stirred at room temperature for a complete reaction time of 432 hr. Normal isolation procedures, using pentane extraction, were used. Product composition of these two solvolysis fractions was determined by differential infrared analysis. The former contained 11 mol % of **2c**, 84.5 mol % of **2d**, and 4.5 mol % of **1b**. Similarly, the product of the solvolysis reaction (after 432 hr) contained 15 mol % of **2c**, 83 mol % of **2d**, and 2 mol % of **1b**.

**Registry No.**—**1a** HCl, 35079-81-3; **1b**, 2975-83-9; **1e**, 35079-83-5; **2c**, 837-65-0; **2d**, 35079-85-7; **2e**, 35079-86-8; **2f**, 35079-87-9; **3e**, 35079-88-0; **4**, 2969-43-9; **5**, 2198-06-3; *N*-dibenzobicyclo[3.2.1]octadien-*exo*-2-ylacetamide, 35079-91-5; *N*-dibenzobicyclo-[3.2.1]octadien-*endo*-2-ylacetamide, 35079-92-6.

**Acknowledgments.**—The authors are indebted to the National Science Foundation and to the Donors of the Petroleum Research Fund, administered by the American Chemical Society, for the support of this research. One of us (J. R. M.) is also indebted to the Phillips Petroleum Company for fellowship support.

# Synthesis of 1,2-Dialkylcyclopropenes, Methyl Malvalate, and Methyl Sterculate[1a]

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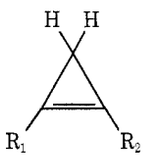
*Received November 5, 1971*

Dipropyl-, dipentyl-, dihexyl-, diheptyl-, and dioctylcyclopropene and methyl malvalate and sterculate have all been synthesized. Ethyl diazoacetate is decomposed in the presence of the appropriate alkyne, followed by hydrolysis to yield a 1,2-disubstituted 3-cyclopropenecarboxylic acid. Exposure to perchloric acid results in decarbonylation to a cyclopropenium ion, which is reduced by sodium borohydride to a 1,2-disubstituted cyclopropene. The absence of any 1,3-disubstituted cyclopropene in the product is consistent with theory. Spectroscopic data is presented. The cyclopropenethiol reaction is discussed.

The 1,2-disubstituted cyclopropene function occurs in the fatty acid chain of lipids from certain plants belonging to the order Malvales, cottonseed oil being the most common. These cyclopropenoid fatty acids have recently been the subject of intense investigation and are held responsible for numerous physiological disorders in farm and laboratory animals.[1]

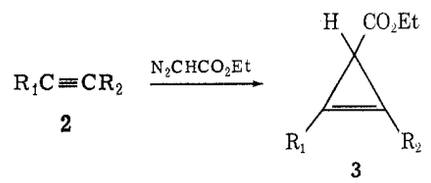
## Results

We have developed a synthesis to produce 1,2-disubstituted cyclopropenes (**1**) in quantities for biological testing and feedings. Gensler and coworkers[2] have reported a comparable route to **1f** and **1g**.



**1a**, $R_1 = R_2 =$ propyl
**b**, $R_1 = R_2 =$ pentyl
**c**, $R_1 = R_2 =$ hexyl
**d**, $R_1 = R_2 =$ heptyl
**e**, $R_1 = R_2 =$ octyl
**f**, $R_1 =$ octyl, $R_2 = -(CH_2)_8CO_2Me$ (methyl malvalate)
**g**, $R_1 =$ octyl, $R_2 = -(CH_2)_7CO_2Me$ (methyl sterculate)

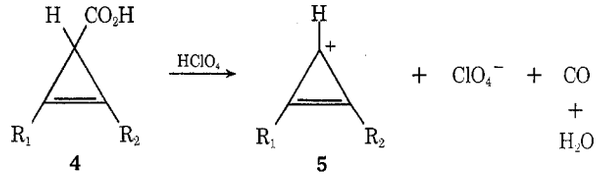
Ethyl diazoacetate, in the presence of a copper catalyst, adds to disubstituted acetylenes (**2**) yielding 1,2-disubstituted cyclopropene-3-carboxylates (**3**).[3] In the



present investigation, alkynes are 40–50% converted to the corresponding cyclopropene by an equal molar amount of diazoacetate. About 90–95% of the unreacted acetylenic compound can be recovered, reflecting the rather high selectivity of the carboxylcarbene. Other workers[2] report a 60–70% conversion for this identical reaction.

All the resulting 1,2-dialkyl-3-carboxylcyclopropenes can be purified by high vacuum distillation ($5 \times 10^{-2}$ mm), with the exception of one, methyl 9,10-(carboxymethano)-9-octadecenate (**3g**), the precursor for sterculate (**1g**). However, unreacted methyl stearolate (**2g**) can be recovered from this latter product by vacuum distillation without significant decomposition of the desired cyclopropene, thus facilitating purification on a column.

After hydrolysis, treatment of the 1,2-disubstituted cyclopropene-3-carboxylic acid (**4**) with strong mineral



acid in acetic anhydride results in decarbonylation[4] to the corresponding cyclopropenium ion (**5**). Cyclopropenium perchlorates are less soluble and easier to purify than the fluoroborates or bromides; therefore, we chose to work with the perchlorates. Mixtures of

(1) (a) Technical Paper No. 3196, Oregon Agricultural Experiment Station; (b) A. M. Abou-Ashour and H. M. Edwards, *J. Nutr.*, **100**, 1347 (1970); (c) W. E. Donaldson and B. L. Fites, *ibid.*, **100**, 605 (1970); (d) S. V. Dande and J. F. Mead, *J. Biol. Chem.*, **245**, 1856 (1970); (e) D. J. Lee, J. H. Wales, and R. O. Sinnhuber, *J. Nat. Cancer Inst.*, **43**, 1037 (1969); (f) R. A. Phelps, *et al.*, *Poultry Sci.*, **44**, 358 (1965); (g) A. M. Miller, E. T. Sheehan, and M. G. Vavich, *Proc. Soc. Exp. Biol. Med.*, **131**, 61 (1969).

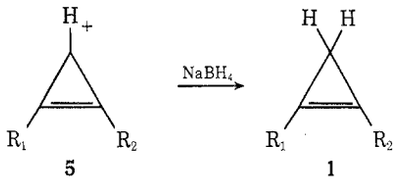
(2) (a) W. J. Gensler, *et al.*, *J. Amer. Chem. Soc.*, **91**, 2397 (1969); (b) *ibid.*, **92**, 2472 (1970); (c) *J. Org. Chem.*, **35**, 2301 (1970); (d) *Chem. Phys. Lipids*, **6**, 280 (1971).

(3) (a) I. A. D'Yakonov, *et al.*, *Zh. Org. Khim.*, **5**, 1742 (1969); *Chem. Abstr.*, **77**, 124556 (1970); (b) *Zh. Obshch. Khim.*, **29**, 3848 (1959); *Chem. Abstr.*, **54**, 195216 (1960); and references cited therein.

(4) (a) R. Breslow and H. W. Chang, *J. Amer. Chem. Soc.*, **83**, 2367 (1961); (b) R. Breslow, *et al.*, *ibid.*, **83**, 2375 (1961); (c) R. Breslow and P. Dowd, *ibid.*, **85**, 2729 (1963); (d) R. Breslow, H. Hover, and H. W. Chang, *ibid.*, **84**, 3168 (1962).

pentane–anhydrous ether at −20° will precipitate dipropyl-, dipentyl-, and dihexylcyclopropenium ions as solids, but in poor yields. Mixtures of chloroform–pentane precipitate all the cyclopropenium ions studied as thick, red-black oils, but in rather good yields.

Reduction[4,5] of 1,2-disubstituted cyclopropenium ions (**5**) can be accomplished with almost any hydride.




5 1

The problem lies in finding an unreactive solvent which will dissolve both the cyclopropenium ion and hydride at low temperatures. Seventeen per cent dimethyl ether of ethylene glycol or 20% pyridine in dimethyl sulfoxide proved to be satisfactory solvents for this reduction with sodium borohydride. The yields of **1** from decarbonylation followed by reduction are variable, but average about 55%. The reduction product consistently carries with it 4–8% of the corresponding dialkyl acetylene. When solid 1,2-dipropylcyclopropenium perchlorate was recrystallized followed by reduction, the product still contained 8% 4-octyne, demonstrating that the alkyne was not carried over from starting materials. Failure to separate the cyclopropenium perchlorate from the acetic anhydride solution before adding it to the hydride solution shifts an alkyne to cyclopropene ratio to 60% alkyne.

The products have all the chemical and spectroscopic[6] properties expected for 1,2-dialkylcyclopropenes. Synthetic malvalate and sterculate are identical in every respect with the acids isolated from natural sources. The infrared, nmr, and mass spectra of the naturally occurring esters are superimposable with those of the synthetic esters. Infrared bands attributable to the cyclopropene ring occur at 1875 and 1005 $cm^{-1}$ for all 1,2-dialkylcyclopropenes, including methyl malvalate and sterculate.

The nmr shows a triplet centered around $\tau$ 7.66 for the two methylene groups attached to the 1 and 2 positions of the ring. The ring methylene hydrogens resonate in a single sharp peak in the area of $\tau$ 9.28–9.12, depending upon solvent. Solutions of $CCl_4$ and $CCl_4$ mixed with the polar solvents methanol or acetonitrile result in absorption farthest upfield. Adding chloroform results in a small (2 cps on a HA-100 instrument) shift downfield, while adding benzene shifts these two protons 10 cps downfield to $\tau$ 9.18. Pyridine–$CCl_4$ shifts the ring methylene protons farthest downfield, $\tau$ 9.12, while slightly shifting the center of the methyl triplet upfield 3 cps to the same frequency. Surprisingly, running a solution of **1a** neat also shifts the ring methylene protons downfield, to $\tau$ 9.18. Changes in chemical shift of protons on a saturated carbon have been observed in other systems and are attributed to *collision complexes*.[7]

(5) D. T. Longone and D. M. Stehouwer, *Tetrahedron Lett.*, 1017 (1970).

(6) (a) G. L. Closs in "Advances in Alicyclic Chemistry," H. Hart and G. J. Karabatsus, Ed., Academic Press, New York, N. Y., 1966, Chapter 2; (b) C. Y. Hopkins, *J. Amer. Oil Chem. Soc.*, **45**, 778 (1968).

(7) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, Elmsford, N. Y., 1969, pp 111–113 and 246–248.

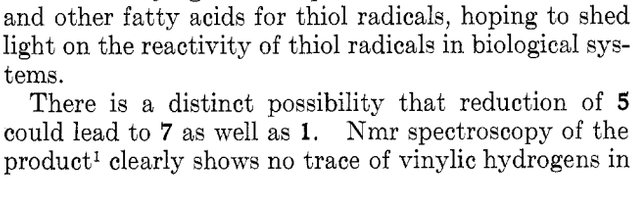
The mass spectra of all the compounds studied are consistent with the 1,2-disubstituted cyclopropene structure. All the 1,2-dialkylcyclopropenes, including methyl malvalate and sterculate, have a base peak of mass 81. Peaks with mass numbers 41, 67, and 95 are intense in all the spectra. In addition, **1e**, **1f**, and **1g** have strong peaks at mass numbers 43 and 55. Doering and Mole[8] report the parent minus one, mass 67, as the base peak for 1,2-dimethylcyclopropene and suggest that it may correspond to the 1,2-dimethylcyclopropenium ion, formed in greatest abundance by virtue of its special aromatic character. None of our spectra show any trace of a parent minus one mass peak.

All 1,2-disubstituted cyclopropenes reported here give a strong Halphen reaction.[9] However, the secondary band[9b] at 540 m$\mu$ is absent, producing more of an orange color for the synthetic compounds. Also, the synthetic compounds assay in excess of 100% compared to natural oils as standards. It is well recognized that the Halphen reaction of natural oils varies with the source and concentration of the cyclopropenoid fatty acid being tested.[9]

There are reports of a spontaneous addition of mercaptans across the strained double bond of 1,2-disubstituted cyclopropenes.[10] Raju and Reiser[11] describe the reaction as an assay method for the cyclopropenoid function in natural oils, but Coleman[9a] and Schneider[12] report that the reaction is not reproducible. We have found that, under an atmosphere of purified nitrogen, methyl mercaptan in benzene does not react with 1,2-dialkylcyclopropenes, even when a large excess of the thiol is left in contact with the olefin at room temperature for several days. Upon the introduction of oxygen, a free-radical initiator, methyl thiol rapidly adds across the double bond of **1b** to form a sulfide (thio ether) in quantitative yield.

The additions of sulfhydryl groups to olefins are well-known reactions involving acidic, nucleophilic, free radical, and photolytic catalyst.[13] It is neither surprising nor unique that they will add to cyclopropenes. We are studying the competition between sterculate and other fatty acids for thiol radicals, hoping to shed light on the reactivity of thiol radicals in biological systems.

There is a distinct possibility that reduction of **5** could lead to **7** as well as **1**. Nmr spectroscopy of the product[1] clearly shows no trace of vinylic hydrogens in




5 6 7

(8) W. Doering and T. Mole, *Tetrahedron*, **10**, 65 (1960).

(9) (a) E. C. Coleman, *J. Ass. Offic. Anal. Chem.*, **53**, 1209 (1970); (b) A. V. Bailey, *et al.*, *J. Amer. Oil Chem. Soc.*, **42**, 422 (1965); (c) T. W. Hammonds, *et al.*, *Analyst*, **96**, 659 (1971).

(10) (a) H. W. Kircher, *J. Amer. Oil Chem. Soc.*, **41**, 4 (1964); (b) H. G. Reilich, *et al.*, *ibid.*, **46**, 305 (1969); (c) R. L. Ory and A. M. Altschul, *Biochem. Biophys. Res. Commun.*, **17**, 12 (1964).

(11) P. K. Raju and R. Reiser, *Lipids*, **1**, 10 (1966).

(12) E. L. Schneider, *J. Amer. Oil Chem. Soc.*, **45**, 585 (1968).

(13) (a) E. N. Prilezhaeva and M. F. Shostakovskii, *Russ. Chem. Rev.*, **32**, 399 (1963); (b) F. W. Stacey and J. F. Harris, Jr., "Organic Reactions," Vol. 13, A. C. Cope, Ed., Wiley, New York, N. Y., 1963, Chapter 4; (c) W. E. Vaughan and F. F. Rust, *J. Org. Chem.*, **7**, 472 (1942).

the area of $\tau$ 2.99 as would be expected for **7**.[14] Breslow and coworkers[4d] report three equivalent propyl groups in the nmr spectrum of tripropylcyclopropenyl perchlorate, indicating that the positive charge is evenly distributed around the ring. Also, the propyl groups in the three cations, tripropylcyclopropenyl, dipropylcyclopropenyl, and propyldiphenylcyclopropenyl perchlorate, are relatively shifted to the same extent. Differences in chemical shift between the $\alpha$- and $\beta$-methylene hydrogens are very similar for the propyl groups in each of these three cations.[4d] This data supports the concept that each carbon of the cyclopropenyl cation has a similar charge structure, with essentially one-third of the charge at each ring carbon.

Our failure here to detect any **7** (less than 1%) from the reduction of **5** does not conflict with Breslow's picture of charge distribution in a cyclopropenyl perchlorate. An attacking nucleophile would certainly attack the unsubstituted position of a cyclopropenium ion more rapidly than at a position substituted with a large alkyl group. A satisfactory model to compare the relative steric effect of substituents on an organic ion during a bimolecular reaction is not available. However, bimolecular displacement reactions (SN2) have been extensively investigated and can be used to demonstrate a large rate-retarding effect when substituents are attached directly to the reacting carbon.[15] For example, methyl chloride reacts with iodide ion in acetone (a pure SN2 reaction) 180 times more rapidly than does *n*-butyl chloride. From a tabulation of some second-order displacements, methyl halides react 11 to 145 times more rapidly than their ethyl counterparts, and the few butyl halides listed react from two to four times more slowly than the ethyl compounds.[15] The bimolecular displacements of some $\alpha$-substituted benzyl halides show a comparable rate-retarding effect.[15]

Competition factors, $k_Y/k_o$, measure the ability of a nucleophile Y to compete with water for a carbonium ion. Triphenylmethyl cation shows marked competition factors, $2.8 \times 10^5$ for azide ion in 50% aqueous acetone and $5.3 \times 10^4$ for hydroxide ion.[15] One expects an ion to become more discriminating as its stability increases. Dipropylcyclopropenium cation,[4d] $pK_{R^+} = 2.7$, is considerably more stable than triphenylmethyl cation,[16] $pK_{R^+} = -6.63$, and should show a correspondingly larger selectivity in its reactions with nucleophiles. The combination of ion selectivity with 1 and 2 substituents accounts for reduction exclusively at the 3 position.

## Experimental Section

**Synthesis of 1,2-Dialkylcyclopropenes and Methyl Malvalate and Sterculate.**—The appropriate alkyne was placed in a flask under an atmosphere of nitrogen with a magnetic stirrer and freshly activated copper dust (approximately 4 g of copper per mole of alkyne). While the flask was immersed in an oil bath at 110–120°, an equal molar amount of ethyl diazoacetate was added slowly enough (while stirring rapidly) so that foaming did not prevent the diazoacetate from dropping directly into the liquid. After the addition was complete, unreacted alkyne was recovered by vacuum distillation followed by vacuum distillation of the ethyl 1,2-dialkyl-3-cyclopropenecarboxylate, except in the synthesis of methyl sterculate. Unreacted methyl stearolate can be recovered from its ethyl diazoacetate adduct, ethyl 1-octyl-2-(7-carbomethoxylheptyl)-3-cyclopropenecarboxylate (**3g**), by vacuum distillation, but the complex cyclopropene itself cannot be distilled without extensive thermal decomposition. The methyl stearolate–ethyl diazoacetate adduct is best separated from polydiazoacetate by column chromatography, preferably on an acid-washed alumina column eluting with pentane–ether. Table I lists the boiling points of some alkynes, their ethyl diazoacetate adducts, and the corresponding 1,2-dialkylcyclopropenes.

TABLE I

DISTILLATION TEMPERATURES AND PRESSURES

| 1,2 Substituent | Acetylene temp, °C (mm) | Ethyl 3-cyclopropene carboxylate temp, °C (mm) | Cyclopropene temp, °C (mm) |
|---|---|---|---|
| Dipropyl | 66 (70) | 96 (0.25)[a] | |
| Dipentyl | 55 (0.4) | 100 (0.25) | |
| Dihexyl | 68 (0.05) | 122 (0.15) | 73 (0.05) |
| Diheptyl | 114 (0.1) | 135 (0.13) | 92 (0.04) |
| Dioctyl | 116 (0.02) | 135 (0.09) | 107 (0.02) |
| 1-Octyl-2-(7-carbomethoxyheptyl) | 114 (0.025) | 134 (0.025) | 125 (0.03) |
| | 128 (0.15) | 159 (0.15) | |
| 1-Octyl-2-(6-carbomethoxylhexyl) | 155 (0.15) | Decomposes | 136 (0.04) |

[a] 3-Cyclopropenecarboxylic acid.

Ester hydrolysis was carried out with 2 equiv of 10% potassium hydroxide in 1-propanol. After heating at 100° for 2 hr under $N_2$, the solution was diluted, adjusted to pH 4, and extracted with ether. The extract was dried and evaporated.

Treatment of the 1,2-disubstituted 3-cyclopropenecarboxylic acid with an equal molar amount of perchloric acid in acetic anhydride (1 g of 70% perchloric acid per 10 g of cold acetic anhydride) decarbonylated it to a 1,2-disubstituted cyclopropenium perchlorate. The decarbonylation may be carried out at room temperature with the dialkyl compounds, but fatty acid percursors must be chilled to below 10°. Decarbonylation was allowed to proceed until gaseous evolution diminished. The entire cyclopropenium perchlorate–acetic anhydride solution was transferred to a large separatory funnel containing chloroform at −20°, and pentane, at the same temperature, was added until a black oil precipitates. Generally, one used 10 ml of cold chloroform for each gram of 70% perchloric acid used, and 70 ml of cold pentane was added. After the black oil was separated, which is mostly cyclopropenium perchlorate, more cold pentane was added and the separatory funnel was allowed to sit at −20° to ensure complete precipitation.

To form the hydride solution, 100 ml of dimethyl sulfoxide, 20 ml of 1,2-dimethoxyethane or 20 ml of pyridine, and 5 g of sodium borohydride were mixed under an inert atmosphere, warmed to dissolve the borohydride, and then cooled to 5–7°; lower temperatures cause sodium borohydride to precipitate. While the hydride solution was rapidly stirred, the cold black oil, 1,2-disubstituted cyclopropenium perchlorate, was slowly added. Too rapid of an addition caused formation of side products, mainly the corresponding alkyne. During the addition of fatty acids, foaming can be arrested by an immiscible layer of pentane over the hydride solution.

After dilution with a large volume of water, neutralization, and extraction with pentane, the 1,2-dialkylcyclopropenes can be distilled (see Table I for distillation data) and/or column chromatographed, eluting with pentane or hexane. The cyclopropene was always eluted before its corresponding alkyne. Acid-washed alumina only partially separated the alkynes from the desired cyclopropenes. Silica gel column gave better separation but a small per cent of the strained ring compound was lost on the column, and although gas chromatography and spectroscopic examination may show the product to be pure, it did not store well and developed a yellow color after several weeks at −20°.

Malvalic and sterculic acids should be converted to esters before further purification or storage, since they are not as stable in the acid form. Esterification may be accomplished with diazomethane or by dissolving the acid in methanol. Esterification of malvalic or sterculic acids in methanol with an acid catalyst leads to the destruction of the cyclopropene function.[17] Chromatogra-

(14) K. B. Wiberg and B. J. Nist, *J. Amer. Chem. Soc.*, **83**, 1226 (1961).

(15) A. Streitwieser, Jr., "Solvolytic Displacement Reactions," McGraw-Hill, New York, N. Y., 1962.

(16) N. Deno, *J. Amer. Chem. Soc.*, **77**, 3047 (1955).

(17) J. R. Nunn, *J. Chem. Soc.*, 313 (1952).

phy of these esters was accomplished on acid-washed alumina or silica gel eluting with pentane, gradually changing to pentane–ether.

All compounds possessed the expected spectral properties as described in the text.

**Alkynes. Methyl stearolate** was prepared from oleic acid by a procedure similar to that reported by Butterfield and Dutton.[18] Gunstone and Hornby[19] report a procedure, which may be superior, utilizing liquid ammonia. A small molar excess of liquid bromine was added to methyl oleate in the dark until the red bromine color persisted for 1 hr. Excess bromine was removed on a vacuum evaporator. The dihalide acid was added to 30% KOH in ethylene glycol (6 mol of KOH per mole of acid) and heated at 206° under an atmosphere of nitrogen for 4 hr. Dilution, acidification, and extraction with hexane was followed by esterification in methanol–1% sulfuric acid. Vaccum distillation afforded a clear oil in 70% yield, bp 155° (0.15 mm). Spectroscopic and physical properties of acetylinic esters are rather passive. Retention on a diethylene glycol succinate column was considerably longer than for methyl oleate and a 300-ft butanediol succinate capillary column showed a single unsplit peak. Absorption in the infrared was at 2940, 2845, 1750, 1470, 1445, 1375, 1260, 1200, and 1178 $cm^{-1}$. The nmr showed no vinylic hydrogens and two overlapping triplets centered around $\tau$ 7.9.

**Methyl 9-heptadecynoate** was synthesized by the method of Ames and Covell.[20] Sodamide (52 g) and 178 g of 1-decyne were dissolved in 4.5 l. of liquid ammonia. After 1 hr, 67 g of 7-bromoheptanoic acid was dissolved in a mixture of tetrahydrofuran and glyme and slowly added. The liquid ammonia was allowed to evaporate, and dilution and acidification was followed by extraction with ether. Esterification was accomplished in methanol–1% sulfuric acid. Vacuum distillation yielded 48 g of a clean oil, bp 114° (0.025 mm). Infrared absorption appeared at 2940, 2845, 1750, 1470, 1445, 1375, 1260, 1200, and 1178 $cm^{-1}$. The nmr shows no vinylic hydrogens and overlapping triplets at $\tau$ 7.9. The mass spectrum shows a parent at $m/e$ 280.

**1,2-Dialkylacetylenes.**—The lower homologs can be purchased from the Chemical Sample Co., Columbus, Ohio. Other alkynes were synthesized by adding the appropriate alkyl bromide to sodium acetylide in liquid ammonia. After work-up and purification the resultant 1-alkyne was added to 1 equiv of sodamide (50 g per 4 l. of $NH_3$) in liquid ammonia followed by addition of 1 equiv of the appropriate alkyl bromide. Distillation data is contained in Table I. Yields of the higher molecular weight alkynes are low, 50% for 9-octadecyne based on 1-decyne.

Attempts to synthesize these alkynes from the appropriate Grignard reagent and 1,4-dichloro-2-butyne (Aldrich) proved unsatisfactory.

**7-Bromoheptanoic Acid.**—One gram-atom of metallic sodium was dissolved in 400 ml of absolute ethanol followed by the addition of 1.05 mol of diethyl malonate. This solution was stirred for 30 min by a strong mechanical stirrer, then added to a freshly prepared solution of 1.25 mol of 1,5-dibromopentane in 100 ml of absolute ethanol. Reaction was exothermic and sodium bromide precipitated. The solution was diluted with a large volume of water and extracted with chloroform. The extract was dried and evaporated. The product was refluxed in 250 ml of acetic acid and 50 ml of sulfuric acid for 1 day, with a warm condenser allowing ethyl acetate to escape. Dilution, extraction, and distillation yielded 7-bromoheptanoic acid in 53% yield, bp 105° (0.08 mm), mp 27–30° [lit.[21] bp 140–142° (1.5 mm), mp 28–29°].

**Registry No.**—**1c**, 35365-52-7; **1d**, 35365-53-8; **1e**, 1089-40-3; **1f**, 5026-66-4; **1g**, 3220-60-8; **2a**, 1942-45-6; **2b**, 6975-99-1; **2c**, 35216-11-6; **2d**, 19781-86-3; **2e**, 35365-59-4; **2f**, 24471-20-3; **2g**, 1120-32-7; **3b**, 35365-62-9; **3c**, 35365-63-0; **3d**, 35365-64-1; **3e**, 35365-65-2; **3f**, 35365-66-3; **3g**, 30689-71-5; methyl 9-heptadecynoate, 25601-39-2; 3-cyclopropenecarboxylic acid 26209-00-7.

**Acknowledgment.**—This work was supported in part by Public Health Service Grants ES 00263 and ES 00256 from the Division of Environmental Health Sciences.

(18) R. O. Butterfield and H. J. Dutton, *J. Amer. Oil Chem. Soc.*, **45**, 635 (1968).

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(20) D. E. Ames and A. N. Covell, *J. Chem. Soc.*, 775 (1963).

(21) D. E. Ames, R. E. Bowman, and R. G. Mason, *J. Chem. Soc.*, 174 (1950).

# Grignard Reagents from Bromobenzo[*h*]quinolines. 13-Substituted Derivatives of 20-Chloronaphtho[2′,1′:12,13](2,4)pyridinophane[1,2]

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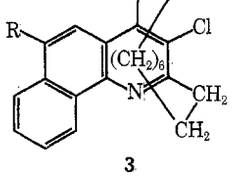
*Received May 10, 1972*

While Grignard reagents are not generally useful intermediates for synthetic conversions in quinoline systems, they are shown to be quite useful in the naphthopyridinophane series (**3**), and to a lesser, but practical extent, useful with 2-alkylbenzo[*h*]quinolines such as **9b**. The stability and utility of such Grignard reagents is not related to decreased acidity of the benzyl bridge methylene groups in **3**, since no metal exchange was noted for the dimethyl analog **9b**. Symmetrical coupling can become the major reaction of Grignard reagents in the benzo[*h*]-quinoline system, as observed for **6**. While the mechanism of this coupling is not known, the lack of coupling parallels steric hindrance at the azomethine linkage. A variety of 13-substituted derivatives of 20-chloronaphtho[2′,1′:12,13][10](2,4)pyridinophane have been prepared and one of these (**3i**) was found to be active (curative at 640 mg/kg) against *Murine Plasmodia–Plasmodium berghei*.

The initial objective of this work was to prepare certain 13-substituted derivatives of 20-chloronaphtho-[2′,1′:12,13][10](2.4)pyridinophane[3] (**3**, Table I),




**3**

specifically the two diastereomeric[3] racemates corresponding to **3g** and **3i** which were of interest as agents against murine malaria. The replacement of aromatic bromine by functional groups of the type shown in **3g** and **3i** has been studied in detail and is usually accom-

(1) Supported by U.S. Army Medical Research Command, DADA-17-70-C-0008. This paper is contribution no. 1048 from the Army Research Program on Malaria.

(2) The methylene-bridged aromatic compounds in this study are named using the rules described by B. H. Smith in "Bridged Aromatic Compounds," Academic Press, New York, N. Y., 1964. There does not exist a universally accepted method for the naming of such compounds; *cf.* F. Vogtle and P. Newmann, *Tetrahedron*, **26**, 5847 (1970). *Chemical Abstracts*' name for **3b**, for example, is 15-bromo-20-chloro-3,4,5,6,7,8,9,10,11,12-decahydro-2,13-metheno-13*H*-1-naphtho[1,2-*b*]azacyclopentadecene.

(3) (a) The pyridinophane ring is asymmetric since the methylene bridge cannot flip to the opposite face. *Cf.* W. E. Parham, R. W. Davenport, and J. B. Biasotti, *Tetrahedron Lett.*, 557 (1969); (b) W. E. Parham, R. W. Davenport, and J. K. Rinehart, *J. Org. Chem.*, **35**, 2662 (1970).