The Preparation of 11-Aryl-11*H*-isoindolo[2,1-*a*]benzimidazol-11-ols

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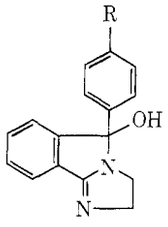
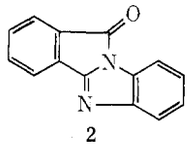
Received June 26, 1973

3-(*p*-Chlorophenyl)-3-methoxyphthalimidine was treated with Meerwein salt to yield the imino ether **4a**. Upon treatment with *o*-phenylenediamine **4a** rearranged to **5a**, which hydrolyzed to **5c** in the presence of hydrochloric acid. Compound **5c** was synthesized independently from **5e**, which was prepared from 2-(*p*-chlorobenzoyl)benzaldehyde and *o*-phenylenediamine.

The recent interest in the anorexic and antidepressant properties[1a-c] of 5-(*p*-chlorophenyl)-2,3-dihydro-5*H*-imidazo[2,1-*a*]isoindol-5-ol (**1a**) and the publication of a paper[2] describing the chemistry of the 5-phenyl analog **1b**[3] prompted us to prepare some 11-aryl-11*H*-isoindolo[2,1-*a*]benzimidazol-11-ols, the 2,3-benz analogs of **1**, for similar studies. The only reported method for preparing these compounds[4] consists in treating benzoylenebenzimidazole **2** with phenyl-



1a, R = Cl
b, R = H



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magnesium bromide. In our studies, we found this procedure to be erratic and unsatisfactory for general use. We therefore wish to report in this work a new method for preparing 11-aryl-11*H*-isoindolo[2,1-*a*]benzimidazol-11-ols.

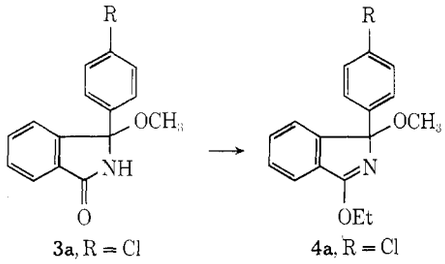
Earlier we had reported[5] the preparation of 1-(*p*-chlorophenyl)-3-ethoxy-1*H*-isoindole and its 1-phenyl analog. Continuing our efforts in this field, we now wish to report the preparation of 1-(*p*-chlorophenyl)-3-ethoxy-1-methoxy-1*H*-isoindole (**4a**) and its 1-phenyl analog **4b**, which served as our starting material.

Results

The reaction of the known[6] 3-aryl-3-methoxyphthalimidines **3a** and **3b** with triethyloxonium fluoroborate[7] and subsequent treatment with sodium carbonate resulted in the formation of the corresponding imino ethers **4a** and **4b** in 90 and 56% yield, respectively. From the reaction of **4a** with *o*-phenylenediamine in refluxing ethanol, 11-amino-11-(*p*-chlorophenyl)-11*H*-isoindolo[2,1-*a*]benzimidazole (**5a**) was isolated in 64% yield. The structural assignment for this compound is in agreement with the analytical data and supported by spectral information. The nmr spectrum of the compound has a broad signal at δ 2.75 ppm, integrating for two protons which readily exchanged with D_2O and therefore are assigned to a primary amino group. The compound dissolved readily in 2 *N* hydrochloric acid and after a few minutes a salt of the composition $C_{20}H_{13}ClN_2O \cdot HCl$ precipitated from the solution. Neutralization with base yielded a $C_{20}H_{13}ClN_2O$ compound that was assigned structure **5c** on the basis of the data given below.

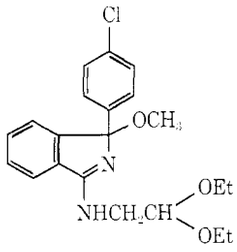
The same sequence of reactions, but starting with 3-ethoxy-1-methoxy-1-phenyl-1*H*-isoindole (**4b**), resulted in the isolation of a free base of the composition $C_{20}H_{14}N_2O$. The properties of this compound compared favorably with those of the known compound **5d**.[4]

To further establish the structure of **5c**, it was synthesized independently by treating 2-(*p*-chlorobenzoyl)-benzaldehyde with *o*-phenylenediamine to give the expected[8] 11-(*p*-chlorophenyl)-11*H*-isoindolo[2,1-*a*]-benzimidazole (**5e**). Oxidation to **5c** was achieved by



3a, R = Cl
b, R = H

4a, R = Cl
b, R = H



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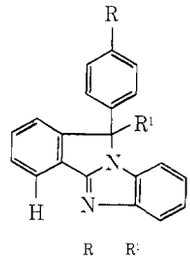


	R	R'
5a	Cl	NH_2
5b	H	NH_2
5c	Cl	OH
5d	H	OH
5e	Cl	H

(1) (a) J. H. Gogerty, W. J. Houlihan, M. Galen, P. Eden, and C. Penberthy, *Fed. Proc., Fed. Amer. Soc. Exp. Biol.*, **27**, 501 (1968); (b) E. A. DeFelice, S. Bronstein, and A. Cohen, *Curr. Res. Therap.*, **11**, 256 (1969); (c) J. H. Goberty and W. J. Houlihan, Abstracts of Papers, Joint Conference, Chemical Institute of Canada and the American Chemical Society, Toronto, Canada, May 24–29, 1970, No. MEDI-016.

(2) W. Metlesics, T. Anton, M. Chaykovsky, V. Toome, and L. H. Sternbach, *J. Org. Chem.*, **33**, 2874 (1968).

(3) This compound was found[2] to coexist in solution with the tautomeric form 2-(2-imidazolin-2-yl)benzophenone.

(4) J. Arient, L. Havlickova, and J. Knizek, *Collect. Czech. Chem. Commun.*, **31**, 4682 (1966).

(5) M. K. Eberle and W. J. Houlihan, *Tetrahedron Lett.*, 3167 (1970).

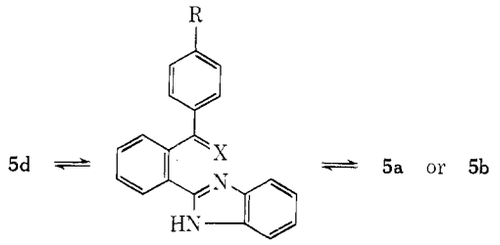
(6) W. Graf, E. Girod, E. Schmid, and W. G. Stoll, *Helv. Chim. Acta*, **42**, 1085 (1959).

(7) H. Meerwein, *Org. Syn.*, **46**, 113 (1966).

(8) A similar reaction has been reported by Metlesics, *et al.*, with ethylenediamine and 2-benzoylbenzaldehyde to give 5-phenyl-2,3-dihydro-5*H*-imidazo[2,1-*a*]isoindole; *cf.* ref 2.

treating **5e** with a stream of air in DMF in the presence of a catalytic amount of sodium hydride.[9] This product was found to be identical in every respect with the compound isolated from hydrolysis of **5a**.

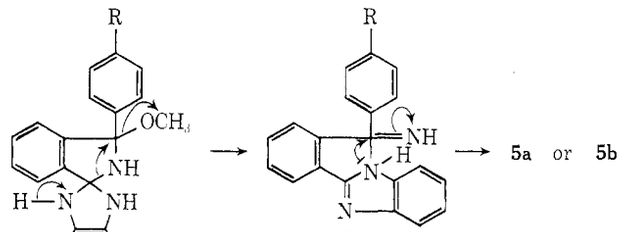
Arient and coworkers[4] have found that compound **5d** displayed an intensive carbonyl band, indicating that the substance exists partly or completely as the benzophenone tautomer **7a**. We have compared the ultraviolet and nmr spectra of amino analogs **5a** and **5b** with those of **5e**, a substance that can only exist in the cyclic form. The similarity of the spectra is in agreement with the cyclic forms **5a** and **5b** and indicates that little or none of the open tautomeric forms **7b** and **7c** are present.



7a, R = H; X = O
b, R = H; X = NH
c, R = Cl; X = NH

Discussion

We assume that the ethoxy group of compounds **4a** and **4b** is more reactive than the methoxy group toward nucleophiles and conclude that the incoming *o*-phenylenediamine replaces first the ethoxy group. Bond reorganization *via* the possible intermediates **8** and **9**



could lead to the products **5a** and **5b**. Support for the reactivity of the iminoethoxy group in **4a** was obtained when it was treated with aminoacetaldehyde diethyl acetal to give 1-(*p*-chlorophenyl)-3-(β-diethoxyethylamino)-1-methoxy-1*H*-isoindole (**6**) in 60% yield.

2-Benzoylbenzoic acid is reported to react with *o*-phenylenediamine to form 4b-phenyl-4b,5-dihydro-11*H*-isoindolo[2,1-*a*]benzimidazol-11-one.[10] Evidence[10,11] has been cited that the keto group of 2-benzoylbenzoic acid reacts with a diamine *via* a Schiff base to form an imidazolidine. Our compounds **4a** and **4b** may therefore be regarded as modifications of 2-benzoylbenzoic acid with a more reactive equivalent of the carboxy group relative to the equivalent of the keto group without change of the oxidation stage.

(9) P. Aeberli and W. J. Houlihan, *J. Org. Chem.*, **33**, 1640 (1968).
(10) P. Aeberli and W. J. Houlihan, *J. Org. Chem.*, **34**, 165 (1969).
(11) T. S. Sulkowski, M. A. Wille, A. Mascitti, and J. L. Diebold, *J. Org. Chem.*, **32**, 2180 (1967).

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting apparatus and have not been corrected. Proton magnetic resonance spectra were obtained on a Varian Associates A-60 spectrometer and are recorded in hertz of δ values (parts per million) relative to tetramethylsilane as internal standard. Infrared spectra were recorded on a Perkin-Elmer spectrophotometer, Model 457. Ultraviolet spectra were determined in 95% ethanol with a Cary recording spectrophotometer, Model 15. Thin layer chromatography (tlc) was carried out on glass plates coated with silica gel HF-254, E. Merck AG.

3-(*p*-Chlorophenyl)-3-methoxyphthalimidine (3a).—A solution of 182 g (0.7 mol) of 3-*p*-chlorophenyl-3-hydroxyphthalimidine in 700 ml of anhydrous methanol saturated with hydrogen chloride was stirred at room temperature for 1 hr. The resultant solid was filtered off to give 135 g (71%) of **3a**: mp 161–163° (CH_2Cl_2–hexane); ir (CH_2Cl_2) 3420 (NH), 1715 cm^{-1} (C=O); nmr ($CDCl_3$) δ 3.12 (3 H, s, OCH_3), 7.10–7.65 (8 H, m, arom + NH), 7.7–8.0 (1 H, C-7 H).

Anal. Calcd for $C_{15}H_{12}ClNO_2$: C, 65.8; H, 4.4; N, 5.1. Found: C, 65.7; H, 4.5; N, 5.4.

3-Methoxy-3-phenylphthalimidine (3b).—A mixture of 36 g (0.16 mol) of 3-phenyl-3-hydroxyphthalimidine and 200 ml of anhydrous methanol, saturated with hydrogen chloride, was stirred at room temperature for 45 min. The solvent was removed *in vacuo* and the residue was chromatographed on silica gel (eluent benzene) to give 10.5 g (27%) of **3b**: mp 139–140° (acetone–hexane); ir (CH_2Cl_2) 3430 (NH), 1715 cm^{-1} (C=O); nmr ($CDCl_3$) δ 3.12 (3 H, s, OCH_3), 7.10–7.75 (9 H, m, arom + NH), 7.75–8.00 (1 H, C-7 H).

Anal. Calcd for $C_{15}H_{13}NO_2$: C, 75.3; H, 5.5; O, 13.4. Found: C, 75.6; H, 5.9; O, 13.7.

1-(*p*-Chlorophenyl)-3-ethoxy-1-methoxy-1*H*-isoindole (4a).—A solution of 21.0 g (0.11 mol) of triethyloxonium fluoroborate and 30.0 g (0.11 mol) of **3a** in 100 ml of methylene chloride was stirred at room temperature for 15 hr under an atmosphere of nitrogen. The solution was poured into 100 ml of 2 *N* sodium carbonate solution and extracted with diethyl ether. The organic phase was separated, dried over anhydrous K_2CO_3, filtered, and evaporated to yield 30.0 g (90%) of liquid **4a**. Distillation in a Kugelrohr under high vacuum gave pure **4a**: tlc ($CHCl_3$); nmr ($CDCl_3$) δ 1.48 (3, t, J = 7.0 Hz, CH_2CH_3), 3.15 (3, s, OCH_3) 4.61 (2, q, J = 7.0 Hz, OCH_2CH_3), 7.1–7.6 (8, m, aromatic H); ir (film) 1625 cm^{-1} (C=N). *Anal.* Calcd for $C_{17}H_{16}ClNO_2$: C, 67.7; H, 5.3; N, 4.6. Found: C, 67.4; H, 5.5; N, 4.8.

3-Ethoxy-1-methoxy-1-phenyl-1*H*-isoindole (4b).—Following the procedure used to prepare **4a**, 10.5 g (0.055 mol) of triethyloxonium fluoroborate, 10.0 g (0.042 mol) of **3b**, and 50 ml of methylene chloride gave 6.3 g (56%) of liquid **4b**: nmr ($CDCl_3$) δ 1.48 (3, t, J = 7.0 Hz, CH_2CH_3), 3.16 (3, s, OCH_3), 4.61 (2, q, J = 7.0 Hz, OCH_2CH_3), 7.1–7.7 (9, m, aromatic H).

11-Amino-11-(*p*-chlorophenyl)-11*H*-isoindolo[2,1-*a*]benzimidazole (5a).—A solution of 9.1 g (0.03 mol) of **4a** and 2.8 g (0.026 mol) of *o*-phenylenediamine in 50 ml of absolute ethanol was refluxed for 15 hr under an atmosphere of nitrogen. The solvent was evaporated under reduced pressure and the residue was crystallized from benzene–hexane to give 5.5 g (64%) of **5a**: mp 200–202°; nmr ($CDCl_3$–DMSO-d_6) δ 2.75 (2, broad, D_2O exchangeable, NH_2), 6.9–7.8 (11, m, aromatic H), 7.8–8.1 (1, m, aromatic H); ir (CH_2Cl_2) 3340, 3400 (NH_2), 1625 cm^{-1} (C=N); uv τ_{max} 222 nm (ε 32,800), 295 infl (14,250), 309 (18,100) 321 (13,600). *Anal.* Calcd for $C_{20}H_{14}ClN_3$: C, 72.4; H, 4.3; Cl, 10.7; N, 12.7. Found: C, 72.0; H, 4.6; Cl, 10.9; N, 12.8.

11-Amino-11-phenyl-11*H*-isoindolo[2,1-*a*]benzimidazole (5b).—In a similar manner as described above, there was obtained from 5.0 g (0.019 mol) of **4b** and 2.3 g (0.021 mol) of *o*-phenylenediamine in 30 ml of ethanol 2.4 g of **5b**, mp 193–195° (benzene–hexane). Chromatography of the filtrate on silica gel gave an additional 0.61 g of **5b** and 1.4 g of starting material: total yield 3.01 g (75% based on recovered starting material); nmr ($CDCl_3$) δ 2.58 (2, broad, D_2O exchangeable, NH_2), 6.8–7.7 (11, m, aromatic), 7.7–8.1 (2, m, aromatic); uv 295 nm infl (ε 14,290), 309 (18,500), 321 (13,990). *Anal.* Calcd for $C_{20}H_{15}N_3$: C, 80.8; H, 5.1. Found: C, 80.5; H, 5.3.

11-(*p*-Chlorophenyl)-11*H*-isoindolo[2,1-*a*]benzimidazol-11-ol (5c). A. From Hydrolysis of 5a.—A solution of 0.40 g of **5a** in 10 ml of 2 *N* hydrochloric acid was allowed to stand at room temperature for 1.5 hr. The resulting solid was filtered off to give 0.17 g (38%) of **5c** HCl, mp 244–245° (from ethanol–water,

four times). *Anal.* Calcd for $C_{20}H_{13}ClN_2O \cdot HCl$: C, 64.9; H, 4.1; Cl, 19.2; N, 7.6. Found: C, 64.7; H, 4.0; Cl, 19.0; N, 7.8.

Treatment of 0.090 g of **5c** HCl in ethanol with 2 *N* NaOH gave 0.055 g (68%) of **5c**: mp 222–223° (from ethanol–water); ir (Nujol) 3060 (OH), 1660 cm^{-1} (C=N or C=O); uv λ_{max} 248 nm (ϵ 18,700) 261 (19,690), 305 infl (12,160). *Anal.* Calcd for $C_{20}H_{13}ClN_2O$: C, 72.2; H, 3.9; Cl, 10.7; N, 8.4. Found: C, 71.9; H, 4.1; Cl, 11.0; N, 8.4.

B. From Oxidation of 5e.—A solution of 0.30 g (0.0095 mol) of **5e** in 10 ml of anhydrous DMF was added to 0.06 g (0.0025 mol) of sodium hydride and stirred at room temperature. The resultant red solution was treated with a stream of dry air until the color had disappeared. The solution was poured on ice water to give 0.21 g (67%) of **5c**: mp 222–224° (ethanol–water); nmr, uv, and ir identical with spectra obtained from **5c** from **5a**; mmp 224–225°.

11-Phenyl-11*H*-isoindolo[2,1-*a*]benzimidazol-11-ol (5d).—A solution of 0.5 g of **5b** in 10 ml of 2 *N* hydrochloric acid was allowed to stand at room temperature for 1.5 hr. The resultant solid was filtered off to give 0.4 g (71%) of **5d** HCl, mp 288–290°. *Anal.* Calcd for $C_{20}H_{14}N_2O \cdot HCl$: C, 71.7; H, 4.5; Cl, 10.6. Found: C, 72.1; H, 4.7; Cl, 10.3.

Treatment of a solution of 0.1 g of **5d** HCl in ethanol with 2 *N* NaOH gave 0.070 g (79%) of **5d**: mp 223–225° (ethanol–water) (lit.[3] mp 220–221°); ir (Nujol) 3060 (OH), 1655 cm^{-1} (C=N); uv λ_{max} 242 nm (ϵ 19,240), 291 (12,300), 305 infl (11,420). *Anal.* Calcd for $C_{20}H_{14}N_2O$: C, 80.5; H, 4.7; N, 9.4. Found: C, 80.9; H, 4.8; N, 9.7.

11-(*p*-Chlorophenyl)-11*H*-isoindolo[2,1-*a*]benzimidazole (5e).—To a stirred suspension of 2.16 g (0.02 mol) of *o*-phenylenediamine in 50 ml of water, sufficient concentrated hydrochloric acid was added to obtain a clear solution. To this a solution of 4.89 g (0.02 mol) of 2-(*p*-chlorobenzoyl)benzaldehyde[12] (mp 108–110°) in 100 ml of acetic acid was added. The resulting solution was held at 80° for 15 min and then concentrated under reduced pressure. The residue was treated first with ethanol followed by ether to give 4.3 g (61%) of **5e** HCl, mp 268–271° (ethanol–ether). Treatment of 1.0 g of **5e** HCl with 2 *N* NaOH gave 0.80 g (89%) of **5e**: mp 207–208° (from ethanol–water); nmr ($CDCl_3$) δ 6.07 (1, s, C_{11} H), 6.8–8.2 (12, m, aromatic); ir (CH_2Cl_2) 1622 cm^{-1} (C=N); uv λ_{max} 222 nm (ϵ 33,420), 242 (14,820), 251 (9660), 306 (22,300), 319 (18,170). *Anal.* Calcd for $C_{20}H_{13}ClN_2$: C, 75.8; H, 4.1; N, 8.8. Found: C, 75.8; H, 4.3; N, 8.8.

1-(*p*-Chlorophenyl)-3-(β-diethoxyethylamino)-1-methoxy-1*H*-isoindole (6).—A mixture of 7.1 g (0.023 mol) of **4a** and 11 g (0.053 mol) of aminoacetaldehyde diethyl acetal was refluxed in 250 ml of absolute ethanol for 4 hr under an atmosphere of nitrogen. The solvent was evaporated under reduced pressure to yield 5.5 g (60%) of **6**: mp 113–114° (ether–pentane); nmr ($CDCl_3$) δ 1.18 (3, t, J = 7 Hz, CH_2CH_3), 1.23 (3, t, J = 7 Hz, CH_2CH_3), 3.10 (3, s, OCH_3), 3.40–4.0 (6, m, 2 CH_2CH_3, NCH_2), 4.79 (1, t, J = 5 Hz, –CHO), 5.4 (1, broad, NH), 7.1–7.6 (8, m, aromatic); ir (CH_2Cl_2) 3440 (NH), 1672 (weak), 1640 cm^{-1}; uv λ_{max} 227 nm (ϵ 24,200). *Anal.* Calcd for $C_{21}H_{23}ClN_2O_3$: C, 64.9; H, 6.5; N, 7.2. Found: C, 65.2; H, 6.8; N, 7.2.

Acknowledgment.—We would like to thank Dr. S. Barcza and his staff for recording the spectra.

Registry No.—**3a**, 730-77-8; **3b**, 28489-08-9; **4a**, 41581-41-3; **4b**, 41581-42-4; **5a**, 41581-43-5; **5b**, 41581-44-6; **5c**, 41581-45-7; **5c** HCl, 41581-46-8; **5d**, 41581-47-9; **5d** HCl, 41581-48-0; **5e**, 41581-49-1; **5e** HCl, 41581-50-4; **6**, 41581-51-5; **7a**, 14539-29-8; **7a** HCl, 41581-53-7; 3-*p*-chlorophenyl-3-hydroxyphthalimidine, 956-92-3; 3-phenyl-3-hydroxyphthalimidine, 6637-53-2; 2-(*p*-chlorobenzoyl)benzaldehyde, 23864-94-0.

(12) Prepared in analogy to the known 2-benzoylbenzaldehyde; *cf.* ref 2.

The Synthesis of the 3a,8a-Dihydrofuro[2,3-*b*]benzofuran-2(3*H*)-one and 1,3,3a,8a-Tetrahydro-2*H*-benzofuro[2,3-*b*]pyrrol-2-one Ring Systems from 4-Formylcoumarin *via* Acyllactone and Iminelactone Rearrangements

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Received April 10, 1973

Syntheses of 3a,8a-dihydrofuro[2,3-*b*]benzofuran-2(3*H*)-ones and 1,3,3a,8a-tetrahydro-2*H*-benzofuro[2,3-*b*]-pyrrol-2-ones by acyllactone and iminelactone rearrangements, respectively, are described.

The rearrangement of α-acyllactones is a well-known synthetic method which has received considerable attention over the past few years for the synthesis of various heterocyclic systems.[1,2] In contrast, there are only two examples of the rearrangement of β-acyl-δ-lactones. Lawson[3] rearranged 4-acetyl-3,4-dihydrocoumarin to 2-methylbenzofuran-3-acetic acid with 3 *N* hydrochloric acid, and Buchi[4] rearranged 4-formyl-5-benzyloxy-7-methoxycoumarin to 4-benzyloxy-6-methoxy-2-oxo-2,3,3a,8a-tetrahydrofuro[2,3-*b*]benzofuran. The difficulties in synthesizing β-acyl-δ-lactones are the probable[3,5] reason for this disparity.

Our earlier work[6] resulted in the first general synthesis of 4-formylcoumarins and made them readily available starting materials to investigate the scope of the rearrangement. The 4-formylcoumarins (**1** and **3** Scheme I) were reduced and rearranged with zinc in acetic acid at 100° to give the expected products (**2** and **4**, respectively). The products are readily converted to benzofuran-3-acetic acids[7] and could also serve as potential intermediates for the synthesis of certain indole alkaloids. Benzofuran derivatives were not detected as by-products from the rearrangement, indicating the ease of formation of the five-membered lactone ring under the reaction conditions.

We were particularly interested in extending the rearrangement to molecules in which the C=O bond of the aldehyde is replaced by C=N. Thus, we subjected imines **5a** and **5b**, oximes **7** and **14**, phenylhydrazone (**16**), and 4-formylcoumarin semicarbazone to the rearrangement conditions.

The imines **5a** and **5b** (Scheme II) were reduced and rearranged to give the pyrrolones **6a** and **6b**, respectively. To our knowledge this constitutes the first case

(1) F. Korte and K. H. Buchel in "Newer Methods of Preparative Organic Chemistry," Vol. III, Academic Press, New York, N. Y., 1964, p 199.
(2) H. Wamhoff and F. Korte, *Synthesis*, **4**, 151 (1972).
(3) A. Lawson, *J. Chem. Soc.*, 144 (1957).
(4) G. Buchi, D. M. Foulkes, M. Kurono, G. F. Mitchell, and R. S. Schneider, *J. Amer. Chem. Soc.*, **89**, 6745 (1967).
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(6) M. von Strandtmann, D. T. Connor, and J. Shavel, Jr., *J. Heterocycl. Chem.*, **9**, 175 (1972).
(7) D. T. Connor and M. von Strandtmann, unpublished work.