Synthesis of 2-Amino-3-carbethoxy-1-hydroxyindoles

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Received April 14, 1977

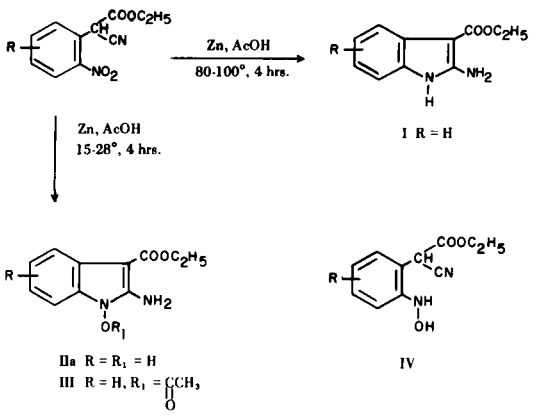
A general method is described for the synthesis of 2-amino-3-carbethoxy-1-hydroxyindoles by the reductive cyclization of 2-nitrophenylcyanoacetates using zinc and acetic acid at temperatures of 15-28°.

J. Heterocyclic Chem., 14, 1145 (1977)

1-Hydroxyindoles are relatively inaccessible and have received scant attention until very recently (1). We describe in this paper a method for the facile synthesis of 2-amino-3-carbethoxy-1-hydroxyindoles.

In the course of the synthesis of 2-amino-3-carbethoxyindole (I) by the reductive cyclization of ethyl 2-nitrophenylcyanoacetate with zinc and acetic acid according to a reported procedure (2), we observed that when the reaction was carried out at 15-28°, the product obtained was not the reported I, but 2-amino-3-carbethoxy-1-hydroxyindole (IIa) (Scheme I). The structure of IIa was readily established by comparison of the mass and pmr spectral data on I and IIa (*vide* Experimental). The molecular ion at m/e 220 in the mass spectrum of IIa and the one proton signal at δ 10.66 in the pmr spectrum of IIa assigned to the >NOH proton clearly distinguished IIa from I. The structure of IIa was confirmed by converting it to the *N*-acetoxyindole (III) which showed a strong absorption band in the ir spectrum at 1825 cm^{-1} indicative of a cyclic >NOAc group, and which on hydrogenolysis readily formed the indole I (3).

Scheme I

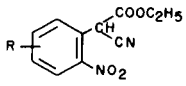


We used the method successfully to synthesize other 2-amino-3-carbethoxy-1-hydroxyindoles (Table II) bearing select substituents in the phenyl nucleus, thereby demonstrating the general applicability of the reaction. Spectral and microanalytical data on Compounds IIb-f were consistent with the assigned structures. The new ethyl 2-nitrophenylcyanoacetates used as starting materials for the reductive cyclization were prepared by a reported method (4) and are listed in Table I. The 2-hydroxyaminophenylcyanoacetates (IV) are apparently the intermediates involved in the cyclization.

The potential of the described 1-hydroxyindoles as intermediates for the synthesis of biologically active molecules has been demonstrated by us in converting them to potent anticonvulsant and antiarrhythmic agents which form the subjects of further papers (5).

Table I

Ethyl 2-Nitrophenylcyanoacetates

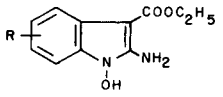


No.	R	M.p. °C	Yield (%)	Formula	Analysis, % Calculated C	H	N	Found C	H	N
1	4-CH_3	56-58 (a)	37.0	$C_{12}H_{12}N_2O_4$	58.05	4.87	11.29	58.43	5.06	11.53
2	4-OCH_3	71-73 (a)	19.6	$C_{12}H_{12}N_2O_5$	54.55	4.58	10.61	54.65	4.78	10.58
3	4-Cl	Viscous liquid	72.6	$C_{11}H_9ClN_2O_4$	49.17	3.37	10.43	49.16	3.35	10.41
4	4-$NHCOCH_3$	163-164 (b)	36.5	$C_{13}H_{13}N_3O_5$	53.59	4.49	14.43	53.70	4.77	14.78
5	5-CH_3	Viscous liquid	50.0	$C_{12}H_{12}N_2O_4$	58.05	4.87	11.29	58.00	5.10	10.97
6	5-Cl	66-67 (c)	26.0	$C_{11}H_9ClN_2O_4$	49.17	3.37	10.43	49.52	3.66	10.57

Solvent of crystallization: (a) ether, (b) methanol, (c) ether-petroleum ether (60-80°).

Table II

2-Amino-3-carbethoxy-1-hydroxyindoles



No.	R	M.p. °C	Yield (%)	Formula	Analysis, % Calculated C	H	N	Found C	H	N
IIa	H	175-176 (a)	53.5	$C_{11}H_{12}N_2O_3$	59.99	5.49	12.73	60.50	5.55	12.41
IIb	5-CH_3	205-207 (b)	37.8	$C_{12}H_{14}N_2O_3$	61.53	6.02	11.97	61.20	5.88	11.58
IIc	6-CH_3	196-197 (a)	54.5	$C_{12}H_{14}N_2O_3$	61.53	6.02	11.97	61.30	6.01	12.21
IId	6-OCH_3	172-174 (a)	32.2	$C_{12}H_{14}N_2O_4$	57.61	5.64	11.20	58.0	5.67	10.94
IIe	6-Cl	192-195 (a)	65.5	$C_{11}H_{11}ClN_2O_3$	51.87	4.35	11.00	52.26	4.31	10.79
IIf	6-$NHCOCH_3$	234-235 (c)	39.0	$C_{13}H_{15}N_3O_4$	56.29	5.45	15.25	56.35	5.59	15.43

Crystallized from (a) ether-benzene, (b) ether-petroleum ether (60-80°), (c) methanol.

EXPERIMENTAL (6)

Melting points were taken on a Boetius micro melting point apparatus and are uncorrected. The ir (potassium bromide) spectra were obtained on a Perkin-Elmer model 157 spectrophotometer, and pmr spectra were recorded on a Varian T-60 spectrometer using tetramethylsilane as an internal standard, s = singlet, t = triplet, q = quartet, m = multiplet, b = broad.

Ethyl 2-Nitrophenylcyanoacetates (Table I).

The compounds were prepared according to a previously reported procedure (4).

2-Amino-3-carbethoxy-1-hydroxyindole (IIa).

A solution of ethyl 2-nitrophenylcyanoacetate (1 g.) (4) in glacial acetic acid (20 ml.) was cooled to 15-20° and zinc dust (4 g.) was added. The reaction mixture was stirred at 15-20° for 30 minutes, and then at room temperature (28°) for 3 hours. The reaction mixture was filtered and the residue washed with 5 ml. of glacial acetic acid. The filtrate was diluted with ice-cold water and the solid which separated was filtered, dried and crystallized. For details of solvents of crystallization, yields and physical data, refer to Table II. This compound had ir: ν 3400, 3200, 2940, 1650, 1630 cm^{-1}; pmr (deuteriochloroform + 1 drop of DMSO-d_6): δ 1.40 (3, t, $COOCH_2CH_3$), 4.33 (2, q, $COOCH_2CH_3$), 6.10 (2, b, NH_2), 7.10 (3, m, aromatic H), 7.75 (1, m, aromatic H), 10.66 (1, b, NOH); ms: m/e (relative intensity) 220 (50, M^+), 204 (42), 174 (39), 158 (100), 130 (44).

2-Amino-3-carbethoxyindole (I).

The procedure described for the preparation of IIa was used with the difference that the solution of 2-nitrophenylcyanoacetate was heated to 100° before the addition of zinc, and the reaction mixture was stirred at that temperature for 5 hours before work-up. The product was crystallized from benzene, m.p. 178-180°; ir: ν 3450, 3350, 3000, 1665, 1650 cm^{-1}; pmr (deuteriochloroform + 2 drops DMSO-d_6): δ 1.41 (3, t, $COOCH_2CH_3$), 4.36 (2, q, $COOCH_2CH_3$), 6.10 (2, b, NH_2), 7.0 (3, m, aromatic H), 7.73 (1, m, aromatic H), 9.93 (1, b, NH); ms: m/e (relative intensity) 204 (88, M^+), 158 (100), 130 (17).

Anal. Calcd. for $C_{11}H_{12}N_2O_2$: C, 64.70; H, 5.92; N, 13.72. Found: C, 65.06; H, 5.48; N, 13.68.

2-Amino-3-carbethoxy-1-hydroxyindoles (IIb-IIf).

The compounds were prepared according to the procedure described above for IIa. In the preparation of IId, a solid material did not separate on dilution with water. The suspension was extracted with ether and the ethereal layer worked up as usual to give the desired product. In the work-up of IIf, acetic acid was removed from the reaction mixture by distillation under vacuum and the residue crystallized.

Acetylation of IIa (III).

Acetic anhydride (1.5 ml.) was added to a cooled solution of IIa (1 g.) in dry pyridine (1.25 ml.) and the mixture was stirred at room temperature for 5 hours. It was poured into an ice-water mixture and the solid which separated was filtered and crystallized from methanol, yield, 30%, m.p. 117-119°; ir: ν 3400, 1825, 1670, 1630 cm^{-1}; pmr (deuteriochloroform + 1 drop of DMSO-d_6): δ 1.41 (3, t, $COOCH_2CH_3$), 2.44 (3, s, $OCOCH_3$), 4.35 (2, q, $COOCH_2CH_3$), 6.58 (2, b, NH_2), 7.00 (3, m, aromatic H), 7.73 (1, m, aromatic H); ms: m/e (relative intensity) 262 (79, M^+), 204 (20), 158 (100), 130 (29).

Anal. Calcd. for $C_{13}H_{14}N_2O_4$: C, 59.51; H, 5.38; N, 10.69. Found: C, 59.24; H, 4.96; N, 10.78.

Hydrogenolysis of III.

A stream of hydrogen was bubbled through a stirred solution of III (0.4 g.) in ethanol (30 ml.) over 5% palladium-charcoal for 0.5 hour. The reaction mixture was filtered and the filtrate evaporated to dryness *in vacuo*. The residue was recrystallized from benzene to give a product which was identical (mixed m.p., ir, nmr) with I.

REFERENCES AND NOTES

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(5) K. L. Munshi, A. N. Dohadwalla, B. K. Bhattacharya, H. Kohl and N. J. de Souza, presented in part at the 2nd Conference of the Commonwealth Pharmaceutical Association at Bombay, India, January 16-20, 1977.

(6) We wish to thank Miss P. Colaco for technical assistance in the preparation of compounds, Dr. P. K. Inamdar and Mr. H. V. Ruparel for microanalytical and spectral determinations, and Dr. S. Selvavinayakam, Ciba-Geigy Research Centre, Goregaon, Bombay, India, for recording the mass spectra.