Synthesis of Benz[*e*]indole and Benz[*g*]indole Carboxaldehydes

R. S. Hosmane (1) and S. P. Hiremath

Department of Chemistry, Karnatak University, Dharwar-3, India

and

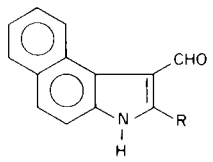
*S. W. Schneller**

Department of Chemistry, University of South Florida, Tampa, Florida 33620

Received October 4, 1973

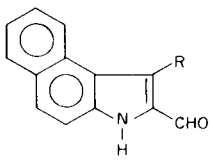
The Vilsmeier-Haack formylation reaction and several additional reactions have been employed to prepare a variety of benz[*e*]- and benz[*g*]indole-2- and 3-carboxaldehydes. Similar conditions have been utilized to prepare several 2,3-disubstituted benz[*g*]indole-5-carboxaldehydes.

As a part of a program (2) designed to expand the chemistry of benzindoles, it became necessary to synthesize a variety of carboxaldehyde derivatives (I, II, III, IV, and V).

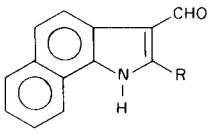


I

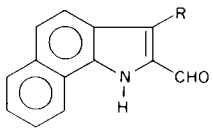
R
a; H
b; CH_3
c; CO_2Et
d; CO_2H
e; C_6H_5



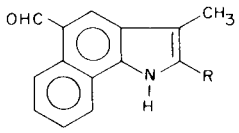
II



III

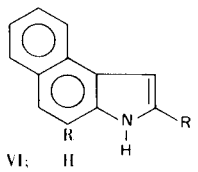


IV

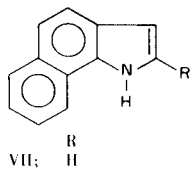


V

Direct Vilsmeier-Haack formylation on the unsubstituted (VI and VII) (3,4) or 2-phenyl (VIII and IX) (5) benzindoles was a fruitful route to Ia, IIIa, Ie, and IIIe. The readily available (4,6) 2-carboethoxy benzindoles (X and XI) could also be converted to Ia and IIIa *via* Vilsmeier-Haack formylation (7,8,9) to Ie and IIIe with subsequent saponification (Id and IIId) and decarboxylation. The aldehydes of the 2-series (*i.e.*, IIa, IVa, IIb,

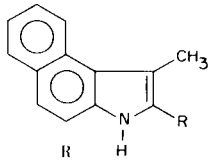


VI; H
VIII; Ph
X; CO_2Et
XII; CH_2OH

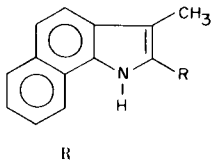


R
VII; H
IX; Ph
XI; CO_2Et
XIII; CH_2OH

and IVb) were readily prepared by direct lithium aluminum hydride reductions of X, XI, XIV, and XV (4,6) to form the corresponding 2-methanols (XII, XIII, XVI, and



XIV; CO_2Et
XVI; CH_2OH
XVIII; CO_2H
XX; H



R
XV; CO_2Et
XVII; CH_2OH
XIX; CO_2H
XXI; H

XVII) which yielded the required 2-carboxaldehydes upon manganese dioxide oxidation. Compound IVb could also be obtained by the direct reduction of IIIe to form XVII and subsequent manganese dioxide oxidation. Saponification of XIV to XVIII and the subsequent decarboxylation afforded a simple route to 3-methyl-1*H*-benz[*e*]indole (XX) also available from Ia *via* lithium aluminum hydride reduction. Likewise, 3-methyl-1*H*-benz[*g*]indole (XXI) was prepared by saponification of XV to XIX and decarboxylation or by lithium aluminum hydride reduction of IIIa. Saponification of Vc (see below) to Vd and subsequent decarboxylation afforded 3-methyl-1*H*-benz[*g*]indole-5-carboxaldehyde (Va).

TABLE I

Benz[*e*]- and Benz[*g*]indole-3- and 5-carboxaldehydes

Compound	Method	M.p., °C	Yield (%)	Purification Solvent	Found % C	H	N	Molecular Formula	Calcd. % C	H	N	Spectra	2,4-DNP (a) Derivative m.p.
Ia	B (b)	192	72	aqueous methanol			7.32	$C_{13}H_9NO$			7.11		>340
Ic	A	245	65	aqueous ethanol	71.83	4.58	5.55	$C_{16}H_{13}NO_3$	71.91	4.87	5.25		>340
Id	C	276-278	87	aqueous ethanol	70.58	3.43	5.78	$C_{14}H_9NO_3$	70.29	3.76	5.85		>340
Ie	B	256	74	ethanol	84.37	4.53	5.10	$C_{19}H_{13}NO$	84.13	4.80	5.16		300
IIa	E	262-263	78	benzene	80.12	4.28	7.33	$C_{13}H_9NO$	80.00	4.61	7.18		>340
IIb	E	291	69	benzene			6.41	$C_{14}H_{11}NO$			6.69		>340
IIIa	B (b)	168	50	aqueous methanol	80.00	4.61	7.18	$C_{13}H_9NO$	80.32	4.46	7.11	ν max 3448 (NH), 1655 (C=O) 1585 (C=C) cm^{-1}	
IIIc	A	218	69	ethylene dichloride	71.68	4.53	5.12	$C_{16}H_{13}NO_3$	71.91	4.87	5.25	ν max 3180 (NH), 1700 (C=O) 1640 (C=O), 1520 (C=C) cm^{-1} τ ($CDCl_3$) 8.55 (3H, t, J = 7.0 Hz, CH_3), 5.5 (2H, q, J = 7.0 Hz, CH_2), -0.8 (1H, s, CHO), m/e 267 (M^+), 238 (M^+-CHO), 194 (M^+-CO_2Et)	328
IIId	C	283-284 (d)	96	aqueous ethanol	70.58	3.47	5.71	$C_{14}H_9NO_3$	70.29	3.76	5.85		>350
IIIe	B	268	75	aqueous ethanol	84.42	4.91	5.38	$C_{19}H_{13}NO$	84.13	4.80	5.16		>350
IVa	E	190	85	benzene	80.25	4.37	7.04	$C_{13}H_9NO$	80.00	4.61	7.18	ν max 3390 (NH), 1650 (C=O) cm^{-1}	
IVb	E	241	81	benzene	80.63	5.12	6.35	$C_{14}H_{11}NO$	80.38	5.26	6.69	ν max 3250 (NH), 1640 (C=O) cm^{-1} τ ($CDCl_3$) 7.3 (3H, s, CH_3), -0.5 (1H, s, CHO)	315
Va	D	238	51	aqueous methanol			6.44	$C_{14}H_{11}NO$			6.69		
Vc	A	228-229	82	nitrobenzene			4.77	$C_{17}H_{15}NO_3$			4.98	τ (DMSO-d_6) 9.31 (t, J = 7.0 Hz, CH_3), 6.3 (q, J = 7.0 Hz, CH_2), 1.8 (s, 4H), -0.12 (s, CHO), m/e 281 (M^+)	
Vd	C	237-239	73	aqueous ethanol			5.38	$C_{15}H_{11}NO_3$			5.53		

(a) Satisfactory nitrogen analysis was obtained for the 2,4-DNP derivatives. (b) Also prepared by method D in 59% and 50% yields for IIIa and Ia, respectively.

TABLE II

Benz[e]- and Benz[g]indole-2-methanols

Compound	M.p., °C	Yield (%)	Found % C	H	N	Molecular Formula	Calcd. % C	H	N
XII	151	87	79.37	5.32	7.39	$C_{13}H_{11}NO$	79.19	5.58	7.11
XIII	149-150	97	79.46	5.68	7.40	$C_{13}H_{11}NO$	79.19	5.58	7.11
XVI	152	67	79.78	6.43	6.37	$C_{14}H_{13}NO$	79.62	6.16	6.63
XVII	146	74	79.38	6.37	6.35	$C_{14}H_{13}NO$	79.62	6.16	6.63

As a means of determining the site of formylation (and, thereby, electrophilic substitution) when both the 2- and 3-positions were substituted, ethyl 3-methyl-1*H*-benz[*g*]indole-2-carboxylate (XV) was subjected to the Vilsmeier-Haack conditions. Proof that substitution occurred at the 5-position (*i.e.*, to form Vc) was discernible from the nmr spectrum which lacked an absorption at a chemical shift attributable to 5-H (10,11) and exhibited a sharp singlet for the 4-proton at τ 1.8.

Finally, employing compounds VII, XI, and XV it is possible to indirectly assign the 2-H, 3-H, and N-H protons in the nmr spectra of benz[*g*]indoles. Based on the observation (11,12) that introduction of a 2-carboethoxy group into indole causes a 0.7-0.8 ppm downfield shift of the 3-H into the region normally occuppied by the 2-H, the sharp doublet for XI at τ 2.65 ($J_{1,3}$ = 2.0 Hz) can be assigned to the 3-H. From this, the triplets at τ 2.85 and τ 3.35 in the spectrum of VII can, respectively, be assigned to the 2-H and 3-H. Neither of these latter bands appeared in the spectrum of XV. The N-H proton for VII occurred at τ 1.35 while it was a broadened signal between τ 0.4 and τ 1.4 for XI and XV.

EXPERIMENTAL

Melting points are uncorrected. A Perkin-Elmer 421 was used to record ir spectra in Nujol. Varian HA-100 instrument was used to record the nmr spectra. Mass spectra were obtained using an A.E.I. MS9 instrument.

General Methods for the Preparation of Benzindolecarboxaldehydes.

Method A.

To a mixture of dimethyl formamide (2 g., 0.0275 mole) and phosphorus oxychloride (2.6 g., 0.013 mole) which had been stirred for 15 minutes under anhydrous conditions, ethylene dichloride (12 g., 0.12 mole) was added followed by the 2-carboethoxybenzindole (X, XI, and XV) (0.016 mole). After stirring and refluxing for one hour on a steam bath, the reaction mixture was poured, with stirring, into a solution of sodium acetate (12 g., 0.15 mole) in ice water (24 ml.). Trituration of the resulting precipitate twice with water and once with ether yielded the crude aldehyde which was recrystallized from the appropriate solvent. The aldehydes thus prepared are described in Table I.

Method B.

Phosphorus oxychloride (9.6 g., 0.05 mole) was added dropwise with stirring to dimethylformamide (16 g., 0.22 mole) in a flask protected from atmospheric moisture and kept at 10-20°. The benzindole (VI, VII, VIII, and IX) (0.05 mole), in dimethylformamide, was slowly added with stirring and the temperature kept at 20-30°. The mixture was then kept at 35° for 45 minutes, poured on crushed ice and the clear solution treated at 20-30° with a solution of sodium hydroxide (9.5 g., 0.24 mole) in water (50 ml.) at such a rate that the solution was always acidic, until about three quarters of alkali had been added. The last quarter was added at once and the solution quickly boiled for 1 minute and cooled. The product that separated was collected by filtration and carefully washed with water. The aldehydes thus prepared are described in Table I.

Method C.

Treatment of the appropriate ester (Ic, IIIc, and Vc) (0.0056 mole) with refluxing potassium hydroxide (2.0 g., 0.036 mole) in methanol (15 ml.) for three hours followed by the removal of the methanol *in vacuo* formed the corresponding potassium carboxylate salt. Dissolution of the salt in water (10 ml.) and resultant acidification with dilute hydrochloric acid, produced a yellowish precipitate which was filtered, washed with water, and yielded the products described in Table I.

Method D.

The necessary carboxybenzindole carboxaldehyde (Id, IIId, and Vd) (0.0042 mole) obtained in Method C was heated at 290-300° for 10 minutes to yield crude product which was purified by vacuum sublimation and subsequent recrystallization to yield the products described in Table I.

Method E.

The appropriate benzindole-2-methanol (XII, XIII, XVI, and XVII) (0.005 mole) and 4 g. of manganese dioxide were stirred in a mixture of solvents containing methylene chloride (50 ml.), tetrahydrofuran (25 ml.), and ethylene dichloride (25 ml.) for 72 hours. Subsequent filtration and evaporation of the solvent, gave the products described in Table I.

Preparation of Benz[e]- and Benz[g]indole-2-methanols.

The appropriate carboethoxyaldehyde (Ic and IIIc) or 3-methyl-2-carboxylic ester (XIV and XV) (0.019 mole) in 40 ml. of dry tetrahydrofuran was added to a suspension of lithium aluminum hydride (0.038 mole) in 80 ml. of dry tetrahydrofuran at a rate sufficient to maintain gentle refluxing. After stirring the solution for 6 hours, water (5 ml.), sodium hydroxide (5 ml., 15%),

and water (10 ml.) were added dropwise with stirring and ice cooling. The resulting white precipitate was filtered, washed with tetrahydrofuran and the combined filtrates dried over potassium hydroxide. Evaporation of the solvent yielded a colorless gummy mass which solidified upon trituration after scratching with petroleum-ether (40-60°). The resulting white products were recrystallized from benzene and are described in Table II.

3-Methyl-1*H*-benz[*g*]indole (XXI).

Treatment of a solution of IIIa (5.0 g., 0.025 mole) in 40 ml. of dry THF with a suspension of LAH (0.95 g., 0.025 mole) in 80 ml. of dry THF produced a white solid which crystallized from benzene as colorless flakes (4.0 g., 88%), m.p. 197° which gave no depression in mixture melting point determination with the authentic sample (3) obtained by hydrolysis and decarboxylation of XV.

3-Methyl-1*H*-benz[*e*]indole (XX).

a) Decarboxylation of XVIII.

3-Methyl-1*H*-benz[*e*]indole-2-carboxylic acid (XVIII) (6) (5 g., 0.022 mole) was heated at 200-220° (oil bath) for 4 to 5 hours. The residue was ether extracted, washed with sodium bicarbonate and dried over anhydrous sodium sulfate. The ether was evaporated and the residual liquid was distilled under pressure at 210°/12 mm. to yield a yellow viscous mass. After cooling, the mass solidified and was crystallized from ethanol as colorless light plates (2.5 g., 63%), m.p. 72°.

Anal. Calcd. for $C_{13}H_{11}N$: N, 8.06. Found: N, 7.94.

b) Reduction of Ia.

Employing the same procedure as used for XXI from IIIa, XX was obtained (80%) from Ia as colorless light plates from ethanol, m.p. 72°, which showed no depression in a mixture melting point determination upon an admixture with the sample obtained above.

Acknowledgements.

Thanks are due to Professor S. Siddappa, Department of Chemistry, Karnatak University, Dharwar for his keen interest and encouragement. We are obliged to Dr. B. D. Tilak, Director and Dr. S. N. Kulkarni, S. S. O., of National Chemical Laboratory, Poona for mass spectra, and to Professor M. V. Bhat of Indian Institute of Science, Bangalore for nmr spectra. One of us (S.W.S.) acknowledges the Research Council of the University of South Florida for a Release Time Award to participate in this project.

REFERENCES

(1) Present address: Department of Chemistry, University of South Florida, Tampa, Florida 33620.

(2) R. S. Hosmane, S. P. Hiremath, and S. W. Schneller, *J. Chem. Soc., Perkin I*, 2450 (1973).

(3) V. A. Desai and S. Siddappa, minor research thesis submitted to Karnatak University, Dharwar, 1962.

(4) H. N. Rydon and S. Siddappa, *J. Chem. Soc.*, 2462 (1951).

(5) A. Bischler, *Ber.*, **25**, 2860 (1892).

(6) G. K. Hughes and F. Lions, *J. Proc. Roy. Soc. N. S. Wales*, **71**, 475 (1937-1938).

(7) A. Vilsmeier and A. Haack, *Ber.*, **60**, 119 (1927).

(8) F. T. Tyson and J. T. Shaw, *J. Am. Chem. Soc.*, **74**, 2273 (1952).

(9) G. F. Smith, *J. Chem. Soc.*, 3843 (1954).

(10) P. J. Black and M. L. Heffernan, *Aust. J. Chem.*, **18**, 357 (1965); R. M. Acheson, *J. Chem. Soc.*, 2630 (1965).

(11) S. P. Hiremath and R. S. Hosmane, "Applications of Nuclear Magnetic Resonance Spectroscopy to Heterocyclic Chemistry. Indole and its Derivatives", in "Advances in Heterocyclic Chemistry", Vol. 15, A. R. Katritzy, Ed., Academic Press, New York, 1973, pp. 310-313.

(12) R. V. Jardine and R. K. Brown, *Can. J. Chem.*, **41**, 2067 (1963).