ACTA CHEMICA SCANDINAVICA 25 (1971) 2865–2870

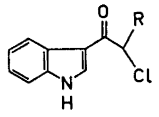
Chlorodeacylation of 3-Acylindoles

JAN BERGMAN

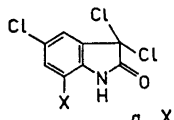
Department of Organic Chemistry, Royal Institute of Technology, S-100 44 Stockholm 70, Sweden

The main product, obtained from the chlorination of a wide range of 3-acylindoles with molecular chlorine in boiling methanol, was found to be 3,3,5,7-tetrachlorooxindole (*2a*). Similar chlorination of 3-methylindole gave a mixture of 3,5,7-trichloro-3-methyloxindole (*7*) and 5,7-dichloro-3-methoxy-3-methyloxindole (*8*).

The reaction of some simple 3-acylindoles with molecular chlorine was studied in connection with the development of a new synthesis[1] of 3-(2-chloroacyl)indoles (*1*). The reaction was at first carried out at low temperatures (0 – 40°) in a wide range of solvents (*cf.* Ref. 2). However, in all cases mixtures were obtained. In contrast to this, chlorination of 3-acetylindole with chlorine in boiling methanol produced 3,3,5,7-tetrachlorooxindole (*2a*) as the readily isolated main product. Only small amounts of 3,3,5-trichlorooxindole (*2b*) and 5-chloroisatin could be detected (TLC).



1

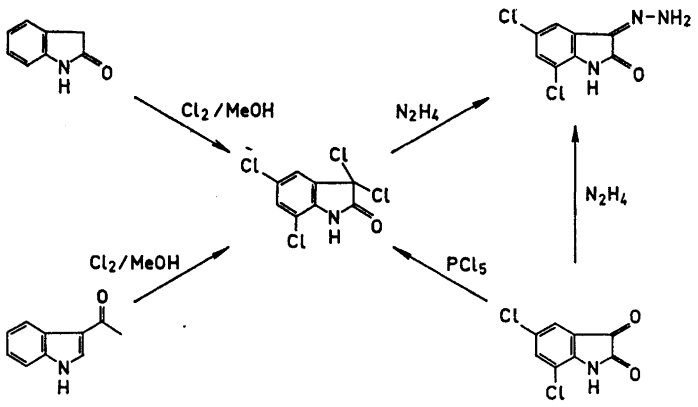


2 a X = Cl
b X = H

The structure of *2a* was proved by the reactions outlined in Scheme 1. The minor product *2b*, has been prepared earlier by chlorination of oxindole with *N,N*-dichlorourethan[3,4] or *N,N*-dichlorocarbamate.[5]

Chlorination of 3-formylindole, 3-trichloroacetylindole, 3-butyrylindole, indole-(3)-carboxylic acid and oxindole, with molecular chlorine in boiling methanol, also gave good yields of *2a*. Chlorodeacylation thus appears to be a general reaction for 3-acylindoles under the given conditions.

No detailed study of the reaction mechanism has been made. The fact that trichloroacetamide could be isolated on addition of ammonia to suitable fractions of the distilled mother liquor from *2a*, does suggest, however, that

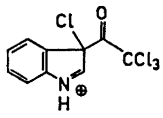


Scheme 1.

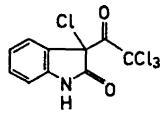
species such as *3* and *4* are possible intermediates. Attempts to detect any ester (*e.g.* methyl trichloroacetate) directly by GLC were unsuccessful.

Simple halodeacylations have been observed previously. Thus Fischer and Bäumler [6] found that 2-bromo-3-ethyl-5-methyl-4-acetylpyrrole on treatment with bromine gave 2,4-dibromo-3-ethyl-5-methylpyrrole. Similarly, 4-amino- and 4-hydroxybenzaldehyde gave 4-bromoaniline and 4-bromophenol, respectively.[7] Recently, Donnelly *et al.*[8] have studied halodeacylations of several aryl ketones.

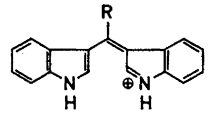
Cleavage of 3-acylindoles under conditions for nucleophilic displacements has frequently been observed.[9] Thus, deacylation, with replacement at the 3-position by a nitro group, occurs during nitration of 3-acetylindole in concentrated nitric acid.



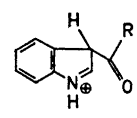
3



4



5 a R = H
b R = CH_3

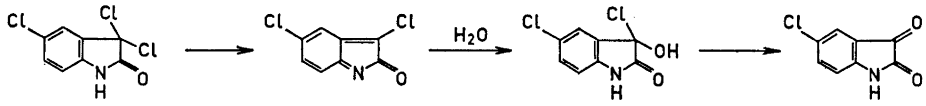


6 a R = H
b R = CH_3

It is known [10] that on treatment with strong acid 3-formylindole gives *5a*, probably *via 6a* (protodeformylation). A similar reaction (protodeacylation) might *a priori* be expected during the chlorination reaction just described. In order to get some information regarding the possibility of the protodeacetylation competing with the chlorodeacylation of 3-acetylindole, the latter compound was boiled in methanol for 6 h with a continuous supply of hydrogen chloride. Most of the starting material, however, could be recovered from the dark-violet solution. Consequently, the protodeacetylation seems to be slow compared with the chlorodeacetylation.

Chlorination of oxindole in boiling carbon tetrachloride gave 3,3,5-trichloro-oxindole (*2b*), which could be further chlorinated in boiling methanol or acetic acid (60°), but not in boiling carbon tetrachloride. To account for this, it is suggested that chlorine or a related species (*e.g.* protonated methyl hypochlorite) act as a strong electrophile in the polar solvents.

According to Foglia and Swern,[4] hydrolysis of *2b* in refluxing aqueous methanol is complete within 5 h. It was therefore very surprising to find that *2a* was nearly unaffected by refluxing 50 % aqueous methanol. Only traces of 5,7-dichloroisatin could be detected. To account for this, it is suggested that the hydrolysis of *2b* proceeds as follows:

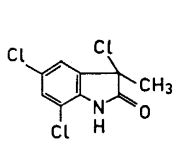


Scheme 2.

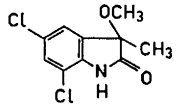
For compound *2a* the rate of deprotonation should be decreased due to the substituent in 7-position. Complete hydrolysis of *2a* could be effected, however, in boiling water.

As unexpected products were obtained from the chlorinations of 3-acyl-indoles, some 3-alkylindoles were also treated with molecular chlorine in boiling methanol.

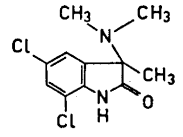
Chlorination of 3-methylindole produced a mixture of 3,5,7-trichloro-3-methyloxindole (*7*) and 5,7-dichloro-3-methoxy-3-methyloxindole (*8*). The



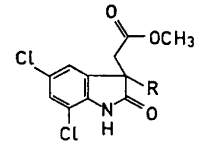
7



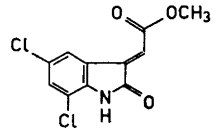
8



9



10 a R = Cl
b R = OCH_3



11

mixture was separated by column chromatography on silica gel; dichloromethane was used as eluent. When refluxed for 5 h in methanol *7* was completely transformed into *8*. Powers,[11] under different conditions, has isolated several less heavily chlorinated oxindole derivatives from the chlorination of 3-methyl indole.

Chlorination of indolyl-3-acetic acid methylester gave *10a*. No formation of *10b* could be detected, probably owing to steric hindrance of the bulky carbomethoxymethyl group. Treatment of *10a* with triethylamine in ethanol gave *11*, which was also obtained by reaction of 5,7-dichloroisatin with methoxycarbonylmethylene triphenylphosphorane.

EXPERIMENTAL

Warning! Chlorinations in methanol are hazardous if the supply of chlorine is not stopped when the reactants (except the methanol) are consumed. If the supply is continued far beyond this point severe explosions may occur. Fire phenomena (*e.g.* in the cooler) occur frequently when the reactants are consumed.

Sources of some starting materials. 3-Trichloroacetylindole,[1] 3-acetylindole,[12] 3-butyrylindole,[12] 5,7-dichloroisatin (Schuchardt), methyl indolyl-3-acetate.[13]

The NMR-spectra were determined with a Varian A-60A spectrometer at 42°, using TMS as internal standard.

3,3,5,7-Tetrachlorooxindole (2a)

Method A. Chlorine was introduced in a rapid stream into a solution 3-acylindole (0.1 mol) in methanol (200 ml) over a period of 2 h at reflux temperature. The reaction mixture was then cooled, finally to −10°. The crystals formed were collected and recrystallized from methanol and dried in vacuum. Yield 75–85 %. (Found: C 35.5; H 1.1; N 5.0; Cl 52.1. Calc. for $C_8H_3Cl_4NO$: C 35.5; H 1.1; N 5.2; Cl 52.4.) NMR (DMSO-d_6): $\tau = 2.37$ (d, 1H, 6–H), $\tau = 2.23$ (d, 1H, 4–H)*, $\tau = -0.9$ (s, 1H, NH); $J_{46} = 2.1$ Hz.

The solvent was driven off from the aforementioned mother liquor. On addition of ammonia to the fractionated (140–170°/760 mmHg) residue, trichloroacetamide (0.9 g, 6 %) was formed.

Method B. Oxindole (0.1 mol), 3,3-dichlorooxindole (0.1 mol) or 5,7-dichlorooxindole (0.1 mol) were chlorinated under the conditions described above. Yield 70–80 %.

Method C. A mixture of 5,7-dichloroisatin (21.6 g, 0.1 mol), PCl_5 (30 g) and toluene (300 ml) was stirred for 48 h at 45°. The almost clear solution was filtered, the solvent removed under reduced pressure, and the residue treated with methanol (500 ml). The solution was filtered, treated with active carbon, concentrated, and finally cooled to −10°. The crystals formed were recrystallized twice from methanol and dried in vacuum. Yield 8.5 g (31 %).

Hydrolysis of 3,3,5,7-tetrachlorooxindole

A mixture of 3,3,5,7-tetrachlorooxindole (1.35 g, 0.005 mol) and water (50 ml) was refluxed for 6 h. The mixture was cooled, the solid collected and recrystallized from ethanol. Another recrystallization from ethanol gave pure 5,7-dichloroisatin (0.65 g, 60 %). M.p. 220–221°.

Attempted hydrolysis with 50 % aqueous methanol for 6 h (or even longer) at reflux temperature only gave traces of 5,7-dichloroisatin.

5,7-Dichloroisatin hydrazone

Method A. A mixture of 3,3,5,7-tetrachlorooxindole (5.4 g, 0.02 mol), ethanol (50 ml) and hydrazine (5 ml) was refluxed for 0.5 h. The mixture was cooled to 35°. The

* It should be noted that the assignment of the signals from the aromatic protons could be reversed (*cf.* Ref. 5).

crystals were collected, dried, and recrystallized from propanol-2. Yield: 3.1 g (67 %). M. p. 250° (dec.) (Found: C 41.4; H 2.9; Cl 30.5; N 18.7. Calc. for $C_8H_5Cl_2N_3O$: C 41.7; H 2.8; Cl 30.8; N 18.3.)

Method B. A mixture of 5,7-dichloroisatin (21.6 g, 0.1 mol), ethanol (200 ml) and hydrazine (10 ml) was refluxed for 0.5 h, cooled to 35°, filtered, dried, and recrystallized from propanol-2. Yield: 14.2 g (62 %).

3,3,5-Trichlorooxindole (*2b*)

Chlorine was introduced in rapid stress stream into a solution of oxindole (13.3 g) in carbon tetrachloride (300 ml) over a period of 2.5 h at reflux temperature. The reaction solution was then cooled, finally to −10°. The crystals formed, recrystallized from benzene, gave 15.5 g (66 %). M.p. 190–192° (Lit.[4] 191–192°).

Hydrolysis of *2b* according to Foglia and Swern [4] gave 5-chloroisatin.

5,7-Dichlorooxindole

5,7-Dichloroisatin (11.5 g, 0.05 mol) was added gradually during 1 h to a stirred mixture of sodium ethylate (13.6 g, 0.2 mol), ethanol (150 ml) and dimethyl sulfoxide (15 ml) at 55°. The mixture was then refluxed for 0.5 h, the ethanol removed under reduced pressure and the residue poured into ice-water, and acidified with hydrochloric acid. The solid formed was collected and recrystallized from propanol-2. Yield: 7.8 g (75 %). M.p. 243–245° (Lit.[5] 244–246°).

Chlorination of 3-methylindole

Chlorine was introduced in a rapid stream into a solution of 3-methylindole (26.2 g) in boiling methanol (300 ml) for 2 h. The cooled reaction mixture was poured into water (900 ml). The thick oil obtained was dissolved in hot methanol. On cooling, finally to −10°, crystals (29 g, m.p. 157–159°) were obtained. TLC (silica gel GF_{254}, CH_2Cl_2) and NMR showed that this material consisted of two compounds, A and B, in the ratio 2:3 ($R_{FA}=0.26$, $R_{FB}=0.12$).

The crystals (25 g) were dissolved in CH_2Cl_2 and chromatographed on silica gel, CH_2Cl_2 being used as eluent.

3-Methyl-3,5,7-trichlorooxindole (*7*)

The fractions, containing compound A above, recrystallized from cyclohexane gave pure 3-methyl-3,5,7-trichlorooxindole. Yield: 9.5 g (19 %). M.p. 166–167°. (Found: C 43.4; H 2.4; Cl 42.2; N 5.6. Calc. for $C_9H_6Cl_3NO$: C 43.2; H 2.4; Cl 42.5; N 5.6.) NMR ($CDCl_3$): $\tau=8.08$ (s, 3H, CH_3), $\tau=2.60$ (s, 2H, 4–H and 6–H), $\tau=0.1$ (s, 1H, NH).

3-Methyl-3-methoxy-5,7-dichlorooxindole (*8*)

Method A. The fractions, containing compound B above, recrystallized from methanol gave pure 3-methyl-3-methoxy-5,7-dichlorooxindole. Yield: 12 g (24 %). M.p. 154–156°. (Found: C 48.5; H 3.7; Cl 29.0; N 5.7. Calc. for $C_{10}H_9Cl_2NO_2$: C 48.8; H 3.6; Cl 28.8; N 5.7.)

Method B. The crystalline mixture (4.0 g) obtained from the chlorination of 3-methylindole (see above) was refluxed with methanol (30 ml) until the solution no longer (5 h) contained 3-methyl-3,5,7-trichlorooxindole. On cooling, crystals of 3-methyl-3-methoxy-5,7-dichlorooxindole were obtained (2.6 g, 65 %). NMR ($CDCl_3$): $\tau=8.46$ (s, 3H, CH_3), $\tau=6.89$ (s, 3H, OCH_3), $\tau=2.70$ (d, 1H, 6–H), $\tau=2.61$ (d, 1H, 4–H),* $\tau=0.3$ (s, 1H, NH). $J_{46}=2.1$ Hz.

* It should be noted that the assignment of the signals from aromatic protons could be reversed (*cf.* Ref. 5).

3-Methyl-3-(*N*,*N*-dimethylamino)-5,7-dichlorooxindole (*9*)

A mixture of 3-methyl-3,5,7-trichlorooxindole (2.5 g, 0.01 mol), 35 % dimethylamine in water (5.0 ml) and methanol (30 ml) was refluxed for 0.5 h, and then poured into water (70 ml). The solid formed was dried and crystallized from methylcyclohexane. Yield: 1.8 g (69 %). M.p. 159–160°. (Found: C 50.6; H 4.6; Cl 27.6; N 10.9. Calc. for $C_{11}H_{12}Cl_2N_2O$: C 51.0; H 4.5; Cl 27.4; N 10.8.) NMR ($CDCl_3$): $\tau = 8.39$ (s, 3H, CH_3), $\tau = 7.57$ (s, 6H, NCH_3), $\tau = 2.63$ (s,* 2H, 6–H and 4–H), $\tau = 0.2$ (s, 1H, NH).

3,5,7-Trichloro-3-carbomethoxymethyloxindole (*10a*)

Methyl indolyl-3-acetate (18.9 g, 0.1 mol) in boiling methanol (200 ml) was treated with chlorine as described above. The reaction mixture was cooled. The crystals formed were collected and recrystallized from methanol. Yield: 22.5 g (73 %). M.p. 146–148°. (Found: 43.1; H 2.5; Cl 34.2; N 4.5. Calc. for $C_{11}H_8Cl_3NO_3$: C 42.8; H 2.6; Cl 34.5; N, 4.5. NMR (acetone-d_6): $\tau = 6.43$ (s, 3H, OCH_3), $\tau = 6.35$ (s, 2H, CH_2), $\tau = 2.54$ (d, 1H, 6–H), $\tau = 2.30$ (d, 1H, 4–H)** $\tau = -0.7$ (s, 1H, NH); $J_{46} = 2.0$ Hz.

5,7-Dichloro-3-carbomethoxymethyleneoxindole (*11*)

Method A. Triethylamine (1.0 ml) was added to a hot solution of 3,5,7-trichloro-3-carbomethoxymethyloxindole (3.1 g, 0.01 mol) in methanol (50 ml). The solution turned red, and crystals soon separated. The mixture was cooled and the red crystals were collected and recrystallized from ethanol. Yield: 2.2 g (81 %). M.p. 243–244°. (Found: C 48.2; H 2.7; Cl 26.3; N 5.2. Calc. for $C_{11}H_7Cl_2NO_3$: C 48.5; H 2.6; Cl 26.0; N 5.2.)

Method B. A solution of 5,7-dichloroisatin (2,2 g, 0.001 mol) and methoxycarbonylmethylene triphenylphosphorane (3.4 g, 0.001 mol) in methanol (75 ml) was refluxed for 2 h. The red crystals formed were collected and recrystallized from ethanol. Yield: 2.1 g (78 %). M.p. 243–244°. NMR (DMSO-d_6): $\tau = 6.74$ (s, 3H, OCH_3), $\tau = 3.79$ (s, 1H, olefinic H), $\tau = 2.23$ (d, 1H, 6–H), $\tau = 1.60$ (d, 1H, 4–H)*; $\tau = -0.9$ (s, 1H, NH). $J_{46} = 2.1$ Hz.

REFERENCES

1. Bergman, J. *J. Heterocycl. Chem.* **7** (1970) 1071.
2. Preobrazhenskaya, M. N., Orlova, M. N. and Suvorov, N. N. *Zh. Vses. Khim. Obshchestva* **13** (1968) 236; *Chem. Abstr.* **69** (1968) 86748 j.
3. Chabrier, P. *Ann. Chim.* **17** (1942) 353.
4. Foglia, T. A. and Swern, D. *J. Org. Chem.* **33** (1968) 4440.
5. Muchowski, J. M. *Can. J. Chem.* **48** (1970) 422.
6. Fischer, H. and Bäumler, R. *Ann.* **468** (1929) 158.
7. Francis, A. W. and Hill, A. S. *J. Am. Chem. Soc.* **46** (1944) 2498.
8. Beirne, J. J., Coyle, A. M. and Donnelly, J. A. *Tetrahedron* **26** (1970) 3809, and references therein.
9. Noland, W. E. and Rush, K. R. *J. Org. Chem.* **31** (1966) 70, and references therein.
10. von Dobeneck, H. *Z. klin. Chem.* **4** (1966) 141, and references therein.
11. Powers, J. *J. Org. Chem.* **31** (1966) 2627.
12. Bergman, J. *Acta Chem. Scand.* **22** (1968) 1063.
13. Stauffer, R. *Helv. Chim. Acta* **49** (1966) 1199.

Received January 7, 1971.

* With tendency to splitting.

** It should be noted that the assignment of the signals from the aromatic protons could be reversed (*cf.* Ref. 5).