

CASHEW NUT SHELL LIQUID. V. THE MONOPHENOLIC FRACTION.
A SYNTHETIC INVESTIGATION OF THE GEOMETRICAL CON-
FIGURATION OF THE MONOÖLEFINIC COMPONENT¹

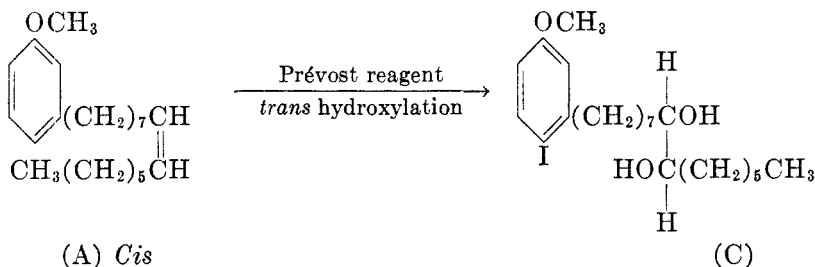
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In a previous communication from these laboratories (1), evidence establishing the heterogeneous olefinic nature of the monophenolic component of commercial cashew nut shell liquid was reported. The monophenol was shown to be a mixture of at least two olefinic components; one a monoölefin and the other a diolefin. It must also be presumed that higher olefinic components were also present in order to account for the unsaturation (equivalent to about two olefinic bonds) of the freshly distilled monophenol. The structure of the monoölefinic component was established as that of a 3-(pentadecenyl-8')phenol.

Two geometrical isomers of 3-(pentadecenyl-8')phenol are possible, (see methyl ethers A and B), and it was the purpose of the present investigation to establish which of these configurations is that of the natural occurring monoölefin.

As the first step toward this objective, the *cis* methyl ether (A) was synthesized employing a method (2) which had previously been developed for the purpose. Because of their liquid nature, it was not advantageous to attempt a comparison of the synthetic *cis* isomer directly with the methyl ether of the natural occurring monoölefinic phenol. Consequently, both were converted into their corresponding crystalline glycols by means of the Prévost reagent, silver iodobenzoate (3). The hydroxylation of an olefinic bond by this reagent is known to be stereospecific and result in a *trans* hydroxylation (3b, 4).³ Thus the spatial configuration of the iodinated glycol⁴ (C) obtained from the synthetic *cis* olefin (A) is deducible *i.e.*,



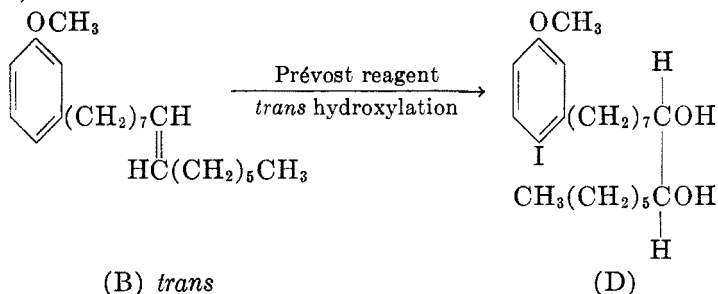
¹ For the fourth article in this series, see Sletzinger and Dawson, *J. Org. Chem.*, **14**, 670 (1949).

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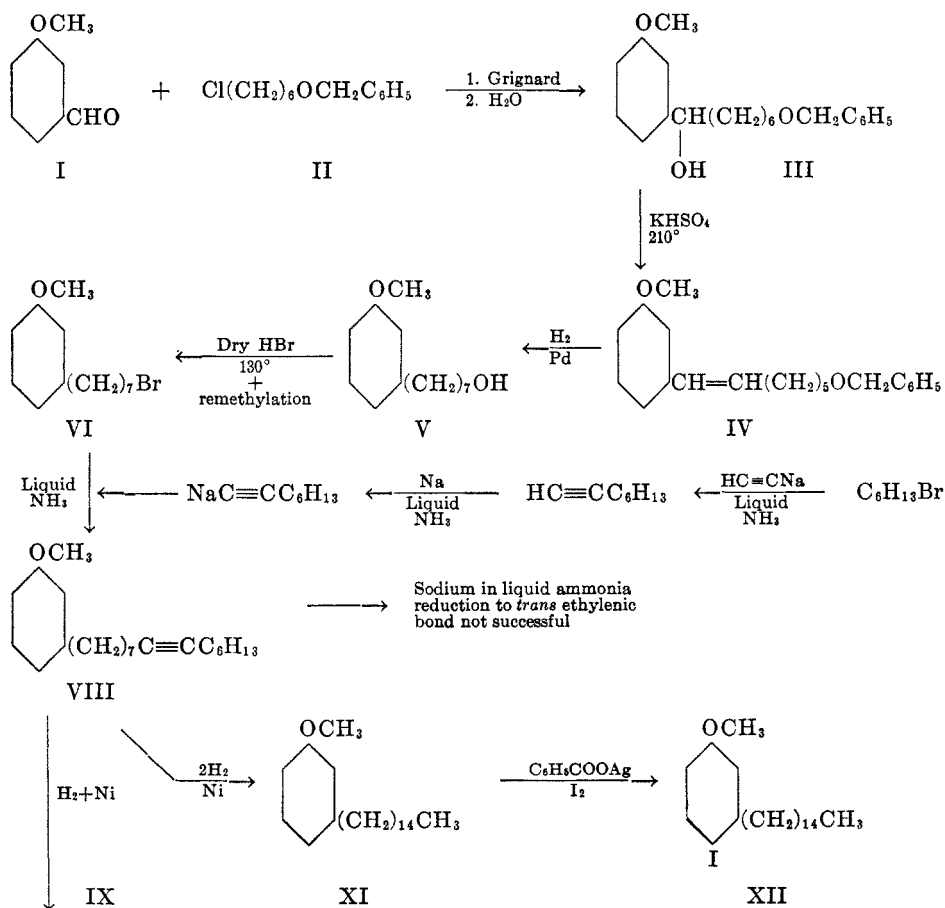
³ The observation (4) that the interaction of silver iodobenzoate with an ester of oleic acid (*cis* double bond) yields upon hydrolysis exclusively the low-melting form of 9,10-dihydroxystearic acid has been confirmed in these laboratories.

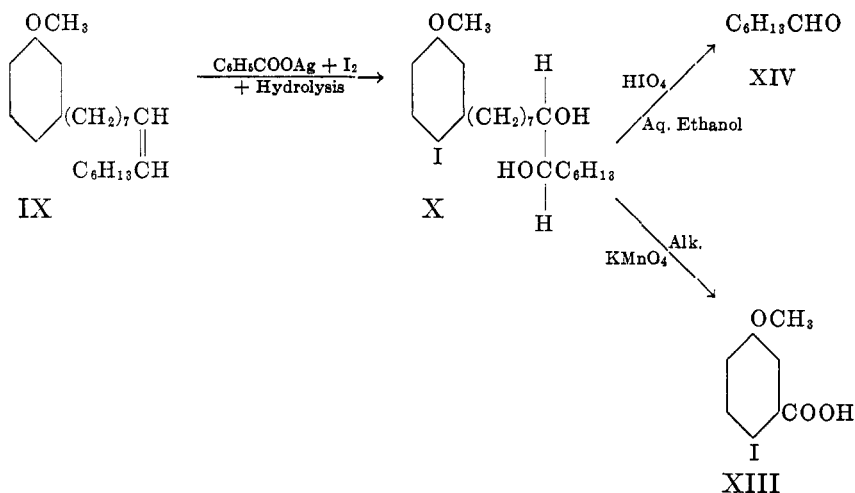
⁴ The hydroxylation of olefinic phenolethers by means of silver iodobenzoate results in the simultaneous iodination of the ring (1).

Furthermore, it can be reasoned that the configuration of the glycol obtained from the natural occurring monoölefin must be either that of (C) or the diastereoisomer (D).



Accordingly, when it was found that the hydroxylation of the synthetic *cis* olefin (A) resulted in an iodinated glycol having different physical properties than that obtained by similarly hydroxylating the natural occurring monoölefin, the geometric structure of the latter was established as that of the *trans* isomer (B).





The desired *cis* olefin (IX) was synthesized starting with *m*-methoxybenzaldehyde (I), using the sequence of reactions outlined on the Flow Sheet. The experimental conditions for the synthesis, which involved as its essential feature the stereospecific reduction of an acetylenic compound (VIII), had been previously developed by Wasserman and Dawson (2) in connection with their investigations of Poison Ivy "Urushiol." However, in the present investigation certain modifications in procedure were introduced which resulted in decided improvements of yield. Thus it was found advantageous to convert the alkyl halide (VI) into the desired acetylene (VIII) by a one-step process involving the sodium salt of octyne-1 (VII) in liquid ammonia, rather than by sodium acetylide and then heptyl bromide as Wasserman and Dawson reported.

Repeated attempts to reduce the acetylenic compound (VIII) to a *trans* olefin with sodium in liquid ammonia (2) at atmospheric pressure, and also at higher pressures in a steel bomb, were not successful. The 3-(pentadecynyl-8')anisole (VIII) was found to be unexpectedly resistant to the sodium liquid ammonia reduction, and no appreciable yield of olefin was obtained, judging from subsequent quantitative hydrogenation data.

The *cis* olefin (IX) was readily obtained by catalytic reduction of the acetylenic compound (VIII) using Raney nickel. Previous investigations (5) established that Raney nickel is stereospecific in catalyzing the hydrogenation of acetylenic bonds. The reduction was allowed to proceed to about 15% in excess of 1 mole equivalent of hydrogen in order to insure that no acetylenic compound remained. The hydrogenated product was then treated with silver iodobenzoate and the resulting benzoates were hydrolyzed. The hydrolysis mixture yielded two crystalline products. One of these, 4-iodo-3-pentadecylanisole (XII), was obtained as the result of the excess hydrogenation. The other product, the expected iodinated glycol (X), melted at 73–74°.

It had been previously established (1) that the action of the Prévost reagent on the methylated monophenolic fraction obtained by vacuum distillation of commercial cashew nut shell liquid resulted in a crystalline iodinated mono-

glycol melting at 92–93°, *i.e.*, nineteen degrees higher than the monoglycol (X) obtained from the synthetic *cis* olefin (IX). The diastereoisomeric character of these two glycols was confirmed by analysis, melting point determination, and the following oxidation experiments. The lower melting glycol (X) (synthetic) on oxidative cleavage with periodic acid yielded *n*-heptaldehyde (XIV) just as previously reported (1) for the glycol derived from the natural oil. Furthermore, oxidation of (X) with alkaline permanganate yielded the same iodomethoxybenzoic acid (XIII).

On the basis of the above results, it may be concluded that the higher-melting monoglycol (92–93°) has the configuration (D), and accordingly the monoolefinic component of the monophenolic fraction of cashew nut shell liquid is a *trans* olefin (see methyl ether, B).

It is clear that the above conclusions are based primarily on the acceptance of a *cis* configuration for the synthetic olefin and a stereospecific hydroxylation by the Prévost reagent. As pointed out earlier, sufficient grounds for such basic assumptions have been provided by previous investigations of the Raney nickel hydrogenation of acetylenic bonds (5) and the action of silver iodobenzoate on olefins (3b, 4). Furthermore, the above conclusions are in line with the fact that a glycol which results from the *cis* hydroxylation of a *cis* double bond or the *trans* hydroxylation of a *trans* double bond is ordinarily higher melting than the glycol which results from the *trans* hydroxylation of a *cis* double bond or the *cis* hydroxylation of a *trans* double bond. Evidence for this is obtained from the tartaric acids, the 2,3-butylene glycols, and the 9,10-dihydroxystearic acids.

EXPERIMENTAL

m-Methoxybenzaldehyde (I). This aldehyde was prepared according to the directions given in Organic Syntheses (6).

1-Chloro-6-benzoyloxyhexane (II). This compound was prepared using the directions given by Wasserman and Dawson (2).

3-(7'-Benzoyloxyheptanol-1')anisole (III). To a two-liter three-necked flask equipped with a dropping-funnel, bulb condenser, and sealed stirrer was added 22 g. of magnesium turnings, 85 cc. of sodium-dried ether, 0.5 g. of methyl iodide, and a crystal of iodine. After the methylmagnesium iodide had formed, a solution of 208 g. of II dissolved in 200 cc. of dry ether was added through the dropping-funnel at such a rate as to keep the reaction going vigorously. After four hours the addition was complete and the black solution was refluxed for an additional hour. A small amount of magnesium remained unreacted. The flask was cooled in an ice-bath and 100 g. of *m*-methoxybenzaldehyde (I) dissolved in 350 cc. of dry ether was slowly added with stirring. The mixture turned white on addition of the aldehyde but cleared on standing overnight. It was hydrolyzed with 600 cc. of 6 *N* sulfuric acid, the ether layer was washed with 10% sodium carbonate, and then with water. It was evaporated, and the remaining liquid dried by the addition of benzene and distillation. A yellow oil remained which was not further purified.

3-(7'-Benzoyloxyheptenyl-1')anisole (IV). The crude secondary alcohol (III) was placed in a 500-cc. flask equipped with a Vigreux column. Five grams of fused potassium bisulfate was added and the flask was heated slowly to 210°. The formation of water was indicated by violent spattering. After 15 minutes the flask was cooled and water was removed by distilling some xylene from the mixture. After filtering from the salt, the brown filtrate was distilled using a six-inch helices-packed column which was electrically heated. The main

fraction distilled at 205–208°/1 mm. (bath temp. 250–280°) and yielded 154 g. (68%) of colorless liquid; n_D^{25} 1.5547.

Anal. Calc'd for $C_{21}H_{26}O_2$: C, 81.29; H, 8.39.

Found: C, 81.10; H, 8.36.

3-(Heptanol-7')anisole (V). A 60-g. sample (0.194 mole) of IV with 0.5 g. of palladium black and 120 cc. of glacial acetic acid was reduced at atmospheric pressure in an Adams shaker for five hours. The theoretical amount of hydrogen (0.387 mole) was absorbed. The catalyst was removed and washed with acetic acid. The solvent was removed *in vacuo* with the toluene formed. The remaining liquid was fractionated with a 6-inch helices-packed electrically-heated column. The main fraction boiled between 148–154°/1.5 mm. (bath temperature, 200°). The yield was 40 g. of clear colorless liquid. This material was used in the next step without further purification.

3-(7'-Bromoheptyl)anisole (VI). A 32-g. sample of V was placed in a 100-cc. flask and dry hydrobromic acid was bubbled through for 9 hours at 130–135°. A water layer soon formed and settled to the bottom. The flask was cooled and the contents poured into a separatory funnel containing water. The mixture was extracted with benzene and washed again with water. The benzene solution was dried over magnesium sulfate, distilled, and the red residue was remethylated at the phenolic hydroxyl groups liberated during the esterification. Dimethyl sulfate (11.2 grams), 100 cc. of methanol, and 20 cc. of dioxane was added to the flask. A solution of 7 g. of KOH in 30 cc. of methanol was then added rapidly, by means of a dropping-funnel with constant stirring. The temperature rose to 50°. Stirring was continued until the reaction was acidic to Alkacid paper. At this point 6 g. of dimethyl sulfate was added to the flask and 3.5 g. of KOH in 15 cc. of methanol as above. The solution was re-refluxed for 15 minutes, when it was acidic again. The reaction mixture was then added to two liters of water and extracted with benzene. The brownish benzene layer was washed with sodium bicarbonate solution, dried over magnesium sulfate, filtered, and evaporated *in vacuo* to a reddish oil. This was then fractionated. The fraction boiling at 159°/1 mm. (bath temperature 198°) yielded 28 g. (63%) of colorless clear liquid, heavier than water; n_D^{25} 1.5240.

Anal. Calc'd for $C_{17}H_{21}BrO$: C, 58.94; H, 7.37.

Found: C, 58.71; H, 7.66.

1-Octyne (VII). Into a three-necked flask containing 300 cc. of liquid ammonia and equipped with a stirrer and gas inlet-tube 17.6 g. of sodium was added in small strips while acetylene was simultaneously bubbled through the solution. The acetylene was obtained from a commercial source and was purified by passing it through a wash bottle of conc'd sulfuric acid, a Dry Ice-methanol bath, and finally a soda-lime drying tower. At no time was a great excess of sodium added. The acetylene was passed through the solution until the blue color was completely discharged and for an additional five minutes in order to insure the conversion to the monosodium acetylide.

A Dry Ice-methanol reflux condenser (cold finger) was then inserted into the apparatus and with stirring 63 g. of *n*-hexyl bromide was added by means of a dropping-funnel over the course of 1.5 hours. The volume of the solution was maintained at 300 cc. by the addition of liquid ammonia when necessary. After all the bromide had been added, stirring and reflux was maintained for an additional two hours. At this point the Dry Ice condenser was removed, and the ammonia was allowed to evaporate, leaving a white solid residue in the flask. This was treated with 50 cc. of 5% ammonium chloride solution, whereupon two layers appeared; an upper yellow organic layer and the bottom water layer. The mixture was extracted with ether and the ether solution washed with dilute hydrochloric acid and water, and dried over magnesium sulfate. The solvent was removed by fractionation through a 10-in. Widmer column. The product was distilled using a helices-packed column; it boiled at 125–126°/759 mm. Yield, 50 g. of octyne-1 (59.5%).

3-(Pentadecynyl-8')anisole (VIII). Into a 500-cc. three-necked flask equipped with a stirrer and containing 100 cc. of liquid ammonia, was added 0.2 g. of hydrated ferric nitrate. To this solution 0.5 g. of sodium was added with stirring. The solution at first turned blue,

but after 15 minutes became grayish, indicating the formation of sodamide. A total of 1.5 g. of sodium was added in small strips with stirring over thirty minutes. When all the sodium was converted to sodamide, as indicated by the disappearance of the blue color, the volume of ammonia was increased to 300 cc. and a Dry Ice-methanol condenser was inserted into the apparatus.

A 7.5-gram sample of 1-octyne was added dropwise over a period of one hour with stirring. A white solid deposited. Throughout the course of the reaction the volume of ammonia was maintained at 300 cc. by the addition of liquid ammonia. After the formation of sodium octyne, the addition of 10 g. of VI dissolved in 15 cc. of dry ether was begun over a period of three hours with stirring and reflux. At the end of this time the reflux was discontinued but stirring was continued without reflux until all the ammonia had evaporated, leaving a grayish solid. The solid was decomposed with 150 cc. of 5% ammonium chloride solution and the organic layer extracted with ether. The ether extract was washed with 30 cc. of 10% hydrochloric acid and water, and dried over magnesium sulfate. It was evaporated to an oil, which was fractionated using a 15-cc. Spitzkolben, b.p. 186–188°/0.8 mm. (bath temp., 230°). The distillate was slightly yellow in color and weighed 4.8 g. (43%); n_D^{25} 1.4958.

Anal. Calc'd for $C_{22}H_{34}O$: C, 84.08; H, 10.82.

Found: C, 83.93; H, 10.96.

3-Pentadecylanisole (XI). A 0.4995-gram sample of VIII (0.00156 mole) was reduced in 25 cc. of ethanol using Raney nickel as a catalyst. The reduction was complete in one hour and resulted in the absorption of 0.00312 mole of hydrogen, thereby confirming the existence of an acetylenic bond in VIII. After filtering the filtrate was concentrated to 2 cc. and cooled. The result was a quantitative yield of hair-like needles melting at 29–30°. A mixed melting point with a sample of the 3-pentadecylanisole (m.p. 29–30°) derived from natural sources showed no depression, thereby confirming the straight chain character of the side chain of VIII.

Cis-3-(pentadecenyl-8')anisole (IX). A 4.7-gram sample of the acetylenic compound VIII was hydrogenated in 75 cc. of ethanol using Raney nickel as a catalyst at 30° and 755 mm. pressure. Under these conditions the theoretical amount of hydrogen required for reduction to the olefinic stage is 380 cc. To insure that no acetylenic compound would remain and thereby complicate subsequent studies of the application of the Prévost reagent to this synthetic *cis*-olefin, the reduction was allowed to proceed until 427 cc. of hydrogen had been absorbed. The catalyst was removed and the alcohol distilled. The residual oil was fractionated; the main fraction boiled at 186–189°/0.8 mm.; yield, 4.2 g. (87%) of a clear colorless liquid.

3-(8', 9'-Dihydroxypentadecyl)-4-iodoanisole (X). A 2.0-gram sample of the *cis*-olefin prepared as described above was added to a solution of 3.26 g. of I_2 in 100 cc. of thiophene-free, anhydrous benzene which contained 4.4 g. of silver benzoate in suspension. The mixture was refluxed for two hours. At the end of this time the iodine color had disappeared. The solution was cooled, filtered from the insoluble silver iodide, and evaporated on a steam-bath, *in vacuo*, to an oil. The oil was dissolved in 50 cc. of 80% ethanol containing 5 g. of KOH and refluxed with occasional stirring for three hours. A brownish solution resulted which was concentrated to a volume of about 5 cc. Then 50 cc. of water was added and the insoluble oil extracted with three 25-cc. portions of ether. The combined ether extracts were washed with water, dried over magnesium sulfate, and evaporated to an oil. The oil was taken up in 75 cc. of hot 95% ethanol and cooled. The crystalline product was recrystallized three times from 95% ethanol. The 1.0-gram yield of crystalline material melted at 43° and analyzed correctly for 4-iodo-3-pentadecylanisole (XII). It presumably resulted from the excess hydrogenation described above.

Anal. Calc'd for $C_{22}H_{37}IO$: C, 59.48; H, 8.3.

Found: C, 59.32; H, 8.35.

The ethanolic mother liquors from the above reaction were evaporated to dryness *in vacuo* and 75 cc. of hot methanol was added in order to dissolve all of the oil. The solution was slowly cooled in an ice-box overnight and the product was recrystallized three times

from Skellysolve B to give a crystalline solid of m.p. 73–74° (yield, 1.3 g.) which analyzed correctly for the iodomonoglycol (X).

Anal. Calc'd for $C_{22}H_{17}IO_3$: C, 55.34; H, 7.74.

Found: C, 55.46; H, 7.78.

Oxidation of X with periodic acid. A 1.0-gram sample of X was oxidized in aqueous methanol using the same procedure as described previously (1) for the oxidation of the iodomonoglycol obtained from the natural oil. A 400 mg. yield of the 2,4-dinitrophenylhydrazone of *n*-heptaldehyde (XIV) proved that the ethylenic bond of IX had not migrated during the hydroxylation reaction. A mixed melting point with an authentic sample of the 2,4-dinitrophenylhydrazone of *n*-heptaldehyde (m.p. 106–107°) showed no depression.

Oxidation of X with alkaline permanganate. A 200-mg. sample of X was oxidized in 25 cc. of water containing 1.0 g. of $KMnO_4$ and 0.2 cc. of 0.2 *N* NaOH using the same procedure as previously described (1) for the oxidation of the iodomonoglycol obtained from the natural oil. The iodomethoxybenzoic acid (XIII) was isolated (30 mg., yield 23%) and melted at 136–137°. A mixed melting point with the acid obtained from the iodomonoglycol of natural origin (1) showed no depression.

ACKNOWLEDGMENT

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SUMMARY

The methyl ether of 3-(pentadecenyl-8')phenol has been synthesized by a method which is believed to yield only the *cis* isomer. Treatment of this synthetic olefin with the Prévost reagent, silver iodobenzoate, yields on subsequent hydrolysis a crystalline iodomonoglycol melting at 73–74°.

Reaction of the Prévost reagent with the methylated monophenolic fraction of cashew nut shell liquid (either commercial or solvent extracted) results in an isomeric monoioglycol melting at 92–93°.

Both glycols have been shown by oxidative degradations to possess the structure of 3-(8',9'-dihydroxypentadecyl)-4-iodoanisole.

On the basis of a *cis* configuration for the synthetic olefin, and a stereo specific hydroxylation by means of the Prévost reagent, it may be concluded that the monoölefinic component of the monophenolic fraction of cashew nut shell liquid possesses a *trans* ethylenic configuration.

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REFERENCES

- (1) SLETZINGER AND DAWSON, *J. Org. Chem.*, **14**, 670 (1949).
- (2) WASSERMAN AND DAWSON, *J. Org. Chem.*, **8**, 73 (1943).
- (3) (a) PRÉVOST, *Compt. rend.*, **196**, 1129 (1933); (b) PRÉVOST, *Compt. rend.*, **197**, 1661 (1933); (c) PRÉVOST AND LUTZ, *Compt. rend.*, **198**, 2264 (1934); (d) PRÉVOST AND WIEMANN, *Compt. rend.*, **204**, 989 (1937); (e) HERSHBERG, *Helv. Chim. Acta*, **17**, 351 (1934).
- (4) WITTCOFF AND MILLER, *J. Am. Chem. Soc.*, **69**, 3138 (1947).
- (5) CAMPBELL AND O'CONNOR, *J. Am. Chem. Soc.*, **61**, 2397 (1939).
- (6) *Org. Syntheses*, **25**, 55 (1945).