AZAINDOLE DERIVATIVES

LI.* SYNTHESIS OF SUBSTITUTED (7-AZA-6-INDOLINYL)DIPHENYLCARBINOLS

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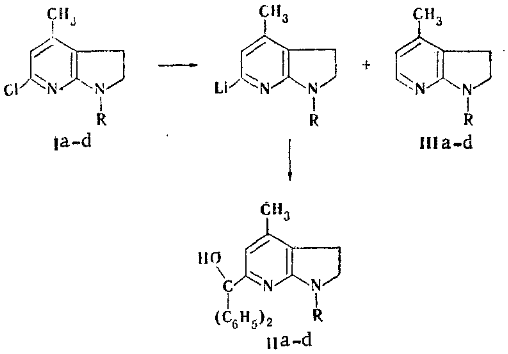
The reaction of 6-chloro-7-azaindolines with naphthyllithium and subsequent treatment with benzophenone give (7-aza-6-indolinyl)diphenylcarbinol and 6-unsubstituted 7-azaindolines, the ratios of the amounts of which are determined by the character of the substituent attached to the nitrogen atom in the 1 position of the azaindoline molecules. In the presence of acidic catalysts (1-butyl-4-methyl-7-aza-6-indolinyl)diphenylcarbinol undergoes dehydration to 1-butyl-4-methyl-6-diphenylmethyl-7-azaindole. Ideas regarding the mechanism of this reaction are expressed.

Substances with psychotropic [2], antiallergic, and antihistamine activity [3, 4] have been found among hetarydiphenylcarbinols. We have studied a method forthe incorporation of a diphenylcarbinol residue in the 7-azaindoline ring. 6-Chloro-7-azaindolines (I) react with nucleophilic reagents only under very severe conditions [5]. Only dehalogenation products III were obtained in the reaction of I with lithium in liquid ammonia [6].



I-III a $R=C_4H_9$; b $R=C_6H_5$; c $R=H$; d $R=COCH_3$

However, if the reaction of chloroazaindolines I is carried out in analogy with the synthesis of diazolyllithium compounds [7] with naphthyllithium at −35 to −40 deg C in tetrahydrofuran (THF) and the resulting azaindolinyllithium compounds are treated with benzophenone, substituted (7-aza-6-indolinyl)diphenylcarbinols (II) are obtained; 6-unsubstituted azaindolines III are simultaneously detected in the reaction products. The yields of carbinols II and the ratios of the amounts of the resulting II and III are determined to a considerable extent by the character of the substituent attached to the pyrroline nitrogen atom. The best yields of carbinols II are observed for N-alkyl(aryl) derivatives Ia, b. In the case of unsubstituted Ic the dehalogenation proceeds quantitatively to give azaindoline IIIc. The acetyl group of Id is removed during the reaction, but there is enough time for a certain amount of the 6-lithio derivative of azaindoline to be formed, and pyrroline nitrogen atom-unsubstituted carbinol IIc is obtained in 12% yield. Absorption bands of a hydroxyl group at 3450-3500 cm^{-1} are observed in the IR spectra of IIa-c, and the spectrum of IIc contains a band at 3380 cm^{-1} that is characteristic for the NH group of the pyrroline ring of 7-azaindolines. The UV spectra of azaindolinyldiphenylcarbinols II are in good agreement with the spectra described [8] for 7-azaindoline derivatives. In addition to signals characteristic for the 4-methyl-7-azaindoline system, a multiplet of phenyl protons at 6.80-7.65 ppm, a singlet

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*See [1] for communication L.

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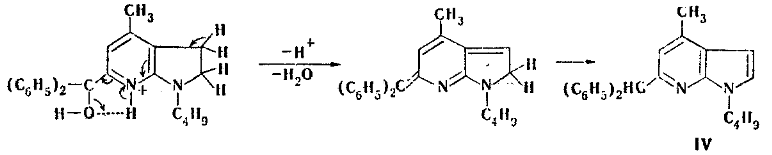
of a 5-H proton (1H) at 5.91-6.19 ppm, and a broad singlet of the proton of the OH group at 6.03-6.48 ppm which disappears on deuteration, are observed in the PMR spectra of carbinols II. A molecular ion peak (M^+) is observed at 392 in the mass spectrum of carbinol IIb,* and the most intense fragment ions are found at 315 ($M^+ - C_6H_5$; *254), 210 [$M^+ - (C_6H_5)_2CO$; *139], 209 [$M^+ - (C_6H_5)_2COH$], 182 [$(C_6H_5)_2CO^+$], and 105 ($C_6H_5CO^+$); this constitutes evidence for the presence in the molecule of a diphenylcarbinol residue, which is most susceptible to fragmentation under the influence of electron impact.

The 6-unsubstituted azaindolines were identified by direct comparison (with respect to the IR spectra and mixed-melting-point determinations) with authentic [6, 9] samples of IIIa-c.

An interesting feature of (1-butyl-4-methyl-7-aza-6-indolinyl)diphenylcarbinol (IIa) is its ability on heating in the presence of acidic catalysts to split out a water molecule to give 1-butyl-4-methyl-6-diphenylmethyl-7-azaindole (IV). In the absence of an acidic catalyst this process practically does not occur, but dehydration proceeds sufficiently completely when, for example, a small amount of p-toluenesulfonic acid or sulfuric acid is added. It may be assumed that dehydration is realized via the following pathway:



IV

An intramolecular hydrogen bond that leads to the formation of a five-membered ring evidently is formed in protonated carbinol IIa. Subsequent redistribution of the electron density is accompanied by splitting out of a water molecule and a proton with realization of a p-quinoid intermediate, which undergoes attack by a proton at the substituent in the 6 position and loses a proton from the 2 position to give azaindole IV; the proton that is split out is tied up by a new molecule of carbinol IIa.

The IR spectrum of IV does not contain absorption in the region of stretching vibrations of OH and NH groups (3100-3550 cm^{-1}), and intense bands of aromatic $C=C$ and $C=N$ bonds are observed at 1490 and 1575 cm^{-1}. The UV spectrum contains three bands with maxima at 232 (log ε 4.51), 272 (log ε 3.76) (shoulder), and 296 nm (log ε 4.06), which are characteristic for 1-alkyl-7-azaindoles [8]. In addition to other signals, a multiplet of phenyl groups (10H) at 7.15 ppm, a singlet of the 5-H proton (1H) at 6.75 ppm, two doublets of pyrrole ring protons (each 1H) at 7.05 ppm (2H) and 6.38 ppm (3H) with $J = 3$ Hz, and a singlet of a methylidyne proton (1H) at 5.67 ppm, which does not vanish on deuteration and is characteristic for the $(C_6H_5)_2CH$ substituent in the 6 position of the azaindole molecule, are observed in the PMR spectrum of azaindole IV.

It should be noted that, in contrast to N-butyl derivative IIa, carbinol IIb, which contains an N-phenyl group, does not undergo dehydration when it is heated in the presence of p-toluenesulfonic acid.

EXPERIMENTAL

The IR spectra of mineral oil suspensions of the compounds were recorded with a UR-10 spectrometer. The UV spectra of ethanol solutions of the compounds were recorded with an EPS-3 spectrophotometer. The PMR spectra of $CDCl_3$ solutions of the compounds were recorded with a JNM-4H-100 spectrometer with tetramethylsilane as the internal standard; the signals are given on the δ scale. The mass spectrum was recorded with an MKh-1303 mass spectrometer with direct introduction of the samples into the ion source at 50 eV. Gas–liquid chromatography (GLC) was carried out with a Pye-Unicam-104 chromatograph with a catharometer and a 2.1 m by 4 mm column filled with 10% SE-30 silicone elastomer on silanized diatomaceous earth (100-200 mesh); the carrier gas was helium, and the temperature was 250 deg C.

(1-Butyl-4-methyl-7-aza-6-indolinyl)diphenylcarbinol (IIa). A 0.29-g (42 mg-atom) sample of granulated lithium was added to a solution of 5.28 g (41 mmole) of naphthalene in 30 ml of anhydrous THF, and the mixture was stirred in a stream of argon at 20-27 deg C for 3 h. A solution of 2.25 g (10 mmole) of 1-butyl-4-methyl-6-chloro-7-azaindoline (Ia) in 20 ml of anhydrous THF was added with vigorous stirring in the course of 20 min to the resulting solution of naphthyllithium cooled to −35 to −40 deg C. The mixture was stirred at the same temperature for another 30 min, after which a solution of 9.6 g (53 mmole) of benzophenone in 25 ml of THF was added in the course of 10 min. The mixture was stirred at −35 to −40 deg C for another 30 min, after which it was heated to room temperature and allowed to stand for 16 h. Ether (60 ml) and 10 ml of water were added, the aqueous layer was separated, and the organic phase was extracted additionally with three 10-ml portions of 17% hydrochloric acid. The combined aqueous and acidic extracts were washed with ether and made

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*Here and subsequently, the m/e values are presented for all of the ion peaks.

alkaline with 25% ammonium hydroxide, and the liberated bases were extracted with ether. The ether extract was dried with magnesium sulfate, the ether was removed by distillation, and the residue (2.79 g) was triturated with hexane to give 1.81 g (49%) of carbinol IIa with mp 97-98 deg C (from hexane). Found: C 81.0; H 7.6; N 7.6%. $C_{25}H_{28}N_2O$. Calculated: C 80.6; H 7.6; N 7.5%.

After separation of carbinol IIa, the hexane mother liquor was evaporated, and the residue was vacuum distilled to give 0.5 g (27%) of 1-butyl-4-methyl-7-azaindoline (IIIa) with bp 114-116 deg C (3 mm). The hydrochloride had mp 158-159 deg C. No melting-point depression was observed for a mixture of the product with an authentic sample. The IR spectra of the two samples were identical.

Reaction of Naphthyllithium with 4-Methyl-6-chloro-7-azaindoline (Ic). A solution of 0.84 g (5 mmole) of Ic in 15 ml of THF was added in the course of 20 min to a cooled (to −35 to −40 deg C) solution of naphthyllithium, obtained from 0.29 g (42 mg-atom) of lithium and 5.28 g (41 mmole) of naphthalene in 60 ml of THF. After 45 min under these conditions, a solution of 9.6 g (53 mmole) of benzophenone in 30 ml of THF was added in the course of 20 min, and the mixture was stirred at −35 to −40 deg C for 30 min. It was then allowed to stand at room temperature for 16 h, after which it was worked up as described in the preceding experiment. Removal of the solvent from the extract by distillation gave 0.65 g (97%) of 4-methyl-7-azaindoline (IIIc) with mp 104-105 deg C. No melting-point depression was observed for a mixture of this product with an authentic sample of IIIc [6]. The IR spectra of the two samples were identical.

The same result was obtained when the reaction of Ic with naphthyllithium was carried out without the addition of benzophenone.

(4-Methyl-7-aza-6-indolinyl)diphenylcarbinol (IIc). This compound was obtained from 2.1 g (10 mmole) of 1-acetyl-4-methyl-6-chloro-7-azaindoline by the procedure used to obtain carbinol IIc. After removal of the solvent from the extract, the residue (1.76 g) was recrystallized from alcohol to give 0.37 g (12%) of carbinol IIc with mp 195-196 deg C. In the IR spectrum the ν_{OH} and ν_{NH} bands appear at 3493 and 3380 cm^{-1}. UV spectrum, λ_{max} (log ε): 255 (3.86) and 309 nm (3.94). Found: C 79.9; H 6.3; N 8.8%. $C_{21}H_{20}N_2O$. Calculated: C 79.7; H 6.4; N 8.8%.

After separation of IIc, the alcohol mother liquor was evaporated to dryness, and the residue was subjected to chromatography with a column (d = 2.3 cm, h = 70 cm) filled with KSK silica gel (100 g) with successive elution with heptane, heptane–ethyl acetate, and ethyl acetate. According to the results of GLC, the ethyl acetate eluate contained primarily IIIc. The eluate was evaporated, and vacuum sublimation of the residue (0.81 g) gave 0.47 g (35%) of IIIc with mp 104-105 deg C. The product was identified by a mixed-melting-point determination with an authentic sample [6] of IIc and comparison of their IR spectra.

(1-Phenyl-4-methyl-7-aza-6-indolinyl)diphenylcarbinol (IIb). A solution of 3 g (12 mmole) of 1-phenyl-4-methyl-6-chloro-7-azaindoline in 30 ml of THF, a solution of naphthyllithium [from 0.36 g (52 mg-atom) of lithium and 6.6 g (52 mmole) of naphthalene] in 90 ml of THF, and a solution of 12 g (66 mmole) of benzophenone in 30 ml of THF were subjected to reaction. Workup gave 2.07 g (43%) of IIb with mp 183-184 deg C (from alcohol). UV spectrum, λ_{max} (log ε): 287 (4.23) and 329 nm (4.16). Found: C 82.7; H 6.2; N 7.0%; M 392 (mass spectroscopically). $C_{27}H_{24}N_2O$. Calculated: C 82.6; H 6.2; N 7.1%; M 392.

After separation of IIb, the alcohol mother liquor was evaporated, and the residue was vacuum distilled to give 0.5 g (24%) of IIIb with bp 178-180 deg C (1 mm) and mp 102-103 deg C. The product was identical to an authentic sample [9] of IIIb with respect to a mixed-melting-point determination and comparison of the IR spectra.

1-Butyl-4-methyl-6-diphenylmethyl-7-azaindole (IV). A 0.29-g (0.8 mmole) sample of carbinol IIa and a catalytic amount of p-toluenesulfonic acid were placed in a Claisen flask, and the mixture was subjected to slow distillation at 50 mm. The distilled substance was recrystallized from alcohol to give 0.2 g (73%) of azaindole IV with mp 83-84 deg C. Found: C 84.3; H 7.4; N 7.9%. $C_{25}H_{26}N_2$. Calculated: C 84.7; H 7.4; N 7.9%.

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AZAINDOLE DERIVATIVES

LII.* SYNTHESIS OF 2-SUBSTITUTED 6-AZAINDOLES

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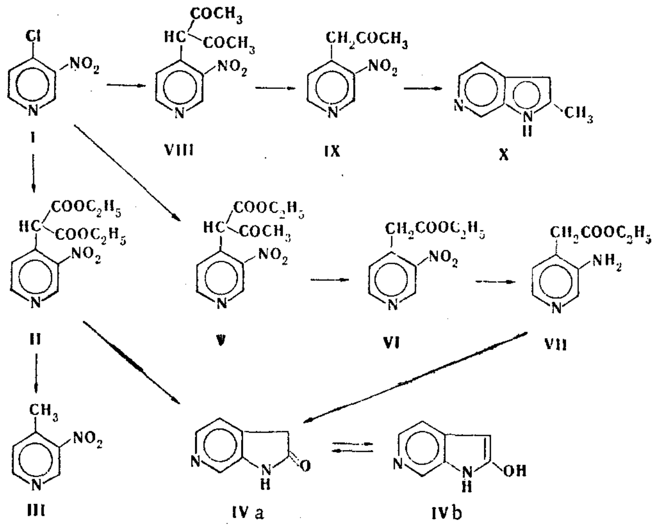
Condensation products, which were converted to 2-substituted (2-hydroxy- and 2-methyl)-6-azaindoles by reductive cyclization, were obtained in high yields from 3-nitro-4-chloropyridine by reaction with malonic and acetoacetic esters and acetylacetone in the presence of sodium hydride in dimethylformamide at room temperature.

Until now a small number of 2-monosubstituted 6-azaindoles have been described [2-4]; most of these compounds were synthesized in low yields by the high-temperature Madelung reaction. In the case of 2-hydroxy-6-azaindole (6-azahydroxyindole) (IV) and 2-methyl-6-azaindole (X) we studied a different method for the preparation of 2-substituted 6-azaindoles on the basis of the accessible 3-nitro-4-chloropyridine (I) [2].



The previously described [2, 5] condensation of I with malonic ester in the presence of sodium alkoxides leads to II in 37-55% yields. Equally low yields were also obtained in the analogous reaction with cyanoacetic ester [6]. According to our data, the low yields are associated with the side reaction to give 3-nitro-4-alkoxypyridines, which are readily saponified on subsequent workup of the reaction mixture. When the reaction was carried out in dimethylformamide (DMF) in the presence of sodium hydride, it was possible to obtain II in practically quantitative yield in 30 min at room temperature. Subsequent saponification and decarboxylation of

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*See [1] for communication LI.

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