Benzoylation of an Enamine[1]

RICHARD D. CAMPBELL AND JOHN A. JUNG

Department of Chemistry, University of Iowa, Iowa City, Iowa

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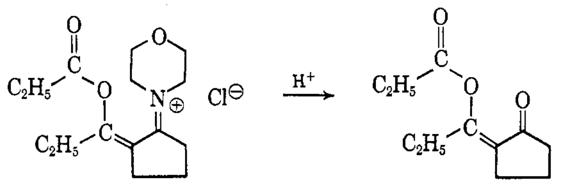
Benzoylation of 1-morpholinocyclohexene-1 with substituted benzoyl chlorides gives moderate to excellent yields of the dibenzoylated enamine, in which both benzoyl groups are attached to the same α-carbon atom. The dibenzoylated enamine is hydrolyzed to the triketone by dilute acid.

The reaction of acid chlorides with enamines has been investigated.[2,3] The expected acylation occurred and the resulting acyl enamines were hydrolyzed to the β-diketones in good yields.[2-5] The intermediate acyl enamine was not isolated or characterized, hence the position of the double bond in the intermediate was left in doubt in most cases.

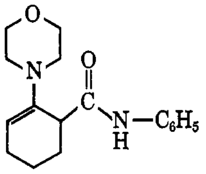
The Stork reaction is characterized by monoalkylation and acylation. However, Hunig[2] has reported the diacylation of 1-morpholinocyclopentene-1 by propionyl chloride, with subsequent hydrolysis to give II. The intermediate I was proposed. Harmer[6] found that dibenzoylation of 1-morpholinocyclopentene-1 occurs in small yield, and produces 2,5-dibenzoylcyclopentanone on hydrolysis.



I

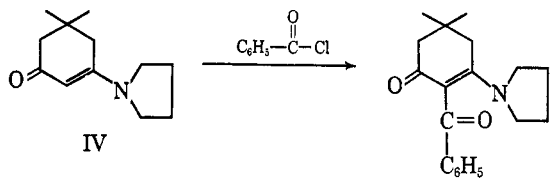
II

Berchtold[7] has established that isocyanates add to cyclic enamines to give a compound III, in which the double bond of the enamine is opposite to, and not in conjugation with, the carbonyl.



III

Alt and Speziale[8] have shown that enamino ketones of the type IV can be benzoylated to give the enamine V, in which the benzoyl chloride has attacked the enamine carbon and not the ketone oxygen. The position of the double bond has been established by n.m.r. spectroscopy (no vinyl proton).

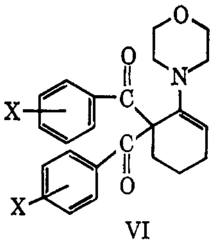


IV

V

These studies provide precedent for possible diacylation of enamines in which the second acyl attack is (a) at the α'-position leading to α,α'-diacylation[7]; (b) at the α-position leading to α,α-diacylation; or (c) at oxygen leading to O-acyl enol.[2]

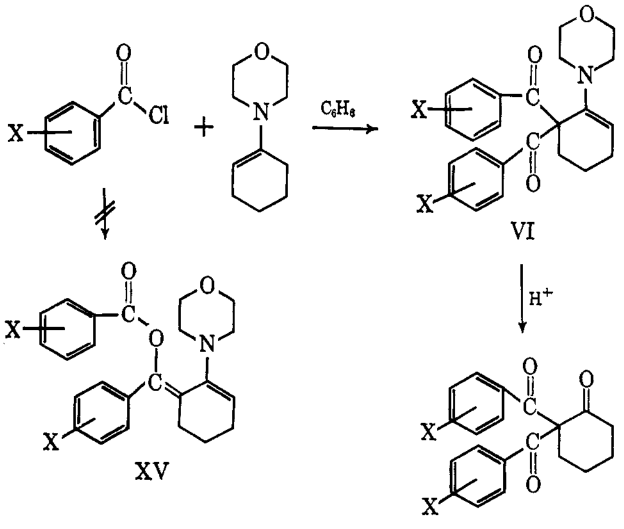
In a study of the synthesis and reactions of benzoylcyclohexanones, we have obtained very low yields of these β-diketones *via* the enamine method. The failure of the Stork reaction to give monobenzoylation was especially acute in the case of the *ortho*-substituted benzoyl chlorides. Investigating the reaction more closely, we have observed that products of structure VI were formed in moderate to excellent yields in the reaction of certain benzoyl chlorides with 1-morpholinocyclohexene-1.



VI

Results and Discussion

Benzoyl chlorides reacted with 2 moles of 1-morpholinocyclohexene-1 in benzene to give the dibenzoylated enamines (see Table I). Hydrolysis of the enamines yielded the triketones VII (see Table II). Had the initial product been the O-benzoyl enol, the hydrolysis step would have yielded monobenzoylcyclohexanone.



VI

XV

VII

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[1] This paper taken in part from the Ph.D. Thesis of J. A. J., University of Iowa, Feb. 1966.

[2] S. Hunig and W. Lendle, *Ber.*, **93**, 909, 913 (1960).

[3] G. Stork, *et al.*, *J. Am. Chem. Soc.*, **85**, 207 (1963).

[4] S. Hunig, *et al.*, *Ber.*, **90**, 2834 (1957).

[5] R. D. Campbell and W. L. Harmer, *J. Org. Chem.*, **28**, 379 (1963).

[6] W. L. Harmer, M.S. Thesis, University of Iowa, 1962.

[7] G. A. Berchtold, *J. Org. Chem.*, **26**, 3043 (1961).

[8] G. H. Alt and A. J. Speziale, *ibid.*, **29**, 798 (1964).

TABLE I

DIBENZOYLATED ENAMINES

Compd.	M.p., °C.	Yield, %	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
o-Fluoro	104–105	40	70.06	70.28	5.63	5.67	3.41	3.44
o-Chloro	150–152	50, 82[a]	64.86	64.63	5.22	5.31	3.15	3.20
o-Bromo	146–148	65	54.05	53.92	4.35	4.40	2.63	2.74
o-Iodo	138–139	70	45.95	45.65	3.69	3.60	2.23	2.13
H	150 dec.	47[a]	76.77	76.75	6.71	6.80		

[a] Prepared without refluxing the reaction mixture.

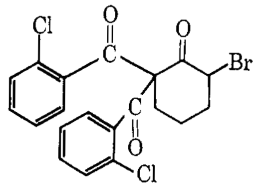
TABLE II

DIBENZOYLATED CYCLOHEXANONES

Compd.	M.p., °C.	Yield, %	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
o-Fluoro	58–59	80	70.17	69.90	4.71	4.55
o-Chloro	70–72	80	64.01	64.02	4.30	4.16
o-Bromo	82–83	86	51.75	51.76	3.47	3.65
o-Iodo	78–80	68	43.03	42.80	2.88	2.93
p-Nitro	162–163	10[a]	60.60	60.63	4.07	4.49

[a] Isolated from the reaction for the preparation of 2-(p-nitrobenzoyl)cyclohexanone, by the procedure for synthesis of these β-diketones as given by Stork.[3] No attempt was made to isolate any enamine intermediates in this reaction.

Bromination of 6,6-di-(o-chlorobenzoyl)-1-morpholinocyclohexene-1 produced compound VIII in 50% yield. Cleavage of the morpholine moiety is expected.[9]



VIII

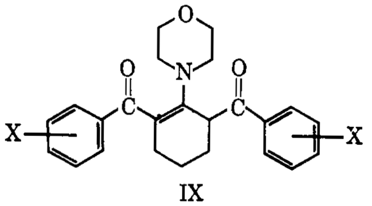
Had the product been the O-benzoylated enol, cleavage of the enol ester function[10] would occur to give a monobenzoylcyclohexanone.

Failure of VI (X = o-Cl) to react with sodium borohydride also argues against O-acylation since enol acetates have been reported to cleave at room temperature with this reagent.[10,11] We would expect enol benzoates to show some cleavage under these conditions. However, the enamine starting material was recovered in 72% yield. An infrared spectrum of the remaining material gives no evidence of reduction.

The ultraviolet spectra of the various dibenzoylated enamines and dibenzoylated cyclohexanones show characteristic benzoyl absorption as indicated by the wave length of maximum absorption and molar extinction coefficient (see Table III). If the hydrolyzed enamines were enol benzoates, we would expect the cinnamoyl chromophore at much longer wave lengths.[12]

Polarographic reduction of the compound believed to be 6,6-di-(o-chlorobenzoyl)-1-morpholinocyclohexene-1 indicates that the compound has the dibenzoyl structure ($E_{1/2}$ = −1.36 v. with respect to the mercury pool electrode). Enol esters should reduce at much higher negative voltages.[13]

The ultraviolet spectrum also eliminates the possible 2,6-dibenzoylated enamine IX. Compound IX contains the β-aminoacrylophenone chromophore which has a strong absorption in the ultraviolet near 330 mμ.[12,14] The product obtained has no band in this region and shows only typical benzoyl absorption (265–270 mμ).



IX

TABLE III

ULTRAVIOLET, INFRARED, AND N.M.R. SPECTRAL DATA

Compd.	Ultraviolet	Infrared	N.m.r.
	Dibenzoylated Enamines		
o-Fluoro	229[a] (22)[b] 270 (13)	5.75[c]	5.20[d]
o-Chloro	230 (23)[e] 268 (8)	5.74	5.05
o-Bromo	230 (23)[e] 265 (10)	5.74	5.05
o-Iodo	220 (26)[e] 265 (9)	5.74	5.05
H	232 (25) 265 (14)	5.77	5.05
	Dibenzoylated Cyclohexanones		
o-Fluoro	232 (16.4)	5.78 6.10	1:1[f]
o-Chloro	250 (13.8)	5.72 6.13	1:1
o-Bromo	242 (13.5)	5.73 6.14	1:1
o-Iodo	248 (13.9)	5.74 6.14	1:1
p-Nitro	264 (26)	5.73 5.88	1:1

[a] Wave length absorption maximum in millimicrons. [b] Extinction coefficient times 10^{-3}. [c] Carbonyl stretching frequency in microns. [d] Triplet parts per million. [e] Shoulder. [f] Ratio of aromatic to aliphatic protons.

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(9) J. Szmuszkovicz, *Advan. Org. Chem.*, **4**, 61 (1963).

(10) W. G. Dauben, *et al.*, *J. Am. Chem. Soc.*, **74**, 3852 (1952).

(11) J. P. Ferris, *et al.*, *J. Org. Chem.*, **29**, 87 (1964).

(12) R. D. Campbell and H. M. Gilow, *J. Am. Chem. Soc.*, **82**, 5426 (1960).

(13) This interpretation made as a result of a discussion with Dr. S. Wawzonek, University of Iowa, Iowa City, Iowa.

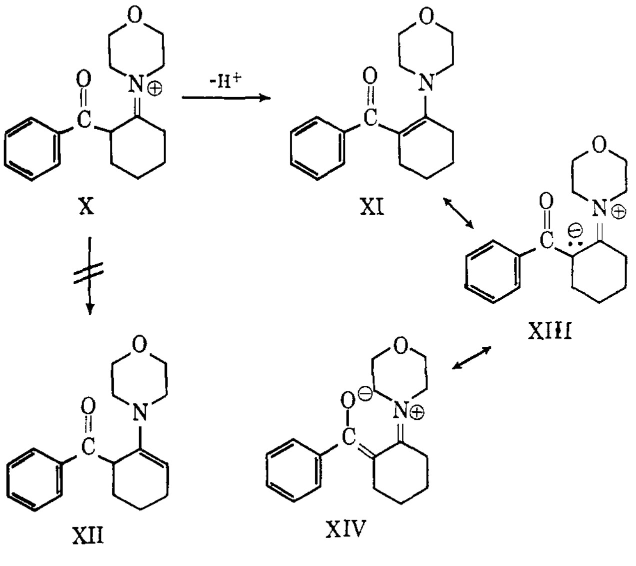
(14) N. H. Cromwell, *Chem. Rev.*, **38**, 83 (1938).

The n.m.r. spectra support the α,α-dibenzoylated enamine structure VI. Integrated intensities of the aromatic and aliphatic signals agree with the ratio of two aromatic rings per morpholino group. The morpholino group provides an excellent calibration standard for intensities.[15] The vinyl proton signal appears at ~5.1 p.p.m. as a triplet, in agreement with VI. The vinyl proton is split by two equivalent vicinal protons. (If the product were IX, the lone proton would appear farther upfield, probably as a doublet or split doublet.)

The hydrolysis products of VI, the triketones VII, provide further proof of structure. The n.m.r. spectra of VII show no enol proton (~17 p.p.m.) and no lone α-proton expected of the 2,6-dibenzoyl ketone. Chemical evidence to support structure VII includes no chelate formation with copper and no enol color reaction with ferric chloride.

In the triketones VII the four aliphatic protons on C-3 and C-6 appear at 2.55 p.p.m., downfield from the four protons on C-4 and C-5. The inductive effect of one carbonyl group (C-1) upon the chemical shift at C-6 is approximately the same as the effect of three carbonyl groups upon the chemical shift at C-3, where the three carbonyl groups are one bond more remote. A similar effect appears in the dibenzoyl enamines VI, in which the downfield shifts of protons on C-3 and C-5 are approximately equal, and the two protons on C-4 appear in the normal upfield position alone.

Some features of the mechanism of the Stork acylation are elucidated by our results. The product of the first benzoylation loses a proton from the α-carbon atom at which attack occurred. In the Stork alkylation[3] the proton loss occurs at the opposite, or α'-carbon atom. In the present case, the formation of the conjugated system of XI is the controlling factor. Subsequent attack at the α'-position by a second molecule of benzoyl chloride[6] is possible only if the nonconjugated benzoyl enamine XII is formed. The second benzoylation must then occur at the α-carbon or at oxygen. The preference for C-acylation over O-acylation can be explained by noting that resonance form XIV must be available for O-acylation. Examination of molecular models reveals that when the $^{+}N{=}C{-}C{=}C{-}O^{-}$ system is coplanar as required, crowding between the carbonyl oxygen and the hydrogens on C-2 of the morpholine moiety exceeds the limits of van der Waals radii. In the *trans* form of XIV, oxygen is more accessible for acylation, but the phenyl-morpholino crowding is prohibitive. Steric inhibition of form XIV resonance suppresses the negative character of oxygen, and the acylation attack occurs at α-C, as suggested by form XIII, and only VI is obtained.



An alternative explanation of the absence of O-acylation products is that while both O- and C-acylation might occur, only the latter leads to products. The O-acylation intermediate could revert to reactants, while the C-acylation intermediate leads to stable product by proton loss to excess base.

The presence of monobenzoyl enamines XI is demonstrated by the isolation of 2-benzoylcyclohexanones from the reaction as their copper chelates. The 2-benzoylcyclohexanones could arise from hydrolysis of XV in the reaction mixture, although no evidence for any O-acylation was obtained.

Experimental Section

Dibenzoylated enamines were prepared by adding the acid chloride (0.25 mole) in 200 ml. of anhydrous benzene dropwise to a solution of 1-morpholinocyclohexene-1 (0.50 mole) in 200 ml. of benzene over a period of 2 hr. with stirring. The mixture was stirred at room temperature for 4 hr. and then refluxed for 2 hr. It was then cooled and filtered to remove the 1-morpholinocyclohexene-1 hydrochloride which was washed several times with anhydrous benzene to remove any color. The benzene washings and filtrate were combined and the benzene was evaporated at reduced pressure with a rotary evaporator, leaving an orange viscous oil. Yellow crystals were visible after several hours. The solid was recrystallized several times from anhydrous methanol, to give the white crystalline dibenzoylated enamine. In the case of the *o*-fluoro and unsubstituted compounds, recrystallizations were made from ether–pentane and ether, respectively.

Hydrolysis of dibenzoylated enamines was carried out by adding to 0.10 mole of the dibenzoylated 1-morpholinocyclohexene-1 in tetrahydrofuran 40 ml. of 3 *N* hydrochloric acid, and refluxing the mixture for 2 hr. This reaction mixture gave a negative ferric chloride test. After cooling, sodium chloride was added and the aqueous layer was separated from the tetrahydrofuran layer after shaking. The tetrahydrofuran was evaporated under reduced pressure leaving a solid. This solid was taken up in ether and the resulting solution was shaken with 5% potassium hydroxide solution. The ether solution was washed with water and dried. After cooling in an ice bath for a few hours, white crystals of triketone VII separated. These were filtered and dried. After concentrating the mother liquor, more crystals were obtained. The potassium hydroxide solution mentioned above was acidified with dilute hydrochloric acid and extracted with ether. Upon drying and evaporating the ether, a small amount of solid remained. It proved to be more VII, by negative enol test and identical infrared spectrum. A further small amount of VII was recovered from the saline hydrolysis mixture, due to the slight water solubility of VII. No other organic product was detected.

However, if the acid hydrolysis mixture was made basic after reflux and allowed to stand for about 2 weeks before work-up of the reaction, the products isolated in addition to the triketone were the corresponding *o*-halobenzoic acid and β-diketone, and *o*-halobenzoylmorpholine. The acid and β-diketone were identified by n.m.r. spectroscopy by comparison with authentic samples. The β-diketone also gave a chelate with cupric acetate solution. The *o*-halobenzoylmorpholine was identified by its n.m.r. spectrum and elemental analysis. Evidently, one benzoyl group can be cleaved in basic solution.

Bromination of 6,6-Di(*o*-chlorobenzoyl)-1-morpholinocyclohexene-1.[9,10]—This reaction was carried out by dissolving 4.4 g. (0.01 mole) of the dibenzoylated enamine in 125 ml. of chloroform and adding 6.4 g. (0.04 mole) of bromine in chloroform.

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[15] Varian N.m.r. Spectra Catalog, Vol. 1, Spectrum No. 84.

The solution was stirred for 1 hr. at room temperature, and after this time, 100 ml. of absolute methanol was added and the resulting solution was stirred for 2 days, again at room temperature. An equal volume of water was added and the mixture was shaken. The organic phase was washed with sodium bicarbonate solution, then twice with water. The solution was dried over magnesium sulfate and filtered, and the solvent was evaporated under reduced pressure leaving an orange oil. Upon addition of anhydrous ether and subsquent cooling at 0° for 1 day, 1.98 g. of a white crystalline material was obtained. After further evaporation of the solvent and cooling, another 0.30 g. of this material was isolated: m.p. 77–78°, 2.28 g. (50%).

Anal. Calcd. for $C_{20}H_{15}BrCl_2O_3$: C, 52.88; H, 3.32. Found: C, 52.55; H, 3.32.

The n.m.r. spectrum indicated that the product was 2,2-di-(*o*-chlorobenzoyl)-6-bromocyclohexanone. There was a multiplet at 5.1 p.p.m., corresponding to one hydrogen, and aromatic and aliphatic areas in a ratio of 8 to 6. The infrared spectrum showed a carbonyl stretch at 5.73 and 6.03 μ; λ_{max}^{EtOH} 245 mμ (ϵ 14,700).

Polarographic Reduction of 6,6-Di(*o*-Chlorobenzoyl)-1-morpholinocyclohexene-1.—A 10^{-3} *M* solution of this dibenzoylated enamine in acetonitrile, with *t*-butylammonium iodide as supporting electrolyte, was reduced using a dropping mercury cathode and mercury pool anode. The resulting polarogram indicated a reduction of the dibenzoylated enamine ($E_{1/2} = -1.36$ v.). A 10^{-3} *M* solution of 1-morpholinocyclohexene-1 showed no reduction under the same conditions. A Sargent Model XXI instrument was used: range, 0–2.5 v.; sensitivity, 0.100 μa./mm.; damping, 2.

The Attempted Reaction of 6,6-Di(*o*-chlorobenzoyl)-1-morpholinocyclohexene-1 with Sodium Borohydride in Ethanol.—To 0.80 g. (0.021 mole) of sodium borohydride in 250 ml. of absolute ethanol, was added 4.40 g. (0.01 mole) of the dibenzoylated enamine and the mixture was stirred for 1 day. After this time it was noticed that some of the enamine had not gone into solution. As a result, 100 ml. of anhydrous tetrahydrofuran was added to increase the solubility. The solution was then stirred for 4 days at room temperature. After this time the solvents were evaporated at reduced pressure leaving a solid residue. The solid was dissolved in anhydrous methanol, and upon cooling in an ice bath, 3.20 g. of a white solid was isolated. A mixture melting point with the starting material showed no depression (149–151°). An infrared spectrum was identical with that of the starting material. (The 3.20 g. of solid corresponds to a recovery of 72%.) An infrared spectrum of the oil which remained did not give any evidence of a reaction. As with the starting material, there was a carbonyl peak at 5.7 μ.

Monobenzoylated cyclohexanones (as the copper chelates) were isolated after hydrolysis of the oily residue remaining when the dibenzoylated enamines were crystallized and removed from the reaction of the benzoyl chlorides with 1-morpholinocyclohexene-1. After hydrolysis, the organic layer was separated from the aqueous layer and the organic solvent was evaporated. The residue was taken up in ether and shaken with sodium bicarbonate solution, washed with water, and shaken with aqueous cupric acetate solution. Upon standing for a few hours, the chelate was visible. It was washed with hot water, then ether, and dried.

All melting points are corrected. The n.m.r. spectra were measured on a Varian A-60 spectrometer. Ultraviolet spectra were obtained from the Cary Model 11 and Model 14 instruments. Infrared spectra were run on a Perkin-Elmer Model 21 and Model 347 Infracord spectrometers.

Electrophilic Substitution Reactions of Triphenylamine[1a]

T. NELSON BAKER, III,[1b] WILLIAM P. DOHERTY, JR.,[1b] WILLIAM S. KELLEY,[1c]
WILLIAM NEWMEYER,[1b] JOSEPH E. ROGERS, JR.,[1b] RICHARD E. SPALDING,
AND ROBERT I. WALTER[1d]

Chemistry Department, Haverford College, Haverford, Pennsylvania

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The conditions for halogenation, sulfonation, and acylation of triphenylamine have been investigated, and the *para* positions have been shown to be those attacked under the conditions used. These reactions in most cases proceed to the trisubstitution stage without formation of isolable amounts of intermediates. These facts are considered in the light of knowledge of the configuration and electronic nature of the triphenylamine molecule.

The electrophilic substitution reactions of triphenylamine afford a route to the synthesis of a number of otherwise difficultly accessible compounds necessary for the preparation of aminium salt free radicals.[2] In addition, they have some theoretical interest in connection with the transmission of substituent effects between aromatic rings through bridging atoms. We report here procedures for carrying out trisubstitution in triphenylamine by most of the usual electrophilic substitution reactions, the proofs of structure of the products, and experimental and theoretical evidence bearing on directive effects in these reactions.

Procedures for a number of trisubstitution reactions of triphenylamine are in the literature. Years ago, the preparation of a trinitrotriphenylamine was described by Heydrich,[3] a trisulfonic acid by Herz,[4] and a tribromo compound by Wieland.[5] More recently, Wilson[6] has patented a synthesis which is claimed to give triformyltriphenylamine. Fox and Johnson have just published a study of acylation reactions of triphenylamine in which trisubstitution products have been identified.[7] In all of these cases, the number of substituents introduced was determined by analysis of the products. The facts that amino groups direct electrophilic aromatic substitution to the *ortho*, *para* positions, that the geometry of triphenylamine is such that *ortho* substitution would be inhibited sterically, and that most reactions are observed to lead to the introduction of no more than three substituents, suggest that reaction occurs at the three *para* positions. Those trisubstitution products which have been described in the literature have been said to be 4,4′,4″-trisubstituted, usually with no experimental support for these claims. The structures

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(1) (a) This work was supported in part by U. S. Army Signal Research and Development Laboratory Contract No. DA-36-039-SC-74917, administered by the University of Pennsylvania, and in the later stages by U. S. Public Health Service Grant GM-10605 to Haverford College. Royalty-free reproduction for purposes of the United States Government is permitted. (b) Senior research participant at Haverford College. (c) Summer research participant sponsored by the National Science Foundation undergraduate research participation program. (d) Inquiries should be sent to this author.

(2) R. I. Walter, *J. Am. Chem. Soc.*, **77**, 5999 (1955).

(3) C. Heydrich, *Ber.*, **18**, 2157 (1885).

(4) R. Herz, *ibid.*, **23**, 2541 (1890).

(5) H. Wieland, *ibid.*, **40**, 4278 (1907).

(6) C. D. Wilson, U. S. Patent 2,558,285 (1951).

(7) C. J. Fox and A. L. Johnson, *J. Org. Chem.*, **29**, 3536 (1964).