. of methanol. When evolution of carbon monoxide ceased (two hours) the solution was kept under a nitrogen atmosphere and 25 ml. of propylene oxide was added. No further evolution of gas was observed but after about 15–20 minutes, the solution was refluxing vigorously from the heat of reaction and it was necessary to cool the flask to prevent flooding the condenser. The reaction was over in about one hour and the reaction mixture was distilled to to give 13.7 g. (70%) of acetone, calculated from peak areas of gas-liquid chromatograms. 2,4-Dinitrophenylhydrazone, m.p. 126–127° (lit.,[5] 126°). A similar reaction in which the methanol was replaced by isopropyl alcohol produced a 75% yield of acetone.

Attempted rearrangements of propylene oxide without a solvent or in benzene as solvent gave much poorer acetone yields, and we believe the formation of a coördinated cobalt cation according to the following reaction[6] between dicobalt octacarbonyl and methanol is necessary for isomerization.

$$3[Co(CO)_4]_2 + 12CH_3OH \longrightarrow 2[Co(CH_3OH)_6]^{++}\,[Co(CO)_4]_2^- + 8\overline{CO}$$

Isomerization could then take place during a reversible exchange between methanol and propylene oxide as coördinating molecule. The lower yields obtained in propylene oxide and benzene were caused by less facile formation of the cation in these solvents. The importance of the coördinated cobalt cation was also demonstrated by the use of pyridine as the solvent. Pyridine reacts with dicobalt octacarbonyl in the same manner as methanol to give cobalt(II) cation with coördinated pyridine molecules, $[Co(C_5H_5N)_6]^{++}[Co(CO)_4]_2^-$. When propylene oxide was added to a solution of dicobalt octacarbonyl in pyridine no temperature rise was noted and 80% of the epoxide was recovered unchanged. Since the same cobalt carbonyl anion was present in both the methanol and pyridine solutions, the cation must be the controlling factor. No isomerization occurred because pyridine is too strongly bound to the cobalt to be replaced by propylene oxide.

Using this isomerization technique, 1,2-butylene oxide was rearranged to methyl ethyl ketone in 77% yield, 2,4-dinitrophenylhydrazone m.p. 108.5–109.5° (lit.,[7] 108–111°), and butylene oxide "S," a mixture of normal butylene oxides sold by Dow Chemical Co., was also isomerized to the single product, methyl ethyl ketone, in 79% yield. Cyclohexene oxide was isomerized to cyclohexanone in 73% yield; 2,4-dinitrophenylhydrazone m.p. 157–159° (lit.,[5] 162°). No products due to ring contraction were found.

Support for this work from Diamond Alkali Co. is gratefully acknowledged.

IONICS, INCORPORATED
152 SIXTH STREET
CAMBRIDGE, MASSACHUSETTS

JOHN L. EISENMANN

RECEIVED FEBRUARY 15, 1962

(1) J. L. Eisenmann, R. L. Yamartino, and J. F. Howard, Jr., *J. Org. Chem.*, **26**, 2102 (1961).

(2) S. Winstein and R. B. Henderson, "Heterocyclic Compounds," Vol. 1, R. C. Elderfield, ed., John Wiley & Sons, New York, N.Y., 1950, p. 1.

(3) R. E. Parker and N. S. Isaacs, *Chem. Rev.*, **59**, 737 (1959).

(4) I. Wender, H. W. Sternberg, and M. Orchin, "Catalysis," Vol. V, P. H. Emmett, ed., Reinhold Publishing Corp., New York, N. Y., 1957, p. 173.

(5) R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," 4th ed., John Wiley and Sons, Inc., New York, N. Y., 1956.

(6) I. Wender, H. W. Sternberg, and M. Orchin, *J. Am. Chem. Soc.*, **74**, 1216 (1952).

(7) H. O. House, *ibid.*, **77**, 5083 (1955).

Partial Asymmetric Synthesis in the Conjugate Addition of a Grignard Reagent to an α,β-Unsaturated Ester

Sir:

A partial asymmetric synthesis in the Diels-Alder condensation of dimenthyl fumarate and

butadiene has recently been reported.[1] These workers also reported that when the reaction was catalyzed by aluminum chloride[2] at lower temperatures the resulting adduct had the opposite sign and configuration from that obtained by the purely thermal condensation. It has been suggested[3] that the 1,4-addition of a Grignard reagent to an α,β-unsaturated ester proceeds through a cyclic intermediate, and in this sense it has some resemblance to the Diels-Alder reaction.

TABLE I

3-PHENYLBUTYRIC ACID

Run	Catalyst	Yield, %	$[\alpha]^{25}D$[a]	Opt. yield, %
1	..	46.1	+3.1°	5.4
2	Cu_2Cl_2	63.5	−5.9°	10.2
3	..	53.0	+3.7°	6.7
4	Cu_2Cl_2	60.1	−3.4°	6.0
5[b]	..	57.9	+3.3°	5.9
6[b]	Cu_2Cl_2	62.6	−3.6°	6.3
7[b]	$CdCl_2$	50.2	+4.6°	8.1

[a] Solvent: benzene. [b] Hydrolyzed with potassium hydroxide in boiling ethylene glycol for 48 hr.

We wish at this time to report that the addition of phenylmagnesium bromide to (−)-menthyl crotonate results in the formation of S-(+)-3-phenylbutyric acid and, furthermore, when this reaction is catalyzed by cuprous chloride the reaction product has the R-(−) configuration.

A solution of phenylmagnesium bromide was prepared (without the use of iodine or other catalysts) from 4.3 g. (0.18 g.-atom) of magnesium and 28.3 g. (0.18 mole) of bromobenzene in 150 ml. of dry ether. To the cooled solution (−8°) of phenylmagnesium bromide was added dropwise a solution of 15.7 g. (0.07 mole) of (−)-menthyl crotonate,[4] and the reaction mixture was worked up in the usual manner. The residual oil was not purified but was hydrolyzed by refluxing with 13 g. of potassium hydroxide in 130 ml. of ethanol for 20 hr. to yield upon acidification 5.3 g. (46%) of 3-phenylbutyric acid, b.p. 113–115° at 3 mm., $n^{25}D$ 1.5150,[5] $[\alpha]^{25}D$ +3.1 (*c*, 10.3, benzene). The infrared spectrum was identical in every respect with that of an authentic sample. The rotation represents 5.4% asymmetric synthesis.[6]

The (+)-enantiomer has previously been assigned the S-configuration by Prelog.[7]

For the cuprous chloride catalyzed reaction, the identical procedure was followed except that the catalytic amount (0.2 g.) of cuprous chloride was added in four portions during the addition of the ester to the phenyl magnesium bromide solution. The resulting product was the R-(−)-3-phenylbutyric acid, as shown in Table I. In contrast to cuprous chloride, cadmium chloride did not alter the stereoselectivity of the reaction.

The effect of other catalysts as well as the general scope of this reaction is currently under investigation and will be the subject of a future publication.

INSTITUTE FOR CHEMICAL RESEARCH Y. INOUYE
KYOTO UNIVERSITY
TAKATSUKI, JAPAN

DEPARTMENT OF CHEMISTRY H. M. WALBORSKY
INSTITUTE OF MOLECULAR-BIOPHYSICS
THE FLORIDA STATE UNIVERSITY
TALLAHASSEE, FLORIDA

RECEIVED APRIL 23, 1962

(1) H. M. Walborsky, L. Barash, and T. C. Davis, *J. Org. Chem.*, **26**, 4778 (1961).

(2) P. Yates and P. Eaton, *J. Am. Chem. Soc.*, **82**, 4436 (1960); G. I. Fray and R. Robinson, *ibid.*, **83**, 249 (1961).

(3) E. E. Royals, "Advanced Organic Chemistry," Prentice-Hall, Inc., New York, 1954; J. Munch-Petersen, *Acta Chem. Scand.*, **13**, 1943 (1959).

(4) H. Rupe, *Ann.*, **369**, 335 (1909).

(5) J. Munch-Petersen, *J. Org. Chem.*, **22**, 170 (1957) report b.p. 104–105° at 0.5 mm. and $n^{25}D$ 1.5147.

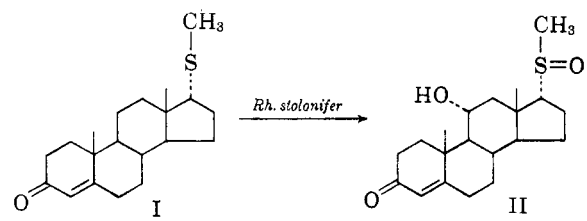
(6) Calculated on $[\alpha]D$ −57° (*c*, 9.8, benzene)[4]: Levene and Marker, *J. Biol. Chem.*, **93**, 761 (1931) report $[\alpha]^{25}D$ −47.92° (benzene).

(7) V. Prelog and H. Scherrer, *Helv. Chim. Acta*, **42**, 2227 (1959).

Microbiological Transformations. XI.[1] The Preparation of Optically Active Sulfoxides

Sir:

Holmlund and co-workers[2] have recently reported the stereospecific oxidation of 17β-acetoxy-7α-methylthioandrost-4-en-3-one to 17β-hydroxy-7α-methylsulfinylandrost-4-en-3-one by fermentation with *Calonectria decora* (CBS). We had previously reported[3] a similar transformation of 17α-methylthioandrost-4-en-3-one (I) to 11α-hydroxy-17α-methylsulfinylandrost-4-en-3-one (II), m.p. 225–226° dec., $[\alpha]D$ −88° ($CHCl_3$), by fermentation with *Rhizopus stolonifer* A.T.C.C. 6227-b. Because of the stereospecificity of this oxidation and of a similar oxidation of 17β-methylthioandrost-4-en-3-one with *Rh. stolonifer*, we investigated the possibility of preparing optically active sulfoxides by the fermentation of optically inactive,



I II

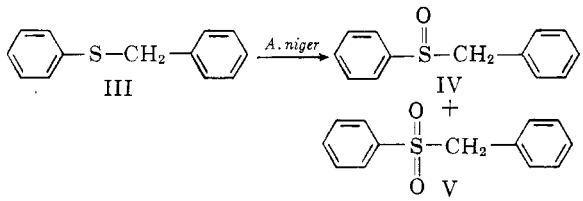
(1) Previous paper in this series: P. F. Guehler, R. M. Dodson, and H. M. Tsuchiya, *Proc. Nat. Acad. Sci.*, **48**, 377 (1962).

(2) C. E. Holmlund, K. J. Sax, B. E. Nielsen, R. E. Hartman, R. H. Evans, Jr., and R. H. Blank, *J. Org. Chem.*, **27**, 1468 (1962).

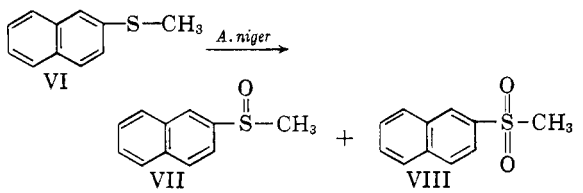
(3) R. M. Dodson and P. B. Sollman, U.S. Patent 2,999,101 (September 5, 1961). We have not found the *exclusive* stereospecificity of the oxidation of sulfides to sulfoxides reported by Holmlund and co-workers (ref. 2). While, in the fermentation of 17α-methylthioandrost-4-en-3-one (I), only one 11α-hydroxy-17α-methylsulfinylandrost-4-en-3-one (II) was isolated, two isomeric 17α-methylsulfinylandrost-4-en-3-ones were obtained in the ratio of 7.5 to 1.

unsymmetrical sulfides. This possibility has now been realized.

Fermentation of phenyl benzyl sulfide (III), by methods similar to those previously described,[4] with *Aspergillus niger*, NRRL 337, produced phenyl benzyl sulfoxide (IV), m.p. and m.m.p. 120–121°, $[\alpha]_D^{21°}$ −20.2° ($CHCl_3$), in 23% yield along with a small quantity (9%) of the corresponding sulfone V, m.p. and m.m.p. 146.5–147.5°. Repeated crystallizations and chromatography of the optically active sulfoxide IV failed to remove



optical activity. Satisfactory analyses were obtained on optically active IV (found: C,



71.98; H, 5.59; S, 14.64), and the infrared spectrum of optically active material was identical with that of the synthetically prepared racemate.

A similar fermentation of methyl β-naphthyl sulfide (VI) with *A. niger* produced methyl β-naphthyl sulfoxide (VII), m.p. and m.m.p. 107.5–108.5°, $[\alpha]_D$ −3.20° ($CHCl_3$), and methyl β-naphthyl sulfone (VIII), m.p. 147.5–148° (found: C, 63.88; H, 4.97; S, 15.50). Inactive methyl β-naphthyl sulfoxide (VII), m.p. 108–109°, (found: C, 69.60; H, 5.34), prepared by the oxidation of the sulfide VI with sodium metaperiodate,[5] proved to be identical (infrared spectrum) with the fermentation product. Because of the low rotation of the methyl β-naphthyl sulfoxide, rotations on a multiply recrystallized sample were determined at lower wave lengths: $[\alpha]_{580}^{22°}$ −3.22°, $[\alpha]_{436}$ −5.25°, $[\alpha]_{405}$ −15.74°, $[\alpha]_{365}$ −23.81° ($CHCl_3$). A similar negative optical rotatory dispersion curve was obtained from the phenyl benzyl sulfoxide (IV).

It is apparent that the optically active sulfoxides obtained *via* fermentation are not optically pure. However, their rotations compare very favorably with those prepared *via* optically active peracids[6] and the fermentations can be run on a relatively large scale. The optical purity and absolute configuration of these sulfoxides as well as possible mechanisms of formation will be discussed in the future.

DEPARTMENTS OF CHEMISTRY AND CHEMICAL ENGINEERING
UNIVERSITY OF MINNESOTA
MINNEAPOLIS 14, MINNESOTA

R. M. DODSON
NORMAN NEWMAN
H. M. TSUCHIYA

RECEIVED MAY 3, 1962

(4) D. H. Peterson, H. C. Murray, S. H. Eppstein, L. M. Reineke, A. Weintraub, P. D. Meister, and, H. M. Leigh, *J. Am. Chem. Soc.*, **74**, 5933 (1952).

(5) N. J. Leonard and C. R. Johnson, *J. Org. Chem.*, **27**, 282 (1962).

(6) (a) A. Maccioni, F. Montanari, M. Secci, and M. Tramontini, *Tetrahedron Letters*, No. 17, 607 (1961); (b) K. Balenović, N. Bregant, and D. Francetić, *ibid.*, No. 6, 20 (1960); (c) K. Balenović, I. Bregovec, D. Francetić, I. Monković, and V. Tomasić, *Chem. Ind.*, 469 (1961); (d) A. Mayr, F. Montanari, and M. Tramontini, *Gazz. chim. ital.*, **90**, 739 (1960).

Pyrimidine Derivatives. III. A Novel Synthesis of 2,4-Diaminopyrimidines[1-4]

Sir:

Derivatives of 2,4-diaminopyrimidine have been of particular interest in these laboratories as potential antimetabolites and antitumor agents because of the various growth-inhibitory properties of compounds possessing this versatile ring system.[3,4] We should now like to report a novel, one-step synthesis of a wide variety of 2,4-diaminopyrimido systems.

Appelquest[5] described the preparation of a condensation product, $C_8H_{12}N_4$, by reaction of dicyandiamide and cyclohexanone for three hours at 150–160°, and, on the basis of elementary analysis only, assumed this compound to be 2,4-diamino-5,6,7,8-tetrahydroquinazoline (Ic). Inasmuch as this reaction, if confirmed and generalized, appeared to offer a direct route in one step to a variety of 2,4-diaminopyrimidine derivatives, we undertook to prove the structure of the condensation product by an alternate synthesis and to investigate the scope of the reaction.

The same product was obtained when this procedure was repeated in these laboratories (colorless prismatic rods from 95% ethanol; 40.0% yield; *Anal.* Calcd. for $C_8H_{12}N_4$: C, 58.51; H, 7.37; N, 34.12. Found: C, 58.5; H, 7.5; N, 33.9). The structure was confirmed by an alternate synthesis. Reaction of guanidine carbonate and 2-carbethoxycyclohexanone gave 2-amino-4-hydroxy-5,6,7,8-tetrahydroquinazoline (Ia),[6,7] which was successively chlorinated (Ib)[7] and aminated to the diamine (Ic). Samples of Ic prepared by the two

(1) This investigation was supported in part by a research grant (CY3335) from the National Cancer Institute, National Institutes of Health, U.S. Public Health Service.

(2) (a) E. J. Modest, S. Chatterjee, H. Kangur, and D. M. Brun, Abstracts of Papers, 137th Meeting, American Chemical Society, Cleveland, Ohio, April 11, 1960, p. 4-N; (b) E. J. Modest, H. Kangur, and S. Chatterjee, Abstracts of Papers, 141st Meeting, American Chemical Society, Washington, D.C., March 27, 1962, p. 26-N.

(3) E. J. Modest, H. N. Schlein, and G. E. Foley, *J. Pharm. Pharmacol.*, **9**, 68 (1957). This is paper I of this series.

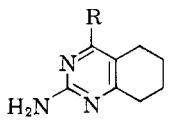
(4) E. J. Modest, G. E. Foley, and S. Farber, *Acta Unio Internat. Contra Cancrum*, **16**, 702 (1960). This is paper II of this series.

(5) A. J. Appelquest, U.S. Patent 2,517,824 (August 8, 1950).

(6) P. C. Mitter and A. Bhattacharya, *Quart. J. Indian Chem. Soc.*, **4**, 149 (1927).

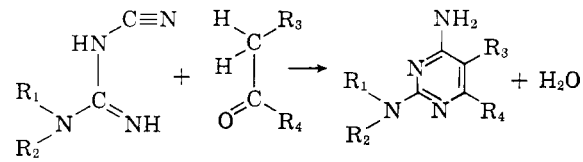
(7) R. Hull, B. J. Lovell, H. T. Openshaw, L. C. Pavman, and A. R. Todd, *J. Chem. Soc.*, 357 (1946).

methods were shown to be identical in all respects, including melting point and mixed melting point (243–245°), and ultraviolet ($\lambda_{max}^{pH\ 1}$ 275 mμ, ε 7850; $\lambda_{max}^{pH\ 10}$ 284 mμ, ε 7620) and infrared (λ_{max}^{KBr} 2.91, 3.00, 3.21, 3.41, 6.02, 6.15, 6.30, 6.96 μ) absorption spectra.



Ia. R = OH
b. R = Cl
c. R = NH_2

This reaction with dicyandiamide has been found to be generally applicable and has been extended to a number of cyclic ketones, including 4-methylcyclohexanone (232–234°, 50.2%),[8] 3-methylcyclohexanone (II, 199–203°, 69.2%), cyclopentanone (231–232°, 8.5%),[9] cycloheptanone (216–217°, 50.5%), cyclopentadecanone (235–236°, 24.7%), α-tetralone (209–210°, 54.8%), β-tetralone (III, 263–264°, 38.0%), *trans*-β-decalone (IV, 254–255°, 61.9%), 1-indanone (262–264°, 45.1%), and 1-keto-1,2,3,4-tetrahydrophenanthrene (V, 311–313°, 34.4%). Cyclohexanone has also been found to undergo this cyclization with N^1-methyl- (204–205°, 56.3%), N^1-(*n*-dodecyl)- (98–100°, 60.5%), and N^1,N^1-dimethyl- (135–136°, 24.1%) dicyandiamide.



Acyclic ketones have been employed successfully in this synthesis. The expected products have been obtained upon reaction of dicyandiamide with phenylacetone (VI, 253–256°, 26.9%),[10] benzyl ethyl ketone (VII, 241–244°, 19.6%),[11] benzylacetone (VIII, 188–190°, 25.3%),[12] 1-cyclohexenylacetone (249–251°, 7.2%), diethyl ketone (168–170°, 4.3%), and acetophenone (164–165°, 32.2%).[13]

The general reaction conditions require maintenance of an internal temperature between 155° and 205° for two to twenty-four hours, the usual reaction time being three to six hours. Where possible, water is removed from the reaction as it is formed. Ketones boiling below 155° are caused to react in a sealed tube or autoclave. Employment of a solvent, 2-ethoxyethoxyethanol or quinoline, has been found to be superior in certain instances to the original conditions without solvent. The reaction of dicyandiamide with α-tetralone is improved by basic catalysts, such as Triton B. With 1-keto-1,2,3,4-tetrahydrophenanthrene, the first isolated product is an equimolecular complex of dicyandiamide and V, which must be disrupted with base. The latter phenomenon is being further investigated with the products from other polycyclic ketones.

The compounds reported are pure, single substances, and all structures have been established except for II, III, and IV. In the latter instances, cyclization can occur theoretically on either side of the carbonyl group of the cyclic, unsymmetrical ketones employed. The product from 3-methylcyclohexanone (II) may be either the 5-methyl or the 7-methyl homolog of Ic. The structures of III, from β-tetralone, and IV, from *trans*-β-decalone, which are reduced diaminobenzo[*g*]quinazolines or diaminobenzo[*f*]quinazolines, are under investigation.

Many of these 2,4-diaminopyrimidine derivatives behave as highly effective antagonists of folic acid in selected microbiological systems.[14] Work is actively in progress on the extension of this synthetic method to the 2,4-diaminopyrimido analogs of steroids and polynuclear carcinogenic hydrocarbons.

THE CHILDREN'S CANCER RESEARCH FOUNDATION, THE CHILDREN'S HOSPITAL MEDICAL CENTER, AND DEPARTMENT OF PATHOLOGY, HARVARD MEDICAL SCHOOL, BOSTON, MASSACHUSETTS

EDWARD J. MODEST
SUPRABHAT CHATTERJEE[15]
HELJO KANGUR

RECEIVED APRIL 27, 1962

(8) Melting points (capillary, uncorrected) and percentage yields of purified 2,4-diaminopyrimidine condensation products are given parenthetically immediately following the reactant. Acceptable analyses have been obtained for all compounds whose melting points are recorded. The subsequent literature references (ref. 9–13) concern alternate syntheses of the 2,4-diaminopyrimidines reported herein.

(9) L. O. Ross, L. Goodman, and B. R. Baker, *J. Am. Chem. Soc.*, **81**, 3108 (1959), report m.p. 230–232° for 2,6-diamino-4,5-trimethylenepyrimidine. Prior to this publication, we had also prepared this compound by amination of 2-amino-6-chloro-4,5-trimethylenepyrimidine.

(10) P. B. Russell and G. H. Hitchings, *ibid.*, **73**, 3763 (1951), report m.p. 249–250° for 2,4-diamino-5-phenyl-6-methylpyrimidine.

(11) P. B. Russell and G. H. Hitchings (ref. 10) report m.p. 237–240° for 2,4-diamino-5-phenyl-6-ethylpyrimidine.

(12) E. A. Falco, S. DuBreuil, and G. H. Hitchings, *J. Am. Chem. Soc.*, **73**, 3758 (1951), report m.p. 181–185° for 2,4-diamino-5-benzyl-6-methylpyrimidine.

(13) P. B. Russell, *J. Chem. Soc.*, 2951 (1954), reports m.p. 162° for 2,4-diamino-6-phenylpyrimidine.

(14) *In vitro* biological studies on these compounds have been done by Dr. George E. Foley and associates and will be reported in detail in a later publication. It should be noted that the inhibitory properties, including folic acid antagonism, of VI, VII, VIII, and related compounds have been studied extensively by Dr. George H. Hitchings and co-workers: *cf.* G. H. Hitchings, E. A. Falco, H. VanderWerff, P. B. Russell, and G. B. Elion, *J. Biol. Chem.*, **199**, 43 (1952); ref. 10 and 12.

(15) Present address: Geophysical Research Directorate, Air Force Cambridge Research Laboratory, Hanscom Field, Bedford, Mass.

Diazotization and Coupling of a Bridgehead Aliphatic Amine[1]

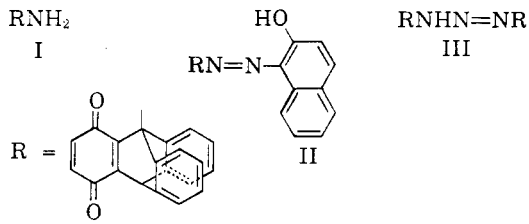
Sir:

It has been generally agreed that aliphatic diazonium ions ordinarily lose a nitrogen molecule

(1) This work was supported in part by the Office of Ordnance Research, U.S. Army.

extremely rapidly with a concurrent or subsequent nucleophilic replacement or elimination reaction.[2] Even when the diazonium ion is located at the bridgehead of a bicyclic system the loss of nitrogen is rapid at temperatures as low as −70°.[3] The diazotization and coupling of a bridgehead amine have now been accomplished with the formation of the aryl alkyl azo compound in a yield of at least 50% after purification (based on unrecovered starting material).

9-Aminotriptycene-1,4-dione (I), bright orange, m.p. 305–306° dec., was prepared from 9-nitroanthracene and *p*-benzoquinone with subsequent isomerization to the hydroquinone, reduction of the nitro group to an amino group, and oxidation of the hydroquinone ring back to the quinone.[4] *Anal.* Calcd. for $C_{20}H_{13}NO_2$: C, 80.3; H, 4.4; N, 4.7. Found: C, 80.1; H, 4.3; N, 4.6. Structural evidence was provided by the infrared spectrum in chloroform which showed absorption maxima at



3400, 3300 (NH), and 1660 cm.$^{-1}$ (C=O). The ultraviolet spectrum in chloroform exhibited maxima at 253 mμ (ε 14,000), 274 mμ (shoulder, ε 3000), and 413 mμ (ε 344). The n.m.r. spectrum in methylene bromide showed absorption at τ 2.65 complex multiplet (ArH), 3.42 singlet (vinyl H), 4.22 singlet (CH), and 6.94 singlet (NH_2) with relative peak areas of 8:2:1:2. Diazotization and coupling of the amine were best carried out in methylene chloride solution at −78°. After addition of an equivalent amount of nitrosyl chloride in methylene chloride the solution was stirred for 30 min. at −78° after which a twofold excess of β-naphthol in 20 ml. of methylene chloride was added, and after 60 min. the solution was allowed to warm to room temperature. In addition to 36% of the starting amine which was recovered, there was obtained 50% (based on unrecovered starting material) of 9-(2-hydroxy-1-naphthaleneazo)-triptycene-1,4-dione (II), m.p. 320–321° dec. *Anal.* Calcd. for $C_{30}H_{18}N_2O_3$: C, 79.3; H, 4.0; N, 6.2; mol. wt., 455. Found: C, 79.2; H, 4.1; N, 6.3; mol. wt., 460. The infrared spectrum in chloroform showed absorption at 3500–3000 (OH) and 1655 cm.$^{-1}$ (C=O). The ultraviolet spectrum in chloroform had maxima at 296 mμ (ε 11,500), 304 mμ (ε 12,500), 396 mμ (ε 10,300), and 413 mμ (ε 10,000). The n.m.r. spectrum in methylene bromide showed absorption at τ −5.95 singlet (OH), 2.67 complex multiplet (ArH), 3.27 singlet (vinyl H), and 4.07 singlet (CH) with relative peak areas of 1:14:2:1. Confirmation of the structure was provided by hydrogenation over platinum in acetic acid which gave 1-acetylamino-2-acetoxynaphthalene and 1,4-diacetoxy-9-acetylaminotriptycene after acetylation of the reaction mixture.

Demonstration of coupling is, of course, not equivalent to a demonstration of the presence of a diazonium ion as an intermediate but repeated attempts to isolate a diazonium fluoroborate or to obtain spectral evidence for the diazonium ion in solution have been unsuccessful. These results suggest that the diazonium ion may be stored in solution as the diazoamino compound which regenerates the diazonium compound just prior to coupling.[6]

It is not clear to what extent the carbonyl groups provide stabilization of the diazonium ion and how much stabilization is provided by the triptycene system. An investigation of this and other aspects of the problem is in progress.

NOYES CHEMICAL LABORATORY
UNIVERSITY OF ILLINOIS
URBANA, ILLINOIS
D. Y. CURTIN
B. H. KLANDERMAN[7]
D. F. TAVARES

RECEIVED MAY 21, 1962

(2) See H. Zollinger, "Diazo and Azo Chemistry, Aliphatic and Aromatic Compounds," Interscience Publishers, Inc., New York, 1961, p. 123 ff. for a very good recent review.

(3) M. Wilhelm and D. Y. Curtin, *Helv. Chim. Acta*, **40**, 2129 (1957).

(4) Most of these steps have been patterned after similar reactions used by previous workers[5] in syntheses of other triptycene derivatives. Since this part of our work was completed a synthesis of 9-aminotriptycene and its treatment with nitrous acid derivatives have been reported [W. Theilacker and K. H. Beyer, *Chem. Ber.*, **94**, 2968 (1961)] but no attempt to intercept the diazonium ion is mentioned.

(5) E. Clar, *Ber*, **64B**, 1676 (1931); P.D. Bartlett, M. J. Ryan, and S. G. Cohen, *J. Am. Chem. Soc.*, **64**, 2649 (1942); P. D. Bartlett and F. D. Greene, *ibid.*, **76**, 1088 (1954).

(6) See ref. 2, pp. 182 ff. for a discussion of analogous behavior of aromatic diazonium compounds.

(7) National Science Foundation Fellow, 1959–present.