Optically Active Heteroaromatic Compounds IX (1). Preparation, Absolute Configuration and Optical Purity of Some Chiral 3-Alkylindoles

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The Fischer and Brunner reactions as well as the Grignard alkylation of isatin have been used to prepare (*S*)-3-*sec*-butyl- and (*S*)-3-(2-methylbutyl)indoles, respectively, starting from (*S*)-1-chloro-2-methylbutane. The stereospecificity of the synthetic sequences followed has been investigated and the stereochemical relationships of the title compounds have been established.

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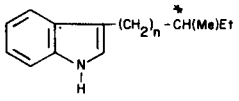
There has been considerable interest, particularly from biological and pharmacological viewpoints, in the chemistry of 3-substituted indole derivatives (2). However, no attempt has been made to prepare simple optically active 3-alkylindoles. As part of our continued study of stereochemical aspects in the synthesis of heteroaromatic compounds (1) and the chiroptical properties of aromatic and heteroaromatic chromophores (3), we have now investigated the synthesis of racemic and optically active 3-*sec*-butyl- (**1**) and 3-(2-methylbutyl)indoles (**2**). These compounds might be useful as relay points in establishing the stereochemistry of more complex indolic natural products and in the investigation of conformational properties (3) of biological macromolecules. This contribution deals with the preparation of racemic **1** and optically active **1** and **2** together with the determination of their stereochemical correlation to known optically active compounds.



1 n=0
2 n=0

Results and Discussion.

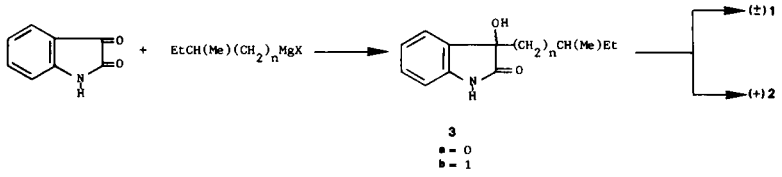
Preparation of (±)-1 and (+)-2 (Scheme I).

The alkylation of isatin with suitable Grignard reagents afforded the corresponding 3-alkyl-3-hydroxyoxindoles (**3**), which by reduction with lithium aluminum hydride in refluxing ether (4), gave compounds (±)-**1** and (+)-**2** (Scheme I) in satisfactory yields (62-70%). In disagreement with literature reported results concerning isatin alkylation by Grignard reagents (5), compounds **3a,b** were obtained (10-14%) only when an ether or dioxane solution of isatin was added (Table I) (6) to the Grignard reagent in ether. By starting from a sample of (*S*)-1-chloro-2-methylbutane, $[\alpha]_D^{25}$ +1.59° (neat) (7), chemically pure (+)-**2**, $[\alpha]_D^{25}$ +9.96° (chloroform), was recovered. The structures of compounds **1,2** and **3** were confirmed by nmr, ir and mass spectra (see Experimental).

Preparation of (+)-1 (Schemes II, III).

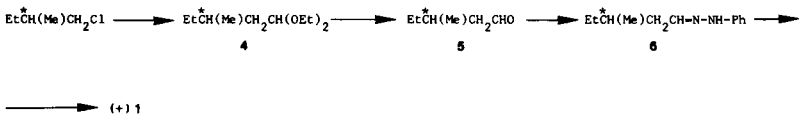
The (*S*)-3-methylpentanal phenylhydrazone (**6**), prepared as usual starting from (*S*)-1-chloro-2-methylbutane, $[\alpha]_D^{25}$ +1.59° (neat), 43% overall yield (8), was dissolved in glacial acetic acid and reacted with boron trifluoride (9) (Scheme II). The reaction mixture, refluxed for 3 hours, afforded after hydrolysis and distillation, 95% chemically pure (+)-**1** (20%). After gc purification, a sample of pure **1**, $[\alpha]_D^{25}$ +11.20° (carbon tetrachloride), was recovered; in a further run, after 30 minutes heating, 95% pure **1** (37%) was obtained. This last sample, after gc purification, showed $[\alpha]_D^{25}$ + 12.98° (carbon tetra chloride).

Scheme I



3
a = 0
b = 1

Scheme II



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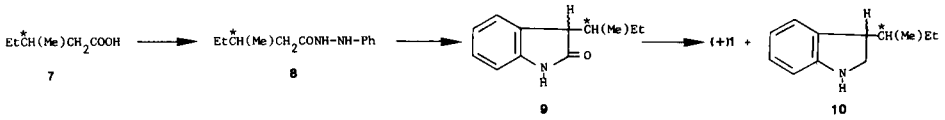
Scheme III

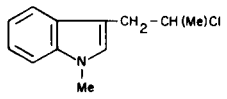


The discrepancy in the optical rotations of compounds (+)-**1** showed that the stereochemical course of the Fischer reaction (9) was affected by reaction conditions. As the evaluation of the enantiomeric purity of (+)-**1**, through its correlation to products of known optical purity, appeared very difficult owing to reasonable racemization phenomena during the oxidative degradation (10), a different and independent preparation of (+)-**1** was accomplished (Scheme III). (*S*)-3-Methylpentanoic acid (**7**), $[\alpha]_D^{25}$ +8.45° (neat) (11,12), was converted into the corresponding phenylhydrazide (**8**) (50-60%) (13), which by heating at *ca.* 200° with calcium oxide (14), yielded (65%) (+)-3-*sec*-butyloxindole (**9**) (15). The reduction of this last compound with sodium in 1-propanol (18) afforded (50%) a 9:1 mixture of (+)-**1** and the corresponding indoline (+)-**10** (Scheme III) (19).

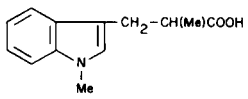
Two subsequent preparations, starting from the same sample of (+)-**7**, afforded after gc purification, samples of (+)-**1** having $[\alpha]_D^{25}$ +12.68° (carbon tetrachloride) and +12.98° (carbon tetrachloride), respectively; in the former run, a sample of pure (+)-**10**, $[\alpha]_D^{25}$ +37.53° (carbon tetrachloride), was recovered. Nmr, ir and mass spectra confirmed the structure of compounds **8**, **9** and **10** (see Experimental).

Since the synthesis, resolution and stereochemical relationships of 2-(3-indolyl)propionic acid (**11a**) have been reported (23), we have also attempted its conversion into optically active **1** (Scheme IV). The alcohol (**12a**) was prepared in good yield (80%) by lithium aluminum hydride reduction of the acid (**11a**) (24), but the conversion of **12a** into the chloride **13a** (25) or into compound **14a** (26) completely failed and only traces of the expected compounds along with a large amount of isomeric and polymeric products were obtained.

In order to correlate (+)-**1** to optically active **11a** through the N-methyl derivative of (+)-**1**, we have attempted the sequence reported in Scheme IV starting from **11b**, prepared from **11a** (27). The conversion of 2-[3-(1-methylindolyl)]propan-1-ol (**12b**) into the corresponding chloride (**13b**) was carried out by adopting the same reaction conditions reported to avoid the isomerization of indolmycenic acid (25b); surprisingly, equimolecular amounts of 1-chloro-2-[3-(1-methyl indolyl)]propane (**13b**) and 1-[3-(1-methylindolyl)]-2-chloropropane (**16b**) were recovered (28) (see Experimental). Owing to the difficulty of separation (29), the chloride mixture was converted, *via* the Grignard reagent, into the corresponding mixture of carboxylic acids. As any attempts to purify the acid (**15b**) from the isomeric **17b** failed, it was impossible to carry out a close correlation of the optically active **11a** to (+)-**1**.



(16b)

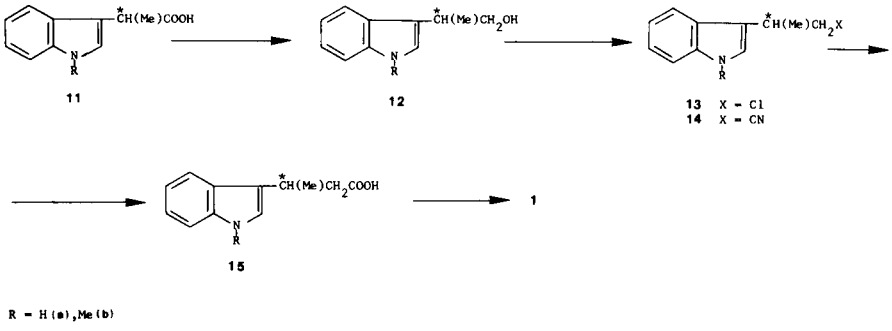


(17b)

Absolute Configurations and Optical Purity of (+)-**1** and (+)-**2**.

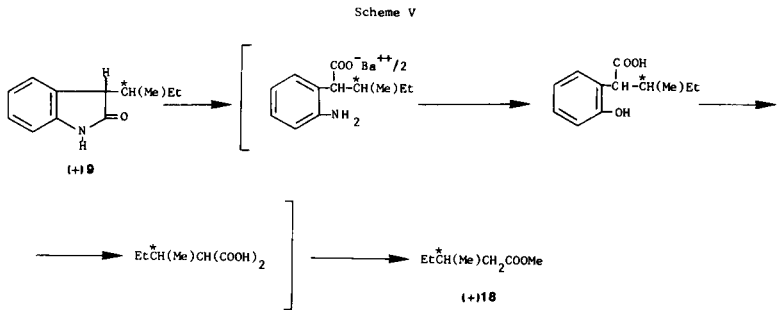
Starting from (*S*)-1-chloro-2-methylbutane, samples of (+)-**1** (Schemes II and III) as well as (+)-**2** (Scheme I) were prepared. Since in principle the adopted sequences should not affect the chiral center, absolute *S* configuration should be obtained for the indole derivatives prepared, especially in the case of compound (+)-**2**, since its synthesis is unambiguous (Scheme I). On this basis it is possible to attribute to (*S*)-**2**, $[\alpha]_D^{25}$ +9.96° (chloroform), the same minimum optical purity (96%) as the starting

Scheme I V



R = H (a), Me (b)

Scheme V



(*S*)-1-chloro-2-methylbutane (7) used in its preparation (Scheme I).

To check this assumption for (+)-**1**, in which the chiral center is directly bound to the heteroaromatic nucleus, the degradation of compound **9** to the acid (**7**) was also accomplished (Scheme V). A sample of compound (+)-**9** was converted, *via* barium 2-(*o*-aminophenyl)-3-methylpentanoate, into the corresponding phenolic derivative (30), and this last compound was reacted without any purification with ozone at 0°. The ozonide, after the usual oxidative decomposition, decarboxylation and esterification with diazomethane, yielded a complex mixture from which, by gc purification, a sample of methyl (*S*)-3-methylpentanoate (**18**) was recovered (Scheme V).

This result confirms the absolute *S* configuration of the chiral center in the 1′-position of (+)-**9** along with those of (+)-**1** and (+)-**10**. Even if the direct correlation between optically active 2-(3-indolyl)propionic acid (**11a**) and (+)-3-*sec*-butylindole (**1**) failed, it is now possible to obtain this relationship through indolmycenic acid (24), since this last compound may be related to (*S*)-2-methylbutan-1-ol (31). Moreover, taking into account the experimental results obtained in the reaction sequences of Schemes II and III and the optical rotation, $[\alpha]^{25}_{365}$ +17.14° (toluene), of the recovered ester (**18**) (Scheme V), it appears reasonable to attribute (*S*)-**1**, $[\alpha]^{25}_{D}$ +12.98° (carbon tetrachloride), with the same optical purity of its precursors (96%)(12).

The capability of the Fischer (9) and Brunner (14) reactions in the synthesis of optically active 3-substituted indoles is so pointed out. The racemization (*ca.* 14%) observed in the Fischer reaction can be attributed to the influence of the acidic reaction medium on (+)-**1**, analogous to what has been observed in the case of some optically active aromatic hydrocarbons in the presence of Lewis acids (32).

EXPERIMENTAL

Melting points were determined on a Kofler bank and boiling points are uncorrected. Gas-liquid chromatographic analyses were carried out on Perkin Elmer F-30 or 3920-B instruments with flame ionization detectors (nitrogen as the carrier gas), using 2 m x 0.29 cm columns packed with 8% Carbowax 20M and 2% potassium hydroxide on 80-100 mesh Chromosorb W (CW 20M), and 2.5% Silicone gum rubber on 80-100 mesh AW-DMCS Chromosorb G (SE 301). Gas-liquid chromatographic purifications were carried out on a Perkin Elmer F21 chromatograph using 2 or 3 m x 0.95 cm columns packed with 3% Silicone gum rubber on Chromosorb G AW-DMCS 60-80 mesh (SE 301). Nmr spectra were recorded on a Jeol PS-100 instrument, TMS being used as internal standard if not otherwise specified. Ir data were determined with a Perkin Elmer 225 spectrophotometer. Optical rotations were measured on a Perkin Elmer 142 or a Schmidt-Haensch polarimeter using 2- or 1-dm cells and neat samples if not otherwise specified. Mass spectra were taken on a Varian Mat CH-7 mass spectrometer operated at 70 eV. The samples were introduced into the ion source by means of a direct insertion probe if not otherwise stated; the temperature at the site of evaporation varied between 50-100° according to the volatility of the individual substances. Microanalyses were obtained from the Micro-Analysis Laboratory of the Faculty of Pharmacy of the Pisa University.

(±)-3-*sec*-Butyl-3-hydroxyoxindole (**3a**).

Table I

Alkylation of Isatin (A) with Grignard Reagents of General Formula $EtCH(Me)(CH_2)_nMgX$(B), X = Cl, Br

n	A/B (a)	Reaction Time (Hours)	Reaction Temperature (°C)	%Yield
0	1 (b,c)/7 (b)	580	35	3.5
0	1 (b,c)/5 (b)	335	35	10
1	1 (e)/5 (b)	10		14
1	1 (e)/5 (b)	10	102	traces
1	1 (f)/5 (f)	10	80	traces

(a) Molar ratio. (b) In ether. (c) Isatin was added by a Soxhlet extractor. (d) The reaction apparatus was equipped with two Soxhlet extractors to add the isatin. (e) In dioxane. (f) In benzene.

To an ethereal boiling solution of the Grignard reagent (1.53 moles), prepared in the usual way from 2-bromobutane, were added by means of a Soxhlet extractor, 21.0 g. (0.140 mole) of purified isatin. After 335 hours, the mixture was cooled and hydrolyzed with water and 5% hydrochloric acid. The organic layer was extracted with ether and dried (sodium sulfate), giving after concentration, a red oil, which was recrystallized from chloroform, yielding (10%) 2.8 g. of **3a**, m.p. 163-173°; nmr (DMSO-d_6): δ 10.1-9.8 (1H, s), 7.3-6.7 (4H, m), 5.8-5.7 (1H, s), 2.0-1.6 (1H, m), 1.2-0.5 (8H, m); ms: m/e (I%) 149 (100), 148 (33), 205 (15, M^+), 65 (12).

Anal. Calcd. for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.35; H, 7.40; N, 6.70.

(2′ *S*)-3-(2′-Methylbutyl)-3-hydroxyoxindole (**3b**).

To an ether solution of the Grignard reagent (1.00 mole) of (*S*)-1-chloro-2-methylbutane, $[\alpha]_D^{25}$ +1.59°, was slowly added through a dropping funnel, a hot solution of 30.0 g. (0.204 mole) of isatin in 600 ml. of anhydrous dioxane. The mixture was heated at reflux for 10 hours and then hydrolyzed with a saturated solution of ammonium chloride and dilute acetic acid. The organic phase, recovered as usual, was concentrated *in vacuo* to give a red oil which was recrystallized from chloroform, yielding (14%) 6.0 g. of **3b**, m.p. 136-140°; nmr (DMSO-d_6): δ 10.1-9.8 (1H, s), 7.4-6.4 (4H, m), 2.2-2.1 (1H, s), 2.0-1.4 (1H, m), 1.4-0.4 (10H, m).

Anal. Calcd. for $C_{13}H_{17}NO_2$: C, 71.20; H, 7.82; N, 6.39. Found: C, 71.35; H, 7.78; N, 6.15.

(±)-3-*sec*-Butylindole (**1**).

By using a Soxhlet extractor, 2.80 g. (13.6 mmoles) of **3a** were added to a suspension of 5.0 g. (0.133 mole) of lithium aluminum hydride in 300 ml. of dry ether. The mixture was refluxed for 10 hours and then hydrolyzed with water and 10% hydrochloric acid solution. The organic phase was washed and dried (sodium sulfate), giving 1.6 g. (70%) of pure (SE 301, 150°) **1**, b.p. 131-132° (0.035 mm); ir (potassium bromide): 3410, 3050, 2960, 2930, 2870, 1640, 1450, 740 cm^{-1}; nmr (carbon tetrachloride): δ 7.6-7.4 (1H, m), 7.1-6.8 (3H, m), 6.6-6.3 (1H, s), 6.3-6.2 (1H, m), 3.0-2.6 (1H, m), 1.4-1.2 (3H, d), 1.8-1.4 (2H, m), 1.0-0.6 (3H, t); ms: m/e (I%) 144 (100), 115 (50), 117 (44), 173 (42, M^+).

Anal. Calcd. for $C_{12}H_{15}N$: C, 83.19; H, 8.73. Found: C, 83.34; H, 8.73.

(+)-3-(2′-Methylbutyl)indole (**2**).

By adopting the above reported procedure, 6.0 g. (27.4 mmoles) of **3b** were reduced with 10.2 g. (0.269 mole) of lithium aluminum hydride to give 3.2 g. (62%) of pure (SE301, 150°) **2**, b.p. 103-105° (0.02 mm), $[\alpha]_D^{25}$ +9.96° (c 2.158, chloroform); ir (potassium bromide): 3420, 3060, 2960, 2920, 2880, 1620, 1410, 740 cm^{-1}; nmr (carbon tetrachloride): δ 7.6-7.2 (1H, m), 7.1-6.5 (3H, m), 6.5-6.3 (1H, s), 6.3-6.1 (1H, m), 2.8-2.2 (2H, dq), 1.8-0.6 (9H, m); ms: m/e (I%) 130 (100), 131 (14), 187 (13, M^+).

Anal. Calcd. for $C_{13}H_{17}N$: C, 83.37; H, 9.15. Found: C, 83.27; H, 9.18.

(*S*)-3-Methylpentanal Phenylhydrazone (**6**).

In a typical run, a mixture of 24.1 g. (0.122 mole) of (*S*)-1,1-diethoxy-3-methylpentane [b.p. 68° (12 mm), n_D^{25} 1.4067, $[\alpha]_D^{25}$ +7.32°, prepared (8) from (*S*)-1-chloro-2-methylbutane, $[\alpha]_D^{25}$ +1.59°] and 42 ml. of 10% sulfuric acid was refluxed, under nitrogen, for 36 hours and then steam distilled. The organic product was recovered with purified ether and dried (sodium sulfate). The solvent was removed at reduced presure and the crude aldehyde was treated with 250 ml. of an aqueous solution of 33.8 g. (0.410 mole) of sodium acetate and 25.0 g. (0.145 mole) of phenylhydrazine hydrochloride. The mixture was heated at 60° for 2 hours and then extracted with ether. The ethereal layer, washed with dilute sulfuric acid, saturated sodium bicarbonate solution and water, was dried (sodium sulfate) and distilled to give 17.0 g. (77%) of 98% chemically pure (SE 301, 140°) **6**, b.p. 135-140° (1mm); nmr (carbon tetrachloride): δ 7.6-6.2 (7H, m), 2.4-1.8 (1H, m), 1.8-0.6 (10H, m).

Anal. Calcd. for $C_{12}H_{18}N_2$: C, 75.74; H, 9.54. Found: C, 75.90; H, 9.65.

(+)-3-*sec*-Butylindole (**1**).

A mixture of 9.6 g. (0.050 mole) of **6** and 13.5 ml. of glacial acetic acid was treated at room temperature, with 5.7 ml. of boron trifluoride etherate. The solution was allowed to reflux and when the spontaneous boiling stopped (10 minutes), refluxing was prolonged for 3 hours by external heating. The mixture, cooled at room temperature, was poured into cold water and the organic products were extracted with ether. The ethereal solution was washed with water, a 10% sodium bicarbonate solution, water and dried (potassium carbonate). The solvent was removed to give, after two distillations, 0.85 g. (20%) of 95% chemically pure (SE 301, 150°) **1**. The sample, purified by preparative gc (SE 301, 130°), b.p. 110° (0.04 mm), $[\alpha]_D^{25}$ +11.20° (c 7.70, carbon tetrachloride), showed ir, nmr and mass spectra identical to those of (∓)-**1**. In a repeated run, starting from 13.6 g. (0.071 mole) of **6** and 6.0 ml. of boron trifluoride etherate, in 14 ml. of glacial acetic acid, after 15 minutes reflux, 4.5 g. (37%) of 95% pure **1** were recovered. This sample, purified by preparative gc, showed $[\alpha]_D^{25}$ +12.98° (c 7.19, carbon tetrachloride).

(+)-3-Methylpentanoyl-β-phenylhydrazide (**8**).

In a representative run, 100 g. (0.860 mole) of (*S*)-3-methylpentanoic acid (**7**), $[\alpha]_D^{25}$ +8.45°, and 225 ml. (2.26 moles) of freshly distilled phenylhydrazine were boiled gently for 2 hours. After cooling, the reaction mixture was taken up in ether and washed with dilute sulfuric acid, 5% sodium hydroxide solution and water. Concentration of the dried (sodium sulfate) extracts left 110 g. of a solid residue which was recrystallized from benzene to yield (57%) 101 g. of **8**, m.p. 117°, $[\alpha]_D^{25}$ +5.88° (c 3.01, chloroform); ir (potassium bromide): 3310, 3240, 1670, 1500, 750, 690 cm^{-1}; nmr (acetone-d_6): δ 8.4 (1H, s), 6.8-6.1 (6H, m), 2.2-1.5 (3H, m), 1.4-1.0 (2H, m), 1.0-0.6 (6H, m).

Anal. Calcd. for $C_{12}H_{18}N_2O$: C, 69.87; H, 8.80; N, 13.58. Found: C, 70.09; H, 8.96; N, 13.60.

From the basic water, 41.0 g. of the acid **7**, $[\alpha]_D^{25}$ +8.45°, were recovered.

(+)-3-*sec*-Butyloxindole (**9**).

In a typical run, 10.0 g. (0.048 mole) of (+)-**8** and 5.4 g. (0.096 mole) of calcium oxide dried at 900° for 12 hours, were stirred under nitrogen at 210-220° for 1.5 hours. During this period a large amount of ammonia was evolved. After cooling at 50°, 20% hydrochloric acid was added and the reaction mixture was stirred until all solid and gummy materials were dissolved. The organic layer, extracted with chloroform, washed with 5% sodium hydroxide solution and water, was dried (sodium sulfate). The solvent was evaporated and the residue yielded (65%) 4.4 g. of >98% pure (SE 301, 180°) **9**, b.p. 142-143° (0.03 mm), $[\alpha]_D^{25}$ +13.10° (c 5.19, benzene); ir (potassium bromide): 3200, 2960, 2930, 2880, 1700, 1660, 1620. 1470, 750 cm^{-1}; nmr (carbon tetrachloride): δ 10.4 (1H, s), 7.2-6.7 (4H, m), 3.4 (1H, m), 2.4-1.9 (1H, m), 1.9-1.2 (2H, m), 1.2-0.6 (6H, m); ms: m/e (I%) 133 (100), 189 (25, M^+), 132 (19).

Anal. Calcd. for $C_{12}H_{15}NO$: C, 76.15; H, 7.99; N, 7.40. Found: C, 76.34; H, 8.08; N, 7.58.

(+)-3-*sec*-Butylindole (**1**).

To a hot solution (80°) of 3.3 g. (17.4 mmoles) of (+)-**9**, in 300 ml. of absolute 1-propanol, 18.5 g. (0.80 g-atom) of sodium were slowly added. The mixture was stirred until all the metal was dissolved. After cooling, 20% sodium chloride solution was added and the organic products, extracted with ether, were washed with water and dried (sodium sulfate). The solvent was removed under reduced pressure and the resulting crude mixture of **9**, **1** and 3-*sec*-butylindoline (**10**), in the ratio of 6:9:1 (SE 301, 150°), was distilled; the recovered **9** was reduced again. The combined reduction mixtures, by preparative gc (SE 301, 145°), gave 1.2 g. (37%) of pure **1**, $[\alpha]_D^{25}$ +12.68° (c 7.73 carbon tetrachloride); this product was spectrally and chromatographically identical with the sample obtained from the Fischer reaction. In a repeated run, starting from the same sample of (+)-**9**, by preparative gc purification, pure **1**, $[\alpha]_D^{25}$ +12.98° (c 7.70 carbon tetrachloride), and **10**, $[\alpha]_D^{25}$ +37.53 (c 3.30, carbon tetrachloride), were recovered. This last product showed nmr (carbon tetra-

chloride): δ 7.2-6.1 (5H, m), 3.7-3.3 (3H, m), 2.1-0.6 (9H, m); ms: m/e (I%) 116 (100) 118 (65), 173 (25), 115 (21), 90 (17), 117 (16), 91 (16), 142 (15), 175 (12, M^+), 65 (11), 128 (8).

(±)-Methyl 2-(3-Indolyl)propanoate (**11a**, Methyl Ester).

In a typical run, a mixture of 12.5 g. (0.067 mole) of **11a** (23a), 6 ml. of methanol, 20 ml. of dichloromethane and 0.2 ml. of concentrated sulfuric acid was refluxed for 36 hours. The reaction mixture, worked up as usual, gave 12.2 g. (91%) of 99% pure (SE 301, 160°) **11a** methyl ester, b.p. 126° (0.005 mm) nmr (carbon tetrachloride): δ 8.9 (1H, s), 7.5 (1H, m), 6.9 (3H, m), 6.5 (1H, d), 3.8 (1H, m), 3.4 (3H, s), 1.5 (3H, d); ms: m/e (I%) 144 (100), 203 (27, M^+), 143 (14), 145 (13).

Anal. Calcd. for $C_{12}H_{13}O_2N$: C, 70.91; H, 6.45; N, 6.89. Found: C, 70.88; H, 6.44; N, 6.92.

(±)-Methyl 2-[3-(1-Methylindolyl)]propanoate (**11b**, Methyl Ester).

A mixture of 2.8 g. (0.012 mole) of benzyltriethylammonium chloride and 13.6 g. (0.096 mole) of methyl iodide in 200 ml. of 50% sodium hydroxide solution were reacted, under stirring at room temperature, with 16.3 g. (0.080 mole) of **11a** methyl ester. After 2 hours the reaction mixture was diluted with water and the organic products were extracted with ether, and washed and dried (sodium sulfate). Distillation gave 15.6 g. (90%) of pure (SE 301, 150°) **11b** methyl ester, b.p. 116° (0.03 mm) (lit. (27) optically active m.p. 59-60°); nmr (carbon tetrachloride): δ 7.5 (1H, m), 7.0 (3H, m), 6.7 (1H, s), 3.8 (1H, m), 3.4 (3H, s), 3.3 (3H, s), 1.5 (3H, d); ms: m/e (I%) 158 (100), 217 (25, M^+), 144 (15), 159 (15).

Anal. Calcd. for $C_{13}H_{15}NO_2$: C, 71.86; H, 6.96; N, 6.45. Found: C, 71.80; H, 7.00; N, 6.35.

(±)-2-[3-(1-Methylindolyl)]propan-1-ol (**12b**).

To an ethereal suspension of 3.7 g. (0.098 mole) of lithium aluminum hydride a solution of 14.6 g. (0.067 mole) of **11b** methyl ester in 120 ml. of ether was added dropwise. The reaction mixture was refluxed for 12 hours and then hydrolyzed as usual. The distillation of the crude material gave 12.0 g. (95%) of **12b**, b.p. 139° (0.01 mm); nmr (carbon tetrachloride): δ 7.4 (1H, m), 6.9 (3H, m), 6.4 (1H, m), 3.5 (3H, m), 3.2 (3H, s), 3.0 (1H, s), 1.2 (3H, d).

Anal. Calcd. for $C_{12}H_{15}NO$: C, 76.15; H, 7.99; N, 7.40. Found: C, 76.20; H, 7.85; N, 7.45.

(±)-1-Chloro-2-[3-(1-methylindolyl)]- and (±)-2-Chloro-1-[3-(1-methylindolyl)]propanes (**13b** and **16b**).

To a solution of 9.8 g. (0.052 mole) of **12b** in 105 ml. of dry pyridine, was added at 0°, a solution of 1.3 g. (0.060 mole) of benzyltriethylammonium chloride in 11.6 ml. of chloroform, followed, dropwise, by 8 ml. (0.103 mole) of methanesulphonyl chloride. The mixture was stored at 0-5° for 56 hours and then poured into iced water. The organic products were extracted with chloroform, washed with 5% hydrochloric acid and water, and dried (sodium sulfate). The solvent was evaporated and the crude product (only one main peak in gc analysis, SE 301, 180°) showed a mass spectrum [m/e (I%) (2m SE 301, glass column at 180°) 144 (100), 207 (20, M^+), 209 (7, M^{+2})] in agreement with the structure of **16b**. On the other hand, the crude product, as well as the distilled one, b.p. 115° (0.005 mm), appeared as an almost equimolecular mixture of **13b** and **16b** by nmr [(carbon tetrachloride, internal standard HMDS) δ 7.10-6.85 (1H, m), 6.76-6.43 (3H, m), 6.06-6.02 (1H, 2s), 4.19-3.98 (0.5H, m), 3.71-3.20 (0.5H, m), 3.11 (3H, 2s), 3.10-2.80 (2H, m), 1.38-1.25 (3H, 2d)] and by ms [(direct introduction, temperature source 100°) m/e (I%), 144 (100), 158 (89), 207 (22, M^+), 209 (7, M^{+2})].

In order to explain these data, a sample of such mixture was heated for 1 minute at the gas-chromatograph injector temperature (200°). 2-Chloro-1-[3-(1-methylindolyl)]propane (**16b**) was quantitatively recovered, b.p. 115° (0.005 mm); nmr (neat, HMDS): δ 7.0-6.9 (1H, m), 6.7-6.4 (3H, m), 6.0 (1H, s), 3.9-3.7 (1H, m), 3.0-2.6 (2H, m), 2.8 (3H, s), 1.2-1.1 (3H,d).

Anal. Calcd. for $C_{12}H_{14}ClN$: C, 69.39; H, 6.79; N, 6.74. Found: C, 69.43; H, 6.81; N, 6.70.

(±)-3-[3-(1-Methylindolyl)]butanoic and (±)-2-Methyl-3-[3-(1-methylindolyl)]propanoic Acids (**15b** and **17b**).

The mixture of isomeric chlorides **13b** and **16b** (5.8 g., 0.028 mole) was reacted with 0.70 g. (0.028 g-atom) of magnesium in dry ether, and the resulting Grignard reagents were carbonated with dry ice. The reaction mixture was processed in the usual way to give 1.5 g. of a mixture of **17b** (retention time 15.5 minutes) and **15b** (retention time 16.5 minutes) in the ratio *ca.* 1:1 (SE 301, 150°, on the corresponding methyl esters). Compound **15b** methyl ester had ms: m/e (I%) (2m SE 301, glass column at 150°) 158 (100), 231 (22, M^+), 144 (10). Compound **17b** methyl ester had ms: m/e (I%) (2 m SE 301, glass column at 150°) 144 (100) 231 (22, M^+), 158 (11).

Any attempts to separate **15b** from **17b** as well as their methyl esters by accurate distillation, fractional crystallization and thin layer chromatography failed.

(+)-Methyl 3-Methylpentanoate (**18**) from (+)-**9**.

A mixture of 5.0 g. (0.026 mole) of **9**, 5.6 g. (0.033 mole) of barium hydroxide, 92 ml. of water and 15 ml. of dioxane was stirred at 150° for 5 hours in a stainless steel autoclave under nitrogen (20 atmospheres). After cooling, the reaction mixture was diluted with 1 l. of water and extracted with chloroform. The aqueous solution was reduced in volume to 250 ml. and treated at 0° with 2.0 g. (0.029 mole) of sodium nitrite and 300 ml. of 2*N* sulfuric acid, and stirred at the same temperature for 12 hours. The mixture was then stirred at 80° for an additional 5 hours. After cooling, the organic products were extracted four times with 75 ml. portions of dichloromethane, dried (sodium sulfate) and ozonized at 0° for 4 hours. The solvent was removed at reduced pressure and the ozonide, in 20 ml. of ethanol, was successively treated with 35 ml. of 10% sodium hydroxide solution and 11 ml. of 35% hydrogen peroxide. After 24 hours of refluxing, the mixture, washed with ether, was acidified and the organic products were extracted continuously with ether, dried and reacted with diazomethane. By preparative gc (SE 301, 70°), chemically pure (CW 20 M, 80°) **18** was recovered, $[\alpha]_{365}^{25}$ +17.14 (c 1.75, toluene). A sample of (+)-**7**, optical purity 96%, by reacting with diazomethane, gave chemically pure (CW 20 M, 80°) **18**, $[\alpha]_{365}^{25}$ +17.16° (c 3.04, toluene).

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REFERENCES AND NOTES

(1) For Part VIII of this series, see C. Botteghi, R. Menicagli, M. L. Wis, L. Lardicci and G. Caccia, *J. Chem. Soc., Perkin Trans. I*, in press.

(2a) R. J. Sundberg, "The Chemistry of Indoles", Academic Press, London, 1970; (b) W. S. Marsh, A. L. Garretson and E. M. Wesel, *Antibiot. Chemother.*, **10**, 316 (1960); (c) M. Julia, J. Igolen and H. Igolen, *Bull. Soc. Chim. France*, 1060 (1962); (d) A. Fredga and L. B. Agenäs, *Ark. Kemi*, **15**, 327 (1960); (e) R. V. Heitnzelman, W. C. Anthony, D. A. Lyttle and J. Szmuszkovicz, *J. Org. Chem.*, **25**, 1548 (1960) and references therein; (f) D. B. Repke and W. J. Ferguson, *J. Heterocyclic Chem.*, **13**, 775 (1976) and references therein.

(3a) P. Salvadori, L. Lardicci, R. Menicagli and C. Bertucci, *J. Am. Chem. Soc.*, **94** 8598 (1972); (b) F. Ciardelli, P. Salvadori, C. Carlini, R. Menicagli and L. Lardicci, *Tetrahedron Letters*, 1779 (1975); (c) F. Ciardelli, E. Chiellini, C. Carlini, O. Pieroni, P. Salvadori and R. Menicagli, *J. Polym. Sci., Polym. Symp.*, **62**, 143 (1978); (d) L. Lardicci, C. Botteghi and P. Salvadori, *Gazz. Chim. Ital.*, **98**, 760 (1968).

(4) M. C. Bettenbuorg and S. David, *Bull. Soc. Chim. France*, 772 (1962).

(5a) J. Bergman, *Acta Chem. Scand.*, **25**, 1277 (1971); (b) B. Mills and K. Schofield, *J. Chem. Soc.*, 5558 (1961).

(6) The solubility of isatin is very low in hot diethyl-, di-(*n*-butyl)-ether and benzene; isatin is fairly soluble in hot dioxane or tetrahydrofuran.

(7) P. Pino, L. Lardicci and L. Centoni, *Gazz. Chim. Ital.*, **91**, 428 (1961).

(8) L. Lardicci, F. Navari and R. Rossi, *Tetrahedron*, **22**, 1991 (1966).

(9) H. R. Snyder and C. W. Smith, *J. Am. Chem. Soc.*, **65**, 2452 (1943).

(10a) B. Witkop, *Ber.*, **77**, 103 (1944); (b) MM. C. Meutzer, D. Molho and Y. Berguer, *Bull. Soc. Chim. France*, 555 (1950); (c) B. Witkop and J. B. Patrick, *J. Am. Chem. Soc.*, **74**, 3855, 3861 (1952); (d) D. W. Ockenden and K. Schofield, *J. Chem. Soc.*, 612 (1953); (e) I. Saito, M. Imuta, S. Matsugo, H. Yamamoto and T. Matsuura, *Synthesis*, 255 (1976); (f) M. N. Dufour-Ricroch and A. Gaudemer, *Tetrahedron Letters*, 4079 (1976).

(11a) K. B. Wiberg and T. W. Hutton, *J. Am. Chem. Soc.*, **78**, 1640 (1956); (b) L. Lardicci and L. Conti, *Ann. Chim. (Rome)*, **51**, 823 (1961).

(12) Its methyl ester (**18**) showed $[\alpha]_{365}^{25}$ +17.16° (toluene), see Experimental

(13a) G. H. Stempel, Jr. and G. S. Schaffel, *J. Am. Chem. Soc.*, **64**, 470 (1942); (b) M. Jacobson and F. Acree, Jr., *ibid.*, **67**, 1621 (1945).

(14a) K. Brunner, *Monatsh. Chem.*, **17**, 479; *ibid.*, **18**, 95, 527 (1896); (b) R. F. Moore and S. G. P. Plant, *J. Chem. Soc.*, 3475 (1951); (c) E. Wenkert, N. K. Bhattacharyya, T. L. Reid and T. E. Stevens, *J. Am. Chem. Soc.*, **20**, 797 (1956).

(15) It is to be noted that the use of calcium hydride in dimethylbenzamide (16), to accomplish the conversion **8** to **9**, yielded (53%) a 3:1 mixture of **9** and the corresponding 2-hydroxindole; the alternative use of sodium methoxide in boiling naphthalene (17) quantitatively gave unreacted **8**.

(16) M. J. Kornet, T. H. Ong and P. A. Thio, *J. Heterocyclic Chem.*, **8**, 999 (1971).

(17) T. Wieland, O. Weiberg, E. Fischer and G. Hörlein, *Ann. Chem.*, **587**, 146 (1954).

(18) G. Tacconi, *Farmaco Ed. Sci.*, **20**, 891, 902 (1965).

(19) The reduction of compound **9** with boron hydride in tetrahydrofuran (20) failed, as well as a reduction carried out using lithium aluminum hydride in boiling ether (21) or dioxane solution (22).

(20) H. Sirowej, S. A. Khan and H. Plieninger, *Synthesis*, 84 (1972).

(21) C. S. Franklin and A. C. White, *J. Chem. Soc.*, 1335 (1963).

(22) B. Robinson, *Chem. Rev.*, **69**, 785 (1969).

(23a) H. E. Johnson and D. G. Crosby, *J. Org. Chem.*, **28**, 1246 (1963); (b) B. Sjöberg, *Ark. Kemi*, **12**, 251 (1958).

(24) T. H. Chan and R. K. Hill, *J. Org. Chem.*, **35**, 3519 (1970).

(25a) K. Eiter and O. Svierak, *Monatsh. Chem.*, **83**, 1453 (1952); (b) M. R. Harden and N. D. Wright, *J. Chem. Soc., Perkin Trans. I*, 1012 (1977).

(26a) M. J. Brienne, C. Ouannes and J. Jacques, *Bull. Soc. Chim. France*, 613 (1967); (b) P. E. Sonnet, *Synth. Commun.*, **6**, 21 (1976).

(27) B. Sjöberg, *Ark. Kemi*, **15**, 419 (1960).

(28) The isomerization we have observed whenever the alcohols **12a** and **12b** or their mesylate or tosylate were reacted with a nucleophilic reagent, may be explained on the basis of the formation of an intermediate cyclopropylium ion (25b).

(29) It is to be noted that the 1-chloro-2-[3-(1-methylindolyl)]propane (**13b**) is converted by heating into the thermodynamically more stable isomer, 1-[3-(1-methylindolyl)]-2-chloropropane (**16b**); this isomerization is quantitative at *ca.* 200° (1 minute) (see Experimental).

(30) C. Marschalk, *Ber.*, **45**, 583 (1912).

(31) W. Klyne and J. Buckingham, "Atlas of Stereochemistry", Chapman and Hall, London, 1974.

(32a) L. E. Eliel, P. H. Wilken and F. T. Fang, *J. Org. Chem.*, **22**, 231 (1957); (b) Our unpublished results.