Preparation and Reactions of 5H-Indeno[1,2-c]-pyridazine Derivatives

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3-Methoxy-5-methyl-5H-indeno[1,2-c]pyriderazine 5a and its 6,9-dimethylated derivative 5b have been prepared. Alkylation in neutral solution takes place at N¹ and at N³, respectively. In basic solution, however, electrophilic attack takes place at position 5 as illustrated by methylation (methyl iodide) and by hydroxylation (oxygen) of 5a to give 5c and 5d, respectively.

Only a single derivative of the indenopyridazine (I, n = 1) has been described, and no chemistry of the ring system has been reported. With a few modifications, the preparation of the ring system I, n = 1, follows that utilized for the preparation of the two similar ring systems, I, n = 2 and 3 (cf. Experimental). Chlorination of the pyridazinones 3a and 3b with phosphorus oxychloride to give the chloropyridazines 4a and 4b is very facile, in contrast to the general conditions obtaining for the preparation of chloropyridazines and to a similar reaction in the indenopyridine series.

The acidity of the C(5)-hydrogen gives rise to a reactive nucleophilic center when the compound is dissolved in, e.g., sodium methoxide as indicated by the formation of an intense blue colour and by the reactions of the anion of 5a with methyl iodide or with oxygen to give the 5-methylated and 5-hydroxylated compounds 5c and 5d, respectively.

Methylation of 5a in neutral solution takes place at N¹ to give the pyridazinium iodide 6, apparently, as judged by ¹H NMR spectroscopy, without attack at position 2, cf. the corresponding reaction of 3-methoxy-6-phenylpyridazine (ratio of quaternization at position...
1 to position 2 = 78/22). In both cases it may be assumed that the phenyl and the pyridazine rings are approximately coplanar, but in the former (compound 5a) the five-membered ring displaces the hydrogen at position 9 so as to render position 1 less hindered. Substitution of H by methyl as in 5b results in quaternization at N2; compound 3c was isolated, see Experimental.

Prolonged heating of the indenopyridazine 5a in basic monodeuteriomethanol gave the 4,5-dideuterated compound.

An improved synthesis of 3,4,7-trimethylindanone 2b is given.

**EXPERIMENTAL**

1H NMR spectra were recorded on a Varian A-60 instrument using CDC13 as a solvent where not otherwise indicated. Boiling points and melting points are uncorrected.

3,4,7-Trimethylindanone 2b. Crotonic acid (65 g) in p-xylene (190 ml) was added to a suspension of aluminum chloride (117 g) in p-xylene (100 ml) (10–15 °C) and then poured onto ice. Work up included a crude distillation (up to 132 °C/0.2 mmHg), a recrystallization from ligroin (200 ml, 80–110 °C), and finally from a mixture of ethanol, water, and acetic acid (55 ml of each) to give 3-(2,5-dimethylphenyl)butyric acid 11 (79 g (60%), m.p. 106–111 °C, lit. 11 111–112 °C). An attempt to prepare the acid by the method given for the synthesis of 3-phenylbutyric acid 12 led only to an inhomogeneous product. Conversion of the acid to the acid chloride 13 and cyclization by addition of aluminum chloride (one mol, cf. Ref. 13) to a molar solution of the acid chloride in benzene at 10–20 °C and subsequent reaction at 20 °C for 30 min gave after work-up the spontaneously crystallizing ketone 2b (yield 73 %, b.p. 92 °C/0.5 mmHg; 30–32 °C after one recrystallization from petroleum ether; lit. 13 32–33 °C).

3-Methoxy-5H-Indeno[1,2-c]pyridazine 5a was prepared from the ketone 2a by lithiation with freshly prepared lithium amide in liquid ammonia, alkylation with bromoacetic acid in ether, cyclization of the crude mixture of diastereomeric keto acids with hydrazine in ethanol and bromination at 80 °C to give hydrobromide of 3a (40.9 g from 172 g of ketone). Two recrystallizations from a mixture of ethanol (300 ml) and water (150 ml) gave the pyridazinone 3a. Yield 18.4 g (8.2%), m.p. 230–234 °C.

The pyridazinone (3a, 5.48 g) was rapidly (ca. 1 min) heated to reflux in phosphorus oxychloride (50 ml) and refluxed for 20 s, cooled by applying vacuum, and the phosphorus oxychloride removed in vacuo. Addition of ice, neutralization with aqueous ammonia, extraction with chloroform, the extract washed with water, treated with Norite, dried, concentrated in vacuo, and the product crystallized from ethanol (20 ml) at 0 °C gave crystals (3.6 g). Recrystallizations from toluene (25 ml, treatment with Norite) and from ethanol (15 ml) gave colourless crystals of 4a. Yield 2.58 g (40%), m.p. 140–144 °C, depending on the rate of heating.

The chloropyridazine (4a, 1.25 g) was methoxylated in a solution of sodium methoxide (680 g of sodium and 10 ml of methanol) in an evacuated ampoule and kept at 80 °C for 20 h. Addition of water, four extractions with chloroform, the combined extracts washed once with water and once with 10% aqueous acetic acid, dried, and concentrated in vacuo gave an oil. The oil was dissolved in ligroin (80–110 °C, 20 ml), treated with Norite at 50 °C, filtered, cooled to 20 °C without inducing crystallization, decanted from a red oil, and allowed to crystallize at −80 °C to give colourless crystals. Yield 780 mg (64%), m.p. 87–90 °C.

Further crystallizations from ligroin as above gave 5a, m.p. 89–91 °C. (Found: C 73.09; H 5.73; N 13.18. Calc. for C12H13N3O: C 73.87; H 5.70; N 13.20).

1H NMR, δ 1.46 (3 H, d, J 7.5 Hz); 3.88 (H2, broadened quartet, J ca. 7.5 Hz); 4.09 (methoxy); 6.95 (H2, d, J 1 Hz); ca. 7.35 (3 H, m); between 7.91 and 8.16 (1 H, m).

The homolog 5b was prepared by the same procedure (above). Recrystallization, finally from ethanol at −80 °C, gave colourless crystals, m.p. 103–104 °C. (Found: C 75.00; H 6.68; N 11.61. Calc. for C13H15N3O: C 74.97; H 6.71; N 11.60).

1H NMR, δ 1.39 (3 H, d, J 7.5 Hz); 2.32 (methyl, at position 6f of toluidine, δ 2.32); 2.83 (methyl, at position 6f); 3.81 (H2, broadened quartet, J ca. 7.5 Hz); 4.12 (methoxy); 6.82 (H2, d, J 1 Hz); 7.02 (H2 and H4, nearly an A2-system; a suspected coupling, J 7.5 Hz, was confirmed on a Bruker instrument at 90 MHz).

N-Methylation. The indenopyridazine (5a, 97 mg) was dissolved in chloroform (0.5 ml) and methyl iodide (0.3 ml) and kept at ca. 25 °C for 27 h. The crystals were washed with chloroform to give the crude quaternary salt 6. Yield 141 mg (86%) m.p. (destr., evolution of gas) between 189–191 °C and 194–195 °C, depending on rate of heating. Recrystallization from acetic acid for analysis. (Found: C 47.12; H 4.26; N 7.76. Calc. for C14H15N3O: C 47.48; H 4.27; N 7.91).

1H NMR, in deuteriochloroform/trifluoroacetic acid 1/1, δ 1.71 (3 H, d, J 7.5 Hz); 4.20 (methoxy); 4.83 (N-methyl); 7.54 to 8.34 (4 H, m).

1H NMR inspection of the crude product from a similar experiment after removal of solvents in vacuo revealed no signals attributable to isomers of 6 or to pyridazinones such as 3d.

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The same procedure applied to the sterically hindered compound 5b gave approximately 40% conversion to 3c. Quaternization in acetonitrile 8 for 3 days at 80 °C gave according to 1H NMR analysis only 3c besides some unidentified products. Recrystallizations from ligroin 80/110 °C and from ethanol at −80 °C gave colourless crystals, m.p. 132–133 °C. (Found: C 74.49; H 6.84; N 11.37. Calc. for C31H34N2O: C 74.37; H 6.71; N 11.66.) 1H NMR, δ 1.48 (3 H, d, J 7.5 Hz); 2.38 and 2.64 (s, two methyl groups); 3.85 (s, N-methyl); 3.94 (broadened and partly hidden quartet, J ca. 7 Hz); 6.84 (d, J 1 Hz); 7.07 (2H apparently, a singlet).

C-Methylation. A solution of the indenopyridazine 5a (220 mg) in ethanol (1.8 ml) and methyl iodide (1.4 ml) was added in vacuo to an ethanolic solution of sodium ethoxide (20 ml, from 1.0 g of sodium). The exothermic reaction was completed within 2 min, and the deep blue colour had faded. Addition of water and extractions with chloroform gave brown crystals (257 mg). Recrystallizations from equal volumes of toluene and ligroin 80/100 °C gave colourless crystals of 5c, m.p. 107–109 °C. (Found: C 73.99; H 6.19; N 12.33. Calc. for C30H36N2O: C 73.31; H 6.24; N 12.38.) 1H NMR, δ 1.48 (6 H, s); 4.14 (methoxy); 6.89 (H4, s); ca. 7.40 (3 H, m), 7.95 to 8.32 (H5, m).

Oxidation. Air was led through a solution of 5a (426 mg, crude) in ethanolic sodium ethoxide (from 200 mg of sodium and 10 ml of ethanol) for 2 h. The blue colour disappeared. Addition of water to the reddish solution and extractions with chloroform and a recrystallization from toluene (5 ml) gave 5d. Yield 221 mg (48%), m.p. 177–185 °C. Recrystallization from toluene and from ethanol gave colourless crystals, m.p. 196–197 °C. (Found: C 68.25; H 5.27; N 12.24. Calc. for C30H36N2O: C 68.41; H 5.30; N 12.27.) 1H NMR, δ (dimethyl sulfoxide-d6): 1.65 (3 H, s); 4.10 (s, methoxy); 6.08 (s, hydroxy, exchangeable with CH3OD); 7.36 (H4, s); 7.45–8.17 (4 H, m). IR (KBr): 3300 cm−1 (OH).

Deuteriation. Sodium methoxide in monodeuteriomethanol (from 170 mg of sodium and 5 ml of monodeuteriomethanol) was added to the indenopyridazine 5a (200 mg) in an evacuated ampoule and kept at 80 °C for 3 days. Addition of water and extraction with chloroform gave crude 3-methoxy-4,5-dideutero-5-methylidenopyridazine. 1H NMR, δ 1.46 (3 H, s); 4.09 (methoxy); 6.95 (weak singlet, indicating that exchange was not complete) and multiplets as for 5a, above.

REFERENCES


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