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BASE-INDUCED REACTIONS OF 3-(α-HALOACYL)INDOLES

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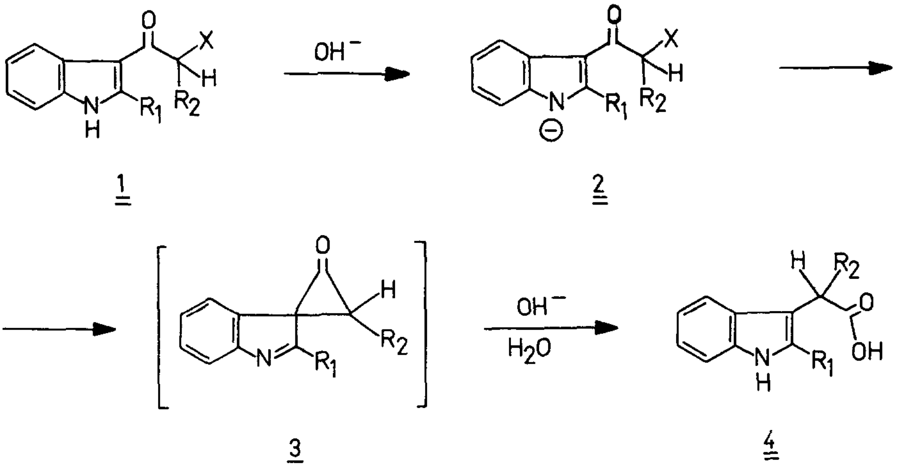
Forcing conditions, such as powdered sodium hydroxide in refluxing xylene[1,2] or silver nitrate in ethanol,[3] are necessary to effect Favorskii rearrangements of aryl α-haloalkyl ketones (RCHXCOAr ⟶ RCHArCOOH). With 3-(α-haloacyl)indoles, which should be relatively strong acids,[4] as reactants we anticipated the formation of indoleacetic acids under mild conditions along the following reaction path:



1 2 3 4

The reactions were carried out as follows: 3-(α-haloacyl)indole[6] (0.02 mol) was added in ten portions to a boiling solution of NaOH (2.4 g 0.06 mol) in 80 % ethanol (200 ml) during 1 h. After another hour of reflux the acid was extracted in moderate yield. Competitive substitutions (RCHXCOAr ⟶ RCHOHCOAr + RCHOEtCOAr) explain the low yields (cf. ref. 7). The yields of substitution products varied in the range of 30 - 80 %.

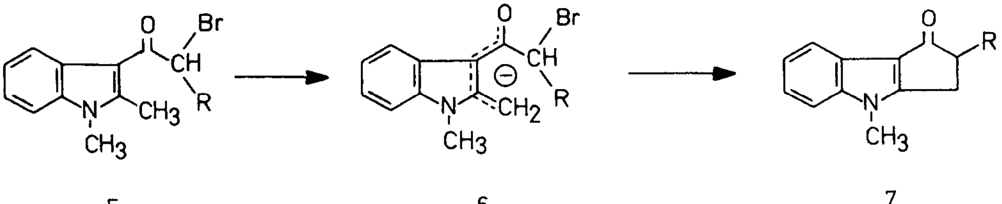
Yields of indole-3-acetic acids (4)

		Yield[a] (%)	M.p.°C	lit. m.p.
4a	R_1=H, R_2=CH_3	15, 11[b]	105-7	102[d], 113-114[e]
4b	R_1=H, R_2=C_2H_5	12	106-7	106[e]
4c	R_1=H, R_2=C_6H_5	18[c]	184-86[f]	
4d	R_1=CH_3, R_2=CH_3	20	135-37[g]	

[a] 1 (X=Br) was used as starting material unless stated otherwise. [b] 1 (R_1=H, R_2=CH_3, X=Cl) was used as starting material. [c] 1 (R_1=H, R_2=C_6H_5, X=Cl) was used as starting material. [d] F. Kögl and D. Kostermans, *Z. Physiol. Chem.*, 235, 201 (1935). [e] K.K. Schlender, M.J.Bukovac, and H.M. Sell, *Phytochemistry*, 5, 133 (1966). [f] Calc. for: $C_{16}H_{13}NO_2$: C, 76.5; H, 5.2; N, 5.6. Found: C, 76.4; H, 5.2; N, 5.7. [g] Calc. for: $C_{12}H_{13}NO_2$: C, 71.0; H, 6.5; N, 6.9. Found: C, 71.1; H, 6.6; N, 7.1.

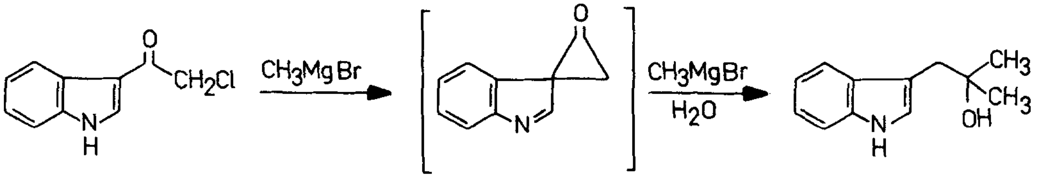
Although the yields of indoleacetic acids are low to moderate, we consider this rapid procedure suitable for the preparation of these compounds for laboratory purposes (e.g. for biological studies). The starting materials (1) are readily available[6] through acylation of indoles by a pyridine α-haloacyl halide reagent.

In accordance with the suggested mechanism N-methylated 3-(α-haloacyl)indoles could not be transformed to Favorskii rearrangement products. The attempted rearrangement of 5 (R=H) and 5 (R=CH_3) gave the cyclization products 7 (R=H) and 7 (R=CH_3) respectively, presumably via the resonance-stabilized anion 6. Compound 7 (R=CH_3) was formed in good yield whereas the yield of 7 (R=H) was low due to competitive substitution. The structure of 7 (R=H) was proved by transformation (LAH reduction) to the known[8] compound N-methyl-2,3-cyclopentanoindole.



5 6 7

The spirocyclic cyclopropane (3) should be an expected intermediate in several reactions performed under basic conditions. In accordance with this 3-chloroacetylindole (8) when treated with CH_3MgI gave α,α-dimethyltryptophol (10) identical with an authentic sample.[9,10] Interestingly enough Bohlmann and Kapteyn[11] have similarly transformed 4-hydroxy-ω-chloroacetophenone to 4-hydroxybenzyldimethylcarbinol.



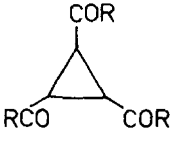
8 9 10

LAH-Reduction of 8 similarly gave tryptophol (30 % yield) together with 3-ethylindol (11). The latter compound is probably formed as follows (8 ⟶ 3-Acetylindole ⟶ 11).[12]

When sodium hydroxide (1.5 g) in 80 % ethanol (60 ml) was added to a boiling solution of 3-(α-brompropionyl)-indole (2.52 g, 0.01 mol) during 1 h (*e.g.* reversed addition), it resulted in a complex (polymeric) mixture. From this mixture one defined product could be isolated (yield: 12 %). From the mass spectroscopic data given below we have assigned it structure 12. The absence of NH vibrations and the presence of strong C=O vibrations at 1658 cm^{-1} further supported structure 12.

MS of 12, *m/e* (rel. intensity) 513 (36, M); 498 (10); 342 (27); 341 (100); 171 (29); 170 (60); 144 (18); 143 (25); 128 (10); 78 (13).

Interestingly Sanna[14] has isolated a trimeric product from the reaction of 2-methyl-3-chloroacetylindole with ammonia at 100°. The Italian worker gave structure 13 (R = 2-methylindol-3-yl) to this product. We will reinvestigate this reaction in connection with further studies of 12.



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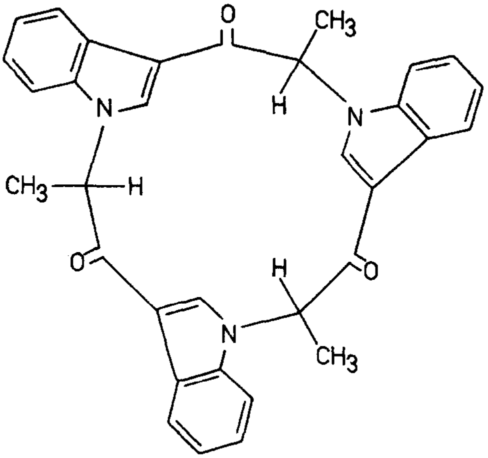

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10. We thank Dr. Szmuszkovicz for a sample of α,α-dimethyltryptophol.
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12. Similar results have recently been obtained[13] in the 4-hydroxy-ω-haloacetophenone series.
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