ALKYLATION OF INDOLES

I. ALKYLATION OF INDOLE WITH TERT-BUTYL CHLORIDE

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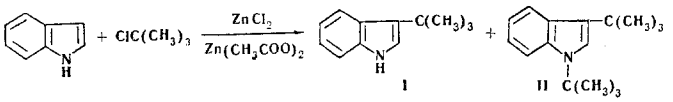
Reaction of indole with tert-butyl chloride in the presence of zinc chloride or acetate gives 3-tert-butylindole, with 1,3-di-tert-butylindole as a by-product.

One of us has previously described a method for the alkylation of acidophobic furans by the Friedel-Crafts reaction with chloro compounds in the presence of a hydrogen chloride acceptor [1]. This paper shows that it is possible to extend this reaction to unsubstituted indole, whose alkylation in the presence of acidic catalysts has not been described.

We have found that the reaction of indole with tert-butyl chloride in the presence of zinc chloride or acetate in ether gives 3-tert-butylindole (I), together with small amounts of 1,3-di-tert-butylindole (II).



Compound I was identified by independent synthesis [2]. The structure of II was established by its NMR spectrum (see Fig. 1). Two tert-butyl groups appear at high field. Their non-equivalence excludes a 3,3-disubstituted indolene. A singlet for the 2-proton is observed at δ 6.85 [3]. The second tert-butyl group is not found in the six-membered ring, since the spectrum still shows, in addition to the signal due to the 2-proton, four aromatic protons not attached to nitrogen.

On distillation of the product, unreacted indole contaminates the higher-boiling fractions. In order to avoid loss of tert-butylindole, it is preferable to take a wide fraction, from which it may be isolated by chromatography or through the picrate as well as by crystallization on prolonged standing. Gas-liquid chromatography shows that I and II are formed in molar proportions of 25 : 1. 2-tert-Butylindole was not observed in the reaction products. In comparison with the method given in [2], I was obtained in higher yields (about 30% compared with 10%) and in a purer state as determined by thin layer chromatography. When the reaction was carried out in the absence of zinc acetate, tarry products formed which were insoluble in benzene and were not further investigated. Thin layer chromatography showed the presence of traces of I, as well as small amounts of indole.

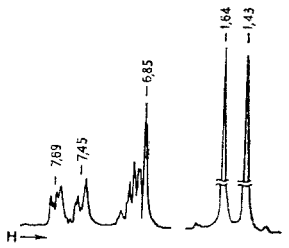


Fig. 1. NMR spectrum of 1,3-di-tert-butylindole; shifts, in ppm on the δ-scale; the spectrum at low field was amplified.

EXPERIMENTAL*

Synthesis and Determination of Purity of tert-Butylindoles. To 11.7 g (0.1 mole) of indole in 30 ml of ether was added 0.5 g of zinc chloride, about 0.5 g of zinc acetate from a total quantity of 11 g (0.06 mole), and about 0.25 ml

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of tert-butyl chloride from a total quantity of 11 g (1.2 mole). The mixture was stirred until the zinc acetate began to dissolve, and small portions of the chloro compound and zinc acetate were added alternately, the latter being kept in excess. The temperature was kept at no more than 20° C by external cooling. After half the chloro compound had been added, an additional 20 ml of ether was added. When addition of the chloro compound was complete, the mixture was stirred for 5 min more, then the mixture was washed with water followed by sodium bicarbonate solution, dried over $MgSO_4$, the ether was removed, and the residue was distilled in vacuo to give 4.6 g (0.022 mole) of indole, and 6 g (0.033 mole) of a fraction, bp 126-136° C (3 mm). From this fraction, on standing, crystals of 3-tert-butylindole (I) separated, mp 67° C. Picrate, mp 107° C ([2]: bp 166-169° C (9 mm), mp 67-68° C. Picrate, mp 105.5-107° C.)

Compound I was also obtained from indolylmagnesium iodide and tert-butyl bromide as described in [2], in 10% yield. A mixed mp with the indoles and their picrates gave no depression.

By gas-liquid chromatography, the fraction described above contained 10% indole, 86% compound I, and 4% compound II (by weight). Conditions for the separation: UKh-1 chromatograph, 10 m × 0.6 cm column, column temperature 205° C. Stationary phase, silicone oil (25% by weight) on diatomaceous brick, 0.2-0.3 mm fraction. Carrier gas H_2, 60 ml/min. Retention times: indole) 6.6 min, 3-tert-butylindole I) 22 min, and 1,3-di-tert-butylindole II) 30 min. The fractions were chromatographed on alumina columns, using a benzene–hexane mixture (1 : 1) as eluent, giving 1,3-di-tert-butylindole (II), mp 67-68° C. Found, %: N 6.13. Calculated for $C_{16}H_{23}N$, %: N 6.11.

The R_f value for I (thin layer chromatography on alumina, eluent 1 : 1 benzene–hexane mixture) was 0.5, and for II it was 0.9.

PMR spectra were taken as 10% solutions in CCl_4 on a JNM-4H-100 (100 MHz) instruments.

The authors than Yu. A. Molin for help in obtaining the PMR spectra.

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