Lithiation of N-(2-Alkylphenyl)alkanamides and Related Compounds. A Modified Madelung Indole Synthesis

William J. Houlihan,* Vincent A. Parrino, and Yasuyuki Uike

Sandoz, Inc., Pharmaceutical Research and Development Department, East Hanover, New Jersey 07936

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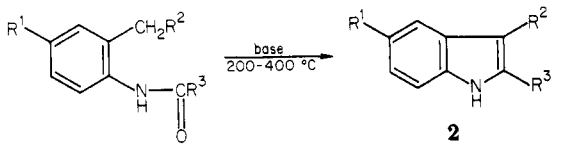
A modified Madelung synthesis for the conversion of *N*-(alkylphenyl)alkanamides and related compounds to indoles, benzindoles, and azindoles has been developed. This procedure consists of treating the amide with 2 or 3 equiv of *n*-butyllithium or lithium diisopropylamide in tetrahydrofuran at temperatures from −20 to +25 °C. Several examples where products other than indoles were formed from the starting amide are also reported.

The Madelung synthesis[1] of indoles (**2**) involves the intramolecular cyclization of an *N*-(2-alkylphenyl)alkanamide (**1**) by a strong base at elevated temperature. The



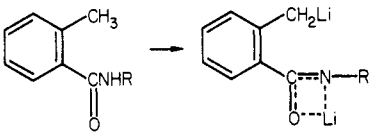
1 **2**

$R^2 = R^3 =$ H, alkyl, aryl

most common conditions given in the literature[1,2] are sodium or potassium alkoxide or sodium amide at temperatures of 200–400 °C. Although these reaction conditions have been used to prepare a variety of indoles, several shortcomings, probably due to the harsh conditions, are apparent. Attempts to effect the reaction with **1** containing a halogen[3] or alkoxy[4] in the benzene ring have failed, and the preparation of highly branched 2-alkylindoles gave poor yields.[5]

Although the mechanism of the Madelung Reaction has not been fully established,[1,6] it seemed to us that an organometallic intermediate such as **3** could be a key intermediate in the formation of **2** via the sequence of steps given in Scheme I.

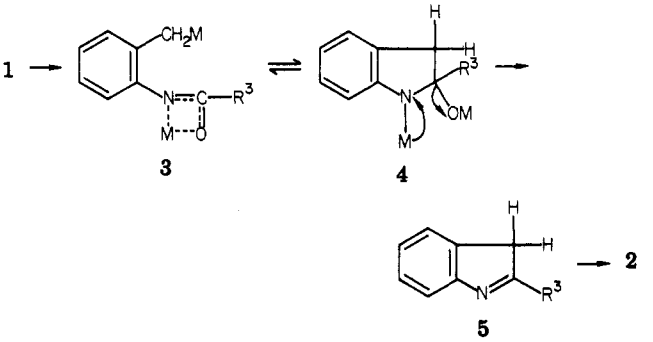
Hauser's report[7] that the isosteric organolithium reagent **7** could be formed by treating **6** with 2 equiv of *n*-butyllithium at room temperature prompted us to extend these conditions to the formation of **3** (M = Li) and thereby effect a Madelung reaction under much milder conditions.



6 **7**

In the present work we report the successful application of Hauser's organolithiation conditions to the synthesis of several indoles, benzindoles, and azaindoles from the requisite *N*-amides.[8]

Scheme I[a]

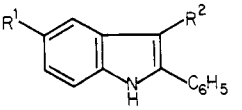


3 **4** **5**

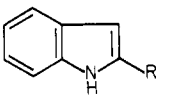
[a] $R^1 = R^2 =$ H; M = Li, Na, K.

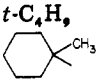
As a model reaction we found that the formation of 5-chloro-2-phenylindole (**8c**) could be effected in >90% yields by treating *N*-(4-chloro-2-methylphenyl)benzamide (**1c**) with 2 or 3 molar equiv of *n*-BuLi in tetrahydrofuran at −20 to +25 °C and then allowing the reaction mixture to stand overnight at room temperature.

Extension of this procedure to *N*-(2-methylphenyl)- and *N*-(4-methoxy-2-methylphenyl)benzamides (**1a** and **1b**) gave 2-phenyl- and 5-methoxy-2-phenylindole (**8a** and **8b**)



8a, $R_1 = R_2 =$ H
b, $R_1 = OCH_3$; R = H
c, R_1 = Cl; R_2 = H
d, R_1 = H; $R_2 = CH_3$



15a, R = *t*-C_4H_9
b, R = 
c, R = 1-adamantanyl

in 90% and 80% yields, respectively. The formation of **8c** and **8b** in these yields is quite gratifying since earlier Madelung reactions with halogen-[3] and methoxy-substituted[4] *o*-toluidides had failed. The 20% yield of 3-methyl-2-phenylindole (**8d**) from *N*-(2-ethylphenyl)benzamide (**1d**) suggests that the present procedure offers no advantage in the synthesis of 3-alkyl-2-phenylindoles (Table I).

When 2-methyl-*N*-(2-methylphenyl)benzamide (**9a**) was treated with 2 or 3 equiv of *n*-BuLi under conditions that gave **8a**, only starting material was recovered. The failure of **9a** to form an indole was at first attributed to a steric effect of the *o*-methyl group that could prevent cyclization of intermediate **3** to **4** (Scheme I). This postulate was shown to be incorrect when the reaction with **9a** and 3 equiv of *n*-BuLi was repeated and the resultant mixture

(1) For a comprehesive review of the Madelung Synthesis see R. K. Brown in "Indoles", W. J. Houlihan, Ed., Wiley, New York, 1972, Part I, pp 385–396.
(2) A. Wu and V. Snieckus, *Tetrahedron Lett.*, 2057 (1957); K. Minoru, Y. Hirosuke and K. Hoshino, Japanese Patent 74 35 268; *Chem. Abstr.*, **83**, 9783 (1975); R. L. Augustine, A. J. Gustavsen, S. F. Wanat, I. C. Pattison, K. S. Houghton, and G. Koletar, *J. Org. Chem.*, **38**, 3004 (1973).
(3) W. E. Noland and C. Reich, *J. Org.* Chem., **32**, 828 (1967).
(4) L. Marion and W. R. Ashford, *Can. J. Res.*, **23**, 26 (1945).
(5) F. Piozzi and M. R. Langella, *Gazz. Chim. Ital.*, **93**, 1382 (1963).
(6) A mechanism similar to that in Scheme I has recently been suggested by W. Fuhrer and H. W. Gschwend, *J. Org. Chem.*, **44**, 1133 (1979).
(7) R. E. Ludt, J. S. Griffiths, K. N. McGrath, and C. R. Hauser, *J. Org. Chem.*, **38**, 1668 (1973).
(8) Additional examples and the proposed mechanism in Scheme I are reported in W. Houlihan, U.S. Patent 3 987 059 (1976); *Chem. Abstr.*, **86**, 43558 (1977).

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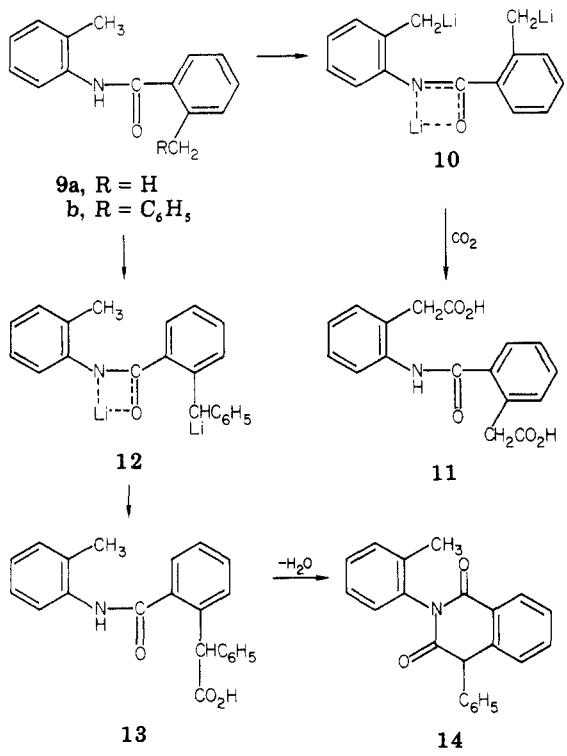
Table I. 2-Alkyl- and 2-Arylindoles

no.	n-BuLi addn temp, °C	n-BuLi molar equiv	time at room temp, h	yield, %	mp, °C (recryst solv)[a]	IR for NH, μm (media)[b]	NMR ($CDCl_3$), δ
8a	20	3	16	90	187-188 (A)[c]	2.87 (C)	
8b	15	2	20	80	158-159 (A)[d]	3.08 (K)	3.85 (3 H, s, OCH_3)
8c	-20	2	15	94	195-196 (A)[e]	2.09 (K)	
8d	15	2	48	20	91-92 (B)[f]	2.88 (C)	2.42 (3 H, s, CH_3)
15a	15	3	16	87	71-72 (C)[g]	2.86 (C)	1.38 (9 H, s, t-C_4H_9), 6.25 (1 H, d, J = 2 Hz, C=CH)
15b	25	2	18	76	49-50 (C)[h]	2.85 (C)	1.28 (s, 3 H, CH_3)
15c	15	3	6	59	146-147 (D)[i]	2.84 (C)	6.20 (1 H, d, J = 4 Hz, C=CH)

[a] Recrystallization solvents: A, Et_2O-C_6H_6; B, cyclohexane; C, Et_2O-cyclohexane; D, Et_2O-pentane. [b] IR spectra media: C, $CHCl_3$; K, KBr. [c] Lit.[11] mp 185-187 °C. [d] Lit.[12] mp 158-160 °C. [e] Lit.[13] mp 196-197 °C. [f] Lit.[14] mp 89.5-91 °C. [g] Lit.[15] mp 77 °C. [h] Anal. Calcd for $C_{15}H_{19}N$: C, 84.5; H, 9.0; N, 6.6. Found: C, 84.6; H, 9.3; N, 6.5. [i] Lit.[16] mp 149 °C.

Scheme II

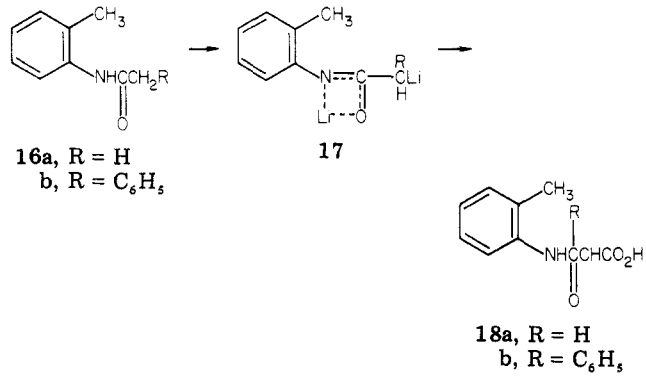


was treated with excess carbon dioxide. From this reaction a 67% yield of a diacid that has been established by ^1H NMR to be **11** was isolated. The formation of **11** can occur only if both methyl groups in **9a** were lithiated to give a dilithio reagent such as depicted by structure **10** (Scheme II). Failure of **10** to cyclize to an indole is possibly due to the electrostatic repulsion of the two CH_2Li groups as they approach each other to form the indole nucleus (**3** → **4** in Scheme I).

When the phenyl analogue (**9b**) of **9a** was treated under similar conditions, it also failed to form an indole. To determine if a trilithio reageant similar to **10** was formed, the reaction mixture was treated with excess carbon dioxide. The only new product, isolated in 60% yield, was established as the isoquinoline-1,3-dione **14** by mass spectral and ^1H NMR data. Formation of **14** rather than a phenyl analogue of **11** suggests that lithiation of the aniline methyl group never occurred. An intermediate such as **12** most likely reacted with CO_2 to form the acid **13** which then cyclized to **14** during processing of the reaction.

To test the reaction for the synthesis of highly branched alkyl or cycloalkyl groups in the 2-position of indole, we treated the *N*-(2-methylphenyl) amides of pivalic acid (**1e**), 1-methylcyclohexanecarboxylic acid (**1f**), and 1-adamantanecarboxylic acid (**1g**) with *n*-butyllithium in THF. In all three examples good yields of the 2-*tert*-butyl-[9] (**15a**, 87%), 2-(1-methylcyclohexyl- (**15b**, 76%), and the 2-(1-adamantanyl)indole (**15c**, 59%) were obtained. These yields represent a considerable improvement of the synthesis of highly α-branched indoles by the Madelung procedure.[5]

Treatment of *N*-(2-methylphenyl)acetamide (**16a**) or phenylacetamide (**16b**) with 3 equiv of *n*-BuLi followed



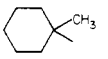
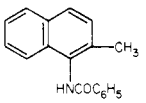
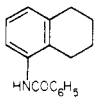
by dilute acid hyrolysis resulted in recovered starting material in both cases. To determine whether metalation had occurred, we treated the lithiated mixture with excess carbon dioxide. In both cases only the malonic acid monoamides **18a** and **18b** were isolated in 62% and 82% yields, indicating that a dianion species such as **17** had formed during lithiation. The formation of this dianion apparently deactivates or hinders the *o*-methyl to further lithiation.

When cinnanamide **19** was treated with 3 equiv of *n*-BuLi, the 1,4-addition product **20** rather than the desired 2-styrylindole was obtained in 77% yield. In order to overcome this problem, the reaction was repeated using LDA as base. The only product that could be isolated from this reaction was a dimer (M^+, 474) that was established by ^1H NMR as structure **22**. Formation of this compound probably occurred by 1,4-attack of an anion such as **21** on a lithiated form of the starting amide **19**. An explanation of the failure of **21** to undergo cyclization to indole is not readily apparent (Scheme III).

Extension of the present cyclization procedure to the *N*-benzoyl derivatives of 1-amino-2-methylnaphthalene

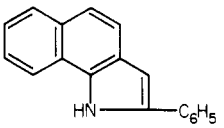
(9) The formation of **15a** in >90% yield from **1e** has been reported in ref 6.

Table II. Amides[a]

no.	R^1	R^2	R^3	method of prepn[b]	yield, %	mp, °C (recryst solv)[c]
1a	H	H	C_6H_5	A	91	142-143 (A)[d]
1b	OCH_3	H	C_6H_5	A	85	202-203 (A)
1c	Cl	H	C_6H_5	A	87	170-171 (B)
1d	H	CH_3	C_6H_5	A	79	151-152 (A)
1e	H	H	t-C_4H_9	B	95	111-112 (B)[e]
1f	H	H		B	87	137-138 (C)
1g	H	H	1-adamantyl	B	90	188-189 (A)
9a				A	70	136-137 (A)[f]
9b				A	45	128-129 (D)
16a				A	75	104 (C)[g]
16b				A	88	157-159 (E)[h]
19				A	90	170-172 (E)
25				B	35	126-128 (F)[i]
 27				A	87	184-185 (B)
 28				B	78	159-160 (B)

[a] Satisfactory (±0.3) elemental analyses (C, H, N) and infrared and ^1H NMR spectra were obtained for all new compounds. [b] See Experimental Section. [c] Recrystallization solvents: A, toluene; B, CH_2Cl_2-toluene; C, Et_2O-petroleum ether; D, EtOAc; E, toluene-pentane; F, Et_2O. [d] Lit.[17] mp 142.5-143 °C. [e] Lit.[6] mp 118-120 °C. [f] Lit.[18] mp 135-136 °C. [g] Lit.[19] mp 112 °C. [h] Lit.[20] mp 156-157 °C. [i] Lit.[9] mp 127-128 °C.

(27) and 1-amino-5,6,7,8-tetrahydronaphthalene (28) gave the benz[*g*]indole **23** and benzo[*cd*]indole **24** in 38% and 41% yields, respectively.



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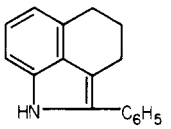

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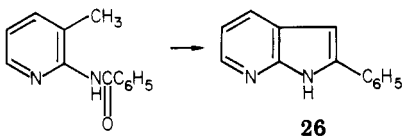
Subjecting the 3-picoline amide **25** to *n*-BuLi cyclization conditions resulted in a dark-colored mixture that failed to yield any stable product. When the *n*-BuLi was replaced by LDA the known[10] 2-phenyl-1*H*-pyrrolo[2,3-*b*]-pyridine (**26**) could be isolated in a modest yield of 22%.



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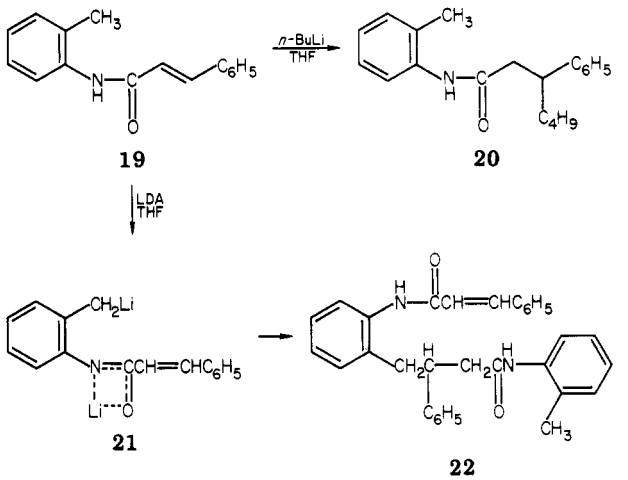
Scheme III



19 20 21 22

Experimental Section

Infrared (IR) spectra were recorded on Perkin-Elmer 257 and 457 grating infrared spectrometers, and nuclear magnetic resonance (NMR) spectra were recorded by using either a Varian T-60 or A-60A spectrometer. Chemical shifts are reported as δ values in parts per million relative to Me_4Si; coupling constants (J) are given in hertz. The mass spectra were obtained on a LKB 900 mass spectrometer. Melting points were obtained on a Thomas-Hoover capillary melting point apparatus and are uncorrected.

Except where noted solvents were reagent grade and were used as received. The organolithium reagents were obtained from Foote Mineral co. and Lithium Corp. of America and used without further purification. The tetrahydrofuran was dried by storage over 3-Å molecular sieves. Silica gel (0.063–0.2 mm) was used in preparing column chromatograms, and analytical thin-layer chromatography was conducted on precoated 40 × 80 mm plastic sheets of silica gel G with fluorescent indicator.

Preparation of Amides (Tables II). Procedures A and B. A mixture of 0.10 mol of amine, 0.10 mol of acid chloride, and 0.10 mol of triethylamine (procedure A) or 0.07 mol of anhydrous

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(20) R. A. Russell and H. W. Thompson, *Spectrochim Acta*, 8, 138 (1956).

potassium carbonate (procedure B) in 150 mL of anhydrous toluene was stirred and refluxed for 3 h and then allowed to stand for ca. 16 h at room temperature. The resulting solids (mixture of product and salts) were filtered off and stirred at room temperature for ca. 1.5 h with 150 mL of H_2O. The solid was filtered off and recrystallized from the appropriate solvent.

General Procedure for the Preparation of Indoles 8a–d and 15a–c. A stirred solution of 0.05 mol of amide **8a–d** or **15a–c** in 100 mL of dry THF maintained under a N_2 atmosphere was maintained at an internal temperature of −20 to +25 °C and treated dropwise with 0.1–0.15 mol of *n*-BuLi as 1.4 or 1.6 M *n*-BuLi in hexane. The stirred mixture was kept at ambient temperature, cooled in an ice bath, and treated dropwise with 60 mL of 2 N HCl. The organic layer was separated and the aqueous layer washed with C_6H_6. The combined organic layers were dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Recrystallization of the residue from the appropriate solvent gave the indoles listed in Table I.

2-[[(2-Carboxymethyl)benzoyl]amino]benzeneacetic Acid (11). To a stirred solution of 50.0 g (0.22 mol) of **9a** in 700 mL of THF under a N_2 atmosphere and cooled to −25 °C was added dropwise 500 mL (0.70 mol *n*-BuLi) of 1.4 M *n*-BuLi in hexane. The mixture was allowed to come to room temperature for 3 h and then poured onto ca. 450 g of crushed CO_2. After the excess CO_2 had evaporated, the mixture was treated with 100 mL of 2 N HCl and then extracted with benzene. The separated organic layer was dried with $MgSO_4$, filtered, and evaporated in vacuo. The residue was crystallized from C_6H_6 to give **11**: 46.3 g (67%); mp 175–176 °C; R_f 0.1 ($CHCl_3$–CH_3OH, 80:20) NMR (Me_2SO-d_6) δ 3.75 (s, 2 H, CH_2), 3.92 (s, 2 H, CH_2), 7.15–7.85 (m, 8 H, $2C_6H_4$), 10.3 (2 H, br, D_2O exchangeable, CO_2H).

Anal. Calcd for $C_{17}H_{15}NO_5$: C, 65.2; H, 4.8; N, 4.5. Found: C, 65.4; H, 5.0; N, 4.3.

2-(2-Methylphenyl)-4-phenylisoquinoline-1,3(2*H*,4*H*)-dione (14). By use of the procedure used to prepare **11**, 25.0 g (0.083 mol) of **9b** in 200 mL of THF and 238 mL (0.332 mol *n*-BuLi) of 1.4 M *n*-BuLi in hexane were poured onto 200 g of crushed CO_2 to give **14**: 15.7 g (60%); mp 166–167 °C (Et_2O–petroleum ether); R_f 0.66 ($CHCl_3$–CH_3OH, 95:5); NMR ($CDCl_3$) δ 2.10 (3 H, s, CH_3), 5.18 (s, 1 H, CH), 6.63–7.63 (m, 12 H, Ar), 8.30 (1 H, m, H-8); IR ($CHCl_3$) 5.85 and 5.95 μm (CONCO). Anal. Calcd for $C_{22}H_{17}NO_2$: C, 80.0; H, 5.4; N, 4.4. Found: C, 80.3; H, 5.4; N, 4.0.

3-[(2-Methylphenyl)amino]-3-oxopropanoic Acid (18a). To a stirred solution of 3.0 g (0.02 mol) of **16a** in 40 mL of dry THF under a N_2 atmosphere and cooled to an internal temperature of −30 °C was added dropwise 43.1 mL (0.06 mol of *n*-BuLi) of 1.4 M *n*-BuLi in hexane. The mixture was allowed to come to room temperature for ca. 16 h and then poured onto ca. 100 g of crushed CO_2. After the excess CO_2 had evaporated, 50 mL of 2 N HCl was added. The organic layer was separated, washed twice with H_2O, dired with anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The crude solid was washed with Et_2O to give **18a**: 2.37 g (62%); mp 130–131 °C dec; NMR (Me_2SO-d_6) δ 2.08 (3 H, s, CH_3), 3.30 (2 H, s, CH_2), 6.64–7.50 (4 H, m, Ar), 9.35 (1 H, br, NH), 11.50 (1 H, br, CO_2H); IR (KBr) 3.08 (NH), 3.28, 3.40, 3.72, 3.91 (**COOH**), 5.82 (**COOH**), 6.02 μm (**CON**). Anal. Calcd for $C_{10}H_{11}NO_3$: C, 63.5; H, 5.9; N, 8.5. Found: C, 63.3; H, 5.9; N, 8.3.

3-[(2-Methylphenyl)amino]-3-oxo-2-phenylpropanoic Acid (18b). By use of the procedure used to prepared **18a**, 4.51 g (0.02 mol) of **16b** in 40 mL of THF, 43.1 mL (0.06 mol of *n*-BuLi) of 1.4 M *n*-BuLi in hexane, and excess solid CO_2 gave after recrystallization from Et_2O, **18b**: 4.43 g (82%); mp 138–139 °C; R_f 0.22 (C_6H_6–acetone, 96:4); NMR ($CDCl_3$) δ 2.15 (3 H, s, CH_3), 4.95 (1 H, s, CH) 6.96–7.65 (9 H, m, C_6H_5, C_6H_4), 10.5 (1 H, s, NH), 12.0 (1 H, br, CO_2H); IR (KBr) 3.08 (NH), 3.15–4.40 (br, **COOH**), 5.83 (**COOH**), 6.05 (**CON**). Anal. Calcd for $C_{16}H_{15}NO_3$: C, 71.4; H, 5.6; N, 5.2. Found: C, 71.5; H, 5.7; N, 5.0.

β-Butyl-*N*-(2-methylphenyl)benzenepropanamide (20). A stirred solution of 4.75 g (0.02 mol) of **19** in 160 mL of dry THF under a N_2 atmosphere was cooled to −20 °C and treated dropwise with 28.7 mL (0.04 mol of *n*-BuLi) of 1.4 M *n*-BuLi in hexane. The deep red solution was stirred for 3 h at room temperature and then carefully treated with 40 mL of 2 N HCl. The organic phase was separated, dried with anhydrous Na_2SO_4, filtered, and evaporated in vacuo to give an oil that failed to crystallize. Chromatography on silica gel (250 g) with a C_6H_6–acetone (96:4) as the eluant gave **20**: 3.64 g (77%); mp 82–83 °C (pentane); R_f 0.6 ($CHCl_3$–CH_3OH, 90:10); NMR ($CDCl_3$) δ 0.63–1.78 (9 H, series of m, *n*-C_4H_9), 1.88 (3 H, s, CH_3), 2.60 (2 H, d, J = 8, CH_2CO), 3.08 (1 H, m, CHAr), 6.95–7.35 (9 H, m, C_6H_4, C_6H_5), 7.40 (1 H, br s, NH); IR ($CHCl_3$) 2.88 (NH), 5.97 μm (CO). Anal. Calcd for $C_{20}H_{25}NO$: C, 81.3; H, 8.5; N, 4.7. Found: C, 81.7; H, 8.5; N 4.6.

***N*-(2-Methylphenyl)-2-[(1-oxo-3-phenyl-2-propenyl)amino]-β-phenylbenzenebutanamide (22).** To a stirred solutiuon of 5.6 g (0.05 mol) of diisopropylamine in 50 mL of THF (N_2 atmosphere) cooled to an internal temperature of 5 °C was added dropwise 36.0 mL (0.05 mol of *n*-BuLi) of 1.6 M *n*-BuLi in hexane. After being stirred for ca. 2 h at room temperature, the solution was then treated dropwise with a solution of 4.75 g (0.02 mol) of **19** in 100 mL of THF and then stirred for an additional 5.5 h. The mixture was cooled in an ice bath and treated with 15 mL of 2 N HCl. The organic layer was separated, dried with $MgSO_4$, filtered, and concentrated in vacuo to give 2.09 g of a yellow foam, R_f (C_6H_6–acetone, 96:4) 0.32, 0.56 (major), 0.76 (trace). Chromatography on alumina with C_6H_6–acetone (90:10) as eluant gave **22**: 1.29 g (23%); mp 210–211 °C; R_f 0.56; NMR (Me_2SO-d_6) δ 2.23 (3 H, s, CH_3), 2.78–3.40 (5 H, m, CH_2CHCH_2), 6.85–8.25 (20 H, m, CH=CH and 18 Ar H), 9.0 (1 H, s, CONH), 9.40 (1 H, s, CONH); IR ($CHCl_3$) 2.92 and 3.03 (NH), 5.98 μm (C=O); mass spectrum, *m/e* 474 (M^+), 456 (M − H_2O), 407, 383, 367 (M − 2-$CH_3C_6H_4NH_2$), 345, 326, 238 (M − 2-$CH_3C_6H_4NHCOCH$=CHC_6H_5) 194, 180, 148. Anal. Calcd for $C_{32}H_{30}N_2O_2$: C, 81.0; H, 6.3; N, 6.0. Found: C, 81.2; H, 6.2; N, 5.8.

2-Phenylbenz[*g*]indole (23). A stirred mixture of 11.1 g (0.043 mol) of **27** in 300 mL of THF was cooled to an internal temperature of 0 °C and treated dropwise with 90 mL (0.086 mol of *n*-BuLi) of 1.6 M *n*-BuLi in hexane. The mixture was stirred for an additional 5 h at 0 °C and 16 h at room temperature, and then with ice cooling it was treated dropwise with 26 mL of saturated NH_4Cl solution. The organic layer was separated, dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Crystallization of the residue from CH_2Cl_2–pentane gave **23**: 4.0 g (38%); mp 169–171 °C; R_f 0.70 (C_6H_6/$CHCl_3$, 98:2); NMR (Me_2SO-d_6) δ 6.8 (1 H, s, H-3), 6.95–8.50 (11 H, m, aromatic), 11.5 (1 H, s, NH, D_2O exchangeable). Anal. Calcd for $C_{18}H_{13}N$: C, 88.9; H, 5.4; N, 5.8. Found: C, 88.8; H, 5.6; N, 5.7.

2-Phenyl-1,3,4,5-tetrahydrobenz[*cd*]indole (24). A stirred mixture of 10 g (0.04 mol) of **28** in 100 mL of dry THF (N_2 atmosphere) was cooled to an internal temperature of 0 °C and treated dropwise with 80 mL (0.12 mol of *n*-BuLi) of 1.6 M *n*-BuLi in hexane. The mixture was stored in a cold room (0 °C) for 18 h and then hydrolyzed with 19 mL of saturated NH_4Cl solution under ice cooling. The organic layer was separated, dried with anhydrous $MgSO_4$, filtered, and evaporated in vacuo to give an oil that failed to crystallize. Chromatography on silica gel (250 g) with $CHCl_3$ as the eluant gave **24**: 3.8 g (41%); mp 118–120 °C; R_f 0.70 (CH_2Cl_2–petroleum ether, 98:2); NMR ($CDCl_3$) δ 1.95 (2 H, m, C(4)H_2), 2.85 (4 H, m, CH_2CCH_2), 6.60 (1 H, s, NH) 6.65–7.75 (8 H, m, aromatic). Anal. Calcd $C_{17}H_{15}N$: C, 87.5; H, 6.5; N, 6.0. Found: C, 87.8; H, 6.9; N, 5.9.

2-Phenyl-1*H*-pyrrolo[2,3-*b*]pyridine (26). To a stirred solution of 10.1 g (0.1 mol) of diisopropylamine in 50 mL of dry THF (N_2 atmosphere) cooled to an internal temperature of −20 °C was added dropwise 66 mL (0.1 mol of *n*-BuLi) of 1.6 M *n*-BuLi in hexane. After the mixture was stirred an additional 0.5 h at −20 °C, a solution of 7.0 g (0.033 mol) of **25** in 50 mL of THF was added dropwise while the temperature was maintained at −20 ± 5 °C. The mixture was allowed to stand for ca. 16 h at room temperature and then treated dropwise with 18 mL of saturated NH_4Cl solution under ice cooling. The organic layer was separated, dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was crystallized from CH_2Cl_2–petroleum ether with charcoal treatment to give 1.5 g (22%) of **26**: mp 203–204 °C (lit.[10] mp 206–207 °C); R_f 0.60 (C_6H_6–$CHCl_3$, 95:5).

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Registry No. **1a**, 584-70-3; **1b**, 61495-08-7; **1c**, 61495-07-6; **1d**, 78987-16-3; **1e**, 61495-04-3; **1f**, 61495-05-4; **1g**, 54898-71-4; **8a**, 948-65-2; **8b**, 5883-96-5; **8c**, 23746-76-1; **8d**, 13228-36-9; **9a**, 22978-49-0; **9b**, 78987-17-4; **11**, 78987-18-5; **14**, 78987-19-6; **15a**, 1805-65-8; **15b**, 61495-03-2; **15c**, 26845-72-7; **16a**, 120-66-1; **16b**, 40748-53-6; **18a**, 78987-20-9; **18b**, 41951-12-6; **19**, 78987-21-0; **20**, 78987-22-1; **22**, 78987-23-2; **23**, 33555-17-8; **24**, 78987-24-3; **25**, 23612-46-6; **26**, 10586-52-4; **27**, 78987-25-4; **28**, 79005-34-8; *o*-toluidine, 95-53-4; 2-methyl-*p*-anisidine, 102-50-1; 4-chloro-*o*-toluidine, 95-69-2; *o*-ethylaniline, 578-54-1; 2-amino-3-picoline, 1603-40-3; 2-mehtyl-1-naphthylamine, 2246-44-8; 5,6,7,8-tetrahydro-1-naphthylamine, 2217-41-6; benzoyl chloride, 98-88-4; pivaloyl chloride, 3282-30-2; 1-methylcyclohexanecarbonyl chloride, 2890-61-1; 1-adamantanecarbonyl chloride, 2094-72-6; *o*-toluoyl chloride, 933-88-0; α-phenyl-*o*-toluoyl chloride, 55810-66-7; acetyl chloride, 75-36-5; phenylacetyl chloride, 103-80-0; cinnamoyl chloride, 102-92-1.

Novel Cycloaddition Products Formed by the Modified Madelung Indole Synthesis

William J. Houlihan,* Yasuyuki Uike, and Vincent A. Parrino

Sandoz, Inc., Pharmaceutical Research and Development Department, East Hanover, New Jersey 07936

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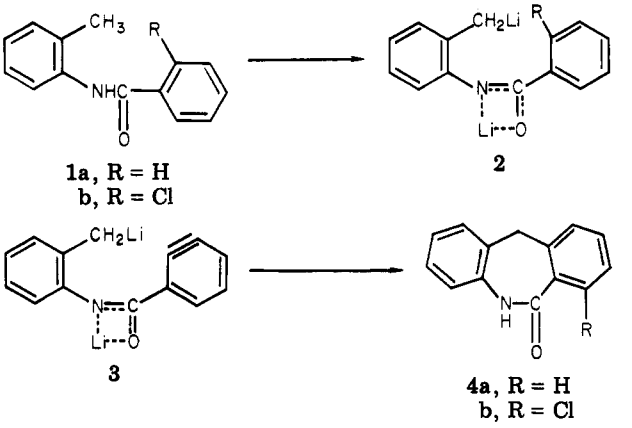
Several *N*-aryl-2,6- or -2,4-dichlorobenzamides when treated with *n*-butyllithium in THF under modified Madelung indole synthesis conditions underwent [4_π + 2_π] cycloaddition reaction to form 6,8a-ethenobenz[*cd*]isoindol-2(1*H*)-ones. *N*-(1-Naphthyl)-2,6-dichlorobenzamide under similar conditions gave rise to the [4_π + 2_π] adduct 3-chloro-6,10b-ethenonaphth[1,2,3-*cd*]isoindol-2(1*H*)-one.

In the preceding paper[1] from this laboratory it was proposed that the dilithio species **2**, formed by treating amide **1** with *n*-BuLi in THF, was an intermediate in the formation of indoles by the Madelung synthesis.[2] In the case where R is a Cl atom (**1b**) we speculated that it might be possible to form the aryne **3** and initiate an internal attack to form the dibenzazepinone **4a** (Scheme I). The present work reports our attempt to form **4** and an unexpected [4_π + 2_π] cycloaddition reaction.

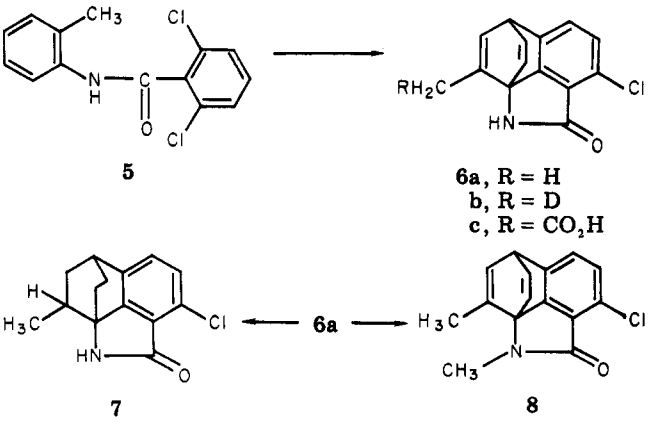
Treatment of **5** with 3 equiv of *n*-BuLi in THF at −60 °C resulted in the formation of a $C_{14}H_{10}ClNO$ compound, A, in 25% yield that gave spectral data inconsistent with the expected **4b**. The mass spectrum of A gave strong M^+ - 26 and M^+ - 40 fragments corresponding to loss of HC≡CH and HC≡CCH$_3$, respectively. The ^{1}H NMR spectrum showed a CH$_3$ doublet at δ 1.95 with a small splitting of 2 Hz, one H at δ 5.00 that was a doublet of triplets, one H at δ 6.50 as a doublet, and four H in the δ 6.82–7.38 region. These data, together with the IR and ^{13}C spectra, are best satisfied by assigning A as the novel tetracyclic 6,8a-ethenobenz[*cd*]isoindol-2(1*H*)-one **6a** (Scheme II). Additional support for this structure was obtained when **6a** absorbed 2 equiv of H_2 on catalytic reduction to form one of the two isomers of **7**. The ^{1}H NMR spectrum of **7** gave a CH$_3$ doublet (J = 6 Hz) at δ 0.4, seven aliphatic protons between δ 0.8–2.50, and a benzyl H at δ 3.20 as an unresolved multiplet. Seven signals in the ^{13}C spectrum between δ 17.8 and 58.3 were consistent with the tetrahedral C atoms found in structure **7**. Methylation of the sodium salt of **6a** afforded a *N*-methyl compound **8** that gave spectral data consistent with the assigned structure.

The formation of **6a** can best be explained by a [4_π + 2_π] cycloaddition of intermediate **9a** or **9b** to form **10a** or **10b** and then hydrolysis to **6a** (Scheme III). In order to distinguish between these possibilities, the reaction of **5** with 3 equiv of *n*-BuLi was quenched separately with D_2O or solid CO_2. In both cases only **6a** was isolated in ca. 25% yield and the deuterated or carboxylated derivatives **6b**

Scheme I



Scheme II



(1) W. J. Houlihan, V. A. Parrino, and Y. Uike, *J. Org. Chem.*, preceding paper in this issue.

(2) For a comprehensive review of the Madelung synthesis see R. K. Brown in "Indoles", W. J. Houlihan, Ed., Wiley, New York, 1972, Part I, pp 385–396.

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