

water, yielding shining needles of umbelliferone, m.p. 230°.

Isolation of Umbelliferone from Oil (R) by Saponification.—To the oil (100 g.) (15°), 200 ml. of 20% methanolic potassium hydroxide was added with constant shaking. The mixture was allowed to stand for forty-five minutes, poured into 1.5 liters of ice-water and extracted five times with ether to remove unsaponifiable matter. The alkaline aqueous portion was acidified with hydrochloric acid (congo red) and distilled *in vacuo* to remove the greater portion of methyl alcohol. The next day the separated oil was extracted with ether and the extract was washed with 2 × 100 ml. of 25% potassium carbonate (W). The ethereal extract was washed with water, dried and distilled. Only a very small, gummy residue was left.

Isolation of Umbelliferone from Fraction (W).—The brown potassium carbonate washings (W) were acidified with hydrochloric acid (congo red) whereby the solution became turbid. It was extracted with 100 ml. of ether; the extract was twice washed with water, dried and distilled. A brownish, solid residue of umbelliferone (0.4 g.), mixed with a little viscous oil, was left, which crystallized

from dilute methanol in silky, colorless needles; m.p. 230°.

Acknowledgment.—It is a pleasure to thank Professor L. M. Parks for suggestions and the laboratory facilities granted, and Professor A. H. Uhl, Professor S. N. Bose, Professor P. C. Mitter, and Dr. P. K. Bose for their interest in this investigation.

Summary

From the matured bark of *Aegle marmelos*, Corréa, three crystalline compounds have been isolated in pure state: 1, The alkaloid γ -fagarine; 2, A coumarin which had not been observed before in the free state in nature. It is an optical isomer of nodakenetin; and 3, Umbelliferone.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF UTAH]

3,4-Dihydro-1,3,2H-Benzoxazines. Reaction of *p*-Substituted Phenols with N,N-Dimethylolamines

BY W. J. BURKE

Major attention in reactions involving phenol and formaldehyde has quite naturally been directed toward polymeric products in view of their wide industrial application. The marked reactivity of the intermediates involved, however, indicates the desirability of investigating further the possibility of isolating well defined monomeric compounds from such systems.

Interaction of secondary aliphatic amines and formaldehyde with phenols has been shown by Caldwell and Thompson,¹ and by Bruson and MacMullen² to result in the introduction of one or more dialkylaminomethyl substituents in positions ortho or para to the hydroxyl group. The reaction involved is shown as

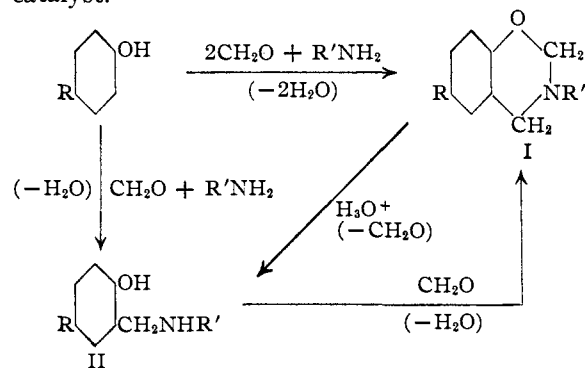


Although generally considered to be a Mannich type of condensation, this and similar reactions involving the interaction of a secondary amine and formaldehyde with a compound containing active hydrogen were studied by others^{3,4} several years before the initial related work of Mannich.⁵

Analogous studies involving primary rather than secondary aliphatic amines appear to have been limited to the use of 2-aminoethanol.⁶ Reaction of equimolar quantities of this amine with formaldehyde and certain *o*- or *p*-substituted phenols resulted in crystalline compounds having *o*- or *p*-beta-hydroxyethylaminomethyl groups. Other phenols, such as the three cresols, gave res-

ins containing nitrogen or sirups which could not be purified. The condensation of selected phenols and formaldehyde with sodium sulfanilate and related aminoaromatic sulfonic acid salts has also been reported⁷ but the exact composition of the products was not determined.

The present work has been concerned with the reaction of *p*-substituted phenols with formaldehyde and primary amines in a molar ratio of 1:2:1, respectively. This procedure led to the formation in good yield of 3,4-dihydro-3,6-disubstituted-1,3,2H-benzoxazines (I), a new series of compounds.⁸ In an alternate method, equimolar quantities of the *p*-substituted phenol, formaldehyde, and primary amine reacted to give as an intermediate an *o*-alkylaminomethyl-*p*-substituted phenol (II). Conversion of II to I took place readily by treatment with formaldehyde in the presence of a basic catalyst.



(1) Caldwell and Thompson, *THIS JOURNAL*, **61**, 765 (1939).

(2) Bruson and MacMullen, *ibid.*, **63**, 270 (1941).

(3) Bayer and Co., German Patent 92,309 (1897).

(4) Einhorn, Bischkopff and Szelinski, *Ann.*, **343**, 223 (1905).

(5) Mannich and Krosche, *Arch. Pharm.*, **250**, 647 (1912).

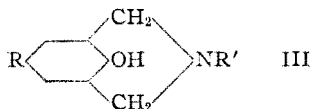
(6) Bruson, *THIS JOURNAL*, **58**, 1741 (1936).

(7) Bruson, U. S. Patent 2,112,434 (1938).

(8) The nomenclature employed in this paper follows that kindly suggested by Dr. Leonard T. Capell of *Chemical Abstracts*.

For values for R and R', see Table I.

Inasmuch as N-methylolamines are capable of attacking *p*-substituted phenols at the free ortho positions^{1,2} the possibility of the alternate structure III



isomeric with I, might be considered. Study of the hydrolysis of the products in the presence of aqueous acid showed that one mole of formaldehyde was readily eliminated with the formation of a compound identical with the corresponding *p*-substituted-*o*-alkylaminomethylphenol II, prepared by an independent synthesis. This behavior is in accord with a 3,4-dihydro-1,3,2H-benzoxazine structure, which contains the labile —O—CH₂—N< group capable of releasing formaldehyde under the mild hydrolytic conditions used. Essentially complete recovery (95%) of starting material when 3,4-dihydro-3-cyclohexyl-6-*t*-butyl-1,3,2H-benzoxazine was treated with acetic anhydride in pyridine is also compatible with the formula assigned.

In the synthesis of 3,4-dihydro-3,6-disubstituted-1,3,2H-benzoxazines, the primary amine and formaldehyde were first condensed to the N,N-dimethylolamine, which was then allowed to react with the *p*-substituted phenol. As a means of obtaining homogeneous reaction media it was found convenient to employ dioxane as solvent. When the reagents were heated under gentle reflux the condensation took place readily and was essentially complete within fifteen minutes in certain instances. Methyl-, cyclohexyl- and benzylamines were used as examples of aliphatic, alicyclic and aralkyl primary amines in condensations with formaldehyde and a variety of *p*-substituted phenols. A summary of the products prepared is given in Table I. Both aqueous formaldehyde and paraformaldehyde were employed satisfactorily. The 3,4-dihydro-1,3,2H-benzoxazines were quite stable toward hot aqueous alkali and formed hydrochlorides readily.

Condensation of benzylamine with 2,6-dimethylol-4-methylphenol might be expected to lead to a compound of the type III. When these two reagents were heated together, however, little or no monomeric condensate appeared to have formed

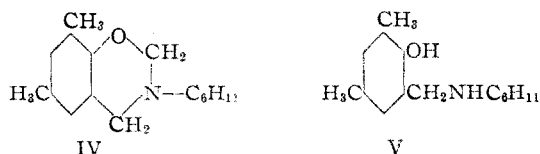
TABLE I

3,4-DIHYDRO-3,6-DISUBSTITUTED-1,3,2H-BENZOXAZINES FROM *p*-SUBSTITUTED PHENOLS AND N,N-DIMETHYLOLAMINES

Y of <i>p</i> -Y-C ₆ H ₄ OH	Primary amine	Yield, %	M. p., °C.	Formula	Analyses, %					
					Carbon		Hydrogen		Nitrogen	
					Calcd.	Found	Calcd.	Found	Calcd.	Found
CH ₃	Benzyl	79	71 ^b	C ₁₆ H ₁₇ NO	80.30	80.18	7.16	7.41	5.85	6.20
C(CH ₃) ₃	Cyclohexyl	92	94 ^c	C ₁₈ H ₂₇ NO	79.07	79.11	9.96	9.70	5.12	5.06
C ₆ H ₅	Cyclohexyl	68	72 ^d	C ₂₀ H ₂₃ NO	4.77	4.80
NHCOCH ₃	Methyl	63	145 ^e	C ₁₁ H ₁₄ N ₂ O ₂	64.06	64.15	6.84	6.54
NHCOCH ₃	Benzyl	61	168 ^c	C ₁₇ H ₁₈ N ₂ O ₂ ^f	9.92	9.98
Br	Cyclohexyl	54	92 ^e	C ₁₄ H ₁₈ NOBr	4.73	4.63

^a Uncorrected. ^b Recrystallized from methanol. ^c Recrystallized from 95% ethanol. ^d Recrystallized from ethyl acetate-methanol (1:1, by vol.). ^e Recrystallized from ethyl acetate-ethanol (95:5, by vol.). ^f This compound was prepared by Mr. Carl Weatherbee.

With a view to obtaining additional information regarding structure, 2,4-dimethylphenol was treated with formaldehyde and cyclohexylamine in a 1:2:1 molar ratio, respectively. The condensation resulted in the elimination of two molecules of water indicating the formation of 3,4-dihydro-3-cyclohexyl-6,8-dimethyl-1,3,2H-benzoxazine (IV), since only a single ortho position was available for reaction. Upon hydrolysis of IV in aqueous acid, formaldehyde was evolved with the formation of V, which was also synthesized by the condensation of equimolar quantities of 2,4-dimethylphenol, formaldehyde, and cyclohexylamine.



The heterocyclic products from *p*-substituted phenols accordingly behave as 3,4-dihydro-1,3,2H-benzoxazines upon hydrolysis.

since the major portion (86%) of the dimethylolphenol was recovered. This behavior is in contrast to the related reactions in which a combination of either dimethylolurea and a primary amine or urea and a dimethylolamine readily resulted in the formation of a tetrahydro-5-substituted-2(1)*s*-triazone.⁹

Acknowledgment.—The assistance given by the Research Corporation in the form of a Frederick Gardener Cottrell Research Grant is gratefully acknowledged.

Experimental

3,4-Dihydro-3-cyclohexyl-6-*t*-butyl-1,3,2H-benzoxazine.—The preparation of this compound by the two procedures given below indicates the general methods used in the synthesis of the 3,4-dihydro-1,3,2H-benzoxazines.

Procedure A.—Cyclohexylamine (39.6 g., 0.4 mole) was added portionwise with cooling to 200 ml. of dioxane containing 60 ml. of aqueous 37% formaldehyde (0.8 mole). After addition of 60 g. of *p*-*t*-butylphenol (0.4 mole), the mixture was heated under reflux for two hours. Upon cooling to room temperature, a crystalline solid (85 g.) separated. The product was recrystallized

(9) Burke, THIS JOURNAL, 69, 2136 (1947).

from 95% ethanol; m.p. 94°, yield 78%. The product was insoluble in water, 10% aqueous hydrochloric acid, and 10% aqueous potassium hydroxide but was soluble in acetic acid, benzene, and chloroform.

Anal. Calcd. for $C_{13}H_{21}NO$: C, 79.07; H, 9.96; N, 5.12. Found: C, 79.11; H, 9.70; N, 5.06.

Procedure B.—Paraformaldehyde (6 g., 0.2 mole) was dissolved in 8 ml. of warm methanol containing 0.1 g. of potassium hydroxide. The solution was cooled during the portionwise addition of 9.9 g. of cyclohexylamine (0.1 mole). After addition of 15 g. *p*-*t*-butylphenol (0.1 mole), the resulting solution was heated under reflux for fifteen minutes. Upon cooling the reaction mixture solidified. Recrystallization from 95% ethanol yielded 23 g. of product; m.p., 94°. An additional 2 g. was obtained from the mother liquor; yield 92%. A mixed m.p. determination with the product prepared by procedure A showed no depression.

In order to determine the effect of acetylating conditions on the product, the following experiment was carried out. A solution of 2.73 g. of the product (0.01 mole) in 10 ml. of pyridine and 6.1 g. of acetic anhydride (0.06 mole) was heated on a boiling water-bath for one and a half hours. The reaction mixture was poured into crushed ice and the resulting solid (2.6 g. or 95% recovery) removed by filtration. The product was recrystallized from ethanol; m.p. 94°. A mixed m.p. determination with starting material showed no depression.

2-Cyclohexylaminomethyl-4-*t*-butylphenol.—To 30 ml. of dioxane containing 7.5 ml. of 37% aqueous formaldehyde (0.1 mole) was added 9.9 g. of cyclohexylamine (0.1 mole) with sufficient cooling to keep the temperature below 25°. After addition of 15 g. of *p*-*t*-butylphenol (0.1 mole) in 20 ml. dioxane with agitation, the resulting solution was heated under gentle reflux for one hour. A sticky mass of crystals was obtained upon removal of dioxane and water at room temperature. The product was recrystallized from ethanol; m.p. 112°; yield, 17 g. (65%).

Anal. Calcd. for $C_{17}H_{27}NO$: C, 78.11; H, 10.41. Found: C, 78.00; H, 10.01.

Hydrolysis of 3,4-Dihydro-3-cyclohexyl-6-*t*-butyl-1,3,2H-benzoxazine.—To 2.73 g. of 3,4-dihydro-3-cyclohexyl-6-*t*-butyl-1,3,2H-benzoxazine (0.01 mole) was added 10 ml. of 95% ethanol and 5 ml. of aqueous hydrochloric acid (0.11 mole). The resulting solution was heated in a 50 ml. modified Claisen flask and 20 ml. of ethanol-water (1:1, by vol.) added during the course of the distillation. The distillate was collected in 25 ml. of water. The distillation was interrupted after a solid began to precipitate out and the volume of the residue was about 10 ml. Ethanol (20 ml.) was added and the resulting solution was removed from the flask. Addition of 6.1 ml. of 10% alcoholic potassium hydroxide (0.11 mole) to the solution resulted in the immediate formation of a precipitate. The product was washed thoroughly with water and recrystallized from ethanol; m.p. 112°; yield 2.2 g. (84%). A mixed melting point determination with 2-cyclohexylaminomethyl-4-*t*-butylphenol showed no depression.

Treatment of a portion of the distillate with 2,4-dinitrophenylhydrazine gave a yellow crystalline product, which was recrystallized from ethanol; m.p. 166°. A mixed m.p. determination with a specimen of the 2,4-dinitrophenylhydrazine of formaldehyde showed no depression.

Reaction of 2-Cyclohexylaminomethyl-4-*t*-butylphenol with Formaldehyde.—To 0.6 g. of paraformaldehyde (0.02 mole) dissolved in 10 ml. of methanol containing 0.05 g. of potassium hydroxide was added 2.61 g. of 2-cyclohexylaminomethyl-4-*t*-butylphenol (0.01 mole). Most of the phenol went into solution but within a minute the reaction mixture became a solid mass. Methanol (35 ml.) was added and the resulting solution heated under reflux for one and a half hours. Upon addition of 4 ml. of water and cooling, a white crystalline product (2.6 g.) separated out. The product was recrystallized from ethanol; m.p., 94°; yield 95%. A mixed m.p. determination with 3,4-dihydro-3-cyclohexyl-6-*t*-butyl-1,3,2H-

benzoxazine, prepared as described above, showed no depression.

3,4-Dihydro-3-cyclohexyl-6,8-dimethyl-1,3,2H-benzoxazine.—To 19.8 g. of cyclohexylamine (0.2 mole) in 100 ml. of dioxane was added 30 ml. of 37% aqueous formaldehyde (0.4 mole) with cooling. After addition of 22.4 g. of 2,4-dimethylphenol (0.2 mole), the resulting solution was heated under reflux for one and a half hours. A light brown liquid (46 g.) was obtained by removal of solvent under reduced pressure. Distillation of the product gave a light-yellow oil; b.p. 140–142° at 0.3 mm., yield 81%.

Anal. Calcd. for $C_{16}H_{23}NO$: C, 78.32; H, 9.45. Found: C, 78.01; H, 9.22.

In another run carried out under analogous conditions, the crude oil was dissolved in ethanol and an equivalent quantity of concentrated aqueous hydrochloric acid added with cooling. The product was isolated as the white crystalline hydrochloride; m.p. 192–195° (dec.); yield 80%.

Anal. Calcd. for $C_{16}H_{24}NOCl$: neut. equiv., 282. Found: neut. equiv., 280.

A mixed m.p. determination with the hydrochloride prepared from the distilled oil showed no depression. Treatment of the hydrochloride with an equivalent quantity of 10% alcoholic potassium hydroxide yielded the free base as a light-yellow oil. The free base was insoluble in water and aqueous 10% potassium hydroxide and was readily soluble in benzene, acetic acid, and chloroform.

Hydrolysis of 3,4-Dihydro-3-cyclohexyl-6,8-dimethyl-1,3,2H-benzoxazine Hydrochloride.—A solution of 2.82 g. of 3,4-dihydro-3-cyclohexyl-6,8-dimethyl-1,3,2H-benzoxazine hydrochloride in 25 ml. of water was heated in a distilling flask. An additional 25 ml. of water was added during the course of the distillation, which was continued until about 10 ml. of liquid remained. Removal of water yielded 2.6 g. of a crystalline product, which was recrystallized from water and then from ethanol; m.p. 214–215°, yield 96%.

Anal. Calcd. for $C_{15}H_{24}NOCl$: neut. equiv., 270. Found: neut. equiv., 268.

The presence of formaldehyde in the distillate was confirmed by the preparation of a 2,4-dinitrophenylhydrazone; m.p., 166°. A mixed melting point determination with the 2,4-dinitrophenylhydrazone of formaldehyde showed no depression.

To 1.0 g. (0.037 mole) of the above 2-cyclohexylaminomethyl-4,6-dimethylphenol hydrochloride in 15 ml. of ethanol was added 2.1 ml. of 10% alcoholic potassium hydroxide (0.037 mole). The precipitate of potassium chloride was removed by filtration and water added to the filtrate to incipient opalescence. Upon cooling, the crystalline free base (0.65 g.) was obtained; m.p. 51°, yield 68%.

Anal. Calcd. for: $C_{15}H_{23}NO$: C, 77.20; H, 9.93. Found: C, 77.36; H, 9.98.

Direct Synthesis of 2-Cyclohexylaminomethyl-4,6-dimethylphenol.—To 40 ml. of dioxane containing 7.5 ml. of 37% aqueous formaldehyde (0.1 mole) and 9.9 g. of cyclohexylamine (0.1 mole) was added 11.2 g. of 2,4-dimethylphenol (0.1 mole). The reaction mixture was heated under reflux for two hours. The solvent was removed under reduced pressure and the resulting solid recrystallized from ethanol; m.p. 51°, yield 8.5 g. (36%). A mixed m.p. determination with the free base obtained indirectly through hydrolysis of 3,4-dihydro-3-cyclohexyl-6,8-dimethyl-1,3,2H-benzoxazine hydrochloride showed no depression.

Reaction of 2-Cyclohexylaminomethyl-4,6-dimethylphenol with Formaldehyde.—To a solution of 0.6 g. of paraformaldehyde (0.02 mole) in 16 ml. of methanol containing 0.05 g. of potassium hydroxide was added 2.33 g. (0.01 mole) of 2-cyclohexylaminomethyl-4,6-dimethylphenol. The reaction mixture was refluxed for one and a half hours and then cooled in ice and water. Addition of 0.87 ml. of concentrated hydrochloric acid (0.01 mole) in 3 ml. of methanol resulted in the formation of a white crystalline product (1.8 g.) which was removed by filtra-

tion, and washed with cold water and then acetone; m.p. 192–195° (dec.). An additional 0.4 g. was obtained from the mother liquor: yield, 78%. A mixed m.p. determination with 3,4-dihydro-3-cyclohexyl-6,8-dimethyl-1,3,2H-benzoxazine hydrochloride showed no depression.

Treatment of 2,6-Dimethylol-4-methylphenol with Benzylamine.—A solution containing 3.36 g. of 2,6-dimethylol-4-methylphenol¹⁰ (0.02 mole), 2.14 g. of benzylamine (0.02 mole) and 5 ml. of benzene was heated under reflux for three hours. Upon cooling and filtering 2.4 g. of solid was obtained, which after crystallization from ethanol melted at 131–132°. Admixture of 2,6-dimethylol-4-methylphenol with either the crude or recrystallized product did not result in a depression of the m. p. of the latter products. An additional 0.4 g. of the same material was obtained from the filtrate; recovery, 86%.

(10) This compound (m. p. 132–133°) was prepared by the procedure of Ullman and Brittner, *Ber.*, **42**, 2539 (1909). These authors recorded a m. p. of 135°.

tallized product did not result in a depression of the m. p. of the latter products. An additional 0.4 g. of the same material was obtained from the filtrate; recovery, 86%.

Summary

1. Reaction of *p*-substituted phenols with formaldehyde and primary aliphatic amines in a molar ratio 1:2:1, respectively, resulted in the formation of a new series of compounds, the 3,4-dihydro-3,6-disubstituted-1,3,2H-benzoxazines.

2. An alternate synthesis for the above compounds involving condensation of formaldehyde with *o*-alkylaminomethylphenols was reported.

SALT LAKE CITY, UTAH RECEIVED OCTOBER 1, 1948

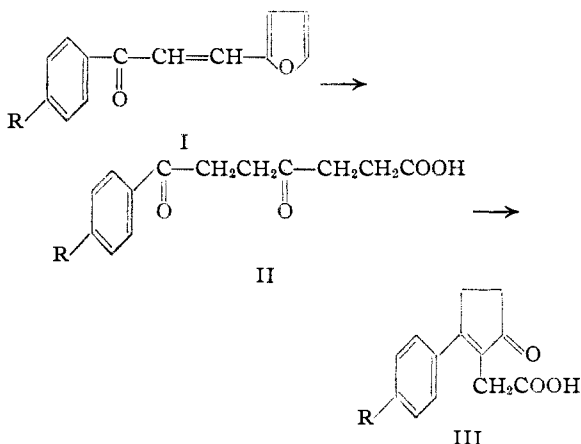
[CONTRIBUTION FROM THE CHARLOTTE DRAKE CARDEZA FOUNDATION, JEFFERSON MEDICAL COLLEGE]

Some Aryl Substituted Cyclopentenones: A New Synthesis of the Cyclopentenophenanthrene Structure

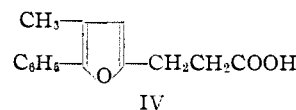
BY D. L. TURNER

The 3-(β -naphthyl)-2-cyclopenten-1-one-2-acetic acid of Robinson¹ has been found to produce myeloid hyperplasia when injected into guinea-pigs in large doses (100 mg.).² This observation led us to prepare a series of similar compounds for biological testing.

The desired compounds were made by the general methods of Robinson, and Kehrer and Iglar,³ from the furfurylidene ketones I (Table I) by way of the phenacyl levulinic acids II (Table II). The cyclopentenones III are formed by the alkaline catalyzed ring closure of the diketoids (Table III).



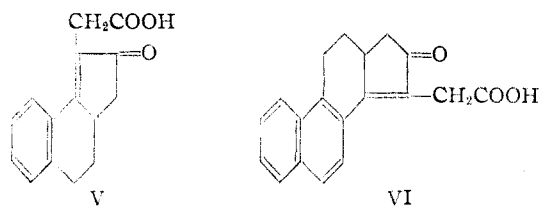
Anomalous behavior was shown by furfurylidene propiophenone; on acid hydrolysis, this substance took up the elements of one molecule of water only, and the product contained no carbonyl group. This substance is evidently 3-methyl-2-phenylfuran-5-propionic acid IV; its



absorption spectrum coincides almost exactly with that of 2-phenylfuran-5-propionic acid^{4a} (Fig. 1). Robinson¹ has suggested that an intermediate naphthylfuranpropionic acid was formed in the hydrolysis of furfurylidene-2-acetylnaphthalene.

A similar furan had been isolated previously by Blicke^{4b} from the hydrolysis of furfurylidene-acetophenone.

The present work provides an easy preparation for the ring systems V and VI, available from α -tetralone and 1-keto-1,2,3,4-tetrahydrophenanthrene, respectively. Similar compounds, lacking



the acetic acid side-chains, have been made by Wilds,^{5,6} who has studied their absorption spectra.⁷ The absorption spectrum of the methyl ester of VI was found to be almost identical with that of Wilds' analogous substance (Fig. 2); slight discrepancies were found at low wave lengths where carboxyl group absorption might be expected to make a difference.

(4) (a) Robinson and Todd, *J. Chem. Soc.*, 1743 (1939); (b) Blicke, Warzynski, Faust and Gearien, *THIS JOURNAL*, **66**, 1675 (1944).

(5) Wilds, *ibid.*, **64**, 1421 (1942).

(6) Wilds and Johnson, *ibid.*, **68**, 86 (1946).

(7) Wilds, *et al.*, *ibid.*, **69**, 1985 (1947).

(1) Robinson, *J. Chem. Soc.*, 1390 (1938).

(2) Turner and Miller, unpublished.

(3) Kehrer and Iglar, *Ber.*, **32**, 1178 (1899); **34**, 1263 (1901).