Constituents of the Cotton Bud. VIII. β-Bisabolol, a New Sesquiterpene Alcohol[1]

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In the course of our investigations of the cotton plant (*Gossypium hirsutum* L. var. Deltapine Smoothleaf) essential oil[3] for constituents attractive to the boll weevil, *Anthonomus grandis* Boheman, we have isolated and established the structure of a new sesquiterpene alcohol, β-bisabolol (**1**). The numbering corresponds to that employed previously.[4] This dextrorotatory, clear, viscous liquid with an apple–floral aroma was separated from the oil β-fraction[3] by column chromatography and purified by distillation. It corresponds to peak 42 in the original SE-30 glpc survey[3] of the cotton bud oil, of which it is the most abundant (5.6% by weight) polar constituent.

The empirical formula, $C_{15}H_{26}O$, ease of dehydration in the mass spectrometer (*m/e* 222–204), ready formation of urethans, and the OH stretch at 3420 cm^{-1} (Figure 1) suggested a tertiary sesquiterpene alcohol. The quite high-field hydroxyl group pmr signal at 1.36 ppm was shifted to as high as 1.15 ppm on dilution with CCl_4 and deshielded by increasing concentration, in accordance with expected hydrogen bonding effects. This high-field signal suggested a shielded hydroxyl, possibly attached axially to a cyclohexyl structure.

The structure of **1** and its relationship to the previously reported[4] cotton component, γ-bisabolene (**6**), were deduced from physical properties, mass, pmr, and infrared spectra. Although **1** could also be considered a derivative of β-curcumene[5] (**7**) or γ-curcumene[6] (**8**), we prefer to emphasize its relationship to the cotton constituent rather than to the curcumenes, neither of which was found in cotton essential oil.

Presence of two double bonds and consequent requirement of a monocyclic skeleton was suggested by the molar refraction exaltation of 3.28 (3.46, theory) and confirmed by the parent masses of **1** (*m/e* 222) and its reduction products, **2** and **3** (*m/e* 226). Dehydration of the tetrahydro alcohols (Scheme I) and a second reduction gave a mixture of two hydrocarbons incompletely resolved by glpc. Kovats indices ($I_K{}^P$, $I_K{}^P$)[7] on polar and apolar glpc columns, infrared, and mass spectra confirmed their identity as *cis*- and *trans*-bisabolane (**4**,**5**).[8] The infrared spectrum of the mixture of **2** and **3** was in nearly complete agreement, except for several small maxima, with that reported[9] for a synthetic product of the same structure. Double bond positions followed from comparison of pmr signals in **1**, **6**, and 4-terpinenol[10] (Table I), particularly the two vinyl protons (C-2, C-10) and the vinylic methyls (C-12, 13, 15). This unsaturation pattern is supported (Figure 1) by the unsplit methyl symmetric bending absorption at 1377 cm^{-1} and δ CH absorption at 825 cm^{-1} (isopropylidene), and the trisubstituted olefinic (cyclohexenyl) proton deformations at 795 and 763 cm^{-1}.

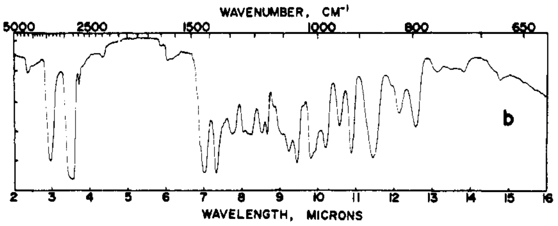
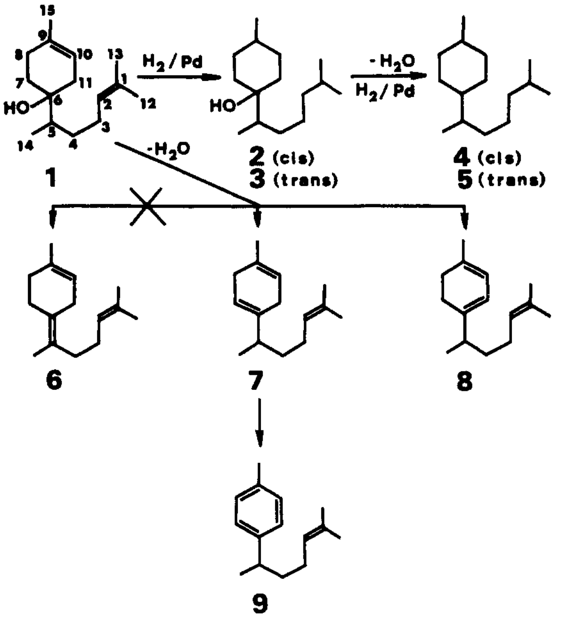


Figure 1.—Infrared spectrum of β-bisabolol; neat liquid between salt plates.

SCHEME I



Hydroxyl group attachment at C-6 in **1** is demanded by comparison of the pmr signals of that group, as well as C-5, 11, and 14 in **1**, **6**, and 4-terpinenol (Table I). Furthermore, after **1** and the mixture of **2** and **3** were transformed to (trichloroacetyl) carbamates in the pmr tube,[11] β-protons C-5, 7, and 11, were all deshielded strongly (Table I). Even the C-14 methyl doublet showed a slight paramagnetic shift.

More evidence for the C-6 location of the hydroxyl function was adduced upon phthalic anhydride dehydration of **1** (Scheme I), which gave **7** and **8** but no **6**.[12]

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[1] (a) Paper VII: P. A. Hedin, J. P. Minyard, and A. C. Thompson, *Phytochemistry*, **6**, 1165 (1967); (b) from the Ph.D. Thesis of J. P. M., Mississippi State University, June 1967; (c) presented at the 154th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1967.

[2] Entomology Research Division, Agricultural Research Service, U. S. Department of Agriculture. Mention of a proprietary product or company does not necessarily imply endorsement of the same by the U. S. Department of Agriculture.

[3] J. P. Minyard, J. H. Tumlinson, A. C. Thompson, and P. A. Hedin, *J. Agr. Food Chem.*, **15**, 517 (1967).

[4] J. P. Minyard, J. H. Tumlinson, A. C. Thompson, and P. A. Hedin, *ibid.*, **14**, 332 (1966).

[5] B. S. Rao and J. L. Simonesen, *J. Chem. Soc.*, 2496 (1928); F. D. Carter, F. C. Copp, B. S. Rao, J. L. Simonsen, and K. S. Subramaniam, *ibid.*, 1504 (1939).

[6] R. D. Blatt and S. N. Slater, *ibid.*, 838 (1949).

[7] E. Kováts, *Z. Anal. Chem.*, **181**, 351 (1961).

[8] J. Plíva, M. Horák, V. Herout, and F. Šorm, "Die Terpene. I. Sesquiterpene," Akademie Verlag, Berlin, 1960, S. 7.

[9] M. Herout, M. Zaoral, and F. Šorm, *Collection Czech. Chem. Commun.*, **18**, 122 (1953).

[10] R. Teranishi, R. E. Lundin, W. H. McFadden, T. R. Mon, T. H. Schultz, K. L. Stevens, and J. Wasserman, *J. Agr. Food Chem.*, **14**, 447 (1966).

[11] V. W. Goodlett, *Anal. Chem.*, **37**, 431 (1965).

[12] Dehydration of 4-terpinenol with a variety of reagents leads to preferential formation (89%) of α-terpinene and γ-terpinene, with some *p*-cymene; K. K. Sugathan and J. Verghese, *Current Sci.*, **33**, 524 (1964).

TABLE I

PMR SPECTRAL ABSORPTIONS OF β-BISABOLOL AND RELATED COMPOUNDS[a]

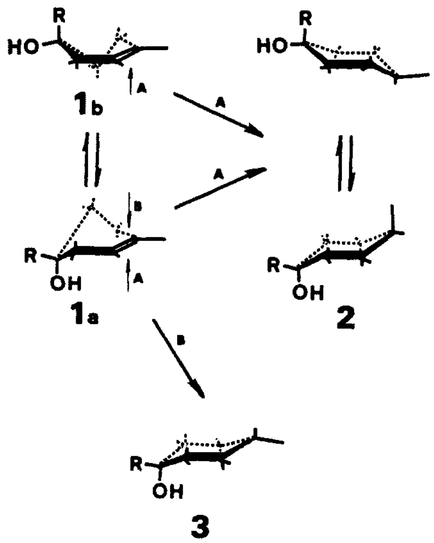
Compound[c]	Proton position[b] C-2	C-3	C-5	C-7	C-8	C-10	C-11	C-12	C-13	C-14	C-15	OH
1	5.01	1.92	2.24	~1.6	1.92	5.20	1.92	1.57	1.64	0.85	1.64	1.36
6	5.02	1.95	. . .	1.95	1.95	5.26	2.65	1.54	1.62	1.62	1.62	. . .
4-Terpinenol	. . .	. . .	2.29	1.55	1.98	5.20	1.98	. . .	. . .	0.90	1.67	1.49
1 carbamate[d]			2.65	2.38			2.38			0.94		8.43[e]
2, 3			1.85	~1.4			~1.4			0.82		1.05
2,3 carbamate[d]			2.38	~1.8			~1.8			0.89		8.61[e]
7				5.32	2.49	5.32	2.49			0.94	1.52	
γ-Terpinene				5.35	2.52	5.35	2.52			0.99	1.53	
8				1.99	1.99	5.48	5.48				1.71	
α-Terpinene				2.03	2.03	5.51	5.51				1.73	
9			2.79	6.93	6.93	6.93	6.93			1.16	2.25	
p-Cymene			2.73	6.89	6.89	6.89	6.89			1.11	2.19	

[a] See ref 13 for conditions; signal multiplicities, coupling constants, and line broadenings given in detail in Experimental Section, but generally are equal for protons in equivalent positions. [b] See numbering of **1**, Scheme I. [c] **1**, β-bisabolol; **2**, **3**, *cis,trans*-tetrahydro-β-bisabolol; **6**, γ-bisabolene; **7**, β-curcumene; **8**, γ-curcumene; **9**, *ar*-curcumene. [d] (Trichloroacetyl) carbamates. [e] Broadened amide singlet.

Table I lists corresponding and distinctive pmr signals of **7** and γ-terpinene, **8** and α-terpinene, and **9** and p-cymene for comparison. Neither **7** nor **8** were obtained in pure form from the dehydration products mixture and attempted glpc purification of **7** resulted in extensive aromatization to *ar*-curcumene, **9**.

Preferential ring hydrogenation of the half-chair conformer **1b** (Scheme II) opposite to the axial side chain would lead to the *cis*-saturated alcohol, **2**. Ring hydrogenation from the side opposite the axial hydroxyl in conformer **1a** would give the *trans* saturate **3** whereas hydrogen addition from the hydroxyl side would give **2**. The comparatively high-field position (1.2–1.8 ppm) of the hydroxyl proton and the more favorable equatorial attachment of the side chain would seem to favor conformer **1a** as β-bisabolol. This configuration correlates well with its modest polarity, exemplified by tlc (R_f 0.28 on silica gel G–benzene) and column chromatographic behavior. On reduction, two principal products were obtained in the ratio 3:1. The major product had an R_f of 0.25 on silica gel–benzene and an I_K^P of 1932; the minor product was less polar (R_f 0.41, I_K^P 1928, same systems). The major product must then have been the *cis* alcohol, **3**, and the minor, **2**, which suggests a possible participation of the hydroxyl in the near side hydrogenation of **1a**. The unequal ratio of **2** and **3** obtained from **1** is believed to account for the minor differences observed in the natural and synthetic tetrahydro-β-bisabolol infrared spectra.

SCHEME II



Experimental Section[13]

Isolation of β-Bisabolol (1).—Cotton essential oil was obtained by steam distillation of 2975 kg of buds of Deltapine Smoothleaf cotton and was fractionated on deactivated silica gel columns as described elsewhere.[3] Girard T removal of the carbonyls from the β (2-chloropropane) fraction thus obtained gave the β_2 (midpolar, noncarbonyl) fraction, 24.0 g from 357.5 g of square oil. Glpc indicated the principal component of this fraction was identical with peak 42 previously found during a glpc survey (SE-30) of the oil.[3] This material was also present in lesser quantities in the γ (methanol) column fraction of the cotton oil, associated with a number of other polar materials.

The β_2 fraction was initially separated by preparative tlc on silica gel G with benzene (visualized by edge streaking with vanillin–sulfuric acid and heating).[14] The adsorbent bands scraped from the plate (**1**, R_f 0.28, purple with spray) were eluted with methylal. In subsequent separations, 2-ml portions of β_2 in CH_2Cl_2 (1:1) were chromatographed (benzene, 29.0 ml) on 2.0 × 10 cm silica gel columns. A 5.5-cm portion starting 1.5 cm from the top of the extruded adsorbent was removed and **1** was eluted from it with methylal. A second crop of **1** was harvested by rechromatography and similar work-up of the methylal eluate from the lower 3 cm of the first columns. Preparative tlc and column fractions were composited according to tlc monitoring evidence. Solvent was removed at reduced pressure to give a total of 13.8 g of **1**; an estimated 5 g more remained in the lower polarity fraction. Vacuum distillation of 9.5 ml of crude **1** gave 7.1 ml of a colorless, viscous liquid with an apple–floral aroma: bp 121–122° (2 mm); $n^{20}{}_D$ 1.4925; $d^{20}{}_4$ 0.9260; $[\alpha]^{20}{}_D$ +23.3° (in $CHCl_3$); MR 69.70; glpc,[8,13] I_K^A

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[13] Melting points are corrected; analyses were performed by Gailbraith Labs., Knoxville, Tenn. Infrared spectra (neat liquids between salts), were performed on Beckman IR-5A and Perkin-Elmer 521 recording spectrometers. Pmr spectra (in CCl_4) were determined on a Varian A-60 recording spectrometer. Chemical shifts were reported as δ (parts per million), TMS = 0. Abbreviations used in describing pmr signals are d, doublet; t, triplet; br, broad, unstructured; m, complex multiplet; unmarked signals are singlets. The figures in parentheses are proton count, followed by line separations in cycles per second if the signal is a multiplet. Mass spectra were determined by Southern Research Institute, Birmingham, Ala., on a P. E.-Hitachi double focusing RMU-6D, fast scan, low resolution, 70 v ionizing potential. Glpc separations were performed on an Aerograph A-700 thermal conductivity chromatograph using the following columns and conditions: A, 4 mm × 3 m, Apiezon L, 20%/Gas Chrom P, silanized, 60/80 mesh, 175°, 75 cc/min He flow; B, 4 mm × 3 m, Carbowax 4000, 28.5%/Gas Chrom P, silanized 60/80 mesh, 175°, 75 cc/min He flow; C, 10 mm × 1.2 m, Carbowax 20M, 20%/Gas Chrom P, silanized, 60/80 mesh, 140°, 150 cc/min He flow.

[14] D. Waldi, "Thin Layer Chromatography," E. Stahl, Ed., Academic Press Inc., New York, N. Y., 1965, p 501.

column A, 1689; I_K^P, column C, 2196; infrared spectrum (Figure 1); 5.6% of oil (8.7 ppm in plant), peak areas from SE-30 glpc.[1] *Anal.* Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 80.83; H, 11.70.

Pmr analyses showed 0.85 d (3, 6.5), 1.36 (1), 1.57 (3), 1.63 (6), 1.92 m, br (6), 2.24 m, br (1), 5.08 t, br (1, 6.5), 5.20 m, br (1); mass spectrum *m/e* (intensity), 222 (2, parent), 204 (23), 122 (21), 121 (39), 119 (40), 111 (38), 93 (61), 82 (33), 81 (100), 72 (31), 69 (44), 67 (26), 55 (31), 41 (55), 32 (40), 28 (36).

The pmr spectrum of the (trichloroacetyl) carbamate of **1**, obtained within 10 min after addition of 4 drops of trichloroacetyl isocyanate to **1** in CCl_4 in the pmr tube,[11] showed the following:[13] 0.94, d (3, 6.5); 1.58 d (3, ~1); 1.67 (6); 1.75 d, br (2, 7); 1.99 m, br (4); 2.37 br, m (4); 2.65 br (1) 5.02 br, t (1, 7.5); 5.23 br (1); 8.43 br (1).

The [*p*-(phenylazo)phenyl]urethan (mp 96–99°, from pentane) formed readily.[15] *Anal.* Calcd for $C_{28}H_{35}N_3O_2$: C, 75.47; H, 7.92; N, 9.43. Found: C, 75.61; H, 7.94; N, 9.61.

Dehydration of 1.—Phthalic anhydride (1.5 g, 10 mmoles) and crude **1** (1.11 g, 5.0 mmoles) were heated at 120–175° for 1 hr under reduced pressure in a Bantamware still without any apparent distillation of hydrocarbon. The reaction mixture was extracted with pentane, filtered, and the solvent removed under reduced pressure. Glpc (column B)[13] of the residue taken up in pentane showed several major peaks. The entire pentane solution (*ca.* 1 ml) was chromatographed (B) in four injections and four fractions were trapped into CCl_4 (Table II). Only fractions D2 and D3 contained enough sample to give useful pmr spectra. The D2 spectrum contained signals interpreted as belonging to **8**; D3 appeared to be principally **7**. Rechromatography and trapping of D2 and D3 into CCl_4 was conducted on column A. I_K^P and I_K^A values of each fraction and subfraction are given in Table II. The signals attributed to **8** in D2 were nearly absent in D2-2, but too little D2-1 (presumed to be **8**) was trapped to obtain a pmr spectrum. D3, initially lacking any aromatic components, gave rise to **7** (D3-2), **9** (D3-1), and an originally present but unidentified component, D3-3. Pmr analyses of **7** showed the following: 0.94 d (3, 6.5); 1.52 (3); 1.60 (8); 1.95 m, br (2); 2.24 m, br (1); 2.49 (4); 5.01 m, br (1); 5.32 br (2). Pmr analyses of **8** showed the following: 0.96 d (3, 6.5); 1.71 (3); 1.99 (4); 5.48 br (2). Pmr analyses of **9** showed the following: 1.16 d (3, 6.5); 1.46 (3); 1.61 br (5); 1.91 br (2); 2.25 (3); 2.79 m, br (1); 5.0 br (1); 6.93 (4).

TABLE II

GLPC FRACTIONS OBTAINED FROM DEHYDRATION OF β-BISABOLOL

Peak (column)[a]	I_K^P, 175°	I_K^A, 175°	Fraction designation	Dehydr prods,[b] %
1(B)	1646	. . .	D1	6
2(B)	1655	. . .	D1	5
3(B), 1(A)	1728	1496	D2-1	3
3(B), 2(A)	1728	1513	D2-2	33
4(B), 1(A)	1775	1489	D3-1	0,[c] 13[d]
4(B), 2(A)	1775	1515	D3-2	25,[c] 14[d]
4(B), 3(A)	1775	1531	D3-3	10,[c] 8[d]
5(B)	1811	. . .	D4	7

[a] See ref 13. [b] Triangulation of peak areas and normalization of total area to 100. [c] % present in D3 mixture before glpc on column A. [d] % present after rechromatography of D3 on column A.

Tetrahydro-β-bisabolol (2, 3).—Quantitative reduction of **1** (2.546 g, 11.5 mmoles) in pentane was accomplished at 3.5 atm of H_2 over Pd on charcoal. Three peaks (I_K^P1837, 1930, 1937) in ratio 1:85:14 appeared upon glpc (column C)[13] of the reduction mixture after solvent removal. Each of these was trapped separately into CCl_4 from 120 μl of the mixture. Tlc of these fractions (silica gel G–benzene) demonstrated that the 1930 peak was a mixture of two materials, **2** and **3**; ratio 3:1, R_f 0.25 and 0.41. Preparative tlc and glpc gave I_K^P (column C) 1932 and 1928; I_K^A (column A) 1621 and 1636, respectively. The infrared spectrum of this mixture matched that of 1-(1′,5′-dimethylhexyl)-4-methylcyclohexanol[10] with only several minor differences: mass spectrum (I_K^P 1930 mixture) m/e (intensity), 226 (1, parent), 208 (3), 124 (17), 123 (13), 113 (100), 95 (44), 81 (12), 69 (5), 67 (5), 55 (7), 41 (7). Pmr analyses (I_K^P 1930 mixture) showed the following: 0.71 (1); 0.82 d (3, 6.5); 0.85 d (9, 6.5); 1.05 (1); 1.21 br (6); 1.54 br, m (2); 1.72 br, m (3).

After the pmr spectrum of the mixture of **2** and **3** had been obtained, 4 drops of trichloroacetyl isocyanate were added to the sample in the pmr tube. The spectrum of the carbamate was run within 10 min of derivatization, which was complete at that time. Pmr analysis (I_K^P 1930 mixture plus isocyanate) showed the following: 0.89 d (3, 6.5); 0.96 d (9, 6.5); 1.27 br (6); 1.43 br (4); 1.75 br (2); 1.92 br (2); 2.21 m, br (3); 8.61 br (1).

Bisabolane (4, 5).—The crude reduction mixture (1.123 g, 4.23 mmoles of **2** plus **3**) and phthalic anhydride (1.5 g, 10 mmoles) were heated together at 135° for 30 min. The mixture was washed with 40 ml of 5% Na_2CO_3 solution and extracted with pentane (50 ml, three portions). After solvent removal under reduced pressure and drying (Na_2SO_4), 0.7 ml of a pale yellow oil was obtained. Tlc on silica gel with benzene revealed only small amounts of nonhydrocarbon impurities. Chromatography on an Alcoa F-20 alumina column (2.0 × 10 cm) with 200 ml of pentane, followed by pentane removal under reduced pressure, afforded 0.5 ml of a pale yellow oil. This was taken up in 15 ml of pentane and hydrogenated at 3.5 atm over palladium on charcoal. Filtration from the catalyst and pentane removal (reduced pressure) gave 0.4–0.5 ml of a crystal clear oil. Glpc (columns B and A) demonstrated that this oil was a mixture of two incompletely resolved components: ratio 4:1; I_K^P 1508, 1526; I_K^A 1475, **5** and **4**, respectively.

Glpc behavior and infrared and mass spectra of this hydrocarbon mixture were identical with those of authentic bisabolane from reduction of **6** from cotton oil.[4] Its infrared spectrum was also identical with a reported spectrum of bisabolane:[9] mass spectrum *m/e* (intensity), 210 (9, parent), 125 (22), 124 (16), 112 (13), 97 (100), 96 (83), 83 (15), 81 (34), 71 (12), 69 (46), 67 (10), 57 (34), 56 (22), 55 (82), 43 (17), 41 (27).

Registry No.—**1**, 15352-77-9; **1** (trichloroacetyl)carbamate, 15352-78-0; **2**, 15352-79-1; **2** (trichloroacetyl)-carbamate, 15352-80-4; **3**, 15352-81-5; **3** (trichloroacetyl)carbamate, 15352-82-6; **4**, 11042-77-6; **5**, 11042-76-5; **6**, 11037-64-2; 4-terpinenol, 562-74-3; **7**, 11037-65-3; γ-terpinene, 99-85-4; **8**, 11037-66-4; α-terpinene, 99-86-5; **9**, 11012-67-2; *p*-cymene, 99-87-6.

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[15] J. A. Attaway, R. W. Wolford, G. E. Alberding, and G. J. Edwards, *Anal. Chem.*, **35**, 234 (1963).

Steroid Hormone Analogs. IV.[1]

C-Nor-D-homoestrone[2]

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Interest continues in the synthesis of modified steroids in a search for analogs with enhanced or more specific pharmacological properties. During the past few years, several groups have reported studies of the synthesis of C-nor-D-homo steroid hormone analogs.[1,3–7] We describe herewith the synthesis of the

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(1) Part III in the series: S. M. Kupchan and M. J. Abu El-haj, *J. Org. Chem.*, **33**, 647 (1968).

(2) This investigation was supported in part by Public Health Service Research Grant HE-02275 from the National Heart Institute.

(3) S. M. Kupchan and S. D. Levine, *J. Am. Chem. Soc.*, **86**, 701 (1964).

(4) S. M. Kupchan, T. Masamune, and G. W. A. Milne, *J. Org. Chem.*, **29**, 755 (1964).

(5) T. Masamune, K. Orito, and A. Murai, *Bull. Chem. Soc. Japan*, **39**, 2503 (1966).

(6) W. F. Johns and I. Laos, *J. Org. Chem.*, **30**, 4220 (1965), and the references cited there.

(7) H. Mitsuhashi and N. Kawahara, *Tetrahedron*, **21**, 1215 (1965), and the references cited there.