the solution was filtered. The zinc was washed once more with 50 ml of hot water and the extracts were combined. Finally, the zinc was washed with two 75-ml portions of warm methylene chloride and these washings were used to extract the combined aqueous filtrates. The combined methylene chloride extracts were rinsed twice with 50 ml of dilute sodium bicarbonate and dried over anhydrous sodium sulfate. Removal of the solvent by evaporation left 0.308 g (33%) of 2-pyrone-3,5-d_2 which was further purified by molecular distillation. The nmr spectrum of the pyrone contains two equal area doublets centered at δ 7.47 and 7.62, both split by 2.4 Hz. Mass spectral analysis showed the product to be 79% doubly deuterated, 20% singly deuterated, and about 1% unlabeled.

3,5-Dibromo-6-fluoro-5,6-dihydro-2-pyrone (13).—Dry nitrogen was bubbled through a solution of 0.927 g of silver fluoroborate in 30 ml of ethylene dichloride while a solution of 1.58 g of 3,5,6-tribromo-5,6-dihydro-2-pyrone (12) in 5 ml of ethylene dichloride was added dropwise. After *ca.* 15 min, evolution of boron trifluoride fumes subsided and the reaction mixture was filtered; the remaining silver bromide was washed with 10 ml of ethylene dichloride. Removal of the solvent from the combined filtrates left 0.946 g of oil which crystallized on standing. After a single recrystallization from carbon tetrachloride, the white crystalline 13 melted at 75–76°. The infrared spectrum (chloroform) of 13 has broad carbonyl absorption at 1745–1775 cm^{-1}. The pmr spectrum is composed of three equal area multiplets centered at δ 4.73, 6.25 (split by 51.0 Hz), and 7.37. The fluorine nmr spectrum shows a quartet centered at 113 ppm upfield of internal fluorotrichloromethane.

Anal. Calcd for $C_5H_3Br_2FO_2$: C, 21.91; H, 1.10. Found: C, 22.21; H, 1.33.

3,4,5,6-Tetrachloro-3,4,5,6-tetrahydro-2-pyrone (15).—While irradiating with a GE 275-W sun lamp, chlorine was slowly bubbled into a solution of 1.979 g of 2-pyrone (0.0207 mol) in 100 ml of methylene chloride which was cooled to −78° in a Dry Ice–acetone bath. After *ca.* 1 hr, the reaction was allowed to warm to −35°, since condensed chlorine was increasing the solution volume. After 1.5 hr at −35°, the solvent and excess chlorine were evaporated to leave *ca.* 5 g of a clear oil ($n^{23}D$ 1.5212) having no noticeable odor of chlorine or hydrogen chloride. The nmr spectrum of the compound is composed of a multiplet at δ 4.4–5.15 (3 H) and a doublet centered at 4.33 (1 H).

Anal. Calcd for $C_5H_4Cl_4O_2$: C, 25.21; H, 1.68. Found: C, 25.20; H, 1.72.

3,5-Dichloro-2-pyrone.—To a solution of 1.776 g of tetrachloride 15 in ether was added dropwise 2 ml of triethylamine in 5 ml of ether. After 5 min, the solution was filtered and the filtrate stripped of solvent, leaving 0.948 g of discolored solid. Chromatography of this product on silica gel resulted in the isolation of 0.735 g of crystalline 3,5-dichloro-2-pyrone melting at 67–70°. After a single sublimation (50°, 0.05 Torr) the melting point was raised to 72.5–73.5° (lit.[24] mp 71–73°).

Registry No.—**1**, 504-31-4; **4**, 19978-32-6; **5**, 19988-79-5; **6**, 19978-33-7; **7**, 19988-77-3; **9**, 19988-78-4; **10**, 19988-73-9; **11**, 19978-41-7; **12**, 19988-74-0; **13**, 19988-75-1; **15**, 19988-76-2.

(24) A. Roedig and G. Markl, *Ann.*, **631**, 1 (1960).

The Synthesis of 9,13b-Dihydroisoindolo[2,1-*d*][1,4]benzodiazepin-6-one

GOETZ E. HARDTMANN AND HANS OTT

Chemistry Research Department, Sandoz Pharmaceuticals, Hanover, New Jersey 07936

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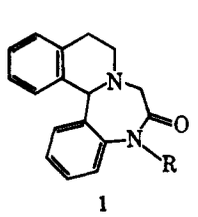
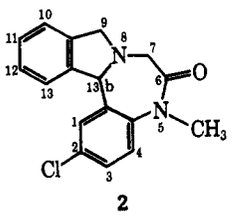
Two independent syntheses for the new isoindolo[2,1-*d*][1,4]benzodiazepine ring system are described. In one approach 2′-bromomethyl-5-chloro-2-nitrobenzophenone is allowed to react with glycine ethyl ester and the reaction product is reduced with zinc in acetic acid yielding 2-chloro-9,13b-dihydro-5H-isoindolo[2,1-*d*][1,4]-benzodiazepin-6(7H)-one. The second approach begins with 3-(5-chloro-2-methylaminophenyl)isoindolin-1-one, which on electrolytic reduction followed by alkylation with ethyl bromoacetate and cyclization on heating in acetic acid gives rise to 2-chloro-5-methyl-9,13b-dihydro-5H-isoindolo[2,1-*d*][1,4]benzodiazepin-6(7H)-one. The syntheses of the respective starting materials are reported. The electrolytic reduction in deuterated solvents is also described.

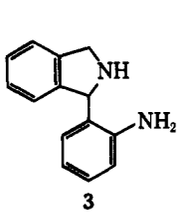
In an earlier publication[1] we reported on the synthesis and the pharmacological activities of tetracyclic benzodiazepines of type **1**. We now[2] wish to report the synthesis of the isoindoline analog **2**, a previously unreported ring system.



1



2



3

In this instance a similar synthetic sequence to that used for the synthesis of **1** would require an N-unsubstituted 1-(*o*-aminophenyl)isoindoline, *e.g.*, **3**, as an intermediate since N alkylation on the isoindoline of this with ethyl bromoacetate and subsequent cyclization would lead to the desired system. Although the synthesis of 1-phenylisoindolines has been described by Veber and Lwowski,[3] we considered **3** not readily available by their reaction sequence. We therefore initially decided to develop a synthesis of **2** not involving the intermediate **3**. This synthesis is outlined in Scheme I.

The structure assigned to **8** is supported by its ir spectrum which showed a strong carbonyl peak at 1740 cm^{-1} and lacked NH or OH absorptions. The nmr spectrum of the crude material was also as expected, showing aromatic and O-ethyl protons as well as an AB quartet for the NCH_2CO protons centered at δ 4.78 (J_{AB} = 16 Hz).

Since larger quantities of **2** were required a second, more economical, sequence was developed as outlined in Scheme II.

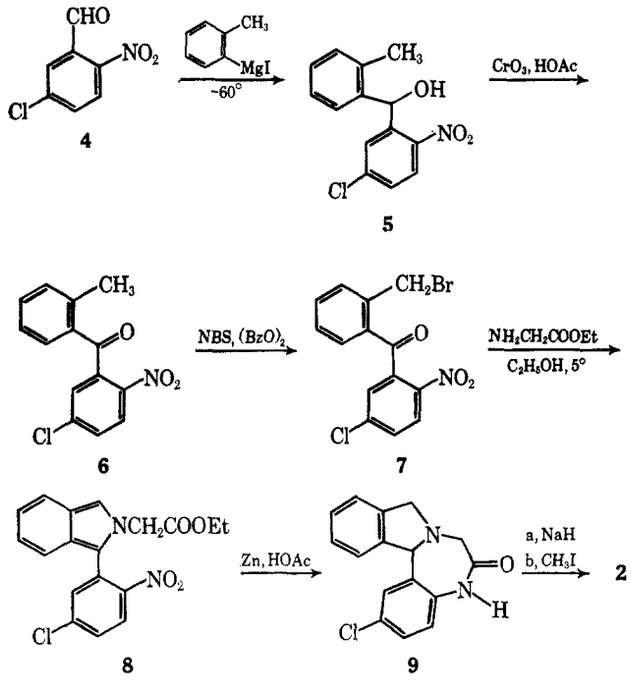
The physical characteristics of the intermediate **13** are in accordance with the structure shown rather than with the corresponding benzophenone imine tautomer (no C=N absorption in ir spectrum). Compound **13**

(1) H. Ott, G. E. Hardtmann, M. Denzer, A. J. Frey, J. H. Gogerty, G. H. Leslie, and J. Trapold, *J. Med. Chem.*, **11**, 777 (1968).

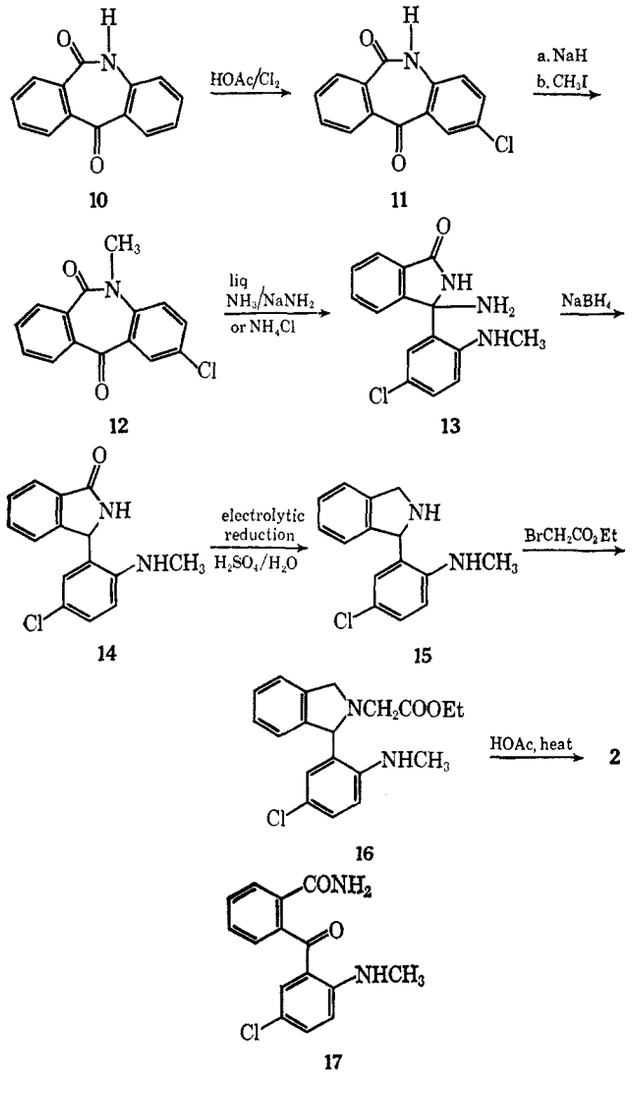
(2) Part of the work described in this paper was published in U. S. Patent 3,375,246 (1968) (to G. E. Hardtmann and H. Ott).

(3) D. F. Veber and W. Lwowski, *J. Amer. Chem. Soc.*, **85**, 646 (1963).

SCHEME I



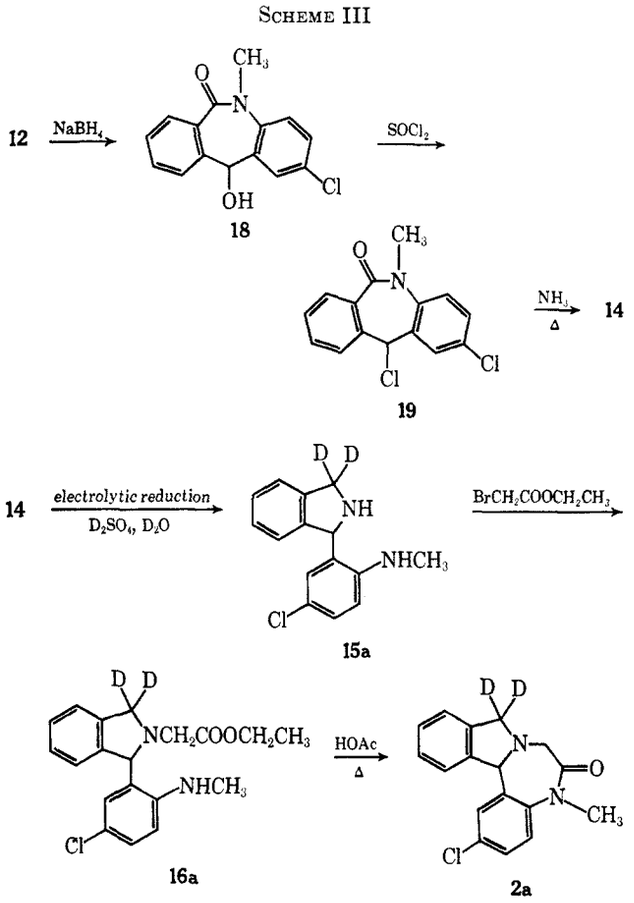
SCHEME II



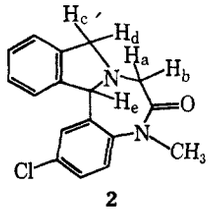
could be reduced to the phthalimidine **14** or could be hydrolyzed to **17**. The phthalimidine **14** was also obtained by the route illustrated in Scheme III. Attempts to reduce **14** with lithium aluminum hydride under various conditions failed. Forcing conditions gave an inseparable mixture while both diisobutylaluminum hydride and diborane reacted only sluggishly with **14**. No isoindoline **15** could be isolated.

It has been reported, however, that phthalimidine can be reduced electrolytically.[4] In this instance, using an apparatus based on that of Coleman and Johnson[5] and aqueous sulfuric acid as the solvent, reduction of **14** was achieved in 50–80% yield. The reduction was also performed in deuterated solvents yielding the dideuterio compound **15a**.

SCHEME III



Compound **2**, prepared by the route shown in Scheme II, was identical in all respects with the material obtained previously. The dideuterated compound **2a** was also prepared.



(4) (a) E. W. Cook and W. G. France, *J. Phys. Chem.*, **36**, 2497 (1932); (b) A. Dunet, R. Ratouis, P. Cadiot, and A. Willemart, *Bull. Soc. Chim. Fr.*, 906 (1956).

(5) G. H. Coleman and H. L. Johnson in "Organic Syntheses," Coll. Vol. III, John Wiley & Sons, Inc., New York, N. Y., 1955, p 60.

The nmr spectrum of **2** is worth mentioning. The N-methyl group appears as a broad singlet (half width = 6 Hz) at δ 3.32 which sharpens considerably when the sample is measured either at a higher temperature (45°) or in pyridine.

The protons H_a and H_b are found as a broadened quartet (δ 3.31) and the protons H_c and H_d appear as a multiplet at δ 4.0. This interesting complexity of the H_c,H_d resonance may be due to homoallylic coupling[6] (J = 1.5 Hz) between H_e and either or both of H_c and H_d, and is analogous to that observed in 3,4-dehydroproline derivatives[7] where the long-range coupling can be as high as 6.6 Hz. In our case the coupling assignment is confirmed by either spin–spin decoupling or measuring the dideuterated compound; in both instances H_e is shown as a singlet. No couplings between H_e and H_a or H_b were observed.

Experimental Section

The nmr spectra were obtained on a Varian A-60 spectrometer, the ir spectra (in $CHCl_3$) using a Perkin-Elmer Model 237, and the mass spectra on a LKB 9000. Melting points were determined with a Hoover melting point apparatus and are uncorrected.

Electrodes for the electrolytical reductions consisted of 99.9% lead sheet, 2.5 mm thick. The anode was separated from the rest of the reaction vessel by a Coors 700 porous cup. An automobile battery served as the power source for the electrolysis.

5-Chloro-2′-methyl-2-nitrobenzhydrol (5).—A Grignard solution prepared from magnesium (2.6 g) and *o*-iodotoluene (24 g) in diethyl ether (100 ml) was added at −65° to a solution of 5-chloro-2-nitrobenzaldehyde (15 g) in toluene (250 ml). The mixture was stirred for 3 hr at −60 to −68°, then brought up to −10°, and 20 ml of saturated ammonium chloride solution was added. After the reaction mixture was allowed to warm to room temperature, water and dilute hydrochloric acid were added. The organic phase was separated and the aqueous phase was extracted with ether. The combined extract was dried (Na_2SO_4) and the solvent was evaporated, yielding 12 g of **5** (54%). A sample was recrystallized from ether: mp 129–131°.

Anal. Calcd for $C_{14}H_{12}NO_3Cl$: O, 17.3; Cl, 12.8. Found: O, 17.0; Cl, 12.7.

5-Chloro-2′-methyl-2-nitrobenzophenone (6).—This material was prepared from **5** as described for 2-nitrobenzophenone.[8] From 95 g of **5**, 82 g (90%) of 5-chloro-2′-methyl-2-nitrobenzophenone were obtained. A sample was sublimed at 110° (0.1 mm) and melted at 115–116°.

Anal. Calcd for $C_{14}H_{10}NO_3Cl$: C, 61.0; H, 3.7; N, 5.1; O, 17.4; Cl, 12.9. Found: C, 61.0; H, 3.9; N, 5.1; O, 17.2; Cl, 12.9.

2′-Bromomethyl-5-chloro-2-nitrobenzophenone (7).—The benzophenone **6** (65 g) was dissolved in anhydrous carbon tetrachloride (1500 ml) and a mixture of N-bromo succinimide (45 g) and dibenzoyl peroxide (1.5 g) was added in 5-g portions over a 20-min period. The mixture was heated under reflux for 4 hr, cooled, extracted with water, and evaporated. The crude crystalline product was washed with ethanol and then recrystallized from methylene chloride–ether: mp 137–139°. The yield varied from 45 to 65% depending on the quality of the brominating agent.

Anal. Calcd for $C_{14}H_9BrClNO_3$: Br, 22.5; Cl, 10.0. Found: Br, 22.9; Cl, 9.8.

2-Chloro-9,13b-dihydro-5H-isoindolo[2,1-*d*][1,4]benzodiazepin-6(7H)-one (9).—A solution of **7** (26.5 g) and glycine ethyl ester (17 g) in a mixture of ethanol (5 l.) and chloroform (400 ml) was stirred at 5° for 30 hr. The solution was concentrated *in vacuo* to about 200 ml after which some starting material, **7** (8 g), could be removed by filtration. The mother liquor was evaporated to dryness *in vacuo*. The residue, dissolved in glacial acetic acid (800 ml), was cooled to 10° and zinc dust (40 g) added in small portions. The mixture was stirred for 3 hr at room temperature and filtered, and the filtrate was evaporated *in vacuo*. The residue was dissolved in methylene chloride and washed twice with sodium carbonate solution and then with water. After drying (Na_2SO_4) the solution was concentrated and the crystalline product which formed was removed by filtration and recrystallized from ethanol to give **9**, 5.9 g (40%), mp 258–262°.

Anal. Calcd for $C_{15}H_{13}ClN_2O$: C, 67.4; H, 4.6; N, 9.8; O, 5.6. Found: C, 67.2; H, 4.8; N, 9.8; O, 5.8.

2-Chloromorphanthridine-6,11(5H)-dione (11).—Morphanthridine-6,11(5H)-dione[9] (100 g) was dissolved in hot glacial acetic acid (2000 ml), a few iodine crystals were added, and a stream of chlorine was introduced into the hot solution (maintained at about 100°). The addition of chlorine was continued until a stiff, porridgelike reaction mixture resulted. After cooling the crystalline product was filtered, washed successively with water, ethanol, and ether, and finally dried under high vacuum. The yields varied between 65 and 85%. Compound **11** melted at 295–298° (lit.[10] mp 293°).

2-Chloro-5-methylmorphanthridine-6,11(5H)-dione (12).—A solution of 2-chloromorphanthridine-6,11(5H)-dione (50 g) in anhydrous dimethylformamide (500 ml) was mixed with a sodium methoxide solution prepared from sodium (5.5 g) and methanol (50 ml). The mixture was evaporated to 125 ml (aspirator) to remove the methanol and warmed to 40°. Methyl iodide (75 ml) was added and the mixture was shaken at room temperature for 1 hr, after which it was poured into water (800 ml) and stirred for an additional hour. The crystals which formed were filtered off, washed with water, and dried to give 35 g (66%) of **12**. After recrystallization from ethanol the product melted at 147–152°. An analytical sample was sublimed at 120° (0.1 mm).

Anal. Calcd for $C_{15}H_{10}ClNO_2$: C, 66.3; H, 3.7; Cl, 13.0; O, 11.8. Found: C, 66.6; H, 3.9; Cl, 13.0; O, 11.5.

3-(5-Chloro-2-methylaminophenyl)isoindolin-1-one (14). Procedure A.—To anhydrous ammonia[11] (150 ml) in a cooled steel vessel, sodium (1 g) was added. After the sodium had all reacted 2-chloro-5-methylmorphanthridine-6,11(5H)-dione (**12**, 22 g) was added and the sealed vessel was heated for 16 hr at 120° (bath temperature). The container was cooled, the ammonia was evaporated, and the crude crystalline product was dissolved in 95% ethanol (400 ml), treated with sodium borohydride (10 g), and heated at reflux temperature for 4 hr. After cooling the excess of sodium borohydride was destroyed with 2 *N* hydrochloric acid (pH 2–3) and the ethanol was evaporated *in vacuo*. The residue was treated with sodium hydroxide (pH 8–9) and extracted several times with ethyl acetate.[12] The crude product was recrystallized from ethanol–chloroform to yield **14** (16 g, 73%): mp 220–226° (recrystallization from chloroform raised the melting point to 229–230°); ir (KBr) 1600, 1610 (C=C), 1700 (amide), 3415, 3200 cm^{-1} (NH).

Anal. Calcd for $C_{15}H_{13}ClN_2O$: C, 66.1; H, 4.8; Cl, 13.0; N, 10.2; O, 5.9. Found: C, 66.2; H, 5.0; Cl, 13.3; N, 9.9; O, 5.9.

3-Amino-3-(5-chloro-2-methylaminophenyl)isoindolin-1-one (13).—The morphanthridine-6,11-dione **12** (9 g) was added to anhydrous liquid ammonia (80 ml) in small portions. Ammonium chloride (1 g) was introduced and the mixture was heated in a steel cylinder (Parr, No. 4721) at 110° for 16 hr. The cylinder was cooled to room temperature, the ammonia was evaporated, and the residue was dissolved in chloroform (250 ml). The chloroform phase was washed twice with 1% acetic acid, dried (Na_2SO_4), and evaporated *in vacuo*. The remaining brownish product was crystallized from acetone yielding **13** (7.5 g, 80%): mp 183–186°; ir ($CHCl_3$) 1600 (C=C), 1700 (amide), 3295 (NH), 3400 cm^{-1} (broad NH).

Anal. Calcd for $C_{15}H_{14}ClN_3O$: C, 62.6; H, 4.9; N, 14.6; O, 5.6. Found: C, 62.6; H, 5.1; N, 14.6; O, 5.9.

1-(5-Chloro-2-methylaminophenyl)isoindoline (15).—A solution of 3-(5-chloro-2-methylaminophenyl)isoindolin-1-one (**14**, 28.5 g)

(6) S. Sternhell, *Rev. Pure Appl. Chem.*, **14**, 15 (1964).
(7) W. R. J. Simpson, Ph.D. Thesis, University of Sydney, 1966.
(8) D. H. Hey and R. D. Mulley, *J. Chem. Soc.*, 2276 (1952).
(9) L. H. Werner, S. Ricca, E. Mohacsi, A. Rossi, and V. P. Arya, *J. Med. Chem.*, **8**, 74 (1965).
(10) (a) A. Wolfram and E. Hausdoerfer, German Patent 551, 256 (1928); *Chem. Abstr.*, **26**, 4344 (1928). (b) A. Drukker and C. I. Judd, *J. Heterocycl. Chem.*, **2**, 276 (1965).
(11) R. W. Chambers and F. H. Carpenter, *J. Amer. Chem. Soc.*, **77**, 1527 (1955).
(12) The product is poorly soluble and on some occasions precipitated in the separatory funnel.

in 65% sulfuric acid (180 ml) was placed into the cathode chamber of the electrolysis apparatus.[10] Water was added (about 150 ml) until the substance just started to precipitate. In the center of the cathode chamber a porous cup (75-mm diameter, Coors porcelain, unglazed) was inserted which was filled with 65% sulfuric acid. The cathode (approximately 180-cm² surface) was inserted into the cathode chamber and the anode of the same size into the porous cup. The mixture was stirred and electrolyzed (6-V automobile battery) with external cooling, keeping the temperature in the cathode chamber between 16 and 22° (to avoid formation of polymers). After 6 hr a fresh battery was connected and the reaction was run an additional 10 hr. The solution in the anode chamber had to be brought back to its original volume by occasional addition of water. While the reaction proceeded samples were removed from time to time and worked up. The reaction was stopped when the carbonyl absorption in the ir spectrum had disappeared. The crude reaction mixture was diluted with twice its volume of ice water, filtered, and neutralized with 50% sodium hydroxide (cooling). The crystalline precipitate which formed was removed by filtration. After drying, the crude product was treated with methylene chloride, the insoluble material was filtered off, and the filtrate was twice extracted with water. The solution was dried (Na_2SO_4), the solvent was evaporated, and the residue was recrystallized from ethanol yielding 19.5 g (72%) of **15**, mp 133–136°.

Anal. Calcd for $C_{15}H_{15}ClN_2$: C, 69.6; H, 5.8; Cl, 13.7; N, 10.8. Found: C, 69.7; H, 6.1; Cl, 13.5; N, 10.8.

2-Chloro-5-methyl-9,13b-dihydro-5H-isoindolo[2,1-*d*][1,4]-benzodiazepin-6(7H)-one (2). Method A.—A hot solution of **9** (7 g) in dimethylformamide (300 ml) was cooled to 60° and sodium hydride (1.32 g, 56% in mineral oil) was added. After the solution was stirred for 30 min, a clear solution was obtained and then methyl iodide (4 g) in dimethylformamide (50 ml) was added dropwise over a period of 30 min. The mixture was heated at 55° for 1 hr followed by evaporation of the solvent. The residue was dissolved in methylene chloride, extracted with water, and dried (Na_2SO_4) and the solvent was evaporated. The remaining oil was treated with 50 ml of diethyl ether–methylene chloride (1:1), after which the starting material **9** (1.2 g) could be removed by filtration. The filtrate was saturated with anhydrous hydrogen chloride causing crystallization of the hydrochloride of **2**. After recrystallization from ethanol the hydrochloride melted at 263–268° dec.

Anal. Calcd for $C_{17}H_{16}Cl_2N_2O$: C, 60.9; H, 4.8; Cl, 21.2; N, 8.4; O, 4.8. Found: C, 61.0; H, 5.1; Cl, 21.0; N, 8.3; O, 5.1.

The free base **2**, prepared from the hydrochloride by standard procedures, was crystallized from ether and melted [after sublimation at 130° (0.2 mm)] at 169–172°.

Anal. Calcd for $C_{17}H_{15}ClN_2O$: C, 68.3; H, 5.1; Cl, 11.9; N, 9.4; O, 5.4. Found: C, 68.3; H, 5.4; Cl, 12.1; N, 9.1; O, 5.5.

Method B.—While a solution of triethylamine (8.4 g) and 1-(5-chloro-2-methylaminophenyl)isoindoline (**15**, 16.9 g) in ethanol (250 ml) was heated at reflux temperature, a solution of ethyl bromoacetate (13.5 g) in ethanol (25 ml) was added (over 10 min). The heating was continued for 2 hr, the solvent was evaporated, and the residue was dissolved in benzene and water. The aqueous phase was extracted with benzene and the combined organic phases were washed with water, dried (Na_2SO_4), and evaporated. A sample of this crude ester (**16**) was crystallized twice from ether to give an analytical sample, mp 78–81°.

Anal. Calcd for $C_{19}H_{21}ClN_2O_2$: C, 66.2; H, 6.1. Found: C, 65.8; H, 6.1.

A solution of the crude product (**16**, 19 g) in glacial acetic acid (150 ml) was slowly concentrated to 50 ml by atmospheric pressure distillation and then evaporated to a solid *in vacuo*. This residue was dissolved in chloroform and, after being washed with sodium hydroxide solution (2 *N*) and with water, the solution was dried (Na_2SO_4) and saturated with hydrogen chloride. Addition of a little ether precipitated the hydrochloride of **2**, which was recrystallized from ethanol (13.5 g), mp 264–269° dec. This material was identical in all respects with that obtained from the methylation of **2**.

2-(2-Methylamino-5-chlorobenzoyl)benzamide (17).—A solution of crude **13** (150 mg) in warm ethanol (8 ml) was treated with dilute hydrochloric acid (2 *N*, 12 ml), giving an instantaneous color change from purple to yellow. After standing for 2 hr at room temperature, the mixture was filtered, and the filtrate was neutralized (2 *N*, NaOH) and extracted twice with chloroform. After being washed with water, the organic phase was evaporated *in vacuo* leaving a residue which was crystallized from methylene chloride–ether. The resulting 52 mg of yellow material melted at 198–201°: uv (CH_3OH) 227.5 mμ (ε 22,000), 399 (4800).

Anal. Calcd for $C_{15}H_{13}ClN_2O_2$: C, 62.4; H, 4.5; Cl, 12.3; N, 9.7; O, 11.1. Found: C, 62.5; H, 4.6; N, 9.5; O, 10.9.

2-Chloro-11-hydroxy-5-methylmorphanthridin-6(5H)-one (18).—A solution of 2-chloro-5-methylmorphanthridine-6,11(5H)-dione (10 g) in ethanol (150 ml) containing a little chloroform was treated with sodium borohydride and the mixture was stirred at 60° (0.5 hr). The cooled reaction mixture was then acidified with acetic acid, evaporated to half of its original volume, and brought back to pH 8–9 with sodium hydroxide solution. Addition of water (300 ml) precipitated the reaction product **18** (9.4 g, 93%), mp 195–198°.

Anal. Calcd for $C_{15}H_{12}ClNO_2$: C, 65.8; H, 4.4; Cl, 12.9. Found: C, 65.9; H, 4.6; Cl, 12.8.

2,11-Dichloro-5-methylmorphanthridin-6(5H)-one (19).—A solution of 2-chloro-11-hydroxy-5-methylmorphanthridin-6-(5H)-one (8.5 g) in thionyl chloride (120 ml) was heated at reflux temperature for 3 hr. After this solution was evaporated to dryness, the residue was dissolved in benzene, and the solution was again evaporated to dryness; the solid remaining was crystallized from methylene chloride–ether to yield 8.8 g (93%) of **19**, mp 188–190°.

Anal. Calcd for $C_{15}H_{11}Cl_2NO$: C, 61.7; H, 3.8; Cl, 24.3. Found: C, 61.4; H, 4.0; Cl, 24.1.

3-(5-Chloro-2-methylaminophenyl)isoindolin-1-one (14). Procedure B.—2,11-Dichloro-5-methylmorphanthridin-6(5H)-one (0.5 g) was heated with liquid ammonia (approximately 10 ml) in a sealed steel vessel at 100° (bath temperature) for 16 hr.[13] After cooling, the ammonia was allowed to evaporate, and the crystalline residue was washed with water, dried, and crystallized from ethanol–acetone (1:1) to give **14** (0.19 g), mp 227–229°, identical with the product obtained by the alternative route above.

1-(5-Chloro-2-methylaminophenyl)isoindoline-3,3-$^2H_2$ (15a).—For this electrolytic reduction an apparatus similar to, but smaller than, that described for the preparation of **15**, was used. The electrodes each had a surface area of 50 cm², and an automobile battery (6 V) was again used as the energy source. The reaction was followed by the periodic working up of samples, the ir spectra of which were checked for the disappearance of carbonyl absorption. A solution of 3-(5-chloro-2-methylaminophenyl)isoindolin-1-one (3.5 g) in a mixture of concentrated dideuteriosulfuric acid (45 ml) and deuterium oxide (45 ml) was diluted with an additional 40 ml of deuterium oxide and electrolyzed at 15–25° until the ir spectrum lacked carbonyl absorption. The reaction mixture was then neutralized with 50% NaOH solution (with cooling) and extracted twice with chloroform. Evaporation of the dried extract followed by recrystallization from ether gave **15a** (2.6 g): mp 134–136°; mass spectrum (70 eV) *m/e* 260 (M^+).

1-(5-Chloro-2-methylaminophenyl)isoindoline-3,3-$^2H_2$-2-acetic Acid Ethyl Ester (16a).—A solution of **15a** (1.8 g) in ethanol (50 ml) containing ethyl bromoacetate (1.8 g) and triethylamine (1.2 g) was heated at reflux temperature for 4 hr. The reaction mixture was evaporated to dryness and the residue was dissolved in ether–benzene (1:1) and a little water. The mixture was then extracted with water and saturated sodium chloride solution, dried, and evaporated *in vacuo*. The residue obtained was dissolved in pentane–ether (9:1) and filtered through silica gel. On partial evaporation of the solvent compound **16a** (2.2 g) crystallized out. A portion was recrystallized from ether–pentane: mp 80–83°.

Anal. Calcd for $C_{19}H_{19}N_2O_2Cl^2H_2$: C, 65.8; H, 6.7; N, 8.1. Found: C, 65.8; H, 6.4; N, 8.1.

2-Chloro-5-methyl-9,13b-dihydro-5H-isoindolo[2,1][1,4]benzodiazepin-9,9-$^2H_2$-6(7H)-one (2a).—A solution of **16a** (0.9 g) in acetic acid (40 ml) was heated at reflux temperature for 4 hr, during which time 6 ml of the solvent were slowly distilled off. The reaction mixture was then evaporated *in vacuo* and a solution of the residue in benzene was washed with water and saturated sodium chloride solution. Evaporation of the solvent left an oil (0.67 g) which was crystallized from ether to give **2a** (0.44 g): mp 171–174°; mass spectrum (70 eV) *m/e* 300 (M^+).

Anal. Calcd for $C_{17}H_{13}N_2OCl^2H_2$: C, 67.9; H, 5.7; Cl, 11.8. Found: C, 67.4; H, 5.7; Cl, 11.8.

(13) A similar reaction was described by F. Hunziker, F. Künzle, and J. Schmutz [*Helv. Chim. Acta*, **49**, 1434 (1966)], who obtained a substituted phthalide from an 11-hydroxymorphanthridine.

Registry No.—**2**, 19991-27-6; **2** hydrochloride, 16175-40-9; **2a**, 20013-27-8; **5**, 19991-29-8; **6**, 16219-20-8; **7**, 16175-45-4; **9**, 16175-46-5; **12**, 16219-18-4; **13**, 16175-31-8; **14**, 16175-32-9; **15**, 19980-11-1; **15a**, 19980-12-2; **16**, 16175-38-5; **16a**, 19980-15-5; **17**, 19980-16-6; **18**, 16175-33-0; **19**, 16219-19-5.

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The Addition of Acetone Dimethylhydrazone to Dimethyl Acetylenedicarboxylate

STEPHEN F. NELSEN

Department of Chemistry, University of Wisconsin, Madison, Wisconsin 53706

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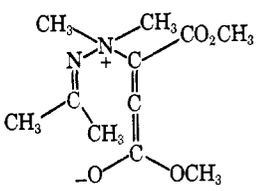
Acetone N,N-dimethylhydrazone and dimethyl acetylenedicarboxylate react at −30° to give 20% of the 1:2 adduct, 1-dimethylamino-2,2-dimethyl-3,4,5,6-tetracarbomethoxy-1,2-dihydropyridine, and 26% of a 1:1 adduct, dimethyl N-isopropylidine-N-dimethylamino-2-aminomaleate. At higher temperatures dimethyl 2-dimethylaminomaleate becomes an increasingly more important product. Dimethyloxalacetate dimethylhydrazone is a minor product at low temperatures. The 1:2 adduct gave upon photolysis the *cis* and *trans* forms of the azahexatriene, the former closing thermally at room temperature.

Hydrazones have three potentially nucleophilic centers: the amino nitrogen, the imino nitrogen, and the imino carbon. Alkylation of dimethylhydrazones takes place exclusively at the amino nitrogen,[1] which clearly ought to be the most nucleophilic center.

Dehydrodimerization of formaldehyde phenylhydrazone to glyoxal osazone, reported by von Pechmann,[2] presumably involves a nucleophilic attack at the carbon in the carbon–carbon bond-forming step. We felt that addition of dimethylhydrazones to dimethyl acetylenedicarboxylate[3] (**1**) would be an example of a nucleophilic reaction of a hydrazone which might give reaction at any of all of the nucleophilic centers. Since the initial addition to form zwitterions should be reversible, the products obtained would reflect the ease of subsequent reactions to give stable products. Dimethylamino nitrogen attack by acetone dimethylhydrazone (**2**) would yield zwitterion **3**, which



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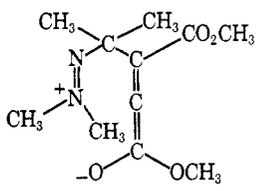

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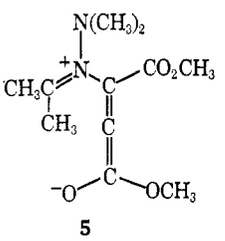

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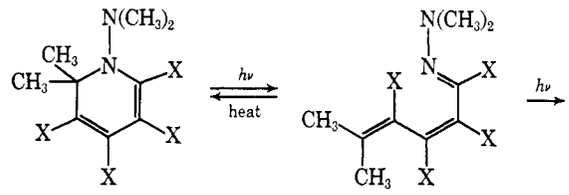
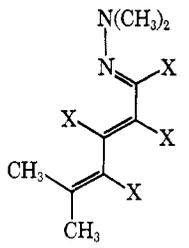
would be expected to undergo N–N$^+$ bond fission and give 2-dimethylamino dimethylmaleate. Attack by the imino carbon would give **4**, which by analogy with enamine adducts[3] might be expected to close to the azacyclobutene structure, which would open to the azabutadiene form easily. Imino nitrogen attack would give **5**, which would be expected to react as adducts of pyridines[3] and other imines,[4] and either add another molecule of dimethyl acetylenedicarboxylate in a "1,4-dipolar" reaction[4a] or transfer a C-methyl hydrogen.

Results and Discussion

When **1** and **2** are mixed in methylene chloride at −30°, the reaction is complete in several hours. To consume all of the hydrazone, a molar ratio of 1.5:1 is required. Removal of solvent affords a yellow solid having spectral and analytical data consistent with **6**, an expected product of initial imino nitrogen attack. The behavior of **6** upon ultraviolet irradiation confirms this structural assignment, for it is partially converted into



6 X = CO_2CH_3 **7**



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an isomer, **7**. The nmr spectrum of **7** shows the downfield shifted dimethylamino absorption and nonequivalent allylic methyls expected for simple ring opening of the azahexadiene ring of **6**. At room temperature in carbon tetrachloride **7** reverts to **6** with a

(1) (a) R. F. Smith and L. E. Walker, *J. Org. Chem.*, **27**, 4372 (1962); (b) P. A. S. Smith and E. E. Most, Jr., *J. Org. Chem.*, **22**, 358 (1957).

(2) H. von Pechmann, *Chem. Ber.*, **30**, 2459 (1897).

(3) For a recent review of such addition reactions, see E. Winterfeldt, *Angew. Chem. Intern. Ed. Engl.*, **6**, 423 (1967).

(4) (a) R. Huisgen and K. Herbig, *Ann. Chem.*, **688**, 98 (1965); (b) J. M. F. Gagan, *J. Chem. Soc., C*, 1966, 1121.