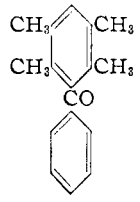
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

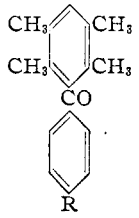
# Para Alkylation of Hindered Ketones by the Grignard Reagent

BY REYNOLD C. FUSON AND ROGER TULL[1]

It was reported earlier[2] that duryl phenyl ketone (I) could be alkylated by the action of *t*-butyl- or benzylmagnesium chloride and that the alkyl radical entered the *para* position of the phenyl group. Subsequently duryl 3-methoxyphenyl ketone and mesityl 3-methoxyphenyl ketone were found to undergo benzylation in a similar way.[3] This unusual type of reaction is all the more remarkable because it does not require "forcing" conditions; the alkylation proceeds in ethyl ether solution at room temperature. The yields of alkylation products, however, were never above 40% and no evidence whatever had



I



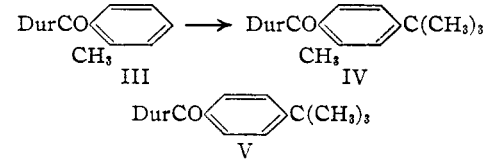
II

been obtained as to the nature of the dihydrobenzenoid condensates presumed to be formed as intermediates or as to the manner by which the aromatic character of the ring is restored.

It has now been found that certain secondary alkylmagnesium halides are even better alkylating agents than *t*-butyl or benzyl Grignard reagents. Isopropylmagnesium bromide converts duryl phenyl ketone into duryl *p*-isopropylphenyl ketone (II, R = $-CH(CH_3)_2$) in 38% yield. Cyclohexylmagnesium chloride affords a similar yield of *p*-cyclohexylphenyl duryl ketone (II, R = $C_6H_{11}$). By far the most effective reagent so far tried is *s*-butylmagnesium bromide, the yield of alkylation product (II, R = $-CH(CH_3)C_2H_5$) being 63%.

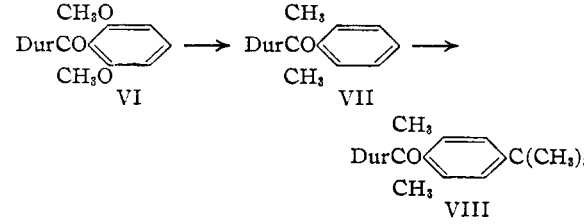
The structures of the isopropyl, cyclohexyl and *s*-butyl derivatives were established by independent syntheses, these ketones being prepared by condensing the appropriate acid chlorides with durene in the presence of aluminum chloride

It is interesting that, although the *para* position of the durene ring is open, alkylation occurs only in the phenyl ring. This result may be attributed to the donation of electrons by the alkyl groups to the durene ring, thus stabilizing it against the attack of the nucleophilic reagent. As would be predicted on this basis, the introduction of methyl groups into the phenyl ring appeared to render alkylation more difficult. Duryl *o*-tolyl ketone (III) reacted with *t*-butylmagnesium chloride to give a low yield of duryl 2-methyl-4-*t*-butylphenyl ketone (IV), the structure of which was established by synthesis of the compound by treatment of *p*-*t*-butylphenyl duryl ketone (V) with methylmagnesium iodide. In this transformation an intermediate dihydro derivative was isolated, which was aromatized by treatment with palladium.



III IV V

Similarly, 2,6-dimethylphenyl duryl ketone (VII) yielded a small amount of the *p*-*t*-butyl derivative (VIII) when allowed to react with *t*-butylmagnesium chloride.



VI VII VIII

The structure of this ketone (VIII) was proved by an independent synthesis involving the condensation of 2,3,5,6-tetramethylbenzoyl chloride with 2,6-dimethyl-4-*t*-butylphenylmagnesium bromide.

The 2,6-dimethylphenyl duryl ketone (VII) was made by an interesting application of the alkoxyl replacement reaction. 2,6-Dimethoxyphenyl duryl ketone (VI), made by condensing the lithium derivative of the dimethyl ether of resorcinol with 2,3,5,6-tetramethylbenzoyl chloride, was transformed to the 2,6-dimethyl derivative (VII) by treatment with methylmagnesium iodide.

As was to be expected in view of foregoing results, duryl mesityl ketone could not be alkylated by the Grignard method.

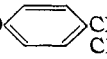
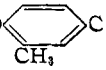
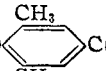
## Experimental

The results of alkylation are shown in the Table. Two different procedures were employed, one of which (A) involved the use of ethyl ether and room temperature; the other (B) provided for a higher reaction temperature. Procedure A is illustrated by the directions for alkylating duryl phenyl ketone with isopropylmagnesium bromide, the conditions being similar to those

(1) Rohm and Haas Fellow, 1948-1949.
(2) Fuson and McKusick, THIS JOURNAL, **65**, 60 (1943).
(3) Fuson and Gaertner, *J. Org. Chem.*, **13**, 496 (1948).

TABLE I

THE REACTION OF GRIGNARD REAGENTS WITH HINDERED KETONES

| Procedure | Ketone | R of RMgX | Product[b] | Yield, % | M. p.[c] (uncor.) | Analyses,[a] % Calcd. C | Calcd. H | Found C | Found H |
|---|---|---|---|---|---|---|---|---|---|
| A | DurCO-C$_6$H$_5$ | $(CH_3)_2CH$— | DurCO-C$_6$H$_4$-$CH(CH_3)_2$ | 38 | 113–113.5° (112–113.5°) | 85.66 | 8.63 | 85.73 | 8.50 |
| A | DurCO-C$_6$H$_5$ |  | DurCO-C$_6$H$_4$-  | 38 | 147–147.5° (145.5–147°) | 86.20 | 8.81 | 86.26 | 8.72 |
| A | DurCO-C$_6$H$_5$ | $CH_3CHCH_2$—  | DurCO-C$_6$H$_4$-$CHCH_2CH_3$  | 63 | 70–71° (66–69°) | 85.67 | 8.90 | 85.71 | 9.20 |
| A | DurCO-C$_6$H$_4$-$CH_3$ | $(CH_3)_3C$— | DurCO-C$_6$H$_4$-$C(CH_3)_3$  | Low | 140.5–141.5° | 85.70 | 9.15 | 85.56 | 9.36 |
| A | DurCO-C$_6$H$_4$-$CH_3$  | $(CH_3)_3C$— | DurCO-C$_6$H$_4$-$C(CH_3)_3$  | Low | 126–127° | 85.68 | 9.38 | 85.73 | 9.38 |
| B | DurCO-C$_6$H$_4$-$CH_3$  | $CH_3CH_2CH$—  | None | | | | | | |
| B | DurCO-C$_6$H$_4$-$OCH_3$  | $CH_3$— | DurCO-C$_6$H$_4$-$CH_3$  | 47 | 143.5–144° (141.5–143.5°) | 85.67 | 8.33 | 85.83 | 8.51 |

[a] The analyses were carried out by Miss Theta Spoor. [b] The products were recrystallized from methanol with the exception of 2,6-dimethylphenyl duryl ketone which was recrystallized from ethanol. [c] The percentage yields correspond to the state of purity indicated by the melting points in parentheses.

employed in the *t*-butylation of duryl phenyl ketone.[2]

**The Action of Isopropylmagnesium Bromide on Duryl Phenyl Ketone.**—A solution of 9.5 g. (0.04 mole) of duryl phenyl ketone in 100 ml. of ether was added over a period of five minutes to a solution of a Grignard reagent containing 0.12 mole of isopropylmagnesium bromide in 75 ml. of ether. The mixture was stirred mechanically during the addition and for three hours afterward, the entire operation being carried out at room temperature. The mixture was then boiled under reflux for thirty minutes and hydrolyzed with dilute hydrochloric acid. The organic layer was washed with water and evaporated to dryness. The crude duryl *p*-isopropylphenyl ketone was recrystallized twice (from methanol).

Procedure B is illustrated by the methoxyl replacement effected by treating 2,6-dimethoxyphenyl duryl ketone with methylmagnesium iodide.

**The Action of Methylmagnesium Iodide on 2,6-Dimethoxyphenyl Duryl Ketone.**—A Grignard reagent was prepared in *n*-butyl ether under an atmosphere of nitrogen from 17 g. (0.12 mole) of methyl iodide and 2.92 g. of magnesium. Nine grams (0.03 mole) of 2,6-dimethoxyphenyl duryl ketone was added to the solution containing the Grignard reagent, and the temperature was raised to 130°. The mixture was stirred at 130° for four hours under an atmosphere of nitrogen. The reaction mixture was cooled and decomposed with dilute hydrochloric acid. Enough ethyl ether was added to dissolve the material which precipitated. The organic layer was washed with water, and the mixed ether extract was evaporated to dryness. The 2,6-dimethylphenyl duryl ketone was recrystallized several times (from ethyl alcohol).

No product was isolated when the reaction was attempted at room temperature.

### Proof of Structures

***p*-*t*-Butylbenzoic Acid.**—This compound was obtained in 50% yield by the carbonation of a Grignard reagent prepared from 106.5 g. of *p*-*t*-butylbromobenzene. The *p*-*t*-butylbenzoic acid melted at 158–164°.[4]

***p*-*t*-Butylphenyl Duryl Ketone.**—*p*-*t*-Butylbenzoyl chloride was prepared in 90% yield by the treatment of *p*-*t*-butylbenzoic acid with thionyl chloride; b. p. 144–146° (25 mm.). A solution containing 19 g. (0.15 mole) of durene and 30.5 g. (0.15 mole) of *p*-*t*-butylbenzoyl chloride in 150 ml. of carbon disulfide was added to a suspension of an equimolecular amount of aluminum chloride in 75 ml. of carbon disulfide over a period of one hour with stirring. The mixture was then stirred for five hours at room temperature. After the reaction mixture was decomposed with dilute hydrochloric acid, the organic layer was washed with 4% sodium carbonate solution and then with water. The carbon disulfide was removed by distillation and the residue was subjected to steam distillation to remove the unchanged durene. The residue was recrystallized from methanol, Darco being used as a decolorizing agent. The *p*-*t*-butylphenyl duryl ketone melted at 127–128°; yield 30 g. (66%).[2]

**Duryl 2-Methyl-4-*t*-butylphenyl Ketone.**—To a Grignard reagent, prepared from 1.09 g. (0.045 atom) of magnesium and 2.8 ml. (0.045 mole) of methyl iodide in 50 ml. of dry *n*-butyl ether, was added 4.4 g. (0.015 mole) of solid *p*-*t*-butylphenyl duryl ketone. The mixture was then heated at 130° for three hours, with stirring. It was then cooled and decomposed with dilute hydrochloric acid. The ether layer was washed with water, then with 5% sodium carbonate, and finally with water. The ether was removed by distillation and the residue recrystallized four times from methanol; m. p. 90–91°.

*Anal.* Calcd. for $C_{22}H_{30}O$: C, 85.02; H, 9.73. Found: C, 84.50; H, 9.15.

This compound decolorized permanganate after ten minutes, and was assumed to be a dihydro derivative of duryl 2-methyl-4-*t*-butylphenyl ketone.

A mixture of the dihydro compound (1.0 g.) and a 5% palladium–charcoal catalyst (0.05 g.) was heated at 350°

(4) Shoesmith and Mackie, *J. Chem. Soc.*, 300 (1936).

for thirty minutes. The mixture was cooled and 15 ml. of ether was added. The catalyst was removed by filtration and the filtrate treated with Darco. The filtrate was evaporated to dryness and the residue was crystallized from methanol. The crude product melted at 127–134°. After several recrystallizations of the compound from methanol its melting point was 139–140°. A mixed melting point with a sample of duryl 2-methyl-4-*t*-butylphenyl ketone prepared by *para* alkylation was not depressed.

**Duryl *p*-Isopropylphenyl Ketone.**—*p*-Isopropylbenzoyl chloride was prepared in 88% yield by the action of thionyl chloride on *p*-isopropylbenzoic acid; b. p. 125–127° (14 mm.).[5] The chloride (8 g.) was condensed with an equimolecular amount (5.9 g.) of durene[6] in the presence of aluminum chloride (6 g.) by a procedure similar to that described for *p*-*t*-butylphenyl duryl ketone. The product melted at 111–112.5°; yield 49%. After two recrystallizations from methanol, the ketone melted at 112.5–113.5°. A mixed melting point with the original sample of *p*-isopropylphenyl duryl ketone showed no depression.

***p*-Cyclohexylbenzoic Acid.**—This acid, prepared according to the procedure of Bodroux and Thomassin,[7] was recrystallized from a mixture of ligroin and benzene; m. p. 193–197°; yield 28%.

**Duryl *p*-Cyclohexylphenyl Ketone.**—*p*-Cyclohexylbenzoyl chloride was prepared by the reaction of 7.2 ml. of thionyl chloride with 6.1 g. of *p*-cyclohexylbenzoic acid. The product boiled at 150–151° (5 mm.); yield 82%. The acid chloride (5.4 g.) was condensed with durene (3.4 g.) by the procedure described for *p*-*t*-butylphenyl duryl ketone. The *p*-cyclohexylphenyl duryl ketone melted at 145–147°; yield 7.1 g. (91%). After two recrystallizations from ethyl alcohol, the product melted at 147–147.5°. A mixture with the *p*-cyclohexylphenyl duryl ketone prepared by the Grignard method melted at 147–147.5°.

***p*-*s*-Butylbenzoic Acid.**—A Grignard reagent, prepared from 29.8 g. (0.14 mole) of *p*-*s*-butylbromobenzene and 3.4 g. of magnesium, was poured into a mixture of solid carbon dioxide and dry ether. The complex was ether decomposed with dilute hydrochloric acid and the ether layer was extracted with 7% sodium hydroxide. The alkaline extract was filtered and acidified with hydrochloric acid (1:1). The *p*-*s*-butylbenzoic acid melted at 90–92.5°; yield 13.7 g. (55%). A melting point of 91–92° has been reported.[8]

***p*-*s*-Butylphenyl Duryl Ketone.**—*p*-*s*-Butylbenzoyl chloride was prepared in 84% yield by the action of thionyl chloride on *p*-*s*-butylbenzoic acid; b. p. 147–149° (28 mm.). The acid chloride (6.5 g.) was condensed with durene (4.45 g.) by the procedure described for *p*-*t*-butylphenyl duryl ketone. The crude product, melting at 66–68°, amounted to 66%. After two recrystallizations from methanol, the ketone melted at 70–71°. A mixed melting point with the original sample of *p*-*s*-butylphenyl duryl ketone showed no depression.

**4-*t*-Butyl-2,6-dimethylphenyl Duryl Ketone from 2,3,5,6-Tetramethylbenzoyl Chloride.**—A solution of 3.9 g. of 2,3,5,6-tetramethylbenzoyl chloride in ether was added, with stirring, over a period of ten minutes to a solution containing a Grignard reagent prepared from an equimolecular amount of 4-*t*-butyl-2,6-dimethylbromobenzene.[9] After the addition was complete, the mixture was stirred and boiled under reflux for one hour and decomposed with dilute hydrochloric acid. The organic layer was washed successively with water, 4% sodium carbonate and with water. The oily residue left by evaporation of the solvent, crystallized after being stored in the refrigerator for eight hours and was recrystallized from ligroin, m. p. 251–252°. The melting point of duril is 250–251°.[10]

The experiment was repeated with the exception that the acid chloride was added dropwise over a period of one hour. After evaporation of the ether, the residue was crystallized from methanol. The 4-*t*-butyl-2,6-dimethylphenyl duryl ketone was collected on a filter and recrystallized twice from methanol; m. p. 126–127°. The melting point of a mixture of this compound and the 4-*t*-butyl-2,6-dimethylphenyl duryl ketone prepared by *para* alkylation was not depressed.

**2,6-Dimethoxyphenyl Mesityl Ketone.**—This compound was prepared in a manner similar to that described for 2,6-dimethoxyphenyl duryl ketone. From 18.2 g. (0.1 mole) of mesitoyl chloride was obtained 18 g. (63%) of 2,6-dimethoxyphenyl mesityl ketone, m. p. 125.5–127.5°. The pure ketone melted at 127.5–128°.

*Anal.* Calcd. for $C_{18}H_{20}O_3$: C, 76.00; H, 7.08. Found: C, 75.96; H, 6.66.

**2,6-Dimethoxyphenyl Duryl Ketone.**—This ketone was synthesized by condensing 2,3,5,6-tetramethylbenzoyl chloride with 2,6-dimethoxyphenyllithium, the lithium compound being prepared by the method of Wittig and Pockels.[11] A solution of 19.3 g. of resorcinol dimethyl ether in 100 ml. of dry ether was added to a solution of phenyllithium prepared from 22 g. of bromobenzene and 2 g. of lithium according to the procedure of Evans and Allen.[12] The exchange reaction was carried out in an atmosphere of nitrogen. To the resulting suspension was added, with mechanical stirring, a solution of 17 g. (0.086 mole) of 2,3,5,6-tetramethylbenzoyl chloride[10] in 100 ml. of dry ether. After the addition of the chloride, which extended over a thirty-minute period, the mixture was boiled, with continuous stirring, for three hours under reflux, and decomposed with dilute hydrochloric acid. The ether layer was washed twice with water, once with 5% sodium carbonate and finally with water. The solution was dried over anhydrous sodium sulfate and the ether was removed by distillation. The crude 2,6-dimethoxyphenyl duryl ketone was recrystallized from ethyl alcohol; yield, 18 g. (70%); m. p. 148–149.5°. The pure ketone melted at 148.5–149.5°.

*Anal.* Calcd. for $C_{19}H_{22}O_3$: C, 76.48; H, 7.43. Found: C, 76.44; H, 7.38.

**Duryl Mesityl Ketone.**—To a Grignard reagent, prepared from 0.48 g. of magnesium and 4 g. (0.02 mole) of bromomesitylene in dry ether, was added with stirring a solution of 3.9 g. (0.02 mole) of 2,3,5,6-tetramethylbenzoyl chloride in ether at a rate that allowed the mixture to reflux gently. The mixture was stirred at room temperature for forty-five minutes after the addition was complete and decomposed with dilute hydrochloric acid. The duryl mesityl ketone was isolated by conventional procedures and recrystallized from methanol; the product melted at 133–134°.

*Anal.* Calcd. for $C_{20}H_{24}O$: C, 85.65; H, 8.63. Found: C, 85.87; H, 8.81.

The sodium carbonate extract, when acidified, yielded 1.5 g. of 2,3,5,6-tetramethylbenzoic acid; m. p. 176–179°.

## Summary

It has been found that duryl phenyl ketone undergoes alkylation in the *para* position of the phenyl group when treated with isopropyl, cyclohexyl or *s*-butyl Grignard reagents.

*t*-Butylation of duryl *o*-tolyl ketone and 2,6-dimethylphenyl duryl ketone has been effected in a similar way.

2,6-Dimethylphenyl duryl ketone has been

(5) Cahours, *Ann. chim. phys.*, [3] **23**, 347 (1848).

(6) The durene used in this investigation was very kindly supplied by the Humble Oil and Refining Company, Baytown, Texas.

(7) Bodtoux and Thomassin, *Compt. rend.*, **205**, 991 (1937).

(8) Hennion and McLeese, THIS JOURNAL, **64**, 2421 (1942).

(9) Fuson, Mills, Klose and Carpenter, *J. Org. Chem.*, **12**, 587 (1948).

(10) Fuson and Kelton, THIS JOURNAL, **63**, 1500 (1941).

(11) Wittig and Pockels, *Ber.*, **72B**, 89 (1939).

(12) Evans and Allen, "Org. Syntheses," Coll. Vol. II, revised edition, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 517.

prepared from 2,6-dimethoxyphenyl duryl ketone by replacement of the methoxyl groups by the action of methylmagnesium iodide.

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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

# Helenalin. I. Isolation and Properties

BY ROGER ADAMS AND WERNER HERZ

Helenalin, the bitter principle of the common sneezeweed *Helenium autumnale*, is reported to be a severe local irritant of nose, eye and stomach.[1] Due to the wide distribution of the plant, its toxicity is of concern to the livestock industry. There are also reports on its activity as a vermifuge,[1] fish poison[2] and insecticide.[3]

According to Clark,[4] helenalin is also found in *Helenium macrocephalum* and *Helenium quadridentatum*, while four other *Helenium* species, *badium*, *tenuifolium*, *elegans* and *montanum*, yield the bitter principle tenulin. Helenalin, m. p. 167°, has been shown by the same author[2] to possess the formula $C_{15}H_{18}O_4$ and contains a hydroxyl group and two double bonds.

Since a supply of yet another *Helenium* species, *Helenium microcephalum*, was made available to us and since extraction of this material was found to give helenalin, a further study of this interesting substance has been undertaken. The present series of papers describes the results obtained to date.[5]

Proof for the identity of our product with helenalin was furnished by comparison with a sample of m. p. 165.5–166° from the collection of the late Dr. E. P. Clark.[6] This sample did not depress the melting point of a product, m. p. 167–168°, whose isolation is described in the experimental part, and the infrared spectra of the two were identical.

The melting point of the material obtained by extraction of *Helenium microcephalum* depends on the manner of crystallization, analytical samples melting fairly sharply at points within the temperature range 167–178°. Combustion of all fractions confirmed the formula $C_{15}H_{18}O_4$ and each sample gave the same derivatives. All fractions had $[\alpha]^{25}D$ in the range −102.0 to −102.8° a value which, within experimental error, coincided with that, $[\alpha]^{20}D$ − 101.9°, given by Clark. Infrared spectra determined in chloroform solution, where differences in crystal structure would be expected to disappear, were identical. This suggests that the material is structurally homogeneous and that variations in melting point may be attributed to differences in crystal structure. Nevertheless, the presence of small amounts of impurities capable of altering the melting point cannot be excluded.

Acetylation of helenalin gave a monoacetyl derivative which melted at 179.5–180.5°; the melting point of acetylhelenalin as given by Clark is 184°. The melting points of tetrahydrohelenalin and acetyltetrahydrohelenalin coincided with those reported by Clark.

Helenalin shows a weak yellow color on treatment with sulfuric acid which changes to deep brown on heating. It gives a positive Legal and Zimmermann test. Attempts to demonstrate the presence of an active methylene group by reaction with aromatic aldehydes have not led to the isolation of pure products. Acetylhelenalin reacts with piperonal in ethanolic hydrogen chloride, but since the product contains a molecule of hydrogen chloride, addition of which may have preceded condensation, the reaction does not provide sufficient evidence for the presence of such a group.

In view of a negative reaction with ferric chloride the hydroxyl group whose presence was demonstrated by Clark[2] is probably not phenolic or enolic. This group was further characterized by the formation of an *o*-bromobenzoate, a *p*-nitrobenzoate and a 3,5-dinitrobenzoate. It did not react with phthalic anhydride or phenyl isocyanate under stringent conditions, but the ease with which it is acetylated and the failure in all attempts at dehydration are arguments against the assumption that it is tertiary. In another paper[7] experimental data demonstrating that it is a secondary hydroxyl will be presented.

Helenalin gives no color with Schiff reagent and thus contains no aldehyde group but rapidly reduces Tollens reagent. This is in harmony with the ultraviolet spectrum[8] (Fig. 1) which is typical of an $\alpha,\beta$-unsaturated ketone.[9] The position of the first maximum ($\lambda$ = 223 m$\mu$; $\epsilon$ = 11900) suggests that helenalin is a mono-

(1) Lamson, *J. Pharmacol. Expti. Therap.*, **4**, 471 (1913).

(2) Clark, THIS JOURNAL, **58**, 1982 (1936).

(3) McGovran, Mayer and Clark, U. S. Dept. Agr. Bur. Entomol. Plant Quarantine, *Entomol. Technic.*, E-572 (1942).

(4) Clark, THIS JOURNAL, **61**, 1836 (1939); **62**, 597 (1940).

(5) We wish to thank Mr. H. R. Reed, Bureau of Animal Industry, U. S. Department of Agriculture, Sonora, Texas, for a supply of this plant. It is noteworthy that tenulin, not helenalin, was obtained by extraction of *Helenium autumnale*, var. *canaliculata*, from the same source, indicating that this variety may actually be a different species. This experiment was carried out by B. F. Aycock and A. E. Senear.

(6) Supplied by Dr. R. C. Roark, Bureau of Entomology and Plant Quarantine, U. S. Department of Agriculture, Washington, D. C.

(7) Adams and Herz, THIS JOURNAL, **71**, 2554 (1949).

(8) Ultraviolet spectra were determined by Mrs. Dorothy C. Brantley on 0.001 *N* solutions in 95% ethanol.

(9) Woodward, THIS JOURNAL, **63**, 1123 (1941); **64**, 76 (1942).