in the separation of a solid which was collected by filtration and crystallized from 75% ethanol; 4.6 g. (0.0198 mole, 78% yield); m.p. 134.5–136°.

A mixture of equal parts of this product and starting material melted between 120 and 127°; a mixture of the product and 5-chloro-2-nitrovanillin, prepared by the method of Raiford and Lichty,[1] melted without depression at 134.5–136°.

Chlorination of 5-Chlorovanillin Triacetate.—5-Chlorovanillin triacetate was chlorinated by the method of Raiford and Lichty[1]; a 78% yield of 5,6-dichlorovanillin triacetate; m.p. 114–115°, was obtained.

Attempted Bromination of 5-Chlorovanillin Triacetate.—5-Chlorovanillin triacetate (10 g., 0.0303 mole) was dissolved in 50 ml. of glacial acetic acid by warming the mixture to 60°; 8.4 g. (0.0525 mole) of bromine was added, and the solution was refluxed for 2 hr. After cooling the reaction mixture, it was poured into 3 vol. of water. The precipitate which formed was crystallized from 30% ethanol; 8.2 g.; m.p. 114–115°. By a mixed melting point determination (m.p. 114–115°) with starting material, the product was identified as 5-chlorovanillin triacetate. The 8.2 g. of material represented an 82% (0.0248 mole) recovery of starting material.

Structures Related to Morphine. XXIII.[1] Stereochemistry of 5,9-Dialkyl-6,7-benzomorphans

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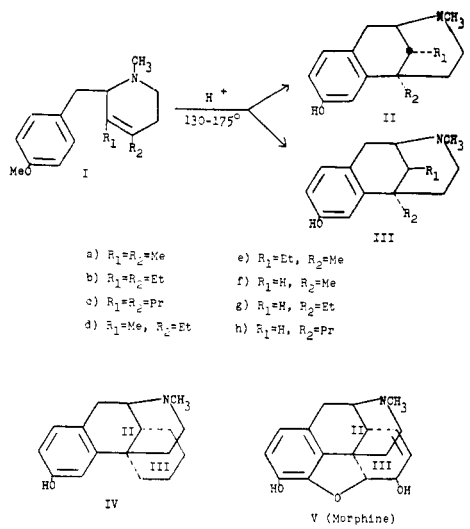
The absolute configuration (at C-9) of several 5,9-dialkyl-6,7-benzomorphans (II, III) has been adduced from methiodide-rate-formation and NMR studies. A nonaqueous titration procedure for determining unchanged II and III, and thus the amount of methiodide formed in a given time, is described.

The acid-catalyzed cyclization of 3,4-dialkyl-2-(*p*-methoxybenzyl)-1-methyl-1,2,5,6-tetrahydropyridines (I) leads to isomeric 5,9-dialkyl-6,7-benzomorphans (II, III) differing in configuration at position 9.[3–6] It has been presumed that the *predominant* isomers[7] resulting from these cyclizations[8] are those in which the 9-alkyl substituents (R_1) are oriented away from the nitrogen, *i.e.*, axial for the hydroaromatic ring, as in II. This assumption followed from analogy with the morphinan synthesis[9] and from consistency with the "*trans* rule" of addition to olefinic bonds,[10] in this instance to the 3,4-double bond of I. In view of the significant pharmacologic behavior of these compounds, particularly the β-isomers,[3,4] it was desired to determine unequivocally their stereochemistry at C-9.



From an examination of molecular models of II and III,[11] it appeared that there would be a substantial difference in the rate of formation of their methiodides, and during the course of degradative experiments in the dimethyl series (IIa and IIIa) such a rate difference was casually observed. It seemed likely also that the methyl signal in the NMR spectrum of IIa would be distinguishable from that of IIIa. These predictions have proved valid and we wish to report a quantitative estimation of the rate of formation of the methiodides of IIa–e and IIIa–e along with NMR spectra of IIa, IIIa, and their *O*-acetyl derivatives. Included as controls in the rate studies are IIf–h

(1) Paper XXII, H. Kugita, S. Saito, and E. L. May, *J. Med. Pharm. Chem.*, **5**, 357 (1962).

(2) Visiting Fellow from the Chelsea School of Pharmacy, England; present address: London, England.

(3) E. L. May and J. H. Ager, *J. Org. Chem.*, **24**, 1432 (1959).

(4) J. H. Ager and E. L. May, *ibid.*, **27**, 245 (1962).

(5) S. E. Fullerton and E. L. May, paper in preparation.

(6) J. H. Ager, S. E. Fullerton, and E. L. May, *J. Org. Chem.*, to be published.

(7) For convenience and clarity the predominant isomers will be designated with the prefix α; the lesser diastereomers will be designated β.

(8) The ratio of predominant (α) to lesser (β) isomers has varied from 12:1 to 6:1 and appears to depend upon the cyclizing agent and temperature used as well as the bulk of the R groups. In general, the higher the temperature and the larger the alkyl groups the lower is this ratio. The yields of the lesser (β) isomers are usually 3–8%.

(9) R. Grewe, A. Mondon, and E. Nolte, *Ann.*, **564**, 161 (1949).

(10) M. S. Newman, "Steric Effects in Organic Chemistry," John Wiley & Sons, New York; Chapman Hall, Ltd., London, 1956, p. 242.

(11) The nitrogen of III is crowded by R_1 while in II there is, of course, no discernible hindrance of the nitrogen by R_1.

which have no alkyl substituent at C-9. The amount of methiodide formed in chloroform in a given time was determined indirectly by non-aqueous titration of unreacted base[12] with acetous perchloric acid using Oracet Blue B indicator.[13]

Experimental

Microanalyses are by Paula Parisius of the Institute's service analytical unit, Harold McCann, director. Melting points (capillary, Hershberg, apparatus) are corrected.

Optical Resolution of β-2′-Hydroxy-2,5,9-trimethyl-6,7-benzomorphan.—β-(±)-2′-Hydroxy-2,5,9-trimethyl-6,7-benzomorphan (IIIa, 0.5 g.),[3] 0.8 g. of (+)-3-bromocamphor-8-sulfonic acid ammonium salt,[14] 10 ml. of water, and 0.5 ml. of 12 *M* hydrochloric acid were boiled to solution and cooled at −5°, giving 0.5 g. of needles, m.p. 255–258°. These were dissolved in hot water and neutralized with ammonium hydroxide to give 0.2 g. (80%) of **β-(−)-2′-hydroxy-2,5,9-trimethyl-6,7-benzomorphan,** oblong prisms from methanol m.p. 179–181°; $[\alpha]^{20}D$ −88.5° (*c* 0.52, absolute alcohol).

Anal. Calcd. for $C_{15}H_{21}NO$: C, 77.88; H, 9.15. Found: C, 78.08; H, 9.16.

The **hydrobromide** crystallized from 90% ethanol-ethyl acetate in prisms, m.p. 295–296° dec.; $[\alpha]^{20}D$ −47.2° (*c* 0.9, water).

Anal. Calcd. for $C_{15}H_{22}BrNO$: C, 57.68; H, 7.10. Found: C, 57.92; H, 7.29.

The filtrate from the 0.5 g. of needles above was made alkaline with ammonium hydroxide giving 0.25 g. of precipitate, m.p. 175–200°. This was dissolved in 7 ml. of boiling methanol and 2 ml. of water was added to the solution. On cooling to 5°, 0.065 g. of prisms [(±)−IIIa], m.p. 210–215°, separated. Further water dilution of the filtrate and cooling to 5° gave 0.14 g. (56%) of **β-(+)-2′-hydroxy-2,5,9-trimethyl-6,7-benzomorphan,** rods or needles from aqueous methanol, m.p. 180–181.5°; $[\alpha]^{20}D$ +88.6° (*c* 0.35, absolute alcohol).

Anal. Calcd. for $C_{15}H_{21}NO$: C, 77.88; H, 9.15. Found: C, 78.02; H, 9.21.

The **hydrobromide,** prisms from alcohol, melted at 293–295° dec.; $[\alpha]^{20}D$ +44.3° (*c* 0.75, water).

Anal. Calcd. for $C_{15}H_{22}BrNO$: C, 57.68; H, 7.10. Found: C, 57.53; H, 7.10.

α-(±)-2′-Acetoxy-2,5,9-trimethyl-6,7-benzomorphan Hydrochloride.—Acetic anhydride (1 ml.) and 0.5 g. of α-(±)-2′-hydroxy-2,5,9-trimethyl-6,7-benzomorphan (IIa)[3] were kept on the steam bath for 30 min., acidified to Congo Red with gaseous hydrogen chloride, and diluted with ether. After decantation, the residue crystallized from acetone in a yield of 0.6 g. (90%). It was decolorized with charcoal (25 ml. of hot acetone) and the solution concentrated to 5 ml. Addition of a few drops of ether and cooling overnight at −5° gave 0.5 g. of small prisms, m.p. 227.5–229°.

Anal. Calcd. for $C_{17}H_{24}ClNO_2$: C, 65.91; H, 7.81; Cl, 11.46. Found: C, 66.30; H, 8.10; Cl, 11.47.

β-(±)-2′-Acetoxy-2,5,9-trimethyl-6,7-benzomorphan Hydrobromide.—Acetic anhydride (1 ml.), 0.1 ml. of pyridine, and 125 mg. of β-(±)-2′-hydroxy-2,5,9-trimethyl-6,7-benzomorphan hydrobromide (IIIa)[3] were refluxed to solution. On cooling, needles separated. Diluted with ether and filtered, the mixture yielded 132 mg. (94%) of hydrobromide of the *O*-acetyl compound; small prisms from acetone, m.p. 252–255° (gas evolution).

Anal. Calcd. for $C_{17}H_{24}BrNO_2$: C, 57.63; H, 6.83. Found: C, 57.56; H, 6.90.

General Procedure Used in the Rate Studies.—The benzomorphan (20 mg.)[15] accurately weighed in a 50-ml. conical flask was dissolved in 20 ml. of chloroform and treated with exactly 0.040 ml. of methyl iodide. The flask was then tightly stoppered and kept at room temperature (25°) with occasional shaking. After a designated period (*cf.*, Table I) of time, the mixture was titrated with 0.0206 *N* acetous perchloric acid (Oracet Blue β as indicator)[13] and the amount of reacted benzomorphan determined by difference. The end point is sharp and is marked by a change in color from blue to mauve. Chloroform as a solvent was found to be more satisfactory than either benzene or acetone. Control titration experiments of II and III in chloroform immediately after addition of the methyl iodide gave accurate equivalent weights, and 20 ml. of chloroform with 0.04 ml. of methyl iodide gave a blank of 0.05 ml. of the standard acid.[16] In several instances heat was required to dissolve the base, in which case the solution was protected with a calcium chloride tube while cooling. Although, with the α-isomers and with IIf–h, the methiodides usually precipitated, the end points were still sharp and the results no less accurate than when a clear solution obtained throughout. Occasionally some color developed during methiodide formation, but again the determination of the titration end points was not unduly difficult. After sufficient experience had been gained it was found advantageous to approximate the amount of acid needed and run most of this in quickly.

Results and Discussion

In Table I are presented percentages of the benzomorphans (II and III) converted to their methiodides during various time intervals ranging from 2–24 hours for the α-isomers and IIf–h and from 4–96 hours for the β-compounds. To facilitate comparison of these data a plot (for each compound) of the percentages as a function of reaction time is shown in Fig. 1. Invariably the α-isomers IIf–h were from 96–99% converted to their methiodides in twenty-four hours, whereas the β-methiodides had formed to the extent of only 13–41% in a similar period. In three instances ($R_1=R_2=Et$; $R_1=R_2=Pr$; $R_1=Et$, $R_2=Me$) with the β-compounds conversion was no more than 35–45% complete after ninety-six hours. Even more striking is the rate difference during the first four hours when the reactivity of the α-isomers and IIf–h is from 5–25 times that of the β-counterparts. There was no substantial difference in the reactivity of the five α-isomers which were also comparable with those compounds bearing no 9-alkyl radical (IIf–h). The order of reactivity of the β-isomers was 5,9-dimethyl > 5-ethyl-9-methyl > 5-methyl-9-ethyl > 5,9-diethyl > 5,9-dipropyl as would be expected if the 9-alkyl substituent is oriented toward nitrogen as in III. It is also apparent that increasing the size of the alkyl substituent at either the 5- or 9- position in III decreases reactivity. Restricted rotation of the 5- and 9-alkyl groups is observed in all molecu-

(12) This technique was also useful in approximating the percentage composition of mixtures of II and III and thus aided in their separation.

(13) A. H. Beckett and E. H. Tinley, "Titration in Non-Aqueous Solvents," The British Drug Houses Ltd., Poole, England, 1957.

NOTE ADDED IN PROOF. Methiodide rate studies have been used by M. Shamma and J. B. Moss, *J. Am. Chem. Soc.*, **83**, 5038 (1961) in determining the stereochemistry of the D/E ring fusion for a series of heteroyohimbines. This publication came to our attention after our manuscript had gone to the Editor.

(14) Sold by the Aldrich Chemical Co. under the name α-D-bromocamphor-π-sulfonic acid.

(15) Allowable limits, ±1 mg.

(16) Accuracy limits after applying this blank were ±2%.

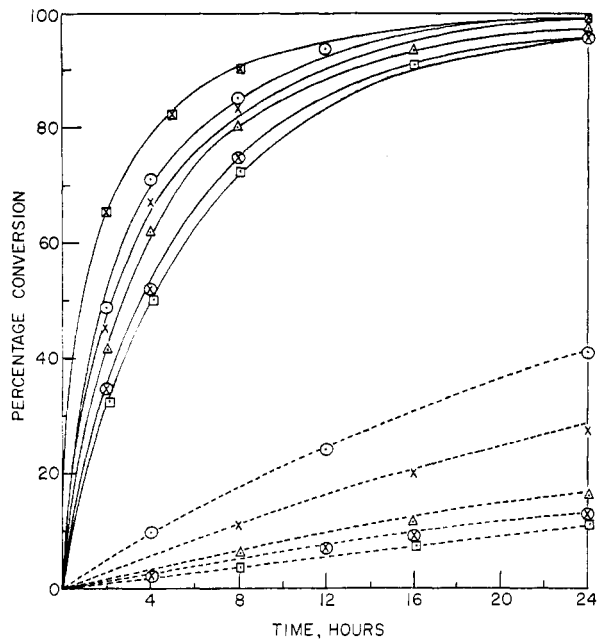


Fig. 1.—⊠ IIf (The points for IIg and IIh are almost identical with those of IIf).

—⊙— IIa - - -⊙- - - IIIa
—×— IId - - -×- - - IIId
—△— IIe - - -△- - - IIIe
—⊗— IIb - - -⊗- - - IIIb
—⊡— IIc - - -⊡- - - IIIc

lar models of III studied excepting IIIa. These results together with the NMR spectra (*vide infra*) leave no doubt that the predominant (α) isomers obtained in the acid cyclization of the tetrahydropyridine derivatives (I) are represented by II, the β-compounds by III.

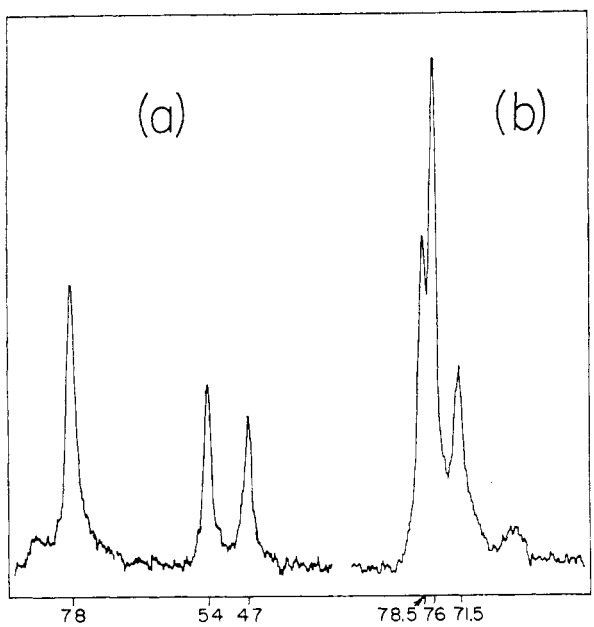


Fig. 2.—NMR spectra of IIa and IIIa (obtained in $CDCl_3$ solution with a Varian HR-60 spectrometer). Frequencies are reported in c.p.s. with respect to internal tetramethylsilane as zero. (a) Predominant isomer, α; (b) β-isomer.

TABLE I

Compound	Reaction Time	% Benzomorphan Converted to Methiodide
IIa[a]	2	48.6
	4	71.0
α-(+)-2′-Hydroxy-2,5,9-trimethyl-6,7-benzomorphan[b]	8	85.0
	24	99.0
IIIa	4	9.9
β-(±)-2′-Hydroxy-2,5,9-trimethyl-6,7-benzomorphan[c]	12	24.0
	24	40.8
IIb[a]	2	35.0
α-(+)-5,9-Diethyl-2′-hydroxy-2-methyl-6,7-benzomorphan[d]	4	52.0
	8	75.2
	16	92.5
	24	96.0
IIIb	4	2.3
β-(±)-5,9-Diethyl-2′-hydroxy-2-methyl-6,7-benzomorphan[c]	12	7.0
	16	9.1
	24	12.5
	30	14.6
	96	35.3
IIc	2	32.5
α-(±)-2′-Hydroxy-2-methyl-5,9-dipropyl-6,7-benzomorphan[e]	4	50.5
	8	75.0
	16	91.9
	24	95.5
IIIc	8	3.9
β-(±)-2′-Hydroxy-2-methyl-5,9-dipropyl-6,7-benzomorphan[e]	16	7.8
	24	11.0
	72	26.8
IId	2	45.2
α-(±)-5-Ethyl-2′-hydroxy-2,9-dimethyl-6,7-benzomorphan[f]	4	67.3
	8	83.2
	24	98.9
IIId	8	10.7
β-(±)-5-Ethyl-2′-hydroxy-2,9-dimethyl-6,7-benzomorphan[f]	16	20.0
	24	27.9
	48	44.8
IIe	2	41.6
α-(±)-9-Ethyl-2′-hydroxy-2,5-dimethyl-6,7-benzomorphan[f]	4	62.0
	8	80.3
	16	93.3
	24	97.3
IIIe	8	6.3
β-(±)-9-Ethyl-2′-hydroxy-2,5-dimethyl-6,7-benzomorphan[f]	16	11.4
	24	16.0
	48	26.1
IIf	2	65.5
(±)-2′-Hydroxy-2,5-dimethyl-6,7-benzomorphan[g]	5	82.4
	8	90.6
	24	98.6
IIg	2	65.0
(±)-5-Ethyl-2′-hydroxy-2-methyl-6,7-benzomorphan[h]	4	78.8
	8	91.6
	24	98.0
IIh	2	63.5
(±)-2′-Hydroxy-2-methyl-5-propyl-6,7-benzomorphan[e]	4	78.5
	8	91.4
	24	99.0

[a] The dextro isomer was used because the racemate was not sufficiently soluble in chloroform. [b] See ref. 18. [c] See ref. 4. [d] See ref. 19. [e] See ref. 6. [f] See ref. 5. [g] See ref. 20. [h] See ref. 21.

Partial proton NMR spectra of the α- and β-isomers (IIa and IIIa)[17] are shown in Fig. 2. The

(17) The *levo* antipodes of IIa and IIIa (*cf.*, Experimental and ref. 18) were used because the racemates were not sufficiently soluble in deuterochloroform.

(18) E. L. May and N. B. Eddy, *J. Org. Chem.*, **24**, 1435 (1959).

strong lines at 78 c.p.s. in α and at 76 c.p.s. in β arise from the 5-methyl, and the doublets at 47 and 54 c.p.s. in α and 71.5 and 78.5 c.p.s. in β are due to the 9-methyl. (In the *O*-acetylated derivatives the 9-methyl frequencies are identical with those given above; the 5-methyl frequencies are 80 and 78 c.p.s., respectively.) The 25 c.p.s. difference in the 9-methyl frequency between α and β is the result of a change in environment of the 9-methyl from a position above the aromatic ring in IIa to one near the nitrogen atom in IIIa. In the former case the "ring current" effect will produce a diamagnetic (upfield) shift[22] of the order of 25 c.p.s.[23] The effect of the nitrogen in IIIa is less readily evaluated quantitatively, but it seems likely that repulsion of the electrons in the C—H bond by the negative nitrogen atom might produce a small paramagnetic shift.[24] Since these two effects appear to be the only significant factors in altering the resonance frequency of the 9-methyl protons in the two molecules, IIa should have its 9-methyl absorption at higher field than IIIa. Thus the predominant isomer (α) has the structure IIa, in agreement with the rate studies discussed above.

By means of stereoselective adsorbents[25] it has been shown that (−)-2′-hydroxy-2,5,9-trimethyl-6,7-benzomorphan, the analgesically active antipode of IIa is related stereochemically to (−)-3-hydroxy - *N* - methylmorphinan (levorphanol, IV) and morphine. Furthermore, a *cis*-fusion of rings B and C for morphine[26] and the morphinans[9,27] and the epimeric relationship of the isomorphinans[28] at C-14 have been rigorously proved. It follows therefore that the α-benzomorphans[7] are comparable in stereochemistry to IV and V, and that the β-compounds conform to the isomorphinan pattern.

In general, these β-compounds (III) are lower melting, more soluble, and from 7–70 times more potent than the α counterparts (II). Assuming that all the activity resides in the *levo*-enantiomorphs the most active III (R_1=Et, R_2=Me) would have twenty to thirty times the analgesic potency of morphine. Experiments designed to render III more readily available are in progress.

(19) S. E. Fullerton, unpublished.

(20) N. B. Eddy, J. G. Murphy, and E. L. May, *J. Org. Chem.*, **22**, 1370 (1957).

(21) S. Saito and E. L. May, *ibid.*, **27**, 948 (1962).

(22) (a) J. A. Pople, *J. Chem. Phys.*, **24**, 1111 (1956); (b) C. E. Johnson, Jr., and F. A. Bovey, *ibid.*, **29**, 1012 (1958).

(23) Using the equations of Johnson and Bovey[22] and distances determined from Dreiding stereo models we calculate a ring current diamagnetic shift of 78 c.p.s. for the proton of the 9-methyl group closest to the aromatic ring in IIa. Averaging due to internal rotation of the methyl group will produce an actual shift of about 1/3 this value, or 26 c.p.s. The almost exact agreement with the observed difference, 25 c.p.s., is undoubtedly fortuitous, but the ring current effect is seen to be of the right magnitude to account for the observed difference.

(24) A somewhat analogous situation occurs, for example, in certain steroids where the angular methyls experience a paramagnetic shift of 6–10 c.p.s. when subjected to the influence of an 11-β-hydroxyl group (*cf.*, J. N. Shoolery and M. T. Rogers, *J. Am. Chem. Soc.*, **80**, 5121 (1958)).

(25) A. H. Beckett and P. Anderson, *J. Pharm. and Pharmacol.*, **12**, **228T** (1960).

(26) H. Rapoport and J. B. Lavigne, *J. Am. Chem. Soc.*, **75**, 5329 (1953).

(27) H. Corrodi, J. Hellerbach, A. Zust, E. Hardegger, and O. Schnider, *Helv. Chim. Acta*, **42**, 212 (1959).

(28) M. Gates and W. G. Webb, *J. Am. Chem. Soc.*, **80**, 1186 (1958).

Studies in Thiazoles. V. Synthesis of Some 2-Chloro- and 2-Hydroxythiazoles

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A number of new 2-hydroxythiazoles and 2-chlorothiazoles have been prepared from the corresponding ω- and α-thiocyanato ketones reported earlier.[1b] The 2-hydroxythiazoles were screened for their *in vitro* activity against *Str. haemolyticus*, *M. pyogenes varaures*, *B. subtilis*, *S. paratyphi*, *S. schottmuelleri*, *S. typhi*, *B. coli*, *Sh. sonnei*, and *S. paradysenteriae* (Flexener), and some of the compounds have been found to inhibit the growth of a wide variety of bacteria at a dilution of 1 in 1000.

The synthesis of some 2-chloro- and 2-hydroxythiazoles required as intermediates in the preparation of therapeutically important 10:11 thiopegans was reported earlier.[2–6] The present paper constitutes an extension of the previous work and describes the synthesis of some 2-hydroxy- and 2-chlorothiazoles, with phenolic, alkoxy, alkyl, and acetamino, phenyl moieties in position 4 of the thiazole system. A number of 5-methyl-substituted thiazole derivatives were also prepared with a view to studying the effect of the alkyl group on

(1)(a) To whom inquiries should be made. Present address: Dept. of Chemistry, University of Western Ontario, London, Ontario, Canada. (b) K. S. Dhami, S. S. Arora, and K. S. Narang, *J. Sci. industr. Res.*, **18B**, 392 (1958).

(2) D. S. Bariana, H. S. Sachdev, and K. S. Narang, *J. Indian Chem. Soc.*, **32**, 427 (1955).

(3) R. Adams, *Org. Reactions*, 377 (1955).

(4) K. Ganapathi and A. Venkataraman, *Proc. Indian Acad. Sci.*, **22A**, 374 (1945).

(5) G. M. Sharma, H. S. Sachdev, and K. S. Narang, *J. Sci. industr. Res.*, **16B**, 411 (1957).

(6) H. S. Sachdev, K. S. Dhami, and K. S. Narang, *ibid.*, **19C**, 9 (1960).