A Novel Ring System from Isoquinoline Methiodide and Active Methylene Compounds II (1)

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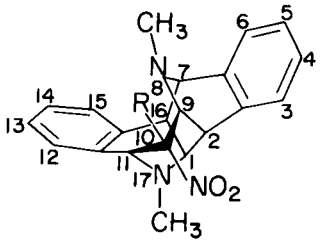
In an earlier communication (1) we reported that the reaction of isoquinoline methiodide with nitroalkanes under alkaline conditions led to the formation of the new diazatetracyclic ring system **1**. We would like to present a summary of the evidence for the proposed structure and an extension of the reaction to include other active methylene compounds.



1a: R = -H
b: R = $-CH_3$

The reaction of two moles of isoquinoline methiodide and one mole of nitroethane in the presence of two moles of sodium methoxide in methanol solution led to the isolation of a colorless compound **1b**, m.p. 213-215° dec. reported (2) m.p. 210-212°. Elemental analysis and mass spectral molecular weight (M^+ 361) indicated an empirical formula of $C_{22}H_{23}N_3O_2$. The nmr spectrum indicated the presence of one tertiary C-CH_3 (1.42 δ), two N-CH_3 (1.45 δ and 1.82 δ), five aliphatic protons (*ca.* 2.2 δ to 3.7 δ), one isolated aliphatic proton (4.67 δ), and eight aromatic protons (*ca.* 6.8 δ to 7.3 δ).

Similar reaction of isoquinoline methiodide with nitromethane led to the isolation of a colorless compound **1a**, m.p. 112-114° dec. Elemental analysis and mass spectral data indicated an empirical formula of $C_{21}H_{21}N_3O_2 \cdot \frac{1}{2}CH_3OH$. The nmr spectrum of this compound was similar to that of compound **1b**, except for the absence of the signal at 1.42 δ and the presence of a new signal centered at 4.48 δ (H-C-NO_2).

To assign the protons in the region from *ca.* 2.2 δ to 4.8 δ (the 1-, 3-, and 4-position protons of the two isoquinoline fragments), we used deuterated isoquinolines. The reaction of isoquinoline-1-d methiodide with nitromethane-d_3 in the presence of sodium methoxide in methanol-d solution, followed by precipitation of the product with water, led to the isolation of **1a**-11, 7-d_2, m.p. 109-110° dec. The nmr spectrum (deuteriobenzene) in the region between *ca.* 2.2 δ and 4.8 δ indicated the loss of two signals originally at 4.71 δ and 3.26 δ in **1a**. These signals were assigned to the two 1-position protons of the isoquinoline fragments. Furthermore, the signal originally centered at 4.48 δ in **1a** appeared as a doublet centered at 4.32 δ (J = 2.5 c/s). These results indicate that reaction with nitromethane occurred at the 1-position of one isoquinoline fragment and at the 3- or 4-position of the other isoquinoline fragment.

The reaction of isoquinoline-4-d methiodide with nitroethane in the presence of sodium methoxide in methanol-d solution yielded **1b**-2, 16-d_2, m.p. 209-210° dec. The nmr spectrum (deuteriobenzene) in the region between *ca.* 2.2 δ and 4.8 δ contained four singlets at 2.43 δ, 3.05 δ, 3.27 δ, and 4.67 δ. These results permit assignment of the signals originally centered at 2.70 δ and 3.53 δ in **1b** to the 4-position protons of the isoquinoline fragments. The remaining signals centered at 2.42 δ and 3.05 δ were assigned to the 3-position protons of the isoquinoline fragments.

The results of spin-decoupling experiments performed on **1a** and **1b** are summarized in Figure 1. In the case of **1a**, the C_{10}-H is coupled to a 3-position proton (C_9-H) of one isoquinoline fragment. This latter proton is coupled (**1b**) to a 4-position proton (adjacent C_2-H), which in turn is coupled to the remaining 3-position proton (C_1-H). These observations, in addition to the other coupling observed in **1b**, support the proposed structure. The formation of the diazatetracyclic ring system has been rationalized elsewhere (1).

The reaction of isoquinoline methiodide with malonic acid derivatives was investigated (Experimental) and led to the isolation of compounds **2a-c**. The reaction failed when it was attempted with diethyl malonate or malon-

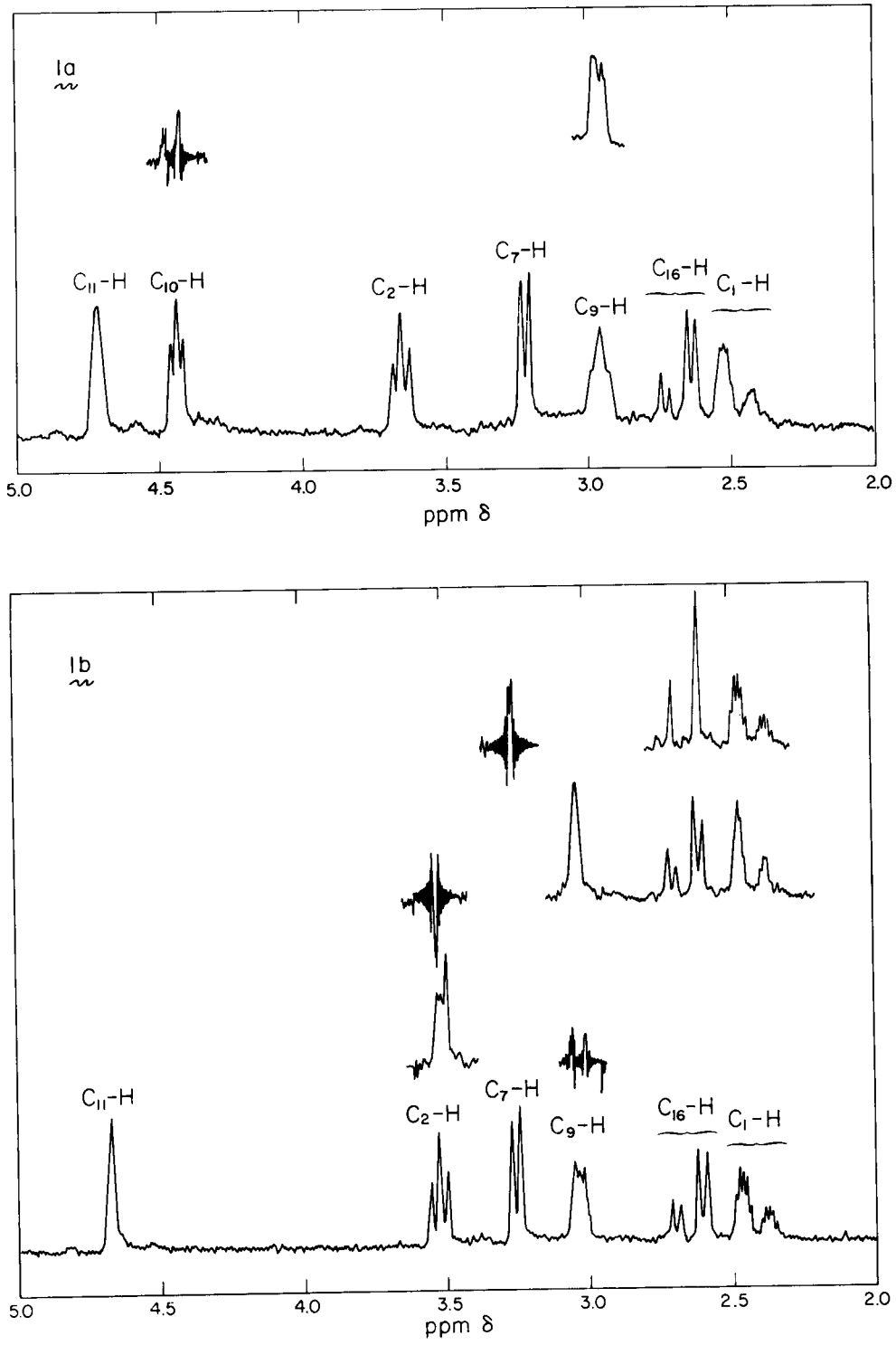
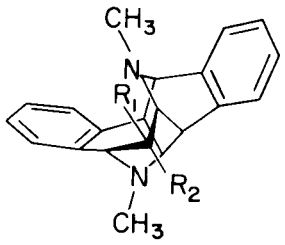


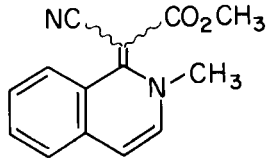
Figure 1. Partial 100 MHz nmr spectra (deuteriobenzene) of 10-substituted 8,17-dimethyl-8,17-diazadibenzo[*c*,*j*]-tetracyclo[7.3.1.$0^{2,9}$.$0^{7,16}$]tridecanes.

amide. The reaction also failed when 4-bromo- or 3-methylisoquinoline methiodide was substituted for isoquinoline methiodide.



2a: R_1, R_2 = -CN, $-CO_2CH_3$
b: R_1, R_2 = -CN, $-CONH_2$
c: $R_1 = R_2$ = -CN
d: R_1, R_2 = $-CONH_2$, $-CO_2CH_3$
e: $R_1 = R_2$ = $-CONH_2$

In the case of the reaction with methyl cyanoacetate, a 7% yield of the anhydrobase **3** was obtained in addition to compound **2a**. Compound **2a** could be converted to the anhydrobase **3** by heating **2a** at its melting point for a short period.



3

Treatment of **2a** with concentrated sulfuric acid at 100° resulted in hydrolysis of the nitrile to yield the carboxamide **2d**. Applying similar conditions to compounds **2b** and **2c** led to the dicarboxamide **2e**.

EXPERIMENTAL

All m.p. and b.p. are uncorrected. Nmr spectra were recorded on a Varian A-60 spectrometer unless otherwise noted. Chemical shifts are expressed in ppm downfield from TMS as internal standard. The following abbreviations were used in reporting nmr spectra: s = singlet; d = doublet; t = triplet; m = multiplet. Spin-decoupling experiments were performed on a Varian HA-100 spectrometer by employing the frequency sweep technique.

General Procedure for the Condensation of Isoquinoline Methiodide with Nitroalkanes and Malonic Acid Derivatives.

A modification of the published procedure (2,3) was employed. To a cooled (ice bath) solution of isoquinoline methiodide (2 moles) and the nitroalkane or malonic acid derivative (1 mole) in anhydrous methanol was slowly added a solution of freshly prepared sodium methoxide (from 2 moles sodium metal) in anhydrous methanol. The mixture was stirred for 3 hours in the cold. In the case of reaction with nitroalkanes, the reaction mixture was reduced in volume and the products were precipitated by the addition of water. In reactions with malonic acid derivatives, the products separated from the reaction mixtures. The products were collected, washed with a small volume of cold methanol and dried. Recrystallization from methanol-acetone mixtures afforded the pure compounds.

8,17-Dimethyl-10-nitro-8,17-diazadibenzo[*c,j*]tetracyclo[7.3.-1.$0^{2,9}$.$0^{7,16}$]tridecane (**1a**).

This compound had m.p. 112-114° dec. (3), yield 44%, mass spectral molecular weight M^+ 347. 100 MHz nmr (deuteriobenzene) ppm 1.48 (s, 3H, N-CH_3), 1.82 (s, 3H, N-CH_3), *ca.* 6.9 to 7.3 (m, 8H, Ar-H).

Anal. Calcd. for $C_{21}H_{21}N_3O_2 \cdot \frac{1}{2}CH_3OH$: C, 71.2; H, 6.1; N, 11.6. Found: C, 71.2; H, 6.5; N, 11.5.

Picrate, m.p. 205-206° dec. (reported (2) m.p. 200° dec.).

8,10,17-Trimethyl-10-nitro-8,17-diazadibenzo[*c,j*]tetracyclo[7.3.-1.$0^{2,9}$.$0^{7,16}$]tridecane (**1b**).

This compound had m.p. 213-215° dec., (reported (2) m.p. 210-212°), yield 41%, mass spectral molecular weight M^+ 361. 100 MHz nmr (deuteriobenzene) ppm 1.42 (s, 3H, $\geqslant$C-CH_3), 1.45 (s, 3H, N-CH_3), 1.82 (s, 3H, N-CH_3), *ca.* 6.8 to 7.3 (m, 8H, Ar-H).

Anal. Calcd. for $C_{22}H_{23}N_3O_2$: C, 73.1; H, 6.4; N, 11.6. Found: C, 73.4; H, 6.4; N, 12.0.

10-Carbomethoxy-10-cyano-8,17-dimethyl-8,17-diazadibenzo[*c,j*]-tetracyclo[7.3.1.$0^{2,9}$.$0^{7,16}$]tridecane (**2a**).

This compound had m.p. 203-204° dec.; yield 75%; nmr (deuteriochloroform) ppm 1.88 (s, 3H, N-CH_3), 2.02 (s, 3H, N-CH_3), *ca.* 2.6 to 3.6 (m, 5H, C_1-H, C_2-H, C_7-H, C_9-H, C_{16}-H), 3.95 (s, 3H, -OCH_3), 4.53 (s, 1H, C_{11}-H), *ca.* 7.1 to 7.5 (m, 8H, Ar-H).

Anal. Calcd. for $C_{24}H_{23}N_3O_2$: C, 74.8; H, 6.0; N, 10.9. Found: C, 74.6; H, 6.3; N, 10.8.

10-Cyano-8,17-dimethyl-8,17-diazadibenzo[*c,j*]tetracyclo[7.3.-1.$0^{2,9}$.$0^{7,16}$]tridecane-10-carboxamide (**2b**).

This compound had m.p. 249-251° dec.; yield 17%; nmr (deuteriopyridine) ppm 1.85 (s, 3H, N-CH_3), 1.98 (s, 3H, N-CH_3), *ca.* 2.5 to 3.3 (m, 3H, C_1-H, C_9-H, C_{16}-H), 3.71 (m, 2H, C_2-H, C_7-H), 4.53 (s, 1H, C_{11}-H), 4.88 (m, 2H, -NH_2), *ca.* 6.9 to 7.5 (m, 8H, Ar-H).

Anal. Calcd. for $C_{23}H_{22}N_4O$: C, 74.6; H, 6.0; N, 15.1. Found: C, 74.6; H, 6.1; N, 15.3.

10-Dicyano-8,17-dimethyl-8,17-diazadibenzo[*c,j*]tetracyclo[7.3.-1.$0^{2,9}$.$0^{7,16}$]tridecane (**2c**).

This compound had m.p. 172-175° dec.; yield 40%; nmr (deuteriobenzene) ppm 1.55 (s, 3H, N-CH_3), 1.72 (s, 3H, N-CH_3), 2.17 to 2.77 (m, 3H, C_1-H, C_9-H, C_{16}-H), 3.20 (d, $J_{7,16}$ = 3 c/s, 1H, C_7-H), 3.45 (t, $J_{2,1} \cong J_{2,9} \cong 3$ c/s, 1H, C_2-H), 3.88 (s, 1H, C_{11}-H), *ca.* 6.8 to 7.3 (m, 8H, Ar-H).

Anal. Calcd. for $C_{23}H_{20}N_4$: C, 78.4; H, 5.7; N, 15.9. Found: C, 78.3; H, 5.9; N, 16.1.

8,17-Dimethyl-10-nitro-8,17-diazadibenzo[*c,j*]tetracyclo[7.3.-1.$0^{2,9}$.$0^{7,16}$]tridecane-7,11-d_2 (**1a**-7, 11-d_2).

Isoquinoline-1-d Methiodide.

2-Benzoyl-1-cyano-1,2-dihydroisoquinoline (4) was subjected to acid hydrolysis employing the variation of Solomon (5) to yield isoquinoline-1-carboxylic acid. A sample (6.24 g.) of this acid was warmed in deuterium oxide (4.0 ml.). The solvent was removed under reduced pressure and a fresh portion of deuterium

oxide (4.0 ml.) was added. The solution was again warmed, then concentrated under reduced pressure. The residue was heated (150°) at atmospheric pressure until gas evolution ceased. The residue was distilled *in vacuo* to yield isoquinoline-1-d, 3.25 g. b.p. 116-117°/16 mm, yield 69%; nmr (deuteriochloroform) ppm 7.30 to 8.05 (m, 5H, C_4-H, C_5-H, C_6-H, C_7-H, C_8-H), 8.50 (d, $J_{3,4}$ = 6 c/s, 1H, C_3-H). The methiodide was prepared by heating isoquinoline-1-d (3.25 g.) with methyliodide (7.0 ml.) in methanol (20 ml.) for 3 hours, followed by dilution with ether. The precipitated product was collected, washed well with ether, and air-dried to yield the desired compound as a pale yellow crystalline solid, 6.75 g., m.p. 157-160° dec., yield 98%. The mass spectrum indicated isotopic purity > 93% (d_0 = 3% max., d_2 = 4% max.); nmr (deuterium oxide) ppm 4.63 (s, 3H, N^+-CH_3), 7.83 to 8.67 (m, 6H, C_3-H, C_4-H, C_5-H, C_6-H, C_7-H, C_8-H).

Reaction of Isoquinoline-1-d Methiodide with Nitromethane-d_3.

The general procedure was used, employing deuteriomethanol as solvent and performing all operations in an atmosphere of dry nitrogen. The crude product was recrystallized from methanol-acetone to yield **1a**-7, 11-d_2 as colorless crystals, m.p. 109-110° dec.; nmr (deuteriobenzene) ppm 1.32 (s, 3H, N-CH_3), 1.68 (s, 3H, N-CH_3), 2.20 to 2.72 (m, 2H, C_1-H, C_{16}-H), 2.68 (m, 1H, C_9-H), 3.55 (t, $J_{2,1} \cong J_{2,9} \cong 3$ c/s, 1H, C_2-H), 4.32 (d, $J_{10,9}$ = 2.5 c/s, 1H, C_{10}-H), *ca.* 6.7 to 7.2 (m, 8H, Ar-H).

8,10,17-Trimethyl-10-nitro-8,17-diazadibenzo[*c,j*]tetracyclo[7.3.-1.$0^{2,9}$.$0^{7,16}$]tridecane-2,16-d_2 (**1b**-2, 16-d_2).

Isoquinoline-4-d Methiodide.

Solid 4-bromoisoquinoline (10.40 g.) was added in small portions to a cold (-70°) solution of freshly prepared *n*-butyllithium (from 1.72 g. of lithium metal and 16.45 g. of *n*-butyl bromide in 300 ml. of 1:1 ether-THF). The solution was stirred 30 minutes, then a solution of deuterium oxide (15 ml.) and THF (20 ml.) was added in one portion. The resulting colorless suspension was stirred 15 minutes at -70°, then allowed to warm slowly to room temperature. The clear liquid was decanted, the solid was washed well with ether, and the combination of washings and ether-THF solution was dried (sodium sulfate) and concentrated. The residue was distilled *in vacuo* to yield isoquinoline-4-d, 3.78 g., b.p. 71-80°/0.75 mm, yield 59%; nmr (deuteriochloroform) ppm 7.05 to 8.22 (m, 4H, C_5-H, C_6-H, C_7-H, C_8-H), 8.58 (s, 1H, C_3-H), 9.30 (s, 1H, C_1-H). The methiodide was prepared in the usual manner to yield a pale yellow crystalline solid, 7.17 g., m.p. 155-157° dec., yield 91%. The mass spectrum indicated isotopic purity > 98% (d_0 < 1%, d_2 = 1% max.); nmr (deuterium oxide) ppm 4.50 (s, 3H, N^+-CH_3), *ca.* 7.7 to 8.4 (m, 5H, C_3-H, C_5-H, C_6-H, C_7-H, C_8-H), 9.55 (s, 1H, C_1-H).

Reaction of Isoquinoline-4-d Methiodide with Nitroethane.

The general procedure was employed. The crude product was recrystallized from methanol-acetone to yield **1b**-2, 16-d_2 as colorless needles, m.p. 209-210° dec.; nmr (deuteriobenzene) ppm 1.42 (s, 3H, ≥C-CH_3), 1.45 (s, 3H, N-CH_3), 1.82 (s, 3H, N-CH_3), 2.43 (s, 1H, C_1-H), 3.05 (s, 1H, C_9-H), 3.27 (s, 1H, C_7-H), 4.67 (s, 1H, C_{11}-H), *ca.* 6.8 to 7.3 (m, 8H, Ar-H).

Anhydrobase **3**.

From the condensation of isoquinoline methiodide and methyl cyanoacetate. After the isolation of **2a** from the reaction of isoquinoline methiodide (20.29 g.) and methyl cyanoacetate (3.77 g.) (general procedure), the mother liquor was taken to dryness. The dark residue was treated with a small volume of chloroform, filtered, and the filtrate chromatographed on Florisil (Floridin Co., 60/100A mesh), with 95:5 chloroform-methanol as the eluent. The orange fraction obtained was taken to dryness and the residue recrystallized from methanol to yield **3** as a deep orange solid, 640 mg., m.p. 194-196° dec., yield 7%.

Anal. Calcd. for $C_{14}H_{12}N_2O_2$: C, 70.0; H, 5.0; N, 11.7. Found: C, 69.6; H, 5.2; N, 11.9.

From the thermal decomposition of **2a**. A sample of compound **2a** (3.85 g.) was heated in an oil bath (200-205°) under a nitrogen atmosphere for 10 minutes. The dark oil was cooled and diluted with water. The solid that separated was collected and recrystallized from methanol to yield the desired compound, 1.72 g., m.p. 194-196° dec., yield 72%. This proved to be identical (tlc, ir spectra, mixture m.p.) with the material isolated above.

Treatment of the dark aqueous solution with sodium perchlorate resulted in the separation of a solid (low yield) that proved to be *N*-methylisoquinolinium perchlorate (compared with an authentic sample prepared from isoquinoline methiodide and sodium perchlorate).

10-Carbomethoxy-8,17-dimethyl-8,17-diazadibenzo[*c,j*]tetracyclo-[7.3.1.$0^{2,9}$.$0^{7,16}$]tridecane-10-carboxamide (**2d**).

A solution of compound **2a** (2.00 g.) in concentrated sulfuric acid (20 ml.) was heated 1 hour on a steam bath. The solution was cooled, poured onto ice, and the resulting solution treated with concentrated ammonium hydroxide until alkaline. The alkaline solution was extracted with chloroform, the extracts were dried (sodium sulfate) and concentrated to yield an oil. The oil was taken up in a small volume of methanol. The crystals that separated were collected, washed with a small volume of methanol and air-dried to yield **2d**, 1.90 g., m.p. 251-256° dec., yield 91%. A portion was recrystallized from methanol-acetone to give colorless crystals, m.p. 257.5-260° dec.; nmr (deuteriochloroform) ppm 1.75 (s, 3H, N-CH_3), 2.00 (s, 3H, N-CH_3), *ca.* 2.5 to 3.4 (m, 4H, C_1-H, C_7-H, C_9-H, C_{16}-H), 3.72 (m, 1H, C_2-H), 3.90 (s, 3H, -OCH_3), 4.60 (s, 1H, C_{11}-H), 6.02 (m, 1H, -NH), 7.29 (m, 8H, Ar-H), 7.60 (m, 1H, -NH); nmr (deuteriopyridine) ppm 1.72 (s, 3H, N-CH_3), 1.98 (s, 3H, N-CH_3), *ca.* 2.4 to 3.2 (m, 2H, C_1-H, C_{16}-H), *ca.* 3.3 to 3.7 (m, 3H, C_2-H, C_7-H, C_9-H), 3.78 (s, 3H, -OCH_3), 4.53 (m, 1H, -NH), 4.93 (s, 1H, C_{11}-H), 7.15 (m, 8H, Ar-H), 7.65 (m, 1H, -NH).

Anal. Calcd. for $C_{24}H_{25}N_3O_3$: C, 71.4; H, 6.2; N, 10.5. Found: C, 71.1; H, 6.4; N, 10.4.

8,17-Dimethyl-8,17-diazadibenzo[*c,j*]tetracyclo[7.3.1.$0^{2,9}$.$0^{7,16}$]-tridecane-10-dicarboxamide (**2e**).

From **2b**.

The procedure for the preparation of **2d** was employed. Thus, from 2.00 g. of **2b** was obtained the dicarboxamide **2e**, 1.15 g., m.p. 276-278° dec., yield 55%; nmr (deuteriopyridine) ppm 1.82 (s, 3H, N-CH_3), 2.02 (s, 3H, N-CH_3), *ca.* 2.5 to 3.2 (m, 2H, C_1-H, C_{16}-H), *ca.* 3.4 to 3.9 (m, 3H, C_2-H, C_7-H, C_9-H), 4.58 (m, 2H, -NH_2), 4.88 (s, 1H, C_{11}-H), *ca.* 6.8 to 7.3 (m, 8H, Ar-H).

Anal. Calcd. for $C_{23}H_{24}N_4O_2$: C, 71.1; H, 6.2; N, 14.4. Found: C, 70.6; H, 6.1; N, 14.1.

From **2c**.

Similar treatment of the dinitrile **2c** afforded a low yield of a compound identical (tlc, ir spectra, nmr spectra, mixture m.p.) to that isolated above.

Acknowledgment.

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REFERENCES

(1) Part I. W. R. Schleigh, *Tetrahedron Letters*, 1405 (1969).

(2) N. J. Leonard and G. W. Leubner, *J. Am. Chem. Soc.*, 71, 3405 (1949).

(3) H. A. DeWalt, Jr., Ph.D. Thesis, University of Illinois, 1950. A compound analyzing for $C_{21}H_{21}N_3O_2$, m.p. 160-163°, picrate m.p. 212° dec. was reported. We were unsuccessful in our attempts to duplicate this isolation of nonsolvated material.

(4) J. J. Padbury and H. G. Lindwall, *J. Am. Chem. Soc.*, 67, 1268 (1945).

(5) W. Solomon, *J. Chem. Soc.*, 129 (1947).