[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA, BERKELEY]

4-Oxo-5,6-dihydro-4*H*-pyrido[3,2,1-*jk*]carbazole and Its Aralkylidene Derivatives

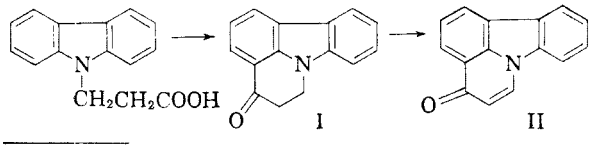
HENRY RAPOPORT AND DOROTHY M. BOWMAN

Received September 15, 1958

4-Oxo-5,6-dihydro-4H-pyrido[3,2,1-*jk*]carbazole (I) was prepared by cyclization of 9-carbazolepropionic acid with anhydrous hydrogen fluoride, in a copper pressure vessel. Condensation of I with several aldehydes in the presence of piperidine led to aralkylidene derivatives which isomerized to the corresponding 4-quinolines on heating with alkali.

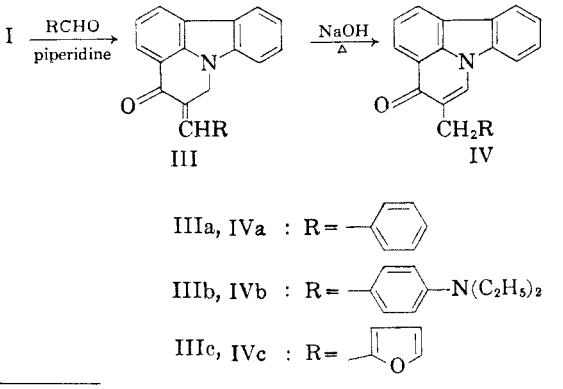
As part of a study of fused ring compounds and the effect of ring strain on aromatic properties and interactions,[1-3] a series of indoles was required for which 4-oxo-5,6-dihydro-4H-pyrido[3,2,1-*jk*]carbazole (I) appeared to be a very attractive intermediate. A convenient synthesis of this compound is described in this paper. Also, the chemistry of some of its α-ylidene derivatives was studied in view of the interesting isomerism recently observed with similar compounds.[4,5]

The synthesis of the pyridocarbazole I from 9-carbazolepropionitrile by fusion with a mixture of aluminum chloride, sodium chloride, and potassium chloride has been reported.[6] However, since others were unable to repeat this cyclization,[7] it was not investigated further. Instead, the cyclization of 9-carbazolepropionic acid, which appeared to offer a more promising path to I, was undertaken. 9-Carbazolepropionic acid was readily prepared by hydrolysis of 9-carbazolepropionitrile, itself easily available from cyanoethylation of carbazole.[8] Hydrolysis with hydrochloric acid has been reported,[7] but was found to be unsatisfactory due to the very low solubility of the nitrile in concentrated hydrochloric acid. Alkaline hydrolysis, using aqueous ethanol as the solvent, proceeded rapidly to give 9-carbazolepropionic acid in quantitative yield.



Three catalysts were investigated for the ring-closure of the acid to the pyridocarbazole I. Polyphosphoric acid, which had been used successfully in the synthesis of 1-ketolilolidine,[4] gave only polymeric material. Trifluoroacetic anhydride[9] gave a small yield of impure ketone. Anhydrous hydrogen fluoride gave the most promising results, but the yield was still low under the reaction conditions usually used,[10] *i.e.*, allowing the reaction mixture to stand at room temperature until all the hydrogen fluoride had evaporated. By carrying out the reaction in a copper pressure vessel, which had the advantage of lengthening the reaction time and of maintaining a high concentration of hydrogen fluoride,[11] the yield of ketone I was raised from 12% to 49%, making I available in quantity.

The condensation of the pyridocarbazole I with various aldehydes was then considered. Benzylidene and *p*-diethylaminobenzylidene derivatives of I have been isolated and have been reported to exist as cis-trans isomers.[6] However, it seems more likely that this isomerism is due to migration of the benzylidene double bond of III into the ring to form the quinolone derivative IV, as has been reported for the derivatives of dihydro-4-quinolone[5] and of 1-ketolilolidine.[4] In order to investi-



(1) H. Rapoport and J. Z. Pasky, *J. Am. Chem. Soc.*, **78**, 3788 (1956).

(2) H. Rapoport and G. Smolinsky, *J. Am. Chem. Soc.*, **79**, 5831 (1957).

(3) H. Rapoport and G. Smolinsky, *J. Am. Chem. Soc.*, **80**, 2910 (1958).

(4) H. Rapoport and J. R. Tretter, *J. Org. Chem.*, **23**, 248 (1958).

(5) P. I. Ittyerah and F. G. Mann, *J. Chem. Soc.*, 467 (1958).

(6) I. G. Farbenindustrie A.-G., French Patent **806,715** (1936).

(7) P. A. S. Smith and T. Y. Yu, *J. Am. Chem. Soc.*, **74**, 1096 (1952).

(8) F. C. Whitmore, H. S. Mosher, R. R. Adams, R. B. Taylor, E. C. Chapin, C. Weisel, and W. Yanke, *J. Am. Chem. Soc.*, **66**, 725 (1944).

(9) R. J. Ferrier and J. M. Tedder, *J. Chem. Soc.*, 1435 (1957).

(10) W. S. Johnson, *Org. Reactions*, **2**, 157 (1944).

(11) A more complex apparatus for refluxing hydrogen fluoride under pressure to attain a higher reaction temperature has been described by L. F. Fieser and E. B. Hershberg, *J. Am. Chem. Soc.*, **62**, 49 (1940).

gate this isomerization with the present compounds, various aralkylidene derivatives of I were prepared. As a model compound containing the quinolone chromophore present in IV, 4-oxo-4H-pyrido-[3,2,1-*jk*]carbazole (II) was prepared by catalytic dehydrogenation of the parent ketone I.

When I was condensed with benzaldehyde, using sodium hydroxide as the catalyst, the product was yellow and melted at 215°, the melting point reported for one of the isomers.[6] Its ultraviolet spectrum (Fig. 1) was very similar to that of II,

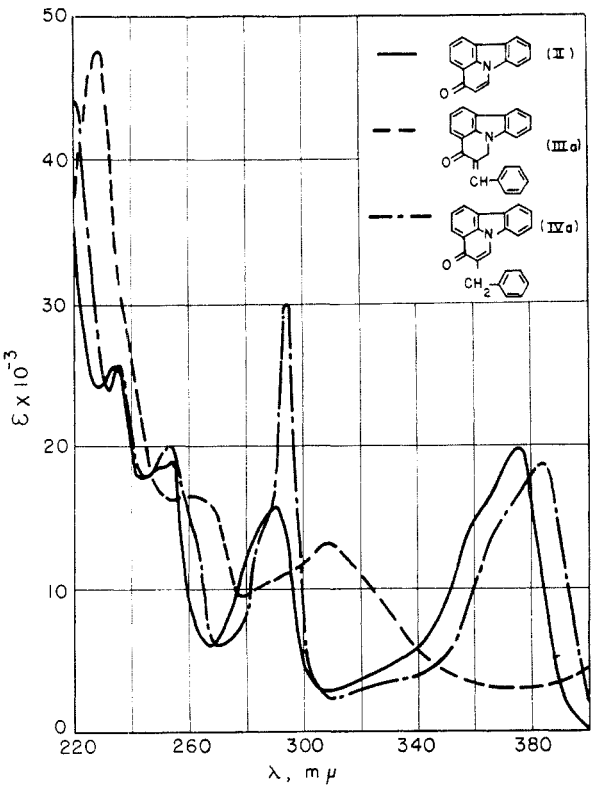
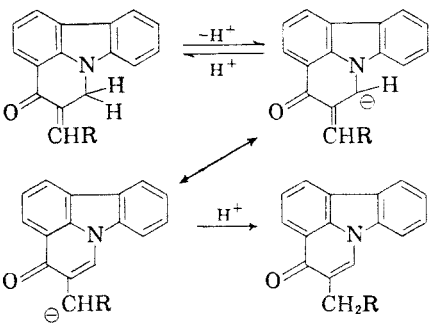


Fig. 1. Ultraviolet absorption spectra in methanol of 4-oxo-4H-pyrido 3,2,1-*jk* carbazole (II) ———, 4-oxo-5-benzylidene-5,6-dihydro-4H-pyrido 3,2,1-*jk*-carbazole (IIIa) — — —, and 4-oxo-5-benzyl-4H-pyrido 3,2,1-*jk* carbazole (IVa) — - —

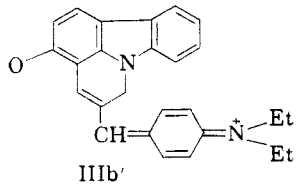
indicating that the compound has the quinolone structure IVa. When piperidine was used as the catalyst for the condensation, the product isolated was orange, and melted at 151°, the melting point reported (148°) for the other isomer.[6] Its spectrum is entirely different from that of the yellow isomer, and it is undoubtedly the expected benzylidene derivative (IIIa). Refluxing the lower-melting orange isomer in alcoholic sodium hydroxide for a few minutes converted it quantitatively to the higher-melting, yellow isomer. When *p*-diethylaminobenzaldehyde or furfural was used instead of benzaldehyde, the same condensation product was obtained with either piperidine or a cold solution of sodium hydroxide as the catalyst. The products were red-orange, and have ultraviolet spectra similar to that of the benzylidene derivative, IIIa. They can therefore be assigned the structures IIIb and IIIc, respectively, with the double bond exocyclic. When these compounds were heated with alcoholic potassium hydroxide, they were converted to lower-melting, yellow isomers having spectra similar to those of the quinolones, II and IVa. The yellow compounds can therefore be assigned structures IVb and IVc, respectively, in which the double bond has migrated into the ring. The isomerization of the furfurylidene derivative (IIIc) to the quinolone (IVc) was also accomplished by refluxing with potassium carbonate in ethanol. Thus, the isomerization on heating takes place whenever a catalyst of sufficient alkalinity is present.

It is interesting that the melting points give no indication of isomer identity; in one instance the quinolone is the higher melting, but in two it is the lower melting. The ultraviolet spectra are the best means of identification, as seen in Fig. 1. When both isomers are available, the color appears to be a reliable guide; the aralkylidene derivatives are always redder than the quinolones. For the three series in which this isomerization has been observed, the quinolones are almost colorless to pale yellow, while the aralkylidenes are orange to red.

The mechanism of the isomerization can be pictured as proceeding by abstraction of a proton by the base, and subsequent return of the proton to the position that leaves the more stable double bond. This would lead to the prediction that the position of equilibrium would be greatly affected by

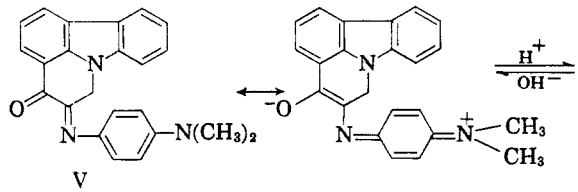


any factors which would stabilize the double bond in one of the two positions. The fact that the benzylidene derivative (IIIa) of I can be isolated, while those of 1-ketolilolidine[4] and of 1,2,3,4-tetrahydro-4-oxoquinoline[5] cannot, shows the effect of conjugation on the isomerization. For the latter two compounds, formation of the quinolone adds significantly to the conjugation of the aromatic system, and therefore occurs with great ease. Compound IIIa, with the stable carbazole system already present, can gain less by formation of the quinolone (IVa) and therefore has less tendency to isomerize. Similarly, IIIb, in which the aralkylidene structure is stabilized by contributions from the resonance form IIIb′, isomerizes less readily than does IIIa.

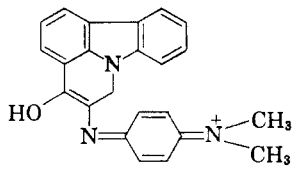


IIIb'

p-Dimethylaminonitrosobenzene was also condensed with I. With sodium hydroxide, piperidine, or potassium carbonate as the catalyst, in refluxing methanol, the product was always the same very deep red compound. This was recovered unchanged on refluxing with potassium hydroxide in ethanol, with potassium *t*-butoxide in *t*-butyl alcohol, or with hydrochloric acid in ethanol. Structure V, with the exocyclic double bond, seems most likely



V



VI

for this compound. If the double bond had migrated into the ring the compound would be expected to be yellow, as is 3-*p*-dimethylaminoanilino-1,4-dihydro-1-methyl-4-oxoquinoline,[5] although comparisons between different ring systems are not necessarily valid. The ultraviolet spectrum does not parallel that of either the aralkylidene derivatives (III) or the quinoline derivatives (IV), but is more similar to the former. In addition, the infrared spectrum did not show an N—H band. The color of V did change to yellow-green in acid, but returned to the original red when the solution was made alkaline. This change can be accounted for by a structure such as VI for the salt. The failure of V to isomerize is not surprising since there would be considerable resonance stabilization of the exocyclic double bond.

EXPERIMENTAL[12]

9-Carbazolepropionic acid. Two hundred g. of 9-carbazolepropionitrile, prepared as described,[8] was mixed with 600 cc. of 95% ethanol and 300 cc. of 3*N* potassium hydroxide, and the solution was heated under reflux in a nitrogen atmosphere for 22 hr. The solution was concentrated until the temperature in the boiling flask reached 98°, diluted with 600 cc. of water, and filtered at 80°. Acidification of the filtrate with 3*N* hydrochloric acid gave a precipitate (241 g.), which was crystallized in 20-g. portions by solution in 500 cc. of benzene, distillation of 50 cc. of the solvent, hot filtration, concentration to 300 cc. and finally cooling to room temperature. After a second recrystallization, the colorless crystals melted at 173–174° (reported[7] m.p. 169–170°).

4-Oxo-5,6-dihydro-4H-pyrido[3,2,1-jk]carbazole (I). A pressure bomb was constructed from a piece of 3 in. o.d. copper pipe, 0.087 in. thick and $6\frac{1}{2}$ in. long, with a copper bottom welded in. The top of the bomb had an exterior threaded band. A Teflon O-ring was set in a groove at the top of the bomb, and a polished copper plate was tightly held against the Teflon ring by a threaded brass head. Ten g. of 9-carbazolepropionic acid and 200 g. of anhydrous hydrogen fluoride were placed in the bomb, and the head was closed tightly so that there was no visible leakage of hydrogen fluoride. The bomb was allowed to stand at room temperature for 48 hr., with occasional shaking, then it was cooled in an ice bath, the top was removed, and the hydrogen fluoride was evaporated rapidly in a stream of nitrogen, the last traces being removed by warming in a water bath. The contents of the bomb were washed out with 100 cc. of boric acid solution and 200 cc. of chloroform, followed by several additional small portions of chloroform. The washings were combined, the layers were separated, and the chloroform phase was washed with 500 cc., then 300 cc., of 0.5*N* sodium hydroxide, followed by 300 cc. of water. The combined aqueous solutions were washed with chloroform, which was added to the original chloroform solution. Acidification of the alkaline solution with acetic acid gave 2 g. of red solid, from which 1.5 g. of unreacted 9-carbazolepropionic acid was recovered on recrystallization. The chloroform solution was dried over sodium sulfate and evaporated to dryness, leaving a dark oil, which was dissolved in hot methanol, filtered, and cooled thoroughly, to give 4 g. (49% yield) of yellow crystals melting at 98–100° (reported[6] m.p. 98°), having an infrared peak at 5.92 μ (KBr pellet). Ultraviolet spectrum: λ_{max} 225 mμ (ϵ 64,700), 293 (14,300), 320 (6330), 289 (7970).

4-Oxo-4H-pyrido[3,2,1-jk]carbazole (II). A solution of 1 g. of 4-oxo-5,6-dihydro-4H-pyrido[3,2,1-*jk*]carbazole (I) in 10 cc. of *p*-cymene was boiled with 15 mg. of 5% palladium on charcoal for 3 hr., at the end of which time hydrogen evolution had stopped. The mixture was cooled to 50° and filtered, using ether to wash the catalyst. The filtrate was evaporated to dryness, and the residue was recrystallized from methanol, then sublimed, to give 480 mg. (49%) of pale yellow crystals, m.p. 177–178°. Ultraviolet spectrum: λ_{max} 217 mμ (ϵ 38,300), 234 (25,600), 254 (19,000), 290 (16,000), 375 (20,000).

Anal. Calcd. for $C_{15}H_9NO$: C, 82.2; H, 4.1; N, 6.4. Found: C, 82.2; H, 4.2; N, 6.3.

Aralkylidene derivatives (III) *of 4-oxo-5,6-dihydro-4H-pyrido[3,2,1-jk]carbazole* (I). One g. of I was dissolved in 50 cc. of refluxing absolute ethanol containing 0.3 cc. of piperidine, and 1 g. of the aldehyde was added. The solution was boiled in a nitrogen atmosphere for 4 hr., then allowed to stand overnight to complete crystallization. The product was recrystallized from a rather large volume of absolute ethanol and dried at 60°/1 mm. for several hours. In this manner the following were prepared:

4-Oxo-5-benzylidene-4,5-dihydro-4H-pyrido[3,2,1-jk]carbazole (IIIa), m.p. 150–151° (reported[6] 148°). Ultraviolet spectrum, 228 mμ (ϵ 47,600), 261 (16,600), 308 (13,300).

4-Oxo-5-p-diethylaminobenzylidene-4,5-dihydro-4H-pyrido-[3,2,1-jk]carbazole (IIIb), m.p. 185–186° (reported[6] m.p. 182°). Ultraviolet spectrum: λ_{max} 229 mμ (ϵ 27,200), 261 (9550), 293 (8750).

4-Oxo-5-furfurylidene-4,5-dihydro-4H-pyrido[3,2,1-jk]-carbazole (IIIc), m.p. 208–208.4°. Ultraviolet spectrum, λ_{max} 228 mμ (ϵ 21,200), 263 (8800), 346 (9350).

Anal. Calcd. for $C_{20}H_{13}NO_2$: C, 80.3; H, 4.4; N, 4.7. Found: C, 80.4; H, 4.6; N, 4.8.

Compounds IIIb and IIIc were also formed when 1 g. of sodium hydroxide dissolved in 10 cc. of 50% ethanol was

(12) All melting points are corrected, and those above 200° were taken in evacuated capillaries. Microanalyses were performed by the Microchemical Laboratory, University of California, Berkeley. Ultraviolet spectra were taken in methanol.

added to a solution of 1 g. of I and 1 g. of the aldehyde in 50 cc. of ethanol, and the resulting solution stirred at room temperature for 2 hr. The product precipitated during this time, and was removed by filtration and washed with ethanol. Under these reaction conditions, benzaldehyde formed the quinolone, isomerization being too rapid to permit isolation of IIIa.

Isomerization of aralkylidene derivatives IIIa,b,c. One hundred mg. of the arylidene derivative was heated under reflux with 20 cc. of a *N* solution of potassium hydroxide in absolute ethanol, for 10 min. As the more soluble quinolone was formed, all of the solid went into solution. Concentration to 10 cc. and cooling gave the crystalline product in quantitative yield. It was recrystallized several times from methanol and dried at 60°/1 mm. for several hours. By this procedure the following were prepared:

4-Oxo-5-benzyl-4H-pyrido[3,2,1-jk]carbazole (IVa), m.p. 214–215° (reported[6] m.p. 215°). Ultraviolet spectrum: λ_{max} 218 mμ (ε 44,500), 236 (25,800), 253 (20,100), 294 (20,900), 384 (18,900). This compound was also formed when benzaldehyde was stirred with I at room temperature, with sodium hydroxide as the catalyst, under the conditions reported above.

4-Oxo-5-p-diethylaminobenzyl-4H-pyrido[3,2,1-jk]carbazole (IVb), m.p. 114.5–115°, unchanged on further recrystallization (reported[6] m.p. 144°). Ultraviolet spectrum, λ_{max} 218 mμ (ε 38,400), 237 (25,000), 243 (23,500), 250 (25,300), 293 (20,900), 384 (15,000).

Anal. Calcd. for $C_{36}H_{24}N_2O$: C, 82.1; H, 6.3; N, 7.4. Found: C, 82.5; H, 6.6; N, 7.4.

4-Oxo-5-furfuryl-4H-pyrido[3,2,1-jk]carbazole (IVc), m.p. 156–156.4°. Ultraviolet spectrum, λ_{max} 213 mμ (ε 40,700), 237 (26,600), 251 (20,600), 294 (18,700), 383 (15,300).

Anal. Calcd. for $C_{20}H_{13}NO_2$: C, 80.3; H, 4.4; N, 4.7. Found: C, 79.7; H, 4.6; N, 4.7.

4-Oxo-5-p-dimethylaminophenylimino-5,6-dihydro-4H-pyrido[3,2,1-jk]carbazole (V). A solution of 0.3 g. of 4-oxo-5,6-dihydro[3,2,1-*jk*]carbazole (I) in 10 cc. of methanol containing 2 cc. of 10% sodium hydroxide solution (or 0.1 cc. of piperidine, or saturated with potassium carbonate) was boiled while a solution of 0.3 g. of *p*-dimethylaminonitrosobenzene in 10 cc. of methanol was added dropwise over 5 min. The solution was boiled for a few minutes longer, filtered, and allowed to cool. Very dark red needles formed, which were recrystallized three times from absolute ethanol and dried at 120°/5 mm., m.p. 180.5–181°. Ultraviolet spectrum: λ_{max} 225 mμ (ε 35,300), 294 (27,900).

Anal. Calcd. for $C_{23}H_{19}N_3O$: C, 78.2; H, 5.4; N, 11.9. Found: C, 78.4; H, 5.5; N, 12.1.

This compound was recovered unchanged when it was allowed to stand with alcoholic hydrochloric acid, or boiled with potassium hydroxide in ethanol, or boiled with potassium *t*-butoxide in *t*-butyl alcohol.

BERKELEY, CALIF.

[CONTRIBUTION FROM THE ENTOMOLOGY RESEARCH DIVISION, AGRICULTURAL RESEARCH SERVICE, U. S. DEPARTMENT OF AGRICULTURE]

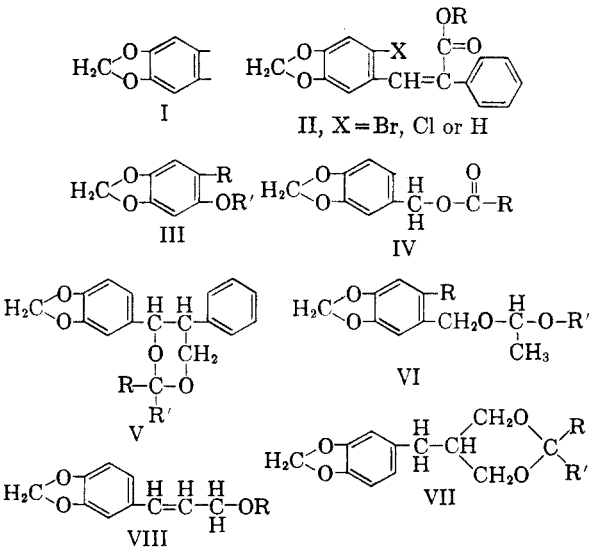
Syntheses of Compounds with the Methylenedioxyphenyl Group

S. I. GERTLER, B. H. ALEXANDER, AND M. BEROZA

Received September 22, 1958

Since the development of several insecticidal substances with the methylenedioxyphenyl group, a variety of new compounds embodying this group has been prepared for insecticidal study. The preparation of these compounds as well as their intermediates is described.

Since a number of compounds with the methylenedioxyphenyl structure I have shown insecticidal or synergistic (with pyrethrins) activity,[1] several other compounds containing this group were prepared for similar testing. Such compounds include types II and III that had not previously been described. The synthesis of the other new methylenedioxyphenyl compounds (IV–VIII) was also undertaken to determine the effect of lengthening the side chain or the inclusion of ring compounds (*m*-dioxanes) on insecticidal activity.



Most of the preparations proceeded smoothly and in good yields to give the expected products. The high yield of 6-nitrosesamol (III, R = NO_2, R′ = H) obtained from the hydrolysis of its acetate

(1) Yuh-Lin Chen and W. F. Barthel, U. S. Dept. Agr., ARS-33-23, 10 pp. (1956); E. K. Harvill, *Contrib. Boyce Thompson Inst.*, **10**, 143 (1939); M. E. Synerholm, U. S. Patent **2,458,656** (1949); Y. Inoue, Y. Katsuda, A. Nishimura, K. Kitagana, and M. Ohno, *Botyu-Kagaku*, **16**, 153 (1951); M. Beroza, *J. Agr. Food Chem.*, **4**, 49 (1956); M. Beroza and W. F. Barthel, *J. Agr. Food Chem.*, **5**, 855 (1957); H. L. Haller, F. B. LaForge, and W. N. Sullivan, *J. Econ. Entomol.*, **35**, 247 (1942); H. L. Haller, F. B. LaForge, and W. N. Sullivan, *J. Org. Chem.*, **7**, 185 (1942); P. G. Piquett, B. H. Alexander, and W. F. Barthel, *J. Econ. Entomol.*, **51**, 39 (1958).