Acta Chemica Scandinavica B 30 (1976) 358—360

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

INGOLF CROSSLAND * and OTTO STEN DYRNUM

Department of Organic Chemistry, The Technical University of Denmark, DK-2800 Lyngby, Denmark

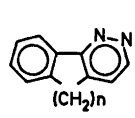
3-Methoxy-5-methyl-5*H*-indeno[1,2-*c*]pyridazine *5a* and its 6,9-dimethylated derivative *5b* have been prepared. Alkylation in neutral solution takes place at N^1 and at N^2, respectively. In basic solution, however, electrophilic attack takes place at position 5 as illustrated by methylation (methyl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

Only a single derivative of the indenopyridazine (*1*, $n=1$) has been described,[1] and no chemistry of the ring system has been reported. With a few modifications, the preparation of the ring system *1*, $n=1$, follows that utilized for the preparation of the two similar ring systems, *1*, $n=2$ and 3 (*cf.* Experimental).[2,3] 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 [2-4] and to a similar reaction in the indenopyridine series.[5]

The acidity [6] 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 N^1 to give the pyridazinium iodide *6*, apparently, as judged by ^{1}H NMR spectroscopy, without attack at position 2, *cf.* the corresponding reaction of 3-methoxy-6-phenylpyridazine (ratio of quaternization at position

* To whom correspondence should be addressed.



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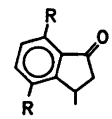

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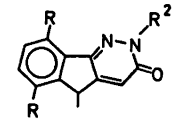
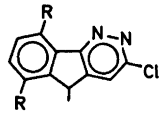
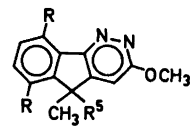
2b R = CH_3



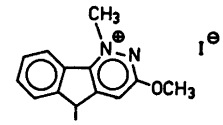
3a R = R^2 = H
3b R = CH_3; R^2 = H
3c R = R^2 = CH_3
3d R = H; R^2 = CH_3



4a R = H
4b R = CH_3



5a R = R^5 = H
5b R = CH_3; R^5 = H
5c R = H; R^5 = CH_3
5d R = H; R^5 = OH



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1 to position 2 = 78/22).[8] In both cases it may be assumed that the phenyl and the pyridazine rings are approximately coplanar,[8,9] 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^9 by methyl as in *5b* results in quaternization at N^2; compound *3c* was isolated,[8] see Experimental.

Prolonged heating of the indenopyridazine *5a* in basic monodeuteriomethanol gave the 4,5-dideuterated compound.[10]

An improved synthesis of 3,4,7-trimethylindanone *2b* is given.[11]

EXPERIMENTAL

^1H NMR spectra were recorded on a Varian A-60 instrument using $CDCl_3$ as a solvent where not otherwise indicated. Boiling points and melting points are uncorrected.

3,4,7-Trimethylindanone 2b.[11] Crotonic acid (65 g) in *p*-xylene (190 ml) was added to a suspension of aluminium chloride (117 g) in *p*-xylene (100 ml) (10–15 °C, 30 min). The mixture was allowed to stand overnight at room temperature (20 °C) and then poured onto ice. Work up [12] 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 cyclisation by addition of aluminium 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 [13] the spontaneously crystallizing ketone *2b* (yield 73 %, b.p. 92 °C/0.5 mmHg; 30–32 °C after one recrystallization from petroleum ether; lit.[11] 32–33 °C).

3-Methoxy-5H-indeno[1,2-c]pyridazine 5a was prepared [2,3] from the ketone *2a* [13] by lithiation with freshly prepared lithium amide in liquid ammonia, alkylation with bromoacetic acid in ether,[2] cyclization of the crude mixture of diastereomeric keto acids with hydrazine in ethanol [4] and bromination [4] 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 2.38 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 $C_{13}H_{12}N_2O$: C 73.57; H 5.70; N 13.20). ^1H NMR, δ 1.46 (3 H, d, J 7.5 Hz); 3.88 (H^5, broadened quartet, J *ca.* 7.5 Hz; 4.09 (methoxyl); 6.95 (H^4, 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 $C_{15}H_{16}N_2O$: C 74.97; H 6.71; N 11.66). ^1H NMR, δ 1.39 (3 H, d, J 7.5 Hz); 2.32 (methyl, at position 6? *cf.* toluene, δ 2.32); 2.83 (methyl, at position 9?); 3 81 (H^5, broadened quartet, J *ca.* 7.5 Hz); 4.12 (methoxy); 6.82 (H^4, d, J 1 Hz); 7.02 (H^7 and H^8, nearly an A_2-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 (0.3 ml) and methyl iodide (0.3 ml) and kept at *ca.* 22 °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 $C_{14}H_{15}N_2OI$: 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);[8] 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*.

The same procedure applied to the sterically hindered compound *5b* gave approximately 40 % conversion to *3c*. Quaternization in acetonitrile [8] for 3 days of 80 °C gave according to ^{1}H 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 $C_{15}H_{16}N_2O$: C 74.97; H 6.71; N 11.66). ^{1}H NMR, δ 1.45 (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 $C_{14}H_{14}N_2O$: C 74.31; H 6.24; N 12.38). ^{1}H NMR, δ 1.48 (6 H, s); 4.14 (methoxy); 6.89 (H^4, s); *ca.* 7.40 (3 H, m), 7.95 to 8.32 (H^9, 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 $C_{13}H_{12}N_2O_2$: C 68.41; H 5.30; N 12.27). ^{1}H NMR, δ (dimethyl sulfoxide-d_6): 1.65 (3 H, s); 4.10 (s, methoxy); 6.08 (s, hydroxy, exchangeable with CH_3OD); 7.36 (H^4, s); 7.45−8.17 (4 H, m). IR (KBr): 3300 cm^{-1} (OH).

Deuteration. 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-dideuterio-5-methylindenopyridazine. ^{1}H 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.

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Received August 27, 1975.