The dimethyl formamide – acyl halide complex. II.[1] A synthesis of selected indole-3-aldehydes

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Received August 7, 1969

The synthesis of selected indole-3-aldehydes from the corresponding indoles and the DMF – acyl halide complex is described.

Canadian Journal of Chemistry, 48, 193 (1970)

The equilibrium formation of a complex **1** on solution of an acyl halide in dimethyl formamide (DMF) was first recognized by Hall in 1956 (2). Bredereck *et al.* (3) subsequently showed that the isolable complexes obtained from certain acid bromides reacted with aniline to give the anilide and *N*,*N*-dimethyl-*N*′-phenylformamidine, i.e. the products of attack at the acyl and formyl carbons of **1**, respectively. We recently (1) described similar results for the nonisolable complexes derived from acid chlorides, and in addition, showed that sodium azide reacted by apparent exclusive attack at the acyl carbon of **1**, to give acyl azides in preparatively useful yields.

We now wish to describe the reaction that occurs between some 3-unsubstituted indoles and the DMF – acyl halide complex.

When indole was added to a solution of benzoyl

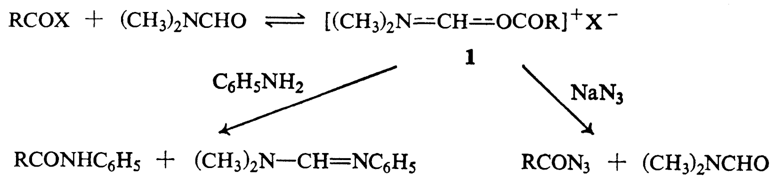

TABLE 1
Yields of indole-3-aldehydes

Starting indole	Acid halide	Reaction* time (h)	Product† yield (%)	Melting points (°C)‡ Observed	Melting points (°C)‡ Reported
Indole	Acetyl chloride	49	48§	181–187 (194–196)§	196–197‖
Indole	Acetyl bromide	88	88.5	189–193 (194–196)§	196–197‖
Indole	Benzoyl chloride	49	85	183–189 (194–196)§	196–197‖
2-Methyl-indole	Benzoyl chloride	67	88	196–201 (200–202)**	202–203††
2-Phenyl-indole	Benzoyl chloride	71	96	240–248 (251–252)**	250–255‡‡

*The reaction times should not be regarded as definitive; 48 h would probably have been sufficient for those indoles which reacted.
†Unless stated otherwise, the yields refer to those of crude products.
‡The figures not in brackets refer to the melting point of the crude products; the values in parentheses represent the melting point observed after one crystallization.
§After one crystallization from benzene – ethanol.
‖See ref. 4.
**After one crystallization from ethanol.
††See ref. 5.
‡‡See ref. 6.

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[1] For Part I, see ref. 1.

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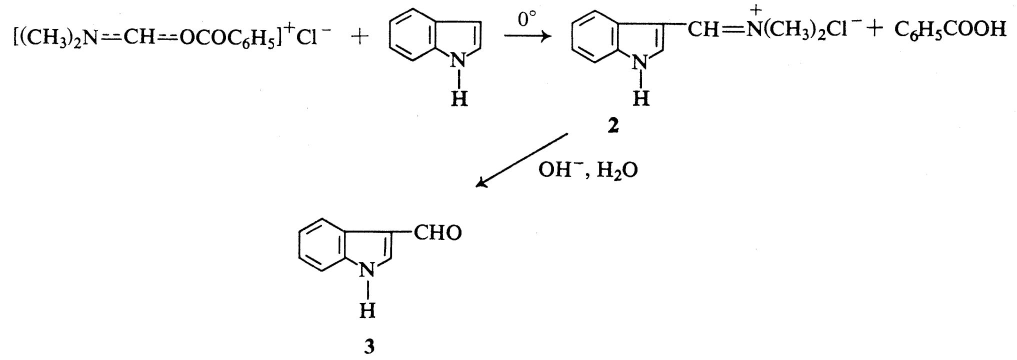

chloride in DMF at 0°, a hygroscopic crystalline solid slowly separated. This material, presumably the iminium salt **2**, gave a good yield of indole-3-aldehyde (**3**) upon alkaline hydrolysis. Acetyl bromide gave similar results, and even acetyl chloride[3] gave a modest yield of the aldehyde (see Table 1).

Under similar conditions, the benzoyl chloride–DMF complex reacted with 2-methyl and 2-phenylindole to give excellent yields of the corresponding 2-substituted indole-3-aldehydes. On the other hand, 2-methoxycarbonylindole and 4-cyanoindole did not react at all, the starting materials being recovered in 60–90% yield after 69 and 116 h, respectively. The inertness of the latter two compounds is probably explicable in terms of an electronic and a steric effect ("peri" cyano group) respectively.

Although the crude products had fairly wide melting point ranges, no contaminants could be detected by thin-layer chromatography (t.l.c.) on alumina, and their infrared (i.r.) spectra were almost identical (minor intensity differences for some of the absorption bands) to those of the authentic aldehydes prepared from the indoles and the DMF – phosphorous oxychloride adduct (4). It was, therefore, unnecessary to effect further purification of these materials before use in subsequent reactions. It should be noted, however, that one crystallization of the crude aldehydes was sufficient to provide samples whose physical properties (mixture melting points, t.l.c. behavior, and i.r. spectra) were indistinguishable from those of the purified authentic specimens.

In conclusion, the interaction of the DMF – acyl halide complexes with certain 3-unsubstituted indoles, provides a convenient, mild, but unhurried route, to the corresponding indole-3-aldehydes.

Experimental

The melting points were determined in a Gallenkamp melting point apparatus and are not corrected.

The acid chlorides were distilled before use; acetyl bromide was a commercial sample (technical grade) used as such. The starting indoles were obtained from commercial sources, or were prepared according to literature methods.

Synthesis of Indole-3-aldehydes

The following procedure was used throughout. A 100 ml three-necked flask containing a magnetic stirring bar, and fitted with a thermometer, a calcium chloride drying tube, and a nitrogen inlet, was flame dried. The apparatus was cooled to 0° in an ice bath and charged with 40 ml of dry DMF. A flow of purified, dry nitrogen through the apparatus was commenced, and when the DMF had reached 0°, 40 mmoles of the acid halide were added all at once from a hypodermic syringe (acetyl bromide was added dropwise to avoid a large temperature rise). The solution was stirred at 0° for 1 h, and then 15 mmoles of the indole were added all at once. After a further hour at 0°, the apparatus was tightly stoppered, affixed with a balloon filled with dry nitrogen, and stored at 0° for the length of time indicated in the table. During this time a crystalline solid separated from the solution. At the end of the specified reaction time the mixture was poured into 300 ml of ice-water, and a solution of 8.0 g of sodium hydroxide in 100 ml of water was added with stirring. The whole was placed in a preheated heating mantle and brought to reflux temperature as rapidly as possible. As soon as the boiling point was reached, heating was discontinued, and the clear solution was cooled with stirring to 0°. The precipitated solid was collected by filtration, washed well with water, and then dried *in vacuo*. The products obtained in this way had the melting points indicated in the Table. One crystallization from a suitable solvent gave materials identical in all respects to the

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[3] Acetyl chloride was not examined in detail because it had previously been shown (1) that the apparent equilibrium concentration of the complex (**1**; R = CH_3; X = Cl) was much lower than that observed for benzoyl chloride or acetyl bromide.

corresponding authentic specimens, but the recovery of pure material from this operation usually did not exceed 80–85%; this behavior is typical for indole-3-aldehydes (e.g. see ref. 4).

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Preparation of 2,7-polymethylene-4,5-benzotropylium perchlorates

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Received August 25, 1969

The first synthesis of 2,7-polymethylene-4,5-benzotropylium perchlorates has been achieved by reduction of the carbonyl function in 2,7-polymethylene-4,5-benzotropones and subsequent treatment with perchloric acid.

Canadian Journal of Chemistry, **48**, 195 (1970)

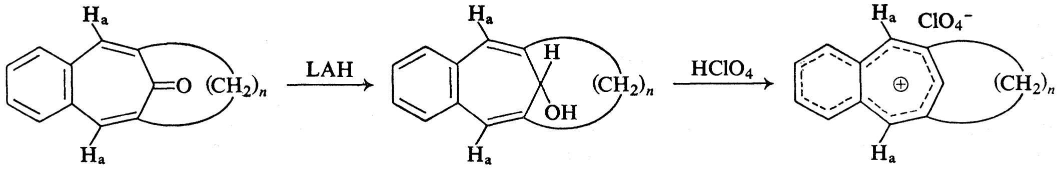
In this communication we wish to report the first synthesis of a new class of organic compounds; namely, 2,7-polymethylene-4,5-benzotropylium perchlorates (**3***a*–**3***b*). Prior to this work Eschenmoser et al. had reported the preparation of some simple benzotropylium perchlorates (1).

2,7-Polymethylene-4,5-benzotropones (**1***a*–**1***e*) were prepared by the reaction of phthalaldehyde (one mole) and cyclic ketones (one mole) (2). By infrared (i.r.) analysis, Kloster-Jensen and coworkers had postulated that the tropone ring system is planar if n is seven or larger (2). We have obtained substantiating evidence for this view from the nuclear magnetic resonance (n.m.r.) spectra of these compounds. For instance, when $n = 9$ (**1***c*), protons H_a resonate at 7.31 p.p.m., which is consistent with a conjugated ring system. However, when $n = 5$ (**1***a*), the protons resonate at 6.78 p.p.m. The downfield shift of the protons in the tropone ring system can be attributed to the increased planarity of the system as n is increased. This was further confirmed by the n.m.r. spectrum of **2***a* where the ring system is no longer planar and the H_a protons resonate at 6.25 p.p.m.

Lithium aluminium hydride reduction of the carbonyl function in **1***c*–**1***e* afforded the corresponding alcohols **2***a*–**2***c* in 60% yield. The 2,7-polymethylene-4,5-benzotropylium perchlorates (**3***a*–**3***b*) were prepared by treating **2***b*–**2***c* with a solution of 70% perchloric acid in ether. The n.m.r. spectra of **3***a*–**3***b* indicated a further downfield shift in the resonance due to the tropone ring protons H_a (9.2 p.p.m.).

Experimental

Melting points were determined with a Thomas-Hoover melting-point apparatus and are corrected. The elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee 37921, U.S.A. A Beckman IR-8 spectrophotometer was used for recording the i.r. spectra. A Cary-14 spectrophotometer was used



1*a* $n = 5$
1*b* $n = 7$
1*c* $n = 9$
1*d* $n = 10$
1*e* $n = 12$

2*a* $n = 9$
2*b* $n = 10$
2*c* $n = 12$

3*a* $n = 10$
3*b* $n = 12$