Procedure 5: Preparation of anthraniloylanthranilic acid. A reaction mix of 1:1:1.5 molar ratios of anthranilic acid, isatoic anhydride and sodium hydroxide are reacted in water at a temperature of 55° until all the reactants are in solution. The anthraniloylanthranilic acid is separated as an insoluble precipitate by acidification of the reaction mix with acetic acid. A methanol-water (4:1) mixture is used for recrystallization.

Picrate salts were prepared from solutions of absolute methanol or methanol-water mixtures.

Catalysts for the reaction of isatoic anhydride with ethanol. Molar ratios of 10:1 of IA to catalyst were used in an excess of 95% ethanol as reactant and solvent. 2.5 g. of IA (0.0153 mole) was tested in 10 ml. of 95% ethanol with the following substances as catalysts: NaOH, KOH, $(CH_3)_3N$, NaOEt, Na_2CO_3 and CaO. All but the last proved to have catalytic activity.

Acknowledgment. The authors wish to express their appreciation to Dr. Joseph Bunnett of Brown University and Dr. Ernest Eliel of the University of Notre Dame for their assistance and suggestions in developing the theory of these reactions.

COLLEGEVILLE, PA.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, SWARTHMORE COLLEGE]

Quinoline Analogs of Podophyllotoxin. III. The Synthesis of a Quinoline Analog of Dehydroanhydropicropodophyllin[1]

EDWARD A. FEHNEL AND JOAN E. STUBER

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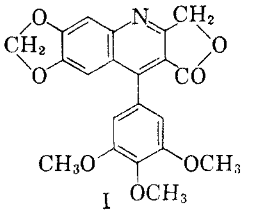
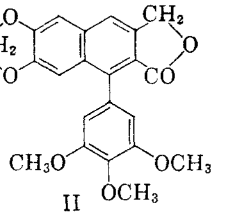
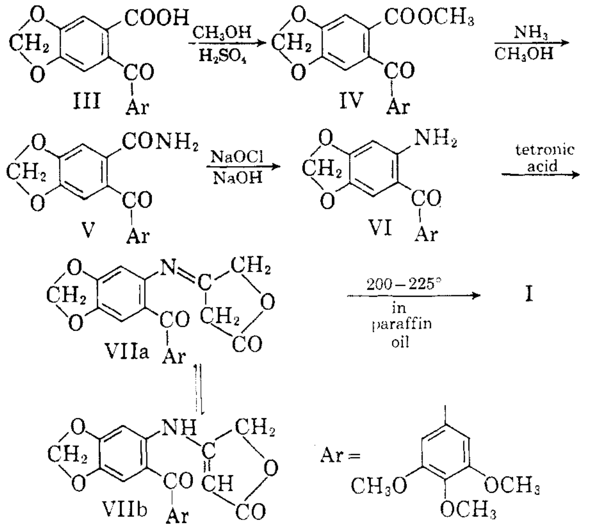
2-Hydroxymethyl-6,7-methylenedioxy-4-(3,4,5-trimethoxyphenyl)-3-quinolinecarboxylic acid lactone, a quinoline analog of dehydroanhydropicropodophyllin, has been synthesized by application of the general method described in Part II to 2-amino-4,5-methylenedioxy-3′,4′,5′-trimethoxybenzophenone. The possible tautomeric nature of the product is discussed.

One of the interim objectives of the present series of investigations has been the synthesis of 2-hydroxymethyl-6,7-methylenedioxy-4-(3,4,5-trimethoxyphenyl)-3-quinolinecarboxylic acid lactone (I), which may be regarded as a quinoline analog of dehydroanhydropicropodophyllin (II). Compound I is of interest both because it bears a much closer structural resemblance to the tumor-damaging lignan, podophyllotoxin, than do any of the quinoline derivatives previously described[2] and because it is a potential precursor of 2-hydroxymethyl-6,7-methylenedioxy-4-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydro-3-quinolinecarboxylic acid lactone, one of the stereoisomers of which should be an exact quinoline analog of podophyllotoxin. We are now able to report that we have succeeded in synthesizing I by an adaptation of the general method described in the preceding paper in this series.[3]


I


II



The sequence of reactions leading to I is outlined in the accompanying diagram. 6-(3,4,5-Trimethoxybenzoyl)piperonylic acid (III), prepared by the method of Gensler and Samour,[4] was esterified and the ester IV was ammonolyzed to give the amide V,[5] which underwent the Hofmann reaction on treatment with sodium hypochlorite to produce the corresponding amine VI. This *o*-aminoketone was condensed with tetronic acid and the resultant anil (VIIa or VIIb) was cyclized to the desired quinoline lactone I. The overall yield was about 10%, with most of the loss oc-

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[1] This investigation was supported by research grant CY-2726(C) from the National Cancer Institute of the National Institutes of Health, U. S. Public Health Service.

[2] E. A. Fehnel, *J. Org. Chem.*, **23**, 432 (1958).

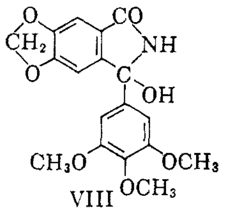
[3] E. A. Fehnel, J. A. Deyrup, and M. B. Davidson, *J. Org. Chem.*, **23**, 1996 (1958).

[4] W. J. Gensler and C. M. Samour, *J. Am. Chem. Soc.*, **73**, 5555 (1951).

[5] Attempts to prepare this amide by way of the corresponding acid chloride failed due to the readiness with which the acid III underwent ring-closure to a substituted anthraquinone in the presence of the usual halogenating agents.

curring in the Hofmann reaction step, in which our best yield was 26%, although numerous experiments were carried out to ascertain the optimum conditions for this reaction.

In the course of attempts to improve the yield in the Hofmann reaction by careful purification of the amide V, the melting point of this substance was observed to fluctuate erratically, even for successive samples obtained during repeated recrystallization of initially homogeneous material. These results, along with the subsequent observation that some of these samples (generally those which had been subjected to several recrystallizations) failed to yield any of the desired amine VI on treatment with sodium hypochlorite, suggested the possibility that the amide might be undergoing rearrangement to the tautomeric "pseudo" form VIII. This type of ring-chain tautomerism has previously been recognized in the o-benzoylbenzoic acid series of compounds, and in the case of at least one amide, o-benzoylbenzanilide, both the "normal" and the "pseudo" forms have been isolated and identified.[6] On the basis of this assumption and of the reported ability of hot acetic anhydride to reconvert the pseudo form of o-benzoylbenzanilide to the normal form,[6] we examined the action of this reagent on samples of the amide V which were known to behave abnormally in the Hofmann reaction and found that in this way it was possible to obtain material which would consistently produce the desired amine on treatment with sodium hypochlorite. The yield in this step, however, remained low (20–25%), the major product of the reaction being a white amorphous water-soluble solid which was not further investigated.



VIII

The quinoline lactone I also exhibited anomalous melting point behavior, although in this case the effect appeared to be due to polymorphism rather than tautomerism. Some recrystallized samples of I melted sharply at 268–269°; others melted first at 260–262°, then (after cooling to permit resolidification) remelted only at the higher temperature. During repeated recrystallizations each of these forms was occasionally observed to undergo spontaneous conversion to the other form. The ultraviolet absorption spectra of the two forms in ethanol (Fig. 1) were identical and showed the expected resemblance to the spectra of both the unsubstituted parent compound, 2-hydroxymethyl-4-phenyl-3-quinolinecarboxylic acid lactone,[3] and the podophyllotoxin series analog, dehydroanhydropicropodophyllin (II).[7] The infrared absorption spectra of the two crystalline forms of I in mineral oil mulls (Fig. 2) were identical, except for slight differences in the relative intensities of a few of the absorption bands,[8] and were consistent with the assigned structure (γ-lactone C=O, 5.61 μ; quinoline C=C and C=N, 6.14, 6.31 μ; no O—H or N—H absorption in 2.7–3.1 μ region).

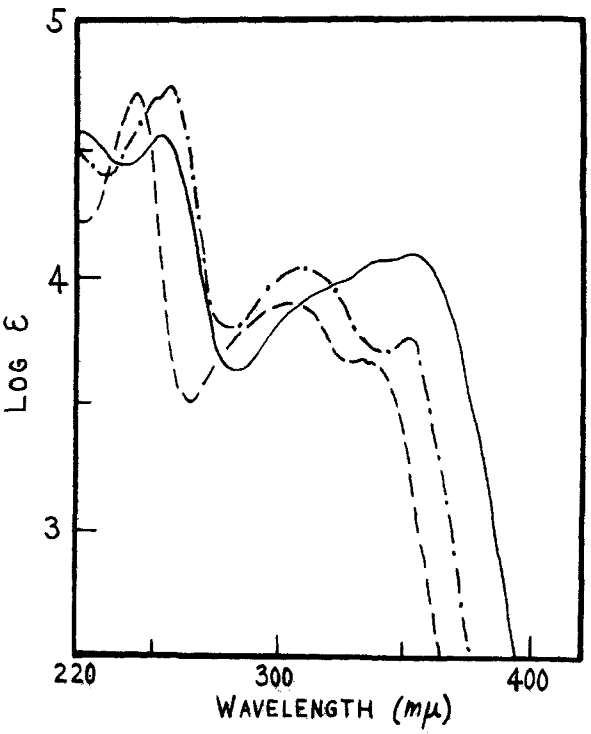


Fig. 1. Ultraviolet absorption spectra of 2-hydroxymethyl-6,7-methylenedioxy-4-(3,4,5-trimethoxyphenyl)-3-quinolinecarboxylic acid lactone (I), ———; 2-hydroxymethyl-4-phenyl-3-quinolinecarboxylic acid lactone, - - - -; and dehydroanhydropicropodophyllin (II), — · — · —

EXPERIMENTAL[9]

Methyl 6-(3,4,5-trimethoxybenzoyl)piperonylate (IV). A mixture of 55.9 g. of 6-(3,4,5-trimethoxybenzoyl)piperonylic acid[4] (III), 2 l. of absolute methanol, and 30 ml. of concentrated sulfuric acid was refluxed for 3 hr. and was then reduced to about half its original volume by distillation under diminished pressure. The residue was diluted with 2 l. of water, neutralized with solid sodium bicarbonate, and filtered to provide 53.5 g. (92%) of light tan microcrystalline powder, m.p. 126–128°. Recrystallization from methanol gave colorless needles melting at 129–130°; λ_{max}^{EtOH} 224 mμ (log ϵ 4.54), 296 mμ (log ϵ 4.17).

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(6) H. Meyer, *Monatsh.*, **28**, 1211, 1231 (1907).

(7) A. W. Schrecker and J. L. Hartwell, *J. Am. Chem. Soc.*, **74**, 5672 (1952).

(8) Concerning differences in the infrared spectra of some polymorphs, see F. A. Miller in H. Gilman's *Organic Chemistry, An Advanced Treatise,* Vol. 3, John Wiley and Sons, Inc., New York, 1953, p. 139; R. N. Jones and C. Sandorfy in A. Weissberger's *Technique of Organic Chemistry,* Vol. 9, Interscience Publishers, Inc., New York, 1956, pp. 295–6.

(9) Microanalyses are by Clark Microanalytical Laboratory, Urbana, Ill.

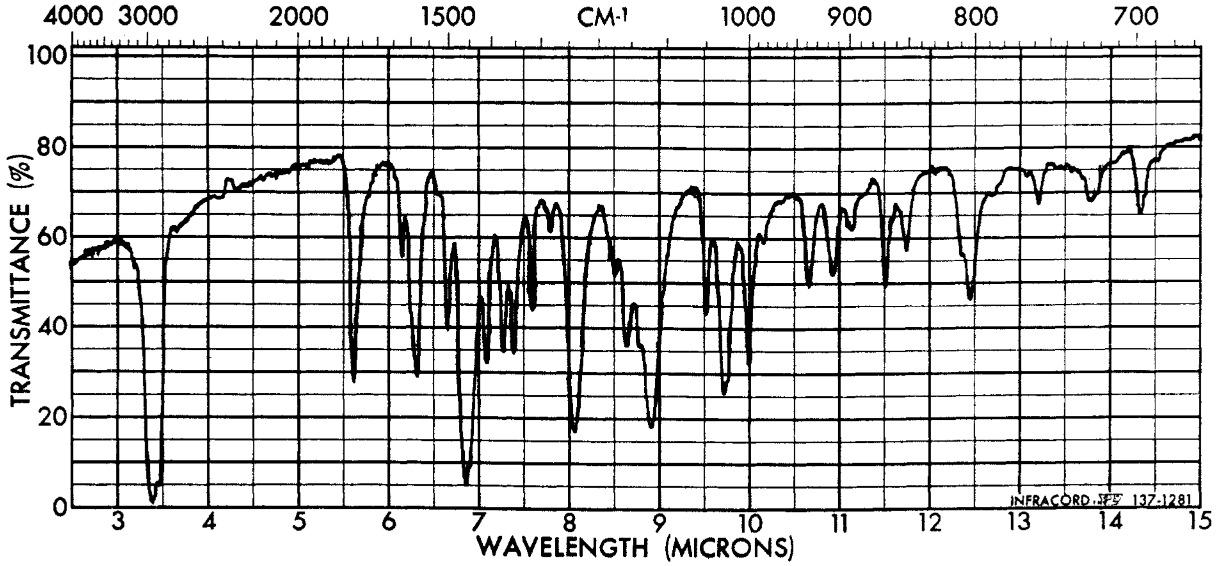

Fig. 2. Infrared spectrum of 2-hydroxymethyl-6,7-methylenedioxy-4-(3,4,5-trimethoxyphenyl)-3-quinolinecarboxylic acid lactone (I).

Anal. Calcd. for $C_{19}H_{18}O_8$: C, 60.97; H, 4.85. Found: C, 61.03; H, 4.89.

6-(3,4,5-Trimethoxybenzoyl)piperonylamide (V). A small piece of sodium (*ca.* 0.1 g.) was dissolved in 100 ml. of absolute methanol, after which the methanol was cooled in an ice bath and saturated with anhydrous ammonia. This solution was mixed with 15.0 g. of methyl 6-(3,4,5-trimethoxybenzoyl)piperonylate in a pressure bottle and the closed container was shaken at room temperature until all the solid had dissolved (4–6 hr.). The excess ammonia and most of the methanol were then removed by distillation under reduced pressure, and the resultant precipitate was collected, washed with a little water, and dried to give 11.5 g. (80%) of the crude amide, m.p. 182–186° (dec.). Recrystallization from benzene provided colorless crystals melting at 194–195° (dec.);[10] $\lambda_{\max}^{\text{EtOH}}$ 299 mμ (log ϵ 3.80).

Anal. Calcd. for $C_{18}H_{17}NO_7$: C, 60.17; H, 4.77. Found: C, 60.39; H, 4.56.

2-Amino-4,5-methylenedioxy-3',4',5'-trimethoxybenzophenone (VI). A mixture of 5.00 g. (0.0139 mole) of 6-(3,4,5-trimethoxybenzoyl)piperonylamide and 33 ml. of acetic anhydride was heated to boiling for 2 min. and was then evaporated to dryness on the steam bath. The residue was cooled, ground to a powder, and treated with a mixture of 60 ml. (0.015 mole) of 0.5*N* sodium hypochlorite solution[11] and 225 ml. of warm (50–60°) water. The resultant suspension was heated immediately to boiling and was then placed on a steam bath for 30 min. The reaction mixture was filtered while hot, and the precipitate was washed several times with hot water and dried to yield 1.06 g. (23%) of bright yellow leaflets, m.p. 144–146°. Recrystallization from ethanol raised the melting point to 147–148°; $\lambda_{\max}^{\text{EtOH}}$ 248 mμ (log ϵ 4.22), 392 mμ (log ϵ 4.00).

Anal. Calcd. for $C_{17}H_{17}NO_6$: C, 61.63; H, 5.17. Found: C, 61.85; H, 5.04.

The *N-acetyl derivative* of VI was prepared by heating a solution of 0.15 g. of the amine in 0.5 ml. of acetic anhydride on a steam bath for 1 hr. The solution was then cooled, diluted with 10 ml. of water, and neutralized with solid sodium bicarbonate. The resultant precipitate was collected, washed with water, and recrystallized from aqueous acetic acid to give pale yellow crystals melting at 173–174°.

Anal. Calcd. for $C_{19}H_{19}NO_7$: C, 61.13; H, 5.13. Found: C, 61.15; H, 5.42.

β-[4,5-Methylenedioxy-2-(3,4,5-trimethoxybenzoyl)phenylimino]-γ-butyrolactone (VII). A mixture of 1.74 g. (5.3 millimoles) of 2-amino-4,5-methylenedioxy-3',4',5'-trimethoxybenzophenone, 0.53 g. (5.3 millimoles) of tetronic acid, and 12 ml. of absolute ethanol was refluxed on a steam bath for 15 min., after which the condenser was removed and the mixture was allowed to boil dry. The solid yellow residue was taken up in boiling methanol, from which it crystallized in the form of matted yellow needles melting at 205–207°; yield 1.74 g. (80%). Recrystallization from methanol raised the melting point to 207–208°; $\lambda_{\max}^{\text{EtOH}}$ 281 mμ (log ϵ 4.32).

Anal. Calcd. for $C_{21}H_{19}NO_8$: C, 61.01; H, 4.63; N, 3.39. Found: C, 61.25; H, 4.68; N, 3.66.

2-Hydroxymethyl-6,7-methylenedioxy-4-(3,4,5-trimethoxyphenyl)-3-quinolinecarboxylic acid lactone (I). A mechanically stirred suspension of 1.50 g. of β-[4,5-methylenedioxy-2-(3,4,5-trimethoxybenzoyl)phenylimino]-γ-butyrolactone in 15 ml. of white paraffin oil was heated in a metal bath at 200–225° for 10 min., after which the reaction mixture was cooled, diluted with an equal volume of petroleum ether, and filtered. The precipitate was washed repeatedly with petroleum ether and dried to give 1.35 g. (94%) of a light brown powder which melted at 259–261° (dec.). Treatment of this material with Nuchar and recrystallization from glacial acetic acid provided colorless needles, which in some experiments melted sharply at 268–269° and in others melted first at 260–262°, then (after cooling to permit resolidification) remelted at 268–269°.

Anal. Calcd. for $C_{21}H_{17}NO_7$: C, 63.79; H, 4.33; N, 3.54. Found: C, 63.85; H, 4.45; N, 3.68.

The *ultraviolet absorption spectra* of the two melting point forms of I in absolute ethanol were identical: $\lambda_{\max}^{\text{EtOH}}$ 253 mμ (log ϵ 4.56), 352 mμ (log ϵ 4.09).

The *infrared absorption spectra* of the two forms of I in mineral oil mulls were identical (within ±0.01 μ) with respect to wave lengths of maximum absorption: $\lambda_{\max}^{\text{mull}}$ 3.39, 3.46, 5.61, 6.14, 6.31, 6.66, 6.86, 7.09, 7.28, 7.39, 7.60, 7.80, 8.05,

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(10) During recrystallization of this material from benzene or methanol, the melting point showed a tendency to vary erratically either upwards or downwards, mostly in the range 185–195°; one sample, however, melted at 202–203° (dec.) after recrystallization from methanol.

(11) Prepared according to the directions given by E. S. Wallis and J. F. Lane, *Org. Reactions*, III, 281–2, (1946).

8.51, 8.65, 8.78, 8.91, 9.52, 9.71, 10.00, 10.16, 10.66, 10.91, 11.12, 11.51, 11.74, 12.46, 13.20, 13.80, 14.35 μ.

The *picrate* of I was prepared by adding 0.10 g. of I to 5 ml. of a saturated solution of picric acid in chloroform, heating the mixture to boiling, and allowing it to cool slowly. The precipitate was collected, washed with a little chloroform, and recrystallized from chloroform to give yellow needles melting at 199–200° (dec.).

Anal. Calcd. for $C_{27}H_{20}N_4O_{14}$: C, 51.93; H, 3.23. Found: C, 52.10; H, 3.37.

SWARTHMORE, PA.

[CONTRIBUTION FROM THE RESEARCH AND DEVELOPMENT LABORATORIES OF THE ETHYL CORPORATION]

Relative Ease of Hydrogenolysis of Some Organometallic Compounds[1]

H. E. PODALL, H. E. PETREE, AND J. R. ZIETZ

Received February 17, 1959

The hydrogenolysis of diethylmagnesium, triethylaluminum, sodium di- and triisobutylaluminum hydrides, diethylzinc, zinc acetylide, and hexaphenyldilead was investigated. The results of this study confirm and extend the generalization that the ease of hydrogenolysis of the metal-carbon bond (as indicated by the minimum temperature at which hydrogenolysis is observed) parallels its degree of polar or ionic character (measured by Pauling's scale of electronegativity). A unified mechanism involving a trapezoidal transition state is proposed for the hydrogenolysis of alkyl- and aryl-metallic compounds, particularly the ionic ones, which is consistent with available hydrogenolysis information. The appreciably greater ease of hydrogenolysis of the trialkylboron-trialkylamine addition compounds over that predicted from electronegativity considerations is considered to be due to relief of steric strain during hydrogenolysis.

In the course of investigating the direct synthesis of tetraethyllead, triethylaluminum, diethylmagnesium,[2] and diethylzinc, the hydrogenolysis of these and some related compounds was studied. The results on the noncatalytic and catalytic hydrogenolysis of diethylmagnesium, triethylaluminum, diethylzinc, sodium di- and triisobutylaluminum hydrides, zinc acetylide, and hexaphenyldilead are summarized in Table I.[3]

The ease of hydrogenolysis of the ethylmetallics (as indicated by the minimum temperature at which hydrogenolysis is first observed) is $Et_2Mg > Et_3Al > Et_2Zn$. In the case of diethylmagnesium in diethyl ether, hydrogenolysis set in at about 50°, and an essentially quantitative conversion to magnesium hydride was obtained within 10 hours at 75°, 800 p.s.i.g. hydrogen pressure. The hydrogenolysis of triethylaluminum in *n*-hexane was found to set in at 140° at 3000 p.s.i.g. hydrogen pressure and was considerably slower than that of diethylmagnesium. Certain metals such as magnesium, however, were found to catalyze the hydrogenolysis to effect a quantitative conversion of triethylaluminum to diethylaluminum hydride within a few hours at 150°, 3000 p.s.i.g. hydrogen

TABLE I

SUMMARY OF TYPICAL HYDROGENOLYSIS RESULTS

RM	Catalyst	Solvent	Temp., °C.	Pressure, atm.	Time, hr.	Products,[a] % Conversion
Et_2Mg	None	Ether	75	68	21	98% MgH_2[b], C_2H_6
Et_3Al	None	None	140	67	4	12% Et_2AlH, C_2H_6
Et_3Al	Mg	*n*-Hexane	150	194	5.5	99% Et_2AlH, C_2H_6
Et_2Zn[c]	None	None	110	720	1.5	5% Zn, C_2H_6
Et_2Zn	Pd/Al_2O_3	Iso-octane[d]	100	680	16	18% ZnH_2, Zn, C_2H_6
ZnC_2	None	Iso-octane[d]	230	67	14	15% Zn, C_2H_6
ZnC_2	None	Iso-octane[d]	180	740	6	12% Zn, 3%$[Zn(CH{=}CH)]_x$[e]
Na(*i*-Bu_2AlH_2)	PtO_2	*n*-Hexane	150	210	3.5	>97% recovery Na(*i*-Bu_2AlH_2)
Na(*i*-Bu_3AlH)[f]	PtO_2	*n*-Hexane	150	210	3.5	100% Na(*i*-Bu_2AlH_2)
(C_6H_5	Raney Ni	Benzene	100	890	6	50% C_6H_5-C_6H_5[b], Pb
C_6H_5	Copper chromite	Benzene	126	770	6	39% $(C_6H_5)_4Pb$[b], Pb

[a] Based on gas evolution and mass spectral analysis unless otherwise indicated. [b] Isolated. [c] In the presence of zinc metal. [d] 2,4,4-Trimethylpentane. [e] Based on ethylene evolution on hydrolysis. [f] 50% Na[*i*-Bu_3AlH] and 50% Na[*i*-Bu_2AlH_2] by analysis.

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[1] Presented before the Symposium on Organometallic Chemistry at the 134th Meeting of the American Chemical Society, Chicago, Sept. 7–12, 1958, Abstracts of Papers, p. 34N.

[2] H. E. Podall and W. E. Foster, *J. Org. Chem.*, **23**, 1848 (1958).

[3] It should be noted that although there was some thermal decomposition of the ethylmetallic compounds here studied, it was negligible relative to the hydrogenolysis reaction. This was evidenced by an uptake of hydrogen rather than an increase in pressure due to thermal decomposition, and by the fact that little or no ethylene was found in the vent gas.