The Synthesis of a 12,13-Dihydro-5*H*-dibenzo[*b*,*g*][1,5]diazonine by a Novel Ring Enlargement Reaction

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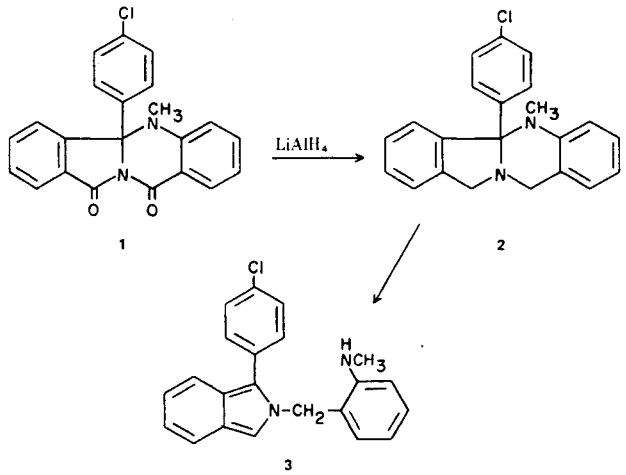
Received January 30, 1978

A novel method for ring expansion of a heterocycle containing a NCN system to a medium sized diaza-heterocycle has been demonstrated for the conversion of an isoindolo[2,1-*a*]-quinazoline derivative **8** to the 5*H*-dibenzo[*b*,*g*][1,5]diazonine (**13**). Attempts to apply this isomerization to heterocyclic systems related to **8** were not successful.

J. Heterocyclic Chem., 15, 1141 (1978)

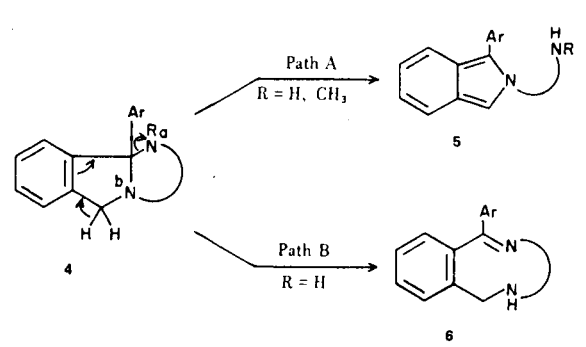
We have reported (1) that certain fused isoindolones such as **1** upon treatment with lithium alumium hydride (LAH) in refluxing diethyl ether or tetrahydrofuran gave labile **2** which on contact with silica gel isomerized to the isoindole **3** (Scheme I).

Scheme I



The formation of **3** can be regarded as an example of a more general isomerization (2) of a fused isoindolinine **4** where the C-N^a cleaves, possibly through the pathway indicated by the solid arrows, to form isoindole **5** (Scheme II, Path A). A second C-N isomerization pathway is possible for **4** when R = H. The cleavage of the C-N^b bond by a N^{a}CN^b pathway could lead to the formation of **6** (Scheme II, Path B). If this type of isomerization could be effected, it would offer a novel method for ring expansion to selected diaza-heterocyclic systems.

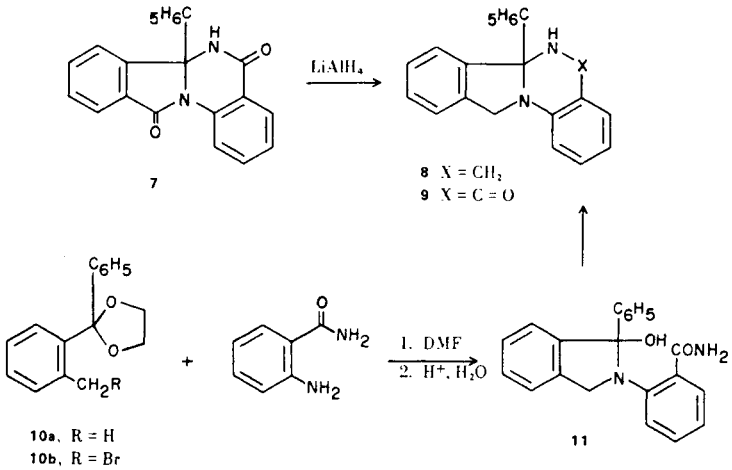
Scheme II



In this work we report the successful application of this concept in preparing the 5*H*-dibenzo[*b*,*g*][1,5]diazonine (**13**) and attempts to extend the reaction to related ring systems.

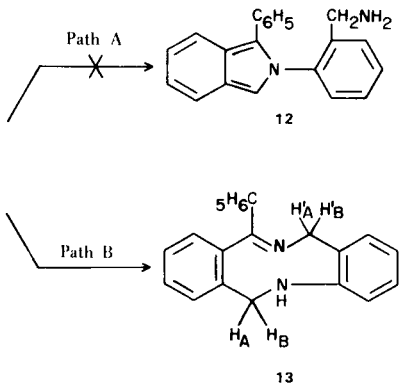
The synthesis of the requisite starting material to form **13** is given in Scheme III. Reduction of the known (3) 5,11-dione **7** with lithium aluminum hydride in refluxing tetrahydrofuran for 126 hours gave a mixture of the desired **8** and the 5-one (**9**). When the reduction was carried out for 25 hours, only **9** was isolated in 82% yield. The structures of **8** and **9** were confirmed by nmr and ir data. In addition, the synthesis of **9** was independently carried out by reacting the bromomethyl ketal (**10b**) with anthranilamide in dimethylformamide (DMF) and hydrolyzing the resultant ketal with dilute acid. Several unsuccessful attempts were made to isolate **11** (4), the most probable precursor of **9**.

Scheme III



When a chloroform solution of **8** was contacted with silica gel for 18 hours and then chromatographed, there was obtained unchanged **8** and 90% of a novel compound isomeric (m/e 298) with **8**. The proton nmr of this compound gave two AB patterns centered at δ 4.19 (J = 15 cps) and 5.77 (J = 3 cps), one deuterium oxide exchangeable and thirteen aromatic protons, while the uv spectrum gave a maximum at 244 mμ. This data is in good agreement with the Path B isomerization product **13** and incompati-

Scheme IV

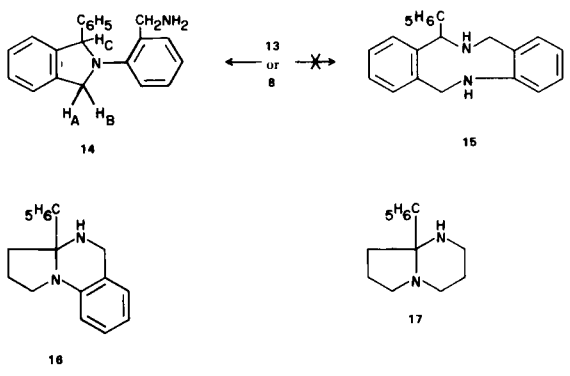


able with the Path A where the isoindole **12** is formed. The high field AB pattern can be assigned to the CH_2N- protons and the low field pattern to the CH_2N= system.

In an attempt to reduce the C=N bond, an acetic acid solution of **12** was hydrogenated in the presence of platinum. The resultant dihydro derivative gave a nmr spectrum that contained two exchangeable protons, one AB pattern (2H), and ABC pattern (3H) an eight aromatic protons. The ABC system consisted of protons located at 4.21 (H_A), 4.96 (H_B) and 5.93 δ (H_C) with coupling constants of J_{AB} 15 cps, J_{AC} 3 cps and J_{BC} 2 cps. Such a pattern has been found (1) to be characteristic of a $H_AH_BCNCH_C$ system in a 1-R-3-phenylisoindolinine and indicates that the dihydro product is **14** rather than **15**. Catalytic hydrogenation of **8** in acetic acid or isopropanol also resulted in the formation of **14**. The formation of **14** from **12** most likely occurs through an acid catalyzed return to **8** followed by hydrogenation.

In an attempt to extend the synthetic usefulness of this isomerization the *nor*-benzo and the bis-*nor*-benzo analogs (**16** and **17**) of **8** were contacted with silica gel for periods up to 96 hours. In both cases only starting material was obtained.

Scheme V



EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and have not been corrected. Proton nmr spectra were obtained on a Varian Associates A-60 spectrometer and are recorded in parts per million from an internal TMS standard. Infrared spectrum were determined on a Perkin-Elmer Infracord spectrophotometer. Ultraviolet spectrum were carried out on a Cary Model 15 spectrometer. Mass spectra were determined on a Consolidated Electronics CO. Mass Spectrometer, Model 21-103C, equipped with an all-glass heated inlet. Thin layer chromatography (tlc) was determined on glass plates coated with silica gel HF-254, Merck AG.

6a-Phenyl-5,6,6a,11-tetrahydroisoindolo[2,1-*a*]quinazoline (**8**) and 6a-Phenyl-5,6,6a,11-tetrahydroisoindolo[2,1-*a*]quinazolin-5-one (**9**).

A. From 6a-Phenyl-5,6,6a,11-tetrahydroisoindolo[2,1-*a*]quinazoline-5,11-dione (**7**).

A slurry of 2.5 g. (0.06 mole) of lithium aluminum hydride and 500 ml. of anhydrous tetrahydrofuran was stirred and refluxed (25 hours) through a Soxhlet apparatus containing 10.0 g. (0.03 mole) of **7** (3). After cooling in an icebath, the reactants were treated with 5.0 ml. of 2*N* sodium hydroxide, 7.5 ml. of water and 10 g. of anhydrous sodium sulfate. The salts were filtered off, washed with tetrahydrofuran and the filtrate concentrated *in vacuo* to give 8.0 g. (82%) of **9**, m.p. 253-255° (methanol); ir (potassium bromide): 3.15 (NH) and 6.03 μ (C=O); uv max (ethanol): 223 mμ (ε 35,490), 262 (6,650), 268 (6,100) and 346 (2,730); nmr (pyridine): δ 3.82 (H_A), 4.18 (H_B, J = 13.0 cps, $ArCH_AH_BN^{11a}$).

Anal. Calcd. for $C_{21}H_{16}N_2O$: C, 80.8; H, 5.1; N, 9.0; O, 5.1. Found: C, 80.6; H, 5.4; N, 9.1; O, 5.3.

When 54.3 g. (0.17 mole) of **7**, 13.6 g. (0.36 mole) of lithium aluminum hydride and 1500 ml. of anhydrous tetrahydrofuran were stirred and refluxed for 168 hours and then processed as above, there was obtained 47.3 g. of solid, m.p. 173-240°. This material (41.5 g.) was stirred for 4 hours at room temperature with 250 ml. of 2*N* hydrochloric acid. The insoluble fraction was filtered off to give 19.9 g. (38%) of a solid that was identified (m.p., uv and ir) as **9**. The acidic filtrate was cooled in an icebath and treated with 2*N* sodium hydroxide until basic to litmus. The resultant solid was filtered off to give 15.6 g. (31%) of **8**, m.p. 149-151° (methanol/water); ir (potassium bromide): 3.10 μ (NH); uv max (ethanol 242 mμ (ε 6,855), 260 (5,515) and 268 (3,395); nmr (chloroform): δ 1.80 (1H, NH, deuterium oxide exchangeable), 3.82 (2H, s, N^5CH_2Ar), 4.61 (H_A), 5.08 (H_B, J = 14.0 cps, $ArCH_AH_B{}^{11a}$), 6.50-7.95 (13H).

Anal. Calcd. for $C_{21}H_{18}N_2$: C, 84.6; H, 6.0 N, 9.4. Found: C, 84.5; H, 6.0 N, 9.2.

B. From 2-Phenyl-2-*o*-tolyl-1,3-dioxolane (**10a**).

A mixture of 82.6 g. (0.43 mole) fo 2-methylbenzophenone, 53.2 g. (0.86 mole) of ethyleneglycol, 2.0 g. of *p*-toluenesulfonic acid and 1000 ml. of benzene was stirred and refluxed in a flask equipped with a Dean-Stark apparatus until the "water layer" (20 ml.) remained constant (52 hours). The solvent was removed *in vacuo* and the residue treated with 500 ml. of 2*N* sodium carbonate. The resultant solid was filtered to give 71.2 g. (69%) of **10a**, m.p. 77-79° (methanol); nmr (deuteriochloroform): δ 2.18 (3H, s, CH_3), 3.80 (4H, s, OCH_2CH_2O), 6.90-7.65 (8H, aromatics).

Anal. Calcd. for $C_{16}H_{16}O_2$: C, 80.0; H, 6.7; O, 13.3. Found: C, 80.0; H, 6.4; O, 13.4.

To a stirred refluxing mixture of 22.5 g. (0.09 mole) of **10a**,

11.5 g. (0.12 mole) of anhydrous sodium bicarbonate and 140 ml. of carbon tetrachloride, irradiated with a high intensity light source, there was added a solution of 16.9 g. (0.11 mole; 5.4 ml.) of bromine in 48 ml. of carbon tetrachloride at such a rate that the bromine color faded rapidly. After an additional hour at reflux, the solvent was removed *in vacuo* and the residue dissolved in 500 ml. of dichloromethane and treated with 45.4 g. (0.33 mole) of anthranilamide. The mixture was stirred for 56 hours at room temperature, filtered, and concentrated *in vacuo* to give a solid (47.6 g.) that was stirred at room temperature for 24 hours with 500 ml. of 2*N* hydrochloric acid. The slurry was treated with 500 ml. of dichloromethane and the organic layer separated, washed with 2*N* sodium bicarbonate, dried (magnesium sulfate), filtered and concentrated *in vacuo* to give 39 g. of solid. Chromatography on silica gel (780 g.; chloroform/methanol, 90:10 eluant) gave 14.1 g. of **9**, m.p. 252-254°, identical (ir, nmr) with **9** prepared by Procedure A.

7-Phenyl-12,13-dihydro-5*H*-dibenzo-[*b*,*g*]diazonine (**13**).

A chloroform solution containing 1.0 g. of **8** was placed on a chromatography column prepared from 20 g. of silica gel (*p*H 6.5; water slurry) and 100 ml. of chloroform. After standing for 18 hours at room temperature the column was developed with chloroform to give 0.90 g. of **13**, Rf 0.60 (chloroform/methanol, 98:2), m.p. 182-183° (dichloromethane/methanol); ir (dichloromethane): 3.05 μ (NH); uv max (ethanol): 244 mμ (ϵ, 9,600), 268 (7,830) and 270 (7,830); nmr (chloroform): δ 3.97 (H_A), 4.52 (H_B' J = 15 cps, NCH_AH_BAr), 4.10 (1H, deuterium oxide exchangeable, NH), 5.62 (H'_A), 5.97 (H'_B J = 3 cps, $NCH'_AH'_BAr$), 6.5-7.7 (13H, aromatic protons).

Anal. Calcd. for $C_{21}H_{18}N_2$: C, 84.5; H, 6.1; N, 9.4. Found: C, 84.4; H, 6.3; N, 9.5.

2-[*o*-(α-Aminotolyl)]-1-phenylisoindoline (**14**) from **8** and **13**.

A mixture of 0.500 g. of **13**, 0.50 g. of platinum oxide and 7 ml. of acetic acid was hydrogenated at room temperature and atmospheric pressure in a shaker apparatus. After hydrogen uptake had ceased (1.0 equivalents of H_2; 1.5 hours), the catalyst was filtered off and the filtrate concentrated *in vacuo*. The residue was made alkaline with 2N sodium carbonate, extracted with dichloromethane, dried (magnesium sulfate), filtered and concentrated *in vacuo* to give 0.400 g. (79%) of **14**, kugelrohr b.p. 180° (0.05 mm.); ir (dichloromethane): 2.75 and 2.98 μ (NH_2); nmr (chloroform): δ 1.50 (2H, deuterium oxide exchangeable, NH_2), 3.60 (H_A), 4.02 (H_B' J = 15 cps, NCH_AH_BAr), 4.21 (H_A), 4.96 (H_B), 5.93 (H_C' J_{AB} = 15 cps, JAC = 3 cps, J_{BC} = 2 cps).

Anal. Calcd. for $C_{21}H_{20}N_2$: C, 84.0; H, 6.9; N, 9.1. Found: C, 83.7; H, 6.8; 9.0.

When a mixture of 1.000 g. of **8**, 0.05 g. of platinum oxide and 20 ml. of acetic acid was hydrogenated as above, there was obtained 0.850 g.(84%) of **14** that was shown by tlc, ir and nmr to be identical with **14** prepared from **13**.

3a-Phenyl-1,2,3,3a,4,5-hexahydropyrrolo[1,2-*a*]quinazoline (**16**) Preparation and Attempted Isomerization.

A mixture of 10 g. (0.036 mole) of 3a-phenyl-1,2,3,3a-4,5-hexahydropyrrolo [1,2-*a*]quinazoline-1,5-dione (**3**), 3.0 g. (0.08 mole) of lithium aluminum hydride in 250 ml. of anhydrous tetrahydrofuran were stirred and refluxed for 78 hours and processed as the preparation of **8**. There was obtained 6.5 g. (72%) of **16**, m.p. 86-88° (ether-pentane), Rf. 0.7 (chloroform); ir (chloroform): 3.05 μ (NH); nmr (deuteriochloroform): δ 1.43 (1H, NH, deuterium oxide exchangeable), 1.60-2.48 (4H, m, CH_2CH_2), 3.15-4.82 (4H, m, NCH_2ArNCH_2), 6.40-7.50 (9H, m, C_6H_4 and C_6H_5).

Anal. Calcd. for $C_{17}H_{18}N_2$: C, 81.6; H, 7.3; N, 11.2. Found: C, 81.5; H, 7.2; N, 11.2.

A chloroform solution containing 1.0 g. of **16** was placed on a chromatography column prepared from 20 g. of silica gel (*p*H 6.5) and 100 ml. of chloroform was allowed to stand at room temperature for either 18, 30 or 72 hours. Elution of the column gave only starting **16** in all three experiments.

8a-Phenyl-1,2,3,4,6,7,8,8a-octahydropyrrolo[1,2-*a*]pyrimidine (**17**) Attempted Isomerization.

A chloroform solution containing 1.0 g. of **17** (5) was placed on a chromatography column prepared from 25 g. of silica gel (*p*H 6.5) and 100 ml. of chloroform was allowed to stand at room temperature for either 24, 48 or 96 hours. Elution of the column with chloroform gave only starting **17** in all three experiments.

Acknowledgment.

The authors express their appreciation to Mr. Urs Stoeckli and his associates for instrumental and analytical data.

REFERENCES AND NOTES

(1) P. Aeberli and W. J. Houlihan, *J. Org. Chem.*, **34**, 1720 (1969).

(2) Additional examples of this type of isomerization are given in reference 1.

(3) P. Aeberli and W. J. Houlihan, *ibid.*, **33**, 2402 (1968).

(4) Compound **11** could also exist in a tautomeric benzophenone form.

(5) P. Aeberli and W. J. Houlihan, *ibid.*, **34**, 165 (1969).