Serendipitous Two-Step Synthesis of a Naphth[3,2,1-*cd*]indole

Milton J. Kornet*

College of Pharmacy, University of Kentucky, Lexington, Kentucky 40506

Alan P. Thio

Division of Regulatory Services, University of Kentucky, Lexington, Kentucky 40506

Laren M. Tolbert

Department of Chemistry, University of Kentucky, Lexington, Kentucky 40506

Received August 28, 1979

Treatment of α-methyl-β-(acetoacetyl)phenylhydrazine (**1b**) or its corresponding *N*-methylphenylhydrazone **1a** with polyphosphoric acid affords the novel naphth[3,2,1-*cd*]indole **5**. This unique transformation includes an arylation and N–N bond cleavage reminiscent of the benzidine rearrangement. Structural assignment is based on decoupling experiments, NMR simulation, and identification of the indole intermediate **3**.

In the course of our continuing investigations in the area of pharmacologically active 1,2-diaza heterocycles,[1,2] we became interested in preparing compounds of structure **2** (Scheme I). Bertho's syntheses of 5-substituted dihydrobenzazepinones from the anilides of levulinic acid and β-benzoylpropionic acid[3,4] were expected to serve as models for the synthesis of **2** by starting from the corresponding diaza precursor **1b**.

Heating **1b** with polyphosphoric acid (PPA)[5] gave after workup and purification compound A as golden crystals which strongly fluoresce yellowish green in most organic solvents. A's molecular formula of $C_{18}H_{16}N_2O$ (microanalysis and mass spectrum) ruled out structure **2**. The higher molecular weight of A relative to **1b** suggested the likelihood of ketone hydrazide (**1b**) to hydrazone hydrazide (**1a**) transformation prior to formation of A. Intermolecular conversions of this type have been reported.[6] When **1a** was similarly heated in PPA, our speculations were borne out by the isolation of A.

Since phenylhydrazones are transformed by acidic reagents into indoles (Fischer indole synthesis) we reasoned that the indole hydrazide **3** (Scheme I) might be an intermediate in the formation of A from phenylhydrazone **1a**. This belief was confirmed upon isolating A from the reaction of **3** with PPA. Indeed, even heating ethyl 1,2-dimethyl-3-indolecarboxylate (**6**), α-methylphenylhydrazine, and PPA[7] together gave A. These experiments strongly suggest that A contains as part of its structure a 1,2-dimethylindole group.

The proton NMR spectrum of A in CF_3COOH exhibits three equally intense singlets at 3.34, 3.55, and 4.26 ppm, suggesting the presence of three distinct methyl groups. In Me_2SO-d_6, one of the singlets becomes a doublet which is coupled to a downfield one-proton resonance as a quartet at 6.11 ppm, suggesting the presence of a methylamino group. The IR spectrum (KBr) shows strong absorption peaks at 1648 and 3367 cm^{-1} which are consistent with the presence of carbonyl and NH functions, respectively. Heating A with picric acid gave a picrate, while refluxing

Scheme I

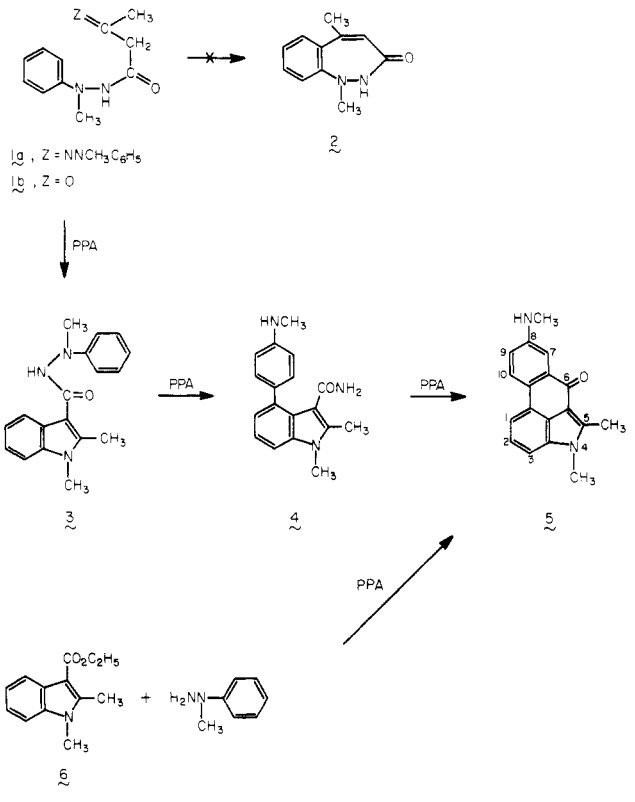

Table I. Coupling Constants and Chemical Shifts from Simulation

	chemical shift ppm			coupling constants, Hz		
ring	ν_A	ν_B	ν_C	J_{AB}	J_{BC}	J_{AC}
indole	7.78	7.46	7.31	0.6	7.5	6.5
anilino	8.08	7.45	6.92	0.0	2.5	8.5

in formic acid afforded a derivative having a molecular ion of *m/e* 304, indicating the incorporation of a single formyl group.[8] These experimental results indicate that A possesses structure **5** in which the position of the methylamino group is indeterminate.

Final structural assignment of A as **5** was based upon a detailed analysis of the aromatic region of the NMR

(1) M. J. Kornet, *J. Pharm. Sci.*, **67**, 1471 (1978).
(2) M. J. Kornet and H. S. I. Tan, *J. Pharm. Sci.*, **61**, 1936 (1972).
(3) A. Bertho, *Chem. Ber.*, **90**, 29 (1957).
(4) A. Bertho and H. Kurzmann, *Chem. Ber.*, **90**, 2319 (1957).
(5) Polyphosphoric acid is often utilized in cyclodehydrations involving a ketone and an aromatic ring. See: (a) J. Koo, *J. Am. Chem. Soc.*, **75**, 1891 (1953); (b) J. Koo, *Org. Synth.*, **40**, 43 (1960).
(6) C. V. Rogers and B. B. Corson, *J. Am. Chem. Soc.*, **69**, 2910 (1947).
(7) A related reagent, phosphoric acid, is used to prepare phenylhydrazides from esters and phenylhydrazine. See T. O. Jones, R. E. Halter, and W. L. Myers, *J. Am. Chem. Soc.*, **75**, 6055 (1953).
(8) The formyl derivative (mp 241–249 °C) was not completely purified; TLC showed contamination by starting material after 3 h of refluxing.

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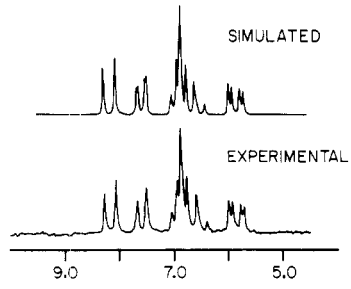

Figure 1. Aromatic region of the ^1H NMR spectra of **5**.

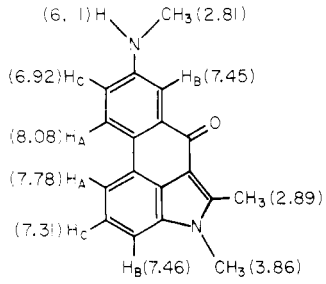

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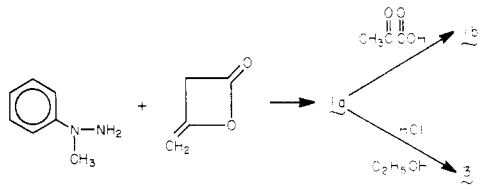
Figure 2. Compound **5** showing proton chemical shifts derived from computer simulation.

spectrum. Decoupling experiments and NMR simulation allowed a complete assignment of all chemical shifts and coupling constants, which are listed in Table I. The aromatic region consisted of two independent ABC patterns. Simultaneous simulation of the six-spin system by using the available first-order coupling constants as the initial values gave, after several iterations, the simulated spectrum shown in Figure 1. The coupling constants and chemical shifts for one ABC pattern indicate protons disposed in a 1, 2, 3 relationship on an aromatic ring and are consistent with a 4-substituted indole.[9] The other ABC pattern indicates an ortho relationship between H_A and H_C (J_{AC} = 8.5 Hz) but a para relationship between H_A and H_B (J_{AB} = 0 Hz). Protons H_B and H_C exhibit typical meta coupling (J_{BC} = 2.5 Hz). Thus this ring has protons disposed in a 1, 2, 4 relationship. Finally, we note that the chemical shift for H_A (8.08 ppm) of the second ring is typical of peri interactions in a phenanthrene system[10] while the chemical shift for H_B (7.45 ppm) is consistent with an ortho benzoyl proton.[10] The chemical shift and coupling constant data, then, enforce the structure given in Figure 2, with appropriately labeled protons. Additional confirmatory evidence was obtained by running the spectra in trifluoroacetic acid, which caused the greatest shift in protons H_B and H_C of the anilino ring.

In the preceding paragraphs, mention has been made of the sequence of the reaction pathway as **1b** → **1a** → **3** → **5**. The final step **3** → **5** warrants some additional comments. This conversion can be rationalized as an arylation accompanied by N–N bond cleavage under acidic conditions and is reminiscent of the benzidine rearrangement.[11] The betaine form of **3** is visualized as a vinyl

Scheme II



analogue of hydrazobenzene which undergoes rearrangement to the intermediate indolecarboxamide **4**. To our knowledge, the rearrangement of the indolehydrazide **3** to **4** is without precedent. The arylation product is analogous in substitution pattern to the diphenyline-type (ortho, para) product of the benzidine rearrangement. Products possessing other substitution patterns seem likely, but we have not isolated them. Intramolecular acid-catalyzed acylation of **4** produces the naphthindole **5**.

The starting material **1a** was obtained from the reaction of diketene with 2 mol of α-methylphenylhydrazine. The hydrazone hydrazide **1a** is analogous to the type of product obtained when phenylhydrazine is used.[12,13] An exchange reaction with pyruvic acid[14,15] readily converted **1a** to the ketone hydrazide (**1b**) (Scheme II). Indole hydrazide **3** was obtained from **1a** via a Fischer indole synthesis catalyzed by alcoholic hydrogen chloride. Interestingly, **5** was not produced in this reaction.

Experimental Section

Melting points were determined on a Fisher-Johns apparatus and are uncorrected. The NMR spectra were recorded on a Varian A-60A or FT-80 spectrometer, using tetramethylsilane as the internal reference. Decoupling experiments were carried out on the FT-80 spectrometer by Mr. John Layton of the Department of Chemistry. NMR spectra were simulated with the SIMEQ program written by C. W. F. Kort, adapted by M. J. A. DeBie, and supplied by Varian Associates. IR spectra were taken on a Perkin-Elmer 700 spectrophotometer using potassium bromide pellets. Mass spectra were obtained on a RMU-7 double-focusing spectrometer by Hitachi Perkin-Elmer. Elemental analyses were performed by Dr. Kurt Eder, Geneva, Switzerland. Solutions were dried over $MgSO_4$.

Ethyl 1,2-Dimethyl-3-indolecarboxylate (6). A solution of 21.8 g (93.5 mmol) of ethyl acetoacetate *N*-methyl-*N*-phenylhydrazone[16] in 240 mL of 2 N ethanolic hydrogen chloride was refluxed for 2.5 h on an oil bath. The mixture was concentrated under reduced pressure, treated with 100 mL of water, and basified by adding solid sodium bicarbonate. The product was extracted with benzene and dried. Evaporation yielded an orange solid which was triturated with petroleum ether and filtered. The off-white crystals weighed 11.8 g (58%): mp 94–94.5 °C (lit.[16] mp 95 °C); IR (KBr) 1683 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.43 (t, 3 H, ethyl CH_3), 2.70 (s, 3 H, $=CCH_3$), 3.58 (s, 3 H, NCH_3), 4.39 (q, 2 H, OCH_2), 7.11–7.33 (m, 3, $H_{4,5,6}$), 7.94–8.30 (m, 1, H_7).

α-Methyl-β-(acetoacetyl)phenylhydrazine *N*-Methyl-*N*-phenylhydrazone (1a). A solution of 20.6 g (0.245 mol) of diketene in 30 mL of dry tetrahydrofuran was added during 1 h to a magnetically stirred refluxing solution of 54.3 g (0.445 mol) of α-methylphenylhydrazine in 100 mL of dry tetrahydrofuran. The reddish solution was refluxed overnight and cooled and the solid filtered. The solid was washed with cold THF to yield 49 g (71%) of white crystals, mp 158–160 °C. A sample was recrystallized (charcoal) from ethanol; mp 160–161.5 °C.

Anal. Calcd for $C_{18}H_{22}N_4O$: C, 69.65; H, 7.14; N, 18.05. Found: C, 69.93; H, 6.67; N, 17.95.

α-Methyl-β-(acetoacetyl)phenylhydrazine (1b). A mixture of 2.0 g (6.45 mmol) of **1a**, 1.31 g (9.61 mmol) of sodium acetate

(9) (a) Although the meta coupling constant (0.6 Hz) is modestly smaller than that for the parent indole ring (1.2 Hz, see ref 9b), this is not surprising in view of the ring deformations caused by the extensive peri interactions; (b) P. J. Black and M. L. Hefferman, *Aust. J. Chem.*, 18, 353 (1965).

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(11) H. J. Shine in "Mechanisms of Molecular Migrations", Vol. 2, B. S. Thyagarajan, Ed., Interscience, New York, 1969, pp 191–247.

(12) H. Z. Lecher, R. P. Parker, and R. C. Conn, *J. Am. Chem. Soc.*, 66, 1959 (1944).

(13) N. T. M. Wilsmore and F. Chick, *J. Chem. Soc.*, 1978 (1910).

(14) E. B. Hershberg, *J. Org. Chem.*, 13, 542 (1948).

(15) H. L. Slates and N. L. Wendler, *J. Org. Chem.*, 22, 498 (1957).

(16) J. Degen, *Justus Liebigs Ann. Chem.*, 236, 157 (1886).

trihydrate, 1.69 g (9.61 mmol) of 50% aqueous pyruvic acid, 8 mL of acetic acid, and 4 mL of water was heated for 45 min on the steam bath. A 100-mL portion of water was then added, and the heating was continued for an additional 15–20 min. The mixture was cooled, basified with $NaHCO_3$, and extracted with chloroform. Evaporation of the dried chloroform solution gave 1.39 g of residue which was recrystallized from benzene–ligroin (bp 66–75 °C) to afford 0.61 g (46%) of ketone: mp 89–90 °C; IR (KBr) 1623, 1597 cm^{-1} (C=O); NMR (CF_3COOH) δ 2.45 (s, 3, CH_3C=O), 3.83 (s, 3, NCH_3), 4.02 (s, 2, CH_2C=O), 7.72 (s, 5, ArH).

Anal. Calcd for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84; N, 13.58. Found: C, 63.96; H, 6.75; N, 13.51.

α-Methyl-β-[(1,2-dimethyl-3-indole)carbonyl]phenylhydrazine (3). A solution of 0.93 g (3.0 mmol) of **1a** in 10 mL of 2 N ethanolic hydrogen chloride was heated at reflux for 80 min. The alcohol was evaporated at reduced pressure, and the residue was suspended in 10 mL of water. The mixture was basified with solid $NaHCO_3$ and extracted with chloroform. After the extract was dried, evaporation of solvent left an oily brown residue which solidified when triturated with petroleum ether and hexane. The resulting solid (0.5 g, 57%) was recrystallized from ethanol and afforded colorless crystals: mp 181.5–182 °C; NMR ($CDCl_3$) δ 2.73 (s, 3, CCH_3), 3.33 (s, 3, $NNCH_3$), 3.65 (s, 3, NCH_3), 6.53–8.10 (m, 10, NH and ArH); mass spectrum (70 eV) *m/e* 293.

Anal. Calcd for $C_{18}H_{19}N_3O$: C, 73.70; H, 6.53; N, 14.32. Found: C, 73.69; H, 6.47; N, 14.25.

4,5-Dimethyl-8-(methylamino)naphth[3,2,1-*cd*]indol-6-(4*H*)-one (5). Method A. From Ketone Hydrazide 1b. A mixture of 2.06 g (0.01 mol) of **1b** and 78 g of polyphosphoric acid was manually stirred and heated on the steam bath for 50 min. After slight cooling the mixture was poured into 350 mL of ice–water with stirring and then basified to pH 6–7 (pHydrion paper) with 50% aqueous NaOH. The precipitated solid was filtered, washed with water, and dried. Trituration with benzene resulted in 0.76 g (28%) of a yellow solid, mp 274–280 °C dec. Two recrystallizations from aqueous dimethylformamide afforded analytically pure golden crystals: mp 283–286 °C dec; IR (KBr) 1648 (C=O), 3367 cm^{-1} (NH); mass spectrum (70 eV) *m/e* 276; NMR (Me_2SO-d_6) δ 2.81 (d, 3 H, J = 1.9 Hz, NCH_3), 2.89 (s, 3 H, 2-indole CH_3), 3.86 (s, 3 H, 1-indole CH_3), 6.11 (q, J = 4.7 Hz, NH), 6.95 (dd, 1 H, J = 8.5, 2.5 Hz, Ar), 7.32–7.56 (m, 3 H, Ar), 7.82 (d, 1 H, J = 6.8 Hz, Ar), 8.12 (d, 1 H, J = 8.6 Hz, Ar); NMR (CF_3CO_2H) δ 3.34 (s, 3 H, CH_3), 3.56 (s, 3 H, CH_3), 4.26 (s, 3 H, CH_3), 7.87–8.45 (m, 4 H, Ar), 8.75 (dd, 1 H, J = 6, 2.5 Hz, Ar), 9.08, (s, 1 H, J = 7 Hz, Ar), 9.18 (br s, 1 H, Ar).

Anal. Calcd for $C_{18}H_{16}N_2O$: C, 78.24; H, 5.84; N, 10.14. Found: C, 78.29; H, 5.76; N, 10.07.

The corresponding picrate was prepared in acetone–methanol and recrystallized from DMF–acetone; mp 228–229 °C dec.

Anal. Calcd for $C_{24}H_{19}N_5O_8$: C, 57.03; H, 3.79; N, 13.86. Found: C, 57.28; H, 3.88; N, 13.81.

Method B. From Hydrazone Hydrazide 1a. A mixture of 3.0 g (9.66 mmol) of **1a** and 100 g of polyphosphoric acid was stirred and heated at 95–105 °C on an oil bath for 75 min. Workup as described under method A gave 1.2 g of crude golden solid. Recrystallization from aqueous DMF afforded crystals, mp 275–280 °C dec. IR and NMR spectra are identical with those of the product obtained from the ketone hydrazide **1b**.

Method C. From Indole Ester 6 and α-Methylphenylhydrazine. A mixture of 1.1 g (5.0 mmol) of ethyl 1,2-dimethyl-3-indolecarboxylate (**6**), 0.61 g (5.0 mmol) of α-methylphenylhydrazine, and 45 g of polyphosphoric acid was heated at 110 °C with stirring for 40 min. Workup as described under method A yielded 0.66 g of crude solid. Two recrystallizations from aqueous DMF gave golden crystals, mp 273–278 °C. A mixture melting point with the product obtained from **1b** was not depressed, and the IR and NMR spectra for the two compounds are identical.

Method D. From Indole Hydrazide 3. Polyphosphoric acid (100 g) and 2.91 g (9.93 mmol) of **3** were heated to 140 °C over a period of 90 min with manual stirring. Workup as described under method A afforded 2.63 g of crude product. Trituration with chloroform followed by recrystallization from DMF–dioxane gave pure crystals, mp 278–281 °C dec. IR and NMR spectra for this compound are identical with those obtained from the product of ketone hydrazide **1b**.

Registry No. **1a**, 72036-43-2; **1b**, 72036-44-3; **3**, 72036-45-4; **5**, 72036-46-5; **5** picrate, 72060-04-9; **6**, 20357-14-6; ethyl acetoacetate *N*-methyl-*N*-phenylhydrazone, 72036-47-6; 4-methylene-2-oxetanone, 674-82-8; α-methylphenylhydrazone, 618-40-6.

Synthesis and Reduction of Pentacyclic Immonium Salts. Application to the Synthesis of (±)-(*E*)-Norvincamone[1]

André Buzas,*[2a] Jean-Pierre Jacquet,[2b] and Gilbert Lavielle[2b]

Laboratoire de Synthèse Organique, UER Sciences, Université d' Orleans, 45045 Orleans, France, and Centre de Recherches SAUBA, 93104 Montreuil, France

Received July 24, 1979

The immonium perchlorates **7** and **10**, prepared by one-step double cyclization of the corresponding amide acids **6** and **9**, were reduced by $Zn/AcOH/H_2O$ to (±)-(*E*)-norvincamone (**8**) and (±)-vincamone (**11**), correspondingly.

We have recently reported the stereoselective reduction of the pentacyclic immonium salts of type **1**[3,4] (see Scheme I). The chemical ($NaBH_4$) or catalytic reduction of this quasi-planar molecule led exclusively the "trans isomer" **2**.[5] This result can be explained by the interaction of the reagent with the immonium carbon atom controlled by the neighboring angular ethyl group, perpendicular to the plane of the molecule. On the other hand, the dissolving-metal reduction ($Zn/CH_3COOH/H_2O$) led mainly to the formation of the "cis isomer" **3**.

We have attempted to apply this specific reduction to the synthesis of vincamine derivatives. This alkaloid family has recently been intensively investigated, as some

(1) Nomenclature and numeration are according to J. Le Men and W. I. Taylor, *Experientia*, **21**, 508 (1965).

(2) (a) Laboratoire de Synthèse Organique, UER Sciences, Université d'Orleans, 45045 Orleans, France; (b) Centre de Recherches SAUBA, 93104 Montreuil, France.

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(5) (a) E. Wenkert and B. Wickberg, *J. Am. Chem. Soc.*, **87**, 1580 (1965); (b) W. I. Taylor, "The Vinca Alkaloids", Marcel Dekker, New York, 1973, p 199.

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