[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF TEMPLE UNIVERSITY]

THE PREPARATION OF 1,1′- AND 3,3′-BIISOQUINOLINE[1]

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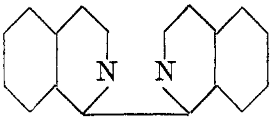
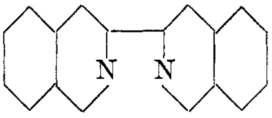
In his discussion of heterocyclic nitrogen compounds likely to give a positive ferroin reaction it was predicted by Smirnoff (1) that 1,1′- and 3,3′-biisoquinoline (I and II respectively) should react positively toward this reagent (Fe^{++}). In 1937 it was pointed out by Diehl (2) that this point had not as yet been tested.


I


II

The synthesis of these two compounds has now been accomplished in this laboratory. I was made by an Ullmann reaction on 1-bromoisoquinoline, and II by a similar reaction on the hitherto unreported 3-bromoisoquinoline. The latter compound was made from the corresponding amino derivative, first reported in 1951 by Teague and Roe (3). It was found that better yields were obtained in this reaction if the usual addition of copper to the diazonium solution was omitted.

In this work the excellent synthesis of 3-aminoisoquinoline from 3-methylisoquinoline by the above authors was modified in several instances in the interests of convenience although the yields suffered somewhat. Thus the hydrated isoquinoline-3-carboxylic acid, for which a much higher melting point was found, [167–168° instead of 134° (dec.)] was conveniently converted to the ethyl ester by the use of a large proportion of sulfuric acid in the esterification mixture. This avoided the use of diazomethane. In the preparation of the amide no liquid ammonia was used, the ester being merely suspended in an alcoholic ammonia solution.

Tests by Dr. G. F. Smith indicate that while I gives no ferroin reaction, an orange color is obtained with II.

EXPERIMENTAL

1-Bromoisoquinoline. This was prepared from isocarbostyril by the method of Jansen and Wibaut (4).

1,1′-Biisoquinoline. To 16.5 g. of 1-bromoisoquinoline in a short test tube provided with a stirrer and a thermometer, 24 g. of copper powder was gradually added at 200°. During the addition the temperature did not increase markedly. The mixture was then heated at 210–230° with stirring for two hours. After cooling, the reaction mixture was crushed and extracted four times with hot concentrated hydrochloric acid. The combined acid extract

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was made alkaline with sodium hydroxide and the resulting precipitate removed. After drying it was extracted repeatedly with hot benzene. The residue remaining after removal of the solvent was crystallized from benzene, yielding 1.8 g. of pure product, melting at 162–163°.

Anal. Calc'd for $C_{18}H_{12}N_2$: C, 84.35; H, 4.72.
Found: C, 84.34; H, 4.74.

Isoquinoline-3-carboxylic acid. The procedure was the same as that of Teague and Roe. From 66.5 g. of the percarboxylic acid, 47.5 g. of the carboxylic acid melting at 164–165° was obtained. The pure acid, crystallized from water, melted at 167–168°. Drying for 20 hours at 100° did not change this melting point.

Anal. Calc'd for $C_{10}H_7NO_2$: C, 69.36; H, 4.07.
Found: C, 69.25; H, 3.90.

For analysis the sample was dried at 65° *in vacuo*. The loss in weight was 6.41%. The calculated loss in weight for $3C_{10}H_7NO_2 \cdot 2H_2O$ is 6.49.

Isoquinoline-3-carboxamide. A mixture of 54 g. of isoquinoline-3-carboxylic acid, 187 ml. of absolute ethanol, and 141 ml. of concentrated sulfuric acid was refluxed for ten hours on the steam-bath. After cooling it was poured on ice, made alkaline with solid Na_2CO_3, and extracted with ether. Removal of the ether yielded 51.5 g. of crude ethyl ester. The entire amount of ester was then mixed with 90 ml. of ethanol and 450 ml. of concentrated ammonium hydroxide, allowed to stand several hours at room temperature with occasional shaking, and finally overnight in the ice box. The resulting crude amide (37 g.) which separated, melted at 206° and was used directly for the preparation of 3-aminoisoquinoline.

3-Bromoisoquinoline. A solution of 10 g. of 3-aminoisoquinoline in 42 ml. of 48% hydrobromic acid and 8 ml. of water, cooled to 5°, was diazotized by the gradual addition of 9 g. of solid sodium nitrite. After being allowed to stand overnight the mixture was made alkaline and extracted with ether. Removal of the ether from two runs carried out as above, followed by crystallization of the residue from petroleum ether, yielded 6.5 g. of product, m.p. 61–62°. The pure product melts at 63–64°.

Anal. Calc'd for C_9H_6BrN: Br, 38.41. Found: Br, 38.61.

3,3'-Biisoquinoline. A procedure similar to that used for 1,1'-biisoquinoline was used. However, more careful temperature control was needed since the reaction tended to warm up very rapidly. From 8.4 g. of 3-bromoisoquinoline and 13 g. of copper, heated for two hours at 260–270°, 0.7 g. of pure product was obtained, melting at 197–198° after crystallization from benzene.

Anal. Calc'd for $C_{18}H_{12}N_2$: C, 84.35; H, 4.72.
Found: C, 84.71; H, 4.93.

SUMMARY

The preparation of 1,1'- and of 3,3'-biisoquinoline is described.

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