The air oxidation of ozonolysis products of Ia, Ib, and Ic to tetrabasic acid derivatives was studied in detail. Varying the temperature from 25 to 100°, the use of several solvents (methanol, isopropyl alcohol, formic acid, acetic acid, propionic acid, acetone, and water) and various catalysts (zinc oxide, ammonium metavanadate, manganese dioxide, potassium permanganate, cobalt acetate, palladium on charcoal, and bromine) never gave yields better than 37%. Higher oxygen pressures and ultraviolet light were not beneficial. The use of chlorine[16] as an oxidizing agent also gave poor results.

Ozonolysis of Dimethyl *cis*-Δ^4-Tetrahydrophthalate (Ic).—A solution of 19.8 g. (0.1 mole) of dimethyl ester Ic in 60 ml. of methanol readily absorbed 0.1 mole of ozone at 0–10°. Immediate titration of the cold solution indicated that 1 equiv. of active oxygen was present. After concentration *in vacuo* the residual oil (28.8 g.) had a molecular weight of 572; infrared bands at 2.9, 5.75, and 11.1–11.5 μ; and an active oxygen content of 3.17% (57% of the original solution). These data coupled with the p.m.r. spectrum (Figure 1, hydroxyl protons replaced with deuterium) are consistent with the dimeric structure V.

3,4-Dicarbomethoxyadipic Acid (IVb).—The ozonolysis product of 20 g. (0.1 mole) of ester Ic (prepared in 60 ml. of methanol) was dissolved in 100 ml. of 98% formic acid and further oxidized with a 6% stream of ozone at 65–95° (MnO_2 catalyst). After removal of the solvent, the semisolid was triturated with ether to yield IVb (5 g.). An analytical sample was obtained from ethyl acetate, m.p. 147–148°.

Anal. Calcd. for $C_{10}H_{14}O_8$: C, 45.80; H, 5.39; neut. equiv., 131. Found: C, 45.67; H, 5.57; neut. equiv., 131.

3,4-Dicarbomethoxyadipic Aldehyde Hemiacetal (VI).—The ozonolysis product of Ic made in methanol at −50° was treated with 1 equiv. of trimethyl phosphite[17] at −50°. The resulting product was an oil which could not be distilled without decomposition. A 2,4-dinitrophenylhydrazone was prepared in the usual manner and recrystallized from ethanol–dimethylformamide, m.p. 230–231°.

Anal. Calcd. for $C_{22}H_{22}N_8O_{12}$: C, 44.74; H, 3.76. Found: C, 45.04; H, 4.19.

Performic acid oxidation of VI (15 g.) gave IVb (9 g.). In addition there was obtained an oil (5 g.), neut. equiv. 136, which appeared to be a mixture of isomeric 1,2,3,4-butanetetracarboxylic acid dimethyl esters. Saponification yielded tetrabasic acid IVa.

Ozonization of *cis*-Δ^4-Tetrahydrophthalic Acid in Acetonitrile.—A mixture of 5.3 g. (0.03 mole) of Ia and 40 g. of acetonitrile absorbed 1 equiv. of ozone at 0°. Immediate titration of the cold solution indicated that 1 equiv. of active oxygen was present. Concentration *in vacuo* followed by thorough drying of the residual powder gave a product free of acetonitrile.

Anal. Calcd. for $C_{16}H_{22}O_{15}$[10]: C, 42.3; H, 4.8. Found: C, 42.4; H, 5.1.

One gram of ozonide yielded 0.9 g. (93%) of IVa (m.p. 186–189°) when refluxed with 5 ml. of 30% hydrogen peroxide and 5 ml. of 98% formic acid.

Ozonization of Norbornylene in Acetonitrile.—Ozonization of a mixture of 4 g. (0.04 mole) of norbornylene and 40 g. of acetonitrile at −10 to −30° resulted in a white gelatinous precipitate. After remaining overnight at room temperature, the product (2 g.) was collected and washed with ether. The acetonitrile filtrate yielded 3.2 g. of an easily pulverizable foam after concentration to a final pressure of 0.2 mm.

Anal. Calcd. for $C_{14}H_{22}O_7$[11]: C, 55.60; H, 7.25. Found: C, 55.2, 54.7; H, 7.20, 7.38.

Ozonization of Hexachlorodicyclopentadiene (VII).—A mixture of 33.9 g. (0.1 mole) of hexachlorodicyclopentadiene,[18] 50 ml. of methanol, and 70 ml. of methylene chloride was cooled to −5°. A 6% ozone stream was admitted to the agitated solution for 3 hr. during which time a slow absorption of ozone occurred. The solution was concentrated *in vacuo* and the semisolid residue (42.6 g.) was mixed with 25 ml. of 98% formic acid. The insoluble crystalline product (21 g., 50%) VIII[12] was collected by filtration and washed with formic acid, m.p. 164° dec. An analytical sample was prepared by recrystallization from benzene. The sample was unchanged after storage for 1 year.

Anal. Calcd. for $C_{11}H_{10}Cl_6O_4$: C, 31.46; H, 2.41; Cl, 50.65; mol. wt., 419. Found: C, 31.61; H, 2.53; Cl, 50.25; mol. wt., 397.

After concentration of the formic acid filtrate there was recovered 21 g. (50%) of viscous oil. This product was not further investigated.

The crystalline ozonolysis product (1 g.), commercial 40% peracetic acid (3 g.), and 4 ml. of acetic acid were heated at 50° for 6 hr. and then allowed to remain overnight at room temperature. After removal of solvent, there was obtained 1 g. of crude product. Recrystallization from water–methanol yielded 0.6 g. of dibasic acid (IX), m.p. 221–222°.

Anal. Calcd. for $C_{10}H_6Cl_6O_4$: C, 29.81; H, 1.50; Cl, 52.80; neut. equiv., 201. Found: C, 29.84; H, 1.86; Cl, 52.55; neut. equiv., 197.

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[16] L. C. King and H. Farber, Abstracts, 136th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept. 1959, p. 89P.

[17] W. S. Knowles and Q. E. Thompson, *J. Org. Chem.*, **25**, 1031 (1960).

[18] R. Riemschneider, *Monatsh.*, **83**, 802 (1952); M. Livar, P. Klucko, and M. Paldan, *Tetrahedron Letters*, **No. 3**, 141 (1963).

On the Reaction of Grignard Reagents with β-Tertiary Amino Ketones

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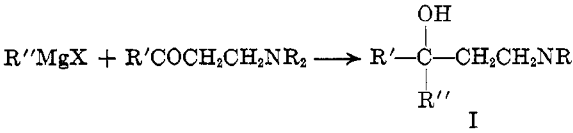
A considerable number of amino alcohols of the general type I have been prepared by the action of



$$R''MgX + R'COCH_2CH_2NR_2 \longrightarrow R'\!-\!\overset{\displaystyle OH}{\underset{\displaystyle R''}{C}}\!-\!CH_2CH_2NR_2 \quad (1)$$

I

Grignard reagents on the appropriate Mannich bases.[1] Although generalization is rather difficult because the yields obtained by various authors are not always comparable, it is evident that in many cases the yields were surprisingly poor. For the case where R″ = cyclohexyl and R′ = phenyl, leading to the commercially important compounds Trihexyphenidyl and Tricyclamol [NR_2 = $N(CH_2)_5$ and $N(CH_2)_4$, respectively], Adamson[1c] suggested that the loss could be due to reduction of the ketone (competing with the addition of the reagent). Since, however, considerable quantities (of the order of 30%) of Mannich base are at times recoverable,[2] it appears more likely that the major loss was due to enolization. This should be especially serious with reagents such as the cyclohexylmagnesium halides which are known to be sluggish in addition. It is consistent with this interpretation that Ruddy and Buckley,[1b] who employed a considerable variety of Grignard reagents and Mannich bases, reported that their yields were much better when there was alkyl substitution on the carbons between the carbonyl and the amino group. Such substitution could not be expected to facilitate addition, but it would be expected to diminish enolization.

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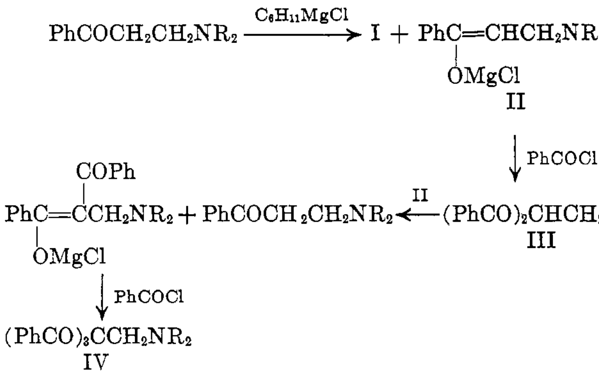
[1] (a) J. J. Denton, *et al.*, *J. Am. Chem. Soc.*, **71**, 2050, 2053, 2054 (1949); (b) W. A. Ruddy and J. S. Buckley, *ibid.*, **72**, 718 (1950); (c) D. W. Adamson, P. A. Barrett, and S. Wilkinson, *J. Chem. Soc.*, 52 (1951); (d) D. W. Adamson, *ibid.*, S-144 (1949); 885 (1950).

[2] E. M. Bottorff, private communication.

Since in approximately equivalent cases it is known that halomagnesium enolates react with acid chlorides to form triketones (C-acylation),[3] there appeared to be a chance of demonstrating the presence of halomagnesium enolate in reaction mixtures such as those discussed above.

Accordingly, an excess of cyclohexylmagnesium chloride was reacted with β-piperidinopropiophenone under semiforcing conditions and the reaction mixture was divided into two halves. The first half was hydrolyzed in the usual way with iced ammonium chloride solution. From this was isolated 1-phenyl-1-cyclohexyl-3-piperidinopropanol (Trihexyphenidyl) in rather better yield than usual, and 27% of the original Mannich base.

The second half of the reaction mixture was added to an excess of benzoyl chloride in ether. The expected immediate products of C-acylation would be the mono- and dibenzoylation products III and IV [$NR_2 = N(CH_2)_5$] corresponding to eq. 2. Kohler and Baltzly[3]



(2)

had obtained only products corresponding to IV, but the influence of the piperidinomethyl group could not be predicted. Both III and IV could be expected to be unstable and could be expected to be cleaved in the presence of water, and perhaps of acid, to dibenzoylmethane and tribenzoylmethane, respectively.[4] In fact, they could not be isolated, although IV, at least, was presumably present initially. Tribenzoylmethane was first observed when an attempt was made to extract basic material from ethereal solution with dilute acid.[5] Dibenzoylmethane was isolated as its copper chelate after removal of the tribenzoylmethane.

Two further experiments were performed in which the entire reaction mixtures from Grignard reagent and Mannich base were allowed to react with excess benzoyl chloride. In II, β-piperidinopropiophenone was used, in III, β-pyrrolidinopropiophenone. The results are shown in Table I, the quantities given in expt. I corresponding to the half of the reaction mixture that was run into benzoyl chloride solution.

TABLE I

Expt. no.	Mannich base, mmoles	Dibenzoylmethane (as Cu chelate), mmoles	Tribenzoylmethane, mmoles
I	150	16	4
II	200	3	22
III	125	3	7.5

The obvious irregularity in these figures is the predominance of dibenzoylmethane in I and of tribenzoylmethane in II and III. We believe this is due to the fact that II and III were worked up rapidly in the knowledge of what fraction was of principal interest, whereas in the first experiment the identity of the tribenzoylmethane was not recognized at once and all the other fractions were examined for products of interest before turning to that one. While tribenzoylmethane has not been reported to be unstable, we have encountered severe losses in recrystallizing it for analysis (from isopropyl alcohol). Further, the mother liquors from the recrystallization yielded copper dibenzoylmethane and benzoic acid, although the sample before recrystallization had been thoroughly extracted with ether. It seems probable, therefore, that all the dibenzoylmethane was formed by cleavage of tribenzoylmethane, wherefore both substances should be equated to *2* equiv. of halomagnesium enolate. On that basis, the products of the three runs were equivalent to 27, 25, and 17%, respectively, of the quantities of Mannich base employed.

This is in reasonable agreement with the amount of Mannich bases that can be recovered in preparations of Trihexyphenylin and Tricyclamol.

Experimental Section

Run II.—A Grignard reagent was prepared from 72 g. (0.6 mole) of cyclohexyl chloride and 15 g. of magnesium turnings, reaction being initiated by 2 g. of cyclohexyl bromide. To this was added in dried (1:1) ether–benzene solution the base from 0.2 mole of β-piperidinopropiophenone hydrochloride. The reaction mixture was refluxed 15 hr., much of the ether being allowed to escape, and then refluxed 2 hr. further. The solution was then filtered rapidly through glass wool into a dropping funnel and added gradually with stirring to 60 g. of benzoyl chloride in 400 ml. of anhydrous ether. The solution became coffee brown in color and a heavy precipitate separated. The reaction mixture was stirred 3 hr. and allowed to stand overnight. The dun-colored precipitate was then filtered and washed with anhydrous ether.

The filtrate from the above precipitate was hydrolyzed and worked up separately. Several compounds, among them trihexylphenidyl, were identified in this fraction, but none was of consequence for the present purpose.

The precipitate was hydrolyzed by shaking in a separatory funnel with ammonium chloride solution and ether. The yellow ethereal layer was washed several times with water, the washings and original aqueous layer being discarded. The ethereal layer was then shaken with 1 *N* hydrochloric acid, whereupon a colorless precipitate separated. This did not all come out at once and over a period of about 4 hr. several crops were obtained. The precipitate was identified by melting point, composition, and

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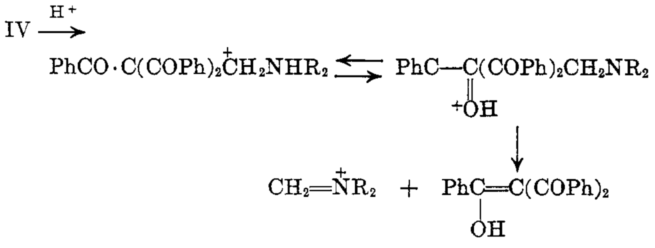
[3] E. P. Kohler and R. Baltzly, *J. Am. Chem. Soc.*, **54**, 4015 (1932).

[4] The cleavage amounts to a reverse Mannich reaction. We have found no reports concerning Mannich bases derived from dibenzoylmethane. Some derived from acetylacetone [L. Neelakatan and W. H. Hartung, *J. Org. Chem.*, **24**, 1943 (1959)], nitroacetone [A. Dornow and W. Sassenberg, *Ann.*, **602**, 14 (1957)], and nitroacetonitrile [W. Ried, E. Köhler, and F. J. Königstein, *ibid.*, **598**, 145 (1956)] appear to have decomposed easily.

[5] Not much tribenzoylmethane, which is very insoluble, could have been present before treatment with acid. The hydroxymethyl derivative could have been, but seems unlikely to be especially sensitive to acid. The behavior during extractions is consistent with a rapid hydrolysis of the piperidinomethyl group to hydroxymethyl on acquiring a positive charge, followed by a slower cleavage to formaldehyde and tribenzoylmethane. An alternative suggestion by J. F. Bunnett amounts to a β-fission. This is also consistent with the observations.



delayed ferric chloride color as tribenzoylmethane, a total of 7 g. (0.022 mole) being obtained.

The ethereal filtrate from the tribenzoylmethane gave a strong ferric chloride test. It was washed free of acid and shaken with cupric acetate solution. The olive green copper chelate of dibenzoylmethane was collected and found to weigh 0.8 g. (equivalent to 3 mmoles of dibenzoylmethane).

Addition of Allylmagnesium Bromide to Hindered Ketones[1]

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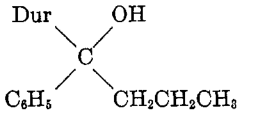
Replacement of methoxyl and other groups by Grignard reagents from *ortho* and *para* positions of hindered ketones has been interpreted to mean that such groups facilitate conjugate addition.[3] It seemed possible that reagents of the allyl type, known to condense with hindered ketones in the 1,2 manner,[4,5] might be induced by such groups to react in the conjugate way.

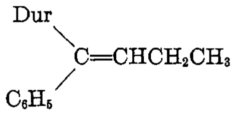
In a study of this question allylmagnesium bromide was allowed to react with duryl *o*-methoxyphenyl ketone, duryl *o*-phenoxyphenyl ketone, duryl *o*-bromophenyl ketone, and mesityl *o*-methoxyphenyl ketone. In no case was there any evidence of group displacement; only the corresponding allyl carbinols were formed. A similar product was obtained from duryl phenyl ketone.

Only the carbinol from the bromo ketone was isolated in pure form, however. The others were viscous oils that failed to crystallize and could not be distilled undecomposed. Infrared spectra showed that in all of them the ketone group was absent and the hydroxyl group was present. It was concluded that only 1,2 addition had occurred.

The unsaturated carbinol from duryl phenyl ketone formed the corresponding saturated carbinol **1** when catalytically hydrogenated. Distillation of the saturated alcohol at diminished pressure gave olefin **2**, and oxidation gave an unconjugated ketone. Pyrolysis of allyldurylphenyldicarbinol produced duryl (Dur) phenyl ketone, a hydrocarbon, and polymeric material.


$(Dur)(C_6H_5)C(OH)CH_2CH_2CH_3$

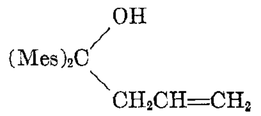
1


$(Dur)(C_6H_5)C{=}CHCH_2CH_3$

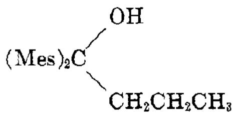
2

Condensation of the allyl reagent with dimesityl ketone gave the carbinol **3**. Neither it nor the saturated carbinol **4** could be induced to crystallize. Distillation of the latter yielded an olefin which by melting point, infrared and n.m.r. spectra, and elemental analysis was identified as 1,1-dimesityl-1-butene (**5**).[6]

1,4 addition of the allyl reagent to a hindered ketone was finally achieved by use of mesityl vinyl ketone (**6**). Mesityl 4-pentenyl ketone (**7**) was the only product isolated. Reduction converted it into known capromesitylene, the identity of which was confirmed by preparation of its dinitro derivative.[7]


$(Mes)_2C(OH)CH_2CH{=}CH_2$

3


$(Mes)_2C(OH)CH_2CH_2CH_3$

4

$(Mes)_2C{=}CHCH_2CH_3$

5

$MesCOCH{=}CH_2$ **6** $MesCOCH_2CH_2CH_2CH{=}CH_2$ **7**

Experimental Section

Reaction of Ketones with Allylmagnesium Bromide.—The reagent was prepared in 75 to 81% yield by the method of Grummitt, Budewitz, and Chudd.[9] The yield was determined each time by acidimetric titration.[10] A solution of 3.17 g. (0.01 mole) of **duryl *o*-bromophenyl ketone** in 100 ml. of ether was placed in a 200-ml., three-necked, round-bottomed flask equipped with a condenser fitted with a drying tube, a pressure-equalized dropping funnel, and a magnetic stirrer. To this solution was added rapidly a solution of allylmagnesium bromide (0.05 mole) in ether. The reaction mixture became cloudy after addition of the first drops. After being stirred 8 hr. at room temperature the gray slurry was poured into cold saturated ammonium chloride solution; the ether layer was washed twice with water, dried over magnesium sulfate, and filtered. The very viscous oil that remained after the solvent had been evaporated crystallized only after standing for many months. The infrared spectrum showed strong hydroxyl absorption at 3560 cm.$^{-1}$, no absorption in the carbonyl region, and terminal methylene absorption at 1638, 1000, and 915 cm.$^{-1}$. Recrystallization from absolute ethanol yielded white crystals, m.p. 69–70°.

Anal. Calcd. for $C_{20}H_{23}BrO$: C, 66.88; H, 6.41. Found: C, 66.99; H, 6.51.

A very similar experiment with **duryl *o*-methoxyphenyl ketone** gave an orange oil which showed infrared absorption at 3540, 1640, 1000, 918, and 1235 cm.$^{-1}$—bands assignable to allylduryl-*o*-methoxyphenylcarbinol. No absorption bands for a carbonyl group were present.

Duryl *o*-phenoxyphenyl ketone likewise gave an oil (73% yield) that showed infrared absorption bands for a terminal double bond (1638, 995, and 915 cm.$^{-1}$), a hydroxyl group (3560 cm.$^{-1}$), and a phenoxyl group (1230 cm.$^{-1}$). Similar results were obtained with **mesityl *o*-methoxyphenyl ketone.**

Dimesityl ketone yielded an oil, the infrared spectrum of which showed absorption bands for a hydroxyl group (3560 cm.$^{-1}$) and a terminal methylene group (1635, 990, and 910 cm.$^{-1}$). Hydrogenation was effected by placing a mixture of 21 g. of crude allyldimesitylcarbinol, 100 ml. of absolute ethanol, and 0.3 g. of platinum oxide in a pressure bottle set in a Parr shaker and charged with 49 lb. of hydrogen pressure. The pressure dropped substantially during the first hour and the treatment was continued for 18 hr. After removal of the catalyst and ethanol, the product was subjected to distillation; 40% of it distilled at 159–160° at 0.55 mm. and solidified. After several recrystallizations from 95% ethanol, the 1,1-dimesityl-1-butene melted at 108–109° (lit.[7] m.p. 109–110°).

Anal. Calcd. for $C_{22}H_{28}$: C, 90.35; H, 9.65. Found: C, 89.95; H, 9.76.

The n.m.r. spectrum showed the presence of a trisubstituted ethylene.

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[1] This investigation was supported in part by a grant from the Office of Ordnance Research, U. S. Army (Contract No. DA-11-022-ORD-874).

[2] To whom correspondence should be addressed: Department of Chemistry, Parsons College, Fairfield, Iowa.

[3] See R. C. Fuson and S. B. Speck, *J. Am. Chem. Soc.*, **64**, 2446 (1942).

[4] W. G. Young and J. D. Roberts, *ibid.*, **66**, 2131 (1944).

[5] K. W. Wilson and W. G. Young, *ibid.*, **72**, 218 (1950).

[6] H. R. Snyder and R. W. Roeske, *ibid.*, **74**, 5820 (1952).

[7] R. C. Fuson, R. J. Hellmann, and W. S. Friedlander, *J. Org. Chem.*, **18**, 1263 (1953).

[8] All melting points are corrected. The infrared spectra were recorded by Mr. Paul E. McMahon and Mrs. John Verkade. The microanalysis were performed by Mr. Josef Nemeth, Miss Claire Higham, and Mrs. Frederick Ju.

[9] O. Grummitt, E. P. Budewitz, and C. C. Chudd, *Org. Syn.*, **36**, 61 (1956).

[10] H. Gilman, E. A. Zoellner, and J. B. Dickey, *J. Am. Chem. Soc.*, **51**, 1577 (1929).