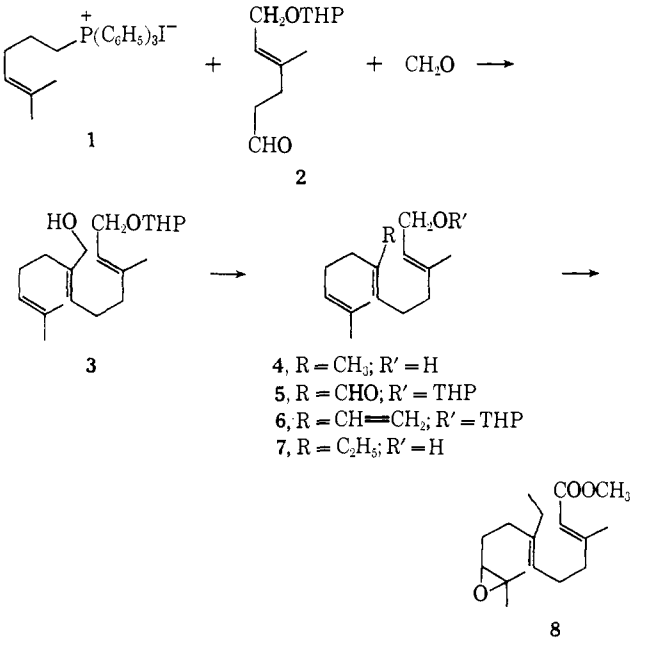
to the corresponding ylide with 1 equiv of *n*-butyllithium in tetrahydrofuran (THF) at 0°;[6] then the mixture was cooled to −78° and the aldehyde **2**[3] was added. After decolorization of the ylide (*ca.* 5 min), the reaction mixture was brought to −25°, treated with 2 equiv of *sec*-butyllithium, brought to 0°, and then treated with 3 equiv of dry paraformaldehyde. The mixture was stirred at 25° for 30 min, and the product was isolated by addition of water, extraction, and chromatographic removal (silica gel) of triphenylphosphine oxide and other much more polar by-products. The hydroxy farnesol derivative **3**[5] was thus obtained in 46% yield. Deoxygenation of the allylic alcohol unit in **3** using the bisulfate ester–hydride method[3,7] with THF as solvent, followed by acid-catalyzed removal of the tetrahydropyranyl group, produced *trans,trans*-farnesol (**4**)[5] free of isomeric impurities as determined by vapor-phase chromatography (vpc) (using a 4 ft × 0.125 in. 3% OV-1 column at 150°) and thin layer chromatography in 75% yield from **3**.[8]

The stereochemical control and the flexibility inherent in this approach to the construction of the farnesol system suggest the application of the method to the synthesis of numerous biologically and biogenetically interesting structures of the acyclic triisoprenoid type. Studies in this area will be reported in future publications. One obvious objective, the synthesis of the position isomer **8** of the C_{17} Cecropia juvenile hormone,[9] has already been attained in the following way using procedures which parallel those described in the accompanying communication[3] for the synthesis of the two known insect juvenile hormones.

The hydroxylated farnesol derivative **3** was oxidized using excess manganese dioxide in hexane at 25° for 1 hr to the aldehyde **5**[5] which was then treated[6] with methylenetriphenylphosphorane (1.2 equiv in THF) to give the tetraene **6**[5] in 93% overall yield from **3**. Exposure of **6** to a moderate excess of diimide at 0° in ethanol (generated from 8.5 equiv of hydrazine and *ca.* 0.05 equiv of copper sulfate in ethanol by slow addition of 7 equiv of 30% aqueous hydrogen peroxide),[10] followed by cleavage of the tetrahydropyranyl ether in methanol containing *p*-toluenesulfonic acid (5 m*M*) at 25° for 1 hr, led to highly selective formation of the homofarnesol **7**[5] (71% yield after isolation). The hydroxymethylene group of **7** was converted to carbomethoxy by oxidation with manganese dioxide, first in hexane then in methanol containing sodium cyanide–hydrogen cyanide,[11,12] and the resulting ester was epoxidized at the terminal olefinic group as previously described for the C_{18} Cecropia juvenile hormone case[12,13] to give the epoxy homofarnesoic acid methyl ester **8**[5] (*ca.* 35% from **7**).

Detailed studies on the biological activity of the synthetic epoxy ester **8** are being conducted by Professor Lynn M. Riddiford and Mr. Alfred M. Ajami[14] and will be reported elsewhere. Their investigation has shown that **8** possesses high biological activity, the level of which varies considerably from one species of insect to another. In some instances, however, the activity shown by **8** is higher than that of the C_{18} Cecropia juvenile hormone. In addition, with certain species of insects the application of **8** results in a striking degree of localization of hormonal effects.



Further studies in this area will be reported in due course.[15]

alcohol is readily available from the reaction of lithium aluminum hydride in tetrahydrofuran with 5-methyl-4-hexenoic acid: G. Büchi, O. Jeger, and L. Ruzicka, *Helv. Chim. Acta*, 31, 241 (1948).

(5) Satisfactory (a) analytical and (b) spectroscopic data were obtained for this substance. Unless indicated otherwise, all intermediates were colorless oils.

(6) Reaction mixture maintained under an inert atmosphere.

(7) E. J. Corey and K. Achiwa, *J. Org. Chem.*, 34, 3667 (1969).

(8) For another recent stereospecific synthesis of farnesol, see E. J. Corey, J. A. Katzenellenbogen, and G. H. Posner, *J. Amer. Chem. Soc.*, 89, 4245 (1967).

(9) A. S. Meyer, H. A. Schneiderman, E. Hanzmann, and J. H. Ko, *Proc. Nat. Acad. Sci. U. S.*, 60, 853 (1968).

(10) E. J. Corey, W. L. Mock, and D. J. Pasto, *Tetrahedron Lett.*, 347 (1961).

(11) E. J. Corey, N. W. Gilman, and B. E. Ganem, *J. Amer. Chem. Soc.*, 90, 5616 (1968).

(12) E. J. Corey, J. A. Katzenellenbogen, N. W. Gilman, S. A. Roman, and B. W. Erickson, *ibid.*, 90, 5618 (1968).

(13) E. E. van Tamelen, M. A. Schwartz, E. J. Hessler, and A. Storni, *Chem. Commun.*, 409 (1966).

(14) Biological Laboratories, Harvard University.

(15) This work was assisted financially by the Hoffmann-La Roche Co.

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Structures of Rubratoxins A and B

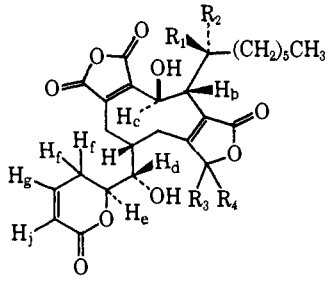
Sir:

Pencillium rubrum has been identified as one of several organisms responsible for fatal poisoning of livestock and poultry fed infected cereals.[1] Attempts to isolate chemical agents associated with the hepatotoxic activity of *P. rubrum*[2] have resulted in characterization of two substances, named rubratoxins A and B.[3] Spectral

(1) J. E. Burnside, W. L. Sippet, J. Forgacs, W. T. Carll, M. B. Atwood, and E. R. Coll, *Amer. J. Vet. Res.*, 18, 817 (1957); J. Forgacs, H. Koch, W. T. Carll, and R. H. White-Stevens, *ibid.*, 19, 744 (1958); A. W. Hayes and B. J. Wilson, *Appl. Microbiol.*, 16, 1163 (1968); G. N. Wogan and R. I. Mateles, *Progr. Ind. Microbiol.*, 7, 149 (1968).

(2) (a) B. J. Wilson and C. H. Wilson, *J. Bacteriol.*, 83, 693 (1962); B. J. Wilson and C. H. Wilson, *ibid.*, 84, 283 (1962); (b) J. D. White, Ph.D. Thesis, Massachusetts Institute of Technology, 1965.

and degradative evidence led Moss, *et al.*, to formulate rubratoxins A and B as the gross structures represented in **1**[4] and **2**,[5] respectively; a partial stereochemical designation was also included for the latter. We report the results of our chemical studies of the two rubratoxins, including an X-ray crystallographic analysis of a derivative of rubratoxin B, which define relative stereostructures **1** and **2** for these substances.



1, $R_1 = H_a$; $R_2 = OH$; $R_3, R_4 = H, OH$
2, $R_1 = H_a$; $R_2 = OH$; $R_3, R_4 = =O$
3, $R_1, R_2 = =O$; $R_3, R_4 = =O$

Crystalline rubratoxin B, mp 170–171° dec, $[\alpha]^{28}D$ +6.25° (*c* 1.12, acetone), was obtained from acetonitrile as the monohydrate, $C_{26}H_{30}O_{11} \cdot H_2O$, and afforded a dihydro derivative, mp 162–163°, $[\alpha]^{28}D$ +31.6° (*c* 2.05, acetone), upon catalytic hydrogenation in acetic acid. The presence of three secondary hydroxyl groups in **2** was revealed by acetylation with isopropenyl acetate and *p*-toluenesulfonic acid. The resulting triacetate, mp 190–191°, which showed no hydroxyl absorptions, had H_a, H_c, and H_d (Table I) shifted to δ 5.5, 6.19, and 5.1,

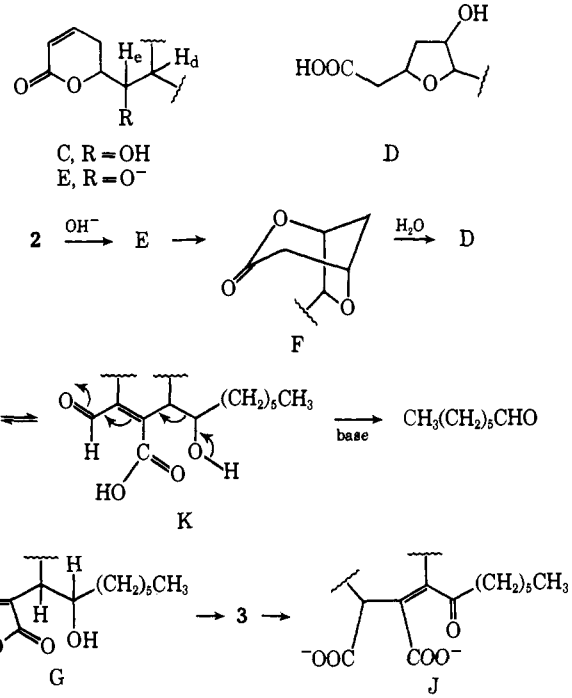
Table I. Proton Chemical Shifts of Rubratoxin B

Proton	Chemical shift (δ)	Multiplicity
H_a	4.44	m
H_b	3.42	d of d J = 11 Hz
H_c	5.64	d J = 11 Hz
H_d	3.84	d of d J = 4, 6 Hz
H_e	4.72	d of t J = 6, 8 Hz
H_f, H_f	2.52	m (eight lines) J = 1.3, 4, 8 Hz
H_g	7.07	d of t J = 4, 10 Hz
H_j	5.95	d of t J = 1.3, 10 Hz

respectively. Two dialkylmaleic anhydride functionalities in rubratoxin B were apparent from the uv spectrum ($\lambda_{max}^{CH_3CN}$ 250 nm, ϵ 10,300),[6] ir spectrum (bands at 1860, 1835, 1780 cm^{-1}), and titration[7] which indicated four masked carboxyl groups. Additional evidence bearing on hydroxyl and anhydride functions in **2** came from formation in 95% yield of a tris(trimethylsilyl) bisimide derivative, mp 108–110°, upon treatment with hexamethyldisilazane in dimethylformamide.

Exhaustive saponification of **2** with 1 *N* NaOH consumed 5 equiv of base and, taken with ir absorption at 1710 cm^{-1} and nmr data in Table I, suggests the presence of a mono-δ-substituted, α,β-unsaturated δ-lactone.[8] Spin decoupling of signals due to H_d and H_e allowed extension to part structure C. Confirmation of this moiety was obtained by basic hydrolysis of dihydrorubratoxin B, followed by sodium periodate cleavage, which gave glutaraldehydic acid (identified as its 2,4-dinitrophenylhydrazone).[9] Acidification of saponified **2** produced isorubratoxin B, mp 180–182° dec, $[\alpha]^{28}D$ +11.2° (*c* 2.49, acetone). This substance was a carboxylic acid and yielded a monomethyl ester, mp 153–156°, containing three secondary hydroxyl groups (triacetate, mp 95–96°). Part structure *D* for isorubratoxin B is consistent with a genesis *via* internal Michael addition of alkoxide E, followed by hydrolysis of the bicyclic intermediate F.

The presence of a heptyl chain in **2** was indicated by Kuhn–Roth oxidation, which gave *n*-heptanoic acid in greater than 70% yield.[10] The base peak at *m/e* 113 in the mass spectrum of **2** corresponded to $CH_3(CH_2)_5CO^+$, indicating oxygenation at C-7, and careful oxidation of **2** with 0.8 *N* chromic acid[11] yielded a monoketone **3**, mp 153–156°, ν_{max} (KBr) 1724 cm^{-1}, $\lambda_{max}^{CH_3CN}$ 249 nm (ϵ 8360), 297 nm (ϵ 2180), in which the carbinol proton H_a was absent and a new signal at δ 4.54 (1 H, d, J = 10 Hz) had replaced that due to H_b.



Appearance of absorption at 272 nm (ϵ 6900) upon exposure of **3** to 0.1 *N* NaOH implied part structure G

(3) (a) R. J. Townsend, M. O. Moss, and H. M. Peck, *J. Pharm. Pharmacol.*, 18, 471 (1966); F. V. Robinson, M. O. Moss, and A. B. Wood, *Chem. Ind. (London)*, 587 (1967); (b) M. O. Moss, F. V. Robinson, and A. B. Wood, *ibid.*, 755 (1967).

(4) M. O. Moss, A. B. Wood, and F. V. Robinson, *Tetrahedron Lett.*, 367 (1969).

(5) M. O. Moss, F. V. Robinson, A. B. Wood, H. M. Paisley, and J. Feeney, *Nature (London)*, 220, 767 (1968).

(6) 1-Cyclohexene-1,2-dicarboxylic anhydride showed $\lambda_{max}^{CH_3CN}$ 250 nm (ϵ 4280).

(7) (a) H. Sutter and N. Wijkman, *Justus Liebigs Ann. Chem.*, 519, 97 (1935); (b) determination of the saponification equivalent of rubratoxin B was carried out by Dr. J. M. Midgley in the M.I.T. laboratories.

(8) D. W. Mathieson, "Interpretation of Organic Spectra," Academic Press, New York, N. Y., 1965, p 64.

(9) R. H. Hall and B. K. Howe, *J. Chem. Soc.*, 2480 (1951).

(10) E. Wiesenberger, *Mikrochim. Acta*, 33, 51 (1948).

(11) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

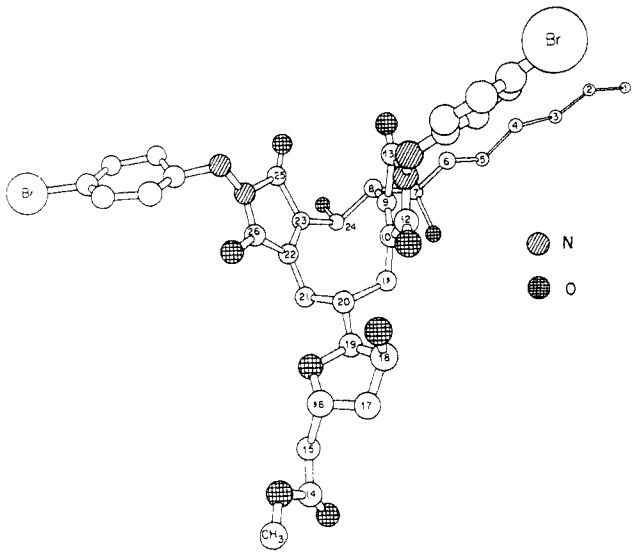


Figure 1. Molecular structure of isorubratoxin B bis-*p*-bromophenylhydrazide methyl ester in the crystal lattice.

for rubratoxin B, with accompanying base-catalyzed rearrangement of **3** to the chromophore represented by J.[12]

The foregoing evidence strongly suggests that rubratoxin B is related structurally to the family of nonadrides,[13] comprising glauconic,[14,15] glaucanic,[14b,15] and byssochlamic acids.[16] Recognition that rubratoxin B is constituted of two C_{13} halves, and application of the biogenetic principle propounded[13a] and elegantly demonstrated[17] for the nonadrides, leads to plane formula **2**. Placement of the third hydroxyl group at C-24 is dictated by the chemical shift of H_c and its coupling with H_b in **2** and **3**.

Rubratoxin A, mp 213–215°, $[\alpha]^{28}D$ +39.7° (*c* 1.12, acetone), obtained from tetrahydrofuran, has the composition $C_{26}H_{32}O_{11}$, and shows uv absorption ($\lambda_{max}^{CH_3CN}$ 250 nm, ϵ 4810) corresponding to only one dialkylmaleic anhydride residue.[6] A new singlet (δ 5.94, 1 H) in the nmr spectrum of toxin A accords with the presence of a γ-hydroxybutenolide,[18] and this was confirmed by oxidation of **1** with CrO_3–AcOH to a mixture of **2** and **3**. Complete formulation of rubratoxin A as **1** derives from a base-catalyzed fragmentation[3b,4] which produced *n*-heptaldehyde presumably *via* retroaldol fission of the tautomeric aldehyde K.

The structural hypothesis was confirmed and allocation of relative stereochemistry was made by a single-crystal X-ray structure determination of isorubratoxin B bis-*p*-bromophenylhydrazide methyl ester, mp 178–180° (from acetonitrile).[19]

The unit cell data for this derivative (a = 14.256, b = 10.605, c = 27.40 Å, β = 97.7°, space group $P2_1$, d_{obsd} = 1.4 g/cm^3) suggested the presence of two molecules per asymmetric unit with F_{000} = 1824. The analysis accordingly required the determination of 110 independent atomic positions, excluding hydrogen; 3200 intensities, of which approximately 2000 were significantly greater than background level, were measured diffractometrically from several different crystals and corrected for the *LP* factor but not for absorption. All atoms of both molecules were located through a combination of Patterson and Fourier methods. Several cycles of least-squares refinements of all coordinates, anisotropic temperature factors for the four bromine atoms, and individual isotropic temperature factors for the other atoms converged to R = 0.14 for the 2000 observed reflections. A perspective drawing of the molecular structure in the crystal lattice is shown in Figure 1.

On the reasonable presumption that conversion of rubratoxin B to isorubratoxin bis-*p*-bromophenylhydrazide methyl ester has involved no change in configuration, rubratoxins A and B are assigned relative stereostructures **1** and **2**, respectively. It is noteworthy that, in disagreement with the assignment by Moss,[5] the C_6 and C_7 chains are found to be cis and are thus in accord with the stereochemical designation previously made to byssochlamic acid.[16]

At this stage of refinement, the two crystallographically independent molecules appear to have virtually identical conformations. Moreover, the conformation of the fused tricyclic bis-*p*-bromophenylhydrazide moiety is very similar to that found in the analogous byssochlamic acid derivative.[16] The two molecules of the asymmetric unit are approximately related by a noncrystallographic translation of $^1/_2\vec{c} + {}^1/_4\vec{b}$. No hydrogen bonds occur between the independent molecules, although each is associated with its symmetry-related neighbor through an intermolecular hydrogen bond between the C-7 hydroxyl group and the C-25 carbonyl oxygen atom. A more detailed description of the molecular geometry will be reported after additional refinements of anisotropic thermal parameters for every atom have been completed.

Acknowledgments. We are indebted to Professors R. I. Mateles and G. N. Wogan, Massachusetts Institute of Technology, for extracts of *P. rubrum* and for obtaining toxicity data. One of us (K. M. S.) thanks Smith, Kline and French Laboratories for a Walter G. Karr Fellowship (1964–1968). Support for this work from the National Cancer Institute (Contract No. PH 43-62-468) and the Air Force Office of Scientific

(12) A similar shift occurs in glauconic acid ketone upon addition of base.[7]

(13) (a) D. H. R. Barton and J. K. Sutherland, *J. Chem. Soc.*, 1769 (1965); (b) J. E. Baldwin, D. H. R. Barton, J. L. Bloomer, L. M. Jackman, L. Rodriguez-Hahn, and J. K. Sutherland, *Experientia*, **18**, 345 (1962).

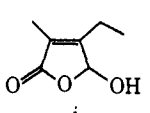
(14) (a) G. Ferguson, G. A. Sim, and J. M. Robertson, *Proc. Chem. Soc., London*, 385 (1962); (b) D. H. R. Barton, L. M. Jackman, L. Rodriguez-Hahn, and J. K. Sutherland, *J. Chem. Soc.*, 1772 (1965).

(15) D. H. R. Barton, L. D. S. Godinho, and J. K. Sutherland, *ibid.*, 1779 (1965).

(16) (a) I. C. Paul, G. A. Sim, T. A. Hamor, and J. M. Robertson, *ibid.*, 5502 (1963); (b) J. E. Baldwin, D. H. R. Barton, and J. K. Sutherland, *ibid.*, 1787 (1965).

(17) C. E. Moppett and J. K. Sutherland, *Chem. Commun.*, 772 (1966); see also R. K. Huff, C. E. Moppett, and J. K. Sutherland, *ibid.*, 1192 (1968).

(18) The model i [J. Schreiber and C. G. Wermuth, *Bull. Soc. Chim. Fr.*, 2242 (1965)] shows a one-proton singlet at δ 6.0.



i

(19) We are indebted to Dr. T. Kamikawa for preparation of this compound.

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Tricyclo[5.3.0.0^{2,10}]deca-3,5,8-triene[1]

Sir:

The title compound (**1**, isobullvalene)[2] appears to have revived interest in some transformations of $(CH)_{10}$ hydrocarbons and has been proposed as an unstable intermediate of some chemical reactions.[3,4] We have recently developed techniques which enable us to purify and characterize thermally unstable compounds such as [10]annulenes[1,5] and oxonins,[6] and the application to the present problem has led to the isolation of **1** without difficulty. We wish to outline briefly the apparatus employed for purification at cold temperatures and further to report the intriguing chemistry of **1** and its related compounds.

Figure 1 shows our typical equipment utilized for precisely temperature-controlled distillation (or sublimation) and low-temperature (down to −80°) chromatography and it is self-explanatory. This apparatus allows one to perform the entire work-up process below −50° and therefore most of the compounds which are surrounded by, at minimum, a 15 kcal/mol energy barrier, can be isolated.

Thus, reaction of cyclononatetraenide (**2**) with methylene chloride and *n*-butyllithium,[3,7] performed at −60° (1.25 hr) and quenched by methanol at −80°, provided a new $(CH)_{10}$ hydrocarbon by distillation at −13° (10^{-4} mm) and alumina chromatography at −80°. Its nmr spectrum (100 MHz, $CDCl_3$ at −40°) is shown in Figure 2 and is obviously compatible with the structure of **1** and corresponds well to that of its 3,4-benzo analog.[4] Catalytic hydrogenation of **1** with Rh-on-carbon at −80°[5,6] afforded three fully saturated compounds, the major product being the tricyclic compound (80%, *m/e* 136) corresponding to **1** and identical with that synthesized through an independent route.[8] The other two minor products were bicyclic (9 and 9%, *m/e* 138). These results clearly demonstrate that compound **1** is tricyclo[5.3.0.0^{2,10}]decatriene, and this structural assignment was further substantiated by its thermal conversion to **4** (*vide infra*). The synthesis is illustrated in Scheme I.

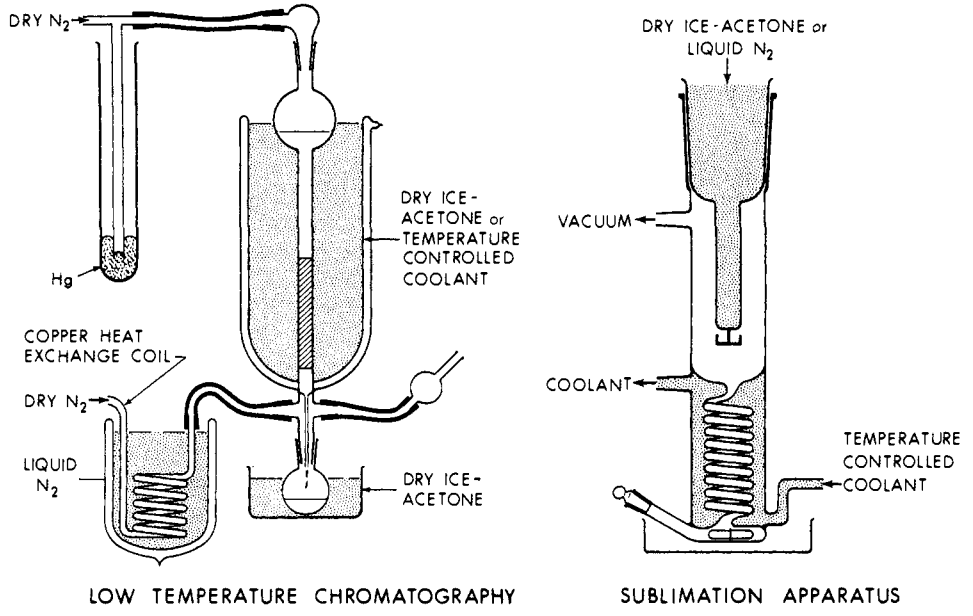

Figure 1. Equipment for low-temperature separation.

A more intriguing finding in the above reaction (**2** + CH_2Cl_2) was that the cold (−60°) reaction mixture con-

(1) Presented on June 17, 1970 before the Gordon Conference (Hydrocarbon) at Andover, N. H., as a part of the general subject entitled "The chemistry of some cyclic systems." The synthesis of pure (*cis*)[5]-[10]annulene was also announced.

(2) This name was suggested for this hydrocarbon by L. A. Paquette and J. R. Malpass, *J. Amer. Chem. Soc.*, 90, 7151 (1968).

(3) T. J. Katz and J. J. Cheung, *ibid.*, 91, 7772 (1969). Compound **2** did not react with CH_2Cl_2 in the absence of butyllithium even at −25° (3 hr). The condensation occurred only after the addition of the last reagent to the reaction mixture.

(4) E. Vedejs, R. A. Shepherd, and R. P. Steiner, *ibid.*, 92, 2158 (1970).

(5) S. Masamune and R. T. Seidner, *Chem. Commun.*, 542 (1969).

(6) S. Masamune, S. Takada, and R. T. Seidner, *J. Amer. Chem. Soc.*, 91, 7769 (1969).

(7) Treatment of 9-chlorobicyclo[6.1.0]nona-2,4,6-triene with lithium at −65° for 3 hr [*cf.* T. J. Katz and P. J. Garratt, *ibid.*, 86, 5194 (1964); G. LaLanatte and R. E. Benson, *ibid.*, 87, 1941 (1965)] provided a lithium salt mixture of mono-*trans*-cyclononatetraenide [3, 70%, see G. Boche, D. Martens, and W. Danzer, *Angew. Chem., Int. Ed. Engl.*, 8, 984 (1969)] and all-cis compound (2, 30%). Geometrical isomerization of **3** to **2** proceeded at 10°. Addition of excess methanol to the cold mixture effected protonation of only anion **3** at −80°, producing *all-cis*-cyclononatetraene, whereas **2** remained anion up to −10°. These results indicate that **3** is far more basic than **2**, as expected, and the site of protonation of **3** is specific.

(8) From 3-bromocycloheptene, using conventional methods: W. von E. Doering, *et al.*, *Tetrahedron*, 21, 25 (1965).