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7-AZAINDOLE DERIVATIVES

XVII. Synthesis of 1-Butyl-3-aminoalkyl-4-methyl-7-azaindoles*

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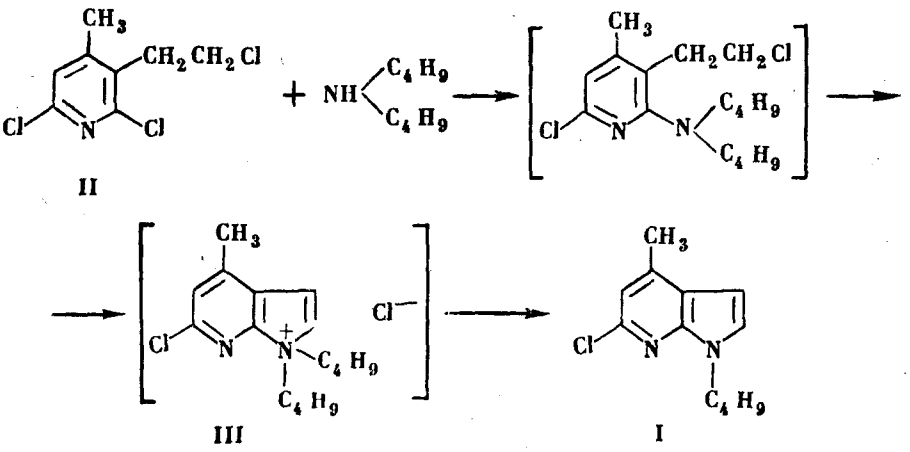
A number of 1-butyl-3-aminoaklyl-4-methyl-7-azaindoles are synthesized, viz. 1-butyl-4-methyl-7-azatryptamine, 1-butyl-3-aminomethyl-4-methyl-7-azaindole, and 1-butyl-3-dimethylaminomethyl-4-methyl-7-azaindole (1-butyl-4-methyl-7-azagramine). It is shown, using butylamine, that aliphatic primary amines behave differently in the reaction with trichlorocollidine from aromatic amines, and similarly to ammonia. The reaction product from trichlorocollidine and butylamine (as well as dibutylamine) is 1-butyl-4-methyl-6-chloro-7-azaindoline. Tributylamine is isolated from among the products of reaction of trichlorocollidine with dibutylamine, and the mechanism of its formation is considered.

Previous papers in this series [1, 2] described the synthesis of various 3-aminoalkyl-4-methyl-7-azaindoles, unsubstituted at the pyrrole nitrogen, or containing a phenyl substituent.

It was of interest, for further study of this series of compounds, to synthesize the corresponding 1-butyl-substituted 3-aminoalkyl-4-methyl-7-azaindoles. The starting compound for these syntheses was 1-butyl-4-methyl-6-chloro-7-azaindoline (I), the product of reaction of trichlorocollidine (II) with dibutylamine [3, 4].

From the previously advanced mechanism for this kind of reaction [5], the formation of I by reaction of trichlorocollidine with dibutylamine can be represented by the following equations:



II III I

The final state in the synthesis of I by the above reactions involves dealkylation of a quaternary azaindoline derivative III. Under the reaction conditions the butyl group splitting off in the dealkylation, will react with excess dibutylamine to give tributylamine. To isolate the latter fraction of low-boiling amines formed in reaction of II with dibutylamine, it was acetylated with acetic anhydride. The tributylamine, incapable of undergoing acetylation, was separated from the N-acetyldibutylamine by extraction with hydrochloric acid, and was characterized as the base, its hydrochloride, and its picrate. Analysis of the starting dibutylamine showed that it did not contain tertiary amines, thus confirming that tributylamine was formed during the synthesis of the azaindoline derivative I.

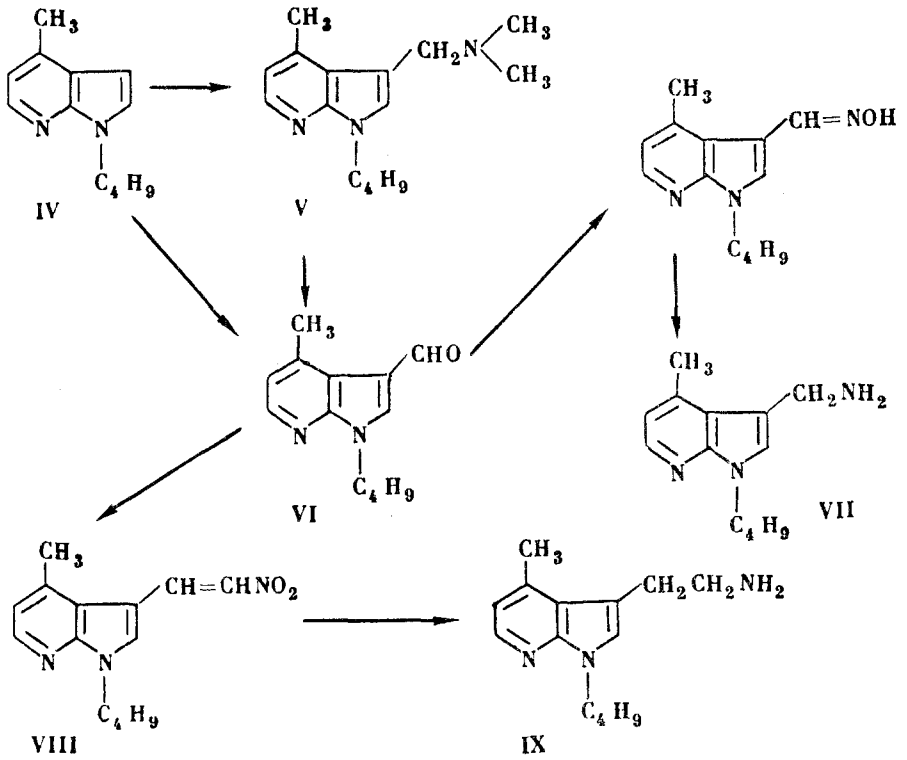
As preparation of I from II and dibutylamine was accompanied by splitting off of a butyl group, it was of interest to use butylamine instead of dibutylamine for reaction with trichlorocollidine, and in that way to cut out the dealkylation stage. Previous work with aromatic amines [3, 6] showed that similar replacement of N-alkylanilines by aniline in a reaction with trichlorocollidine leads, independent of the amount of amine taken, to formation of only 1-phenyl-4-methyl-6-phenylamino-7-azaindoline instead of 1-phenyl-4-methyl-6-chloro-7-azaindoline. Hence in the aromatic series, change from secondary to primary amines is accompanied by replacement of the position 6 chlorine atom of the azaindoline derivatives by an amino group. Furthermore, only 4-methyl-6-chloro-7-azaindoline [7] is formed when trichlorocollidine reacts with ammonia, and the position 6 chlorine atom is not replaced.

*For Part XVI see [1].

Investigation of the reaction of trichlorocollidine with butylamine and dibutylamine showed that one and the same product, 1-butyl-4-methyl-6-chloro-7-azaindoline (I), was formed in both cases. Hence primary aliphatic amines behave, in reaction with trichlorocollidine, like ammonia, and unlike primary aromatic amines.

1-Butyl-4-methyl-6-chloro-7-azaindoline (I) was converted by a previously described method [8] into 1-butyl-4-methyl-7-azaindole (IV). The UV spectrum plot for azaindole IV is displaced towards the short wave region in comparison with that for the azaindoline I, as in all other cases [6, 7](Fig. 1).

1-Butyl-4-methyl-7-azaindole (IV), like 1-phenyl-4-methyl-7-azaindole [9], showed a capacity for electrophilic substitution at position 3. Reaction with paraform and dimethylamine hydrochloride IV converted it to 1-butyl-4-methyl-7-azagramine (V), while a Wilsmeyer reaction with phosphorus oxychloride and dimethylformamide converted it to 1-butyl-3-formyl-4-methyl-7-azaindole (VI). The latter was also prepared by reacting the azagramine V with urotropine in boiling propionic acid.



Condensing 1-butyl-3-formyl-4-methyl-7-azaindole (VI) with nitromethane gave the nitrovinyl derivative VIII, lithium aluminum hydride reduction of which in boiling tetrahydrofuran gave 1-butyl-4-methyl-7-azatryptamine IX. The lower homolog of that compound, 1-butyl-3-aminomethyl-4-methyl-7-azaindole VII was obtained by zinc and hydrochloric acid reduction of the oxime of the aldehyde VI.

Experimental*

Isolation of tributylamine from the reaction of trichlorocollidine II with dibutylamine. 53.8 g (0.24 mole) II and 58.2 g (0.45 mole) dibutylamine were heated together at 140° for 7 hr. Then 70 ml water was added to the reaction products, and the whole extracted with ether. The ether solution was extracted with 240 ml 15% HCl, then twice with 70 ml water each time. Distillation of the ethereal extract, as previously described [3], gave 13.1 g (29%) 2, 6-dichloro-3-vinyl-4-methylpyridine, 23.3 g (43%) trichlorocollidine, and 6.8 g (9%) 2-chloro-3-(β-chloroethyl)-4-methyl-6-dibutylaminopyridine. The HCl and water solutions obtained by extraction were bulked, made alkaline to phenolphthalein with 50% aqueous K_2CO_3, and extracted with ether, after which the extract was dried over K_2CO_3, the ether distilled off, and the mixed low-boiling amines distilled off on a water bath under reduced pressure. Mass 45.8 g. The residue distilled at 147-148° (1 mm) to give 9.15 g (17%) 1-butyl-4-methyl-6-chloro-7-azaindoline (I). UV spectrum:** λ_{max} mμ (lg ε): 263 (3.97), 318 (3.73). The mixture of low-boiling amines was boiled for 3 hr with

*Yu. M. Viktorov participated in the experimental work.

**All UV spectra were determined with a SF-4 spectrophotometer, in ethanol solution.

250 ml acetic anhydride, 500 ml ether added to the reaction products, and the whole extracted twice with 150 ml 10% HCl each time. A 50% solution of K_2CO_3 was carefully added to the ether extract until the free acid was neutralized, the ether layer separated off, washed with water, dried over K_2CO_3, and evaporated under reduced pressure. The residue was distilled, bp 125-125.5° (16 mm), yield of N-acetylbutylamine, 61 g. It formed a colorless oily liquid, readily soluble in the usual organic solvents, less soluble in water, n_D^{20} 1.4557. Found: C 70.15; H 12.23; N 8.15, 8.05%. Calculated for $C_{10}H_{21}NO$: C 70.17; H 12.28; N 8.18%. The HCl solution was thrice extracted with ether, and the ether extracts evaporated under reduced pressure, to give 1.5 g tributylamine hydrochloride, mp 235° (sinters). Picrate, mp 104-105° (ex EtOH).

The base was a colorless oily liquid bp 204-206°, readily soluble in the usual organic solvents, and in water, n_D^{20} 1.4288. Found: N 7.68%. Calculated for $C_{12}H_{27}N$: N 7.56%.

Reaction of trichlorocollidine II with butylamine. 8.7 g (39 mmole) II and 6 g (82 mmole) butylamine was heated at 190° for 7 hr in a sealed tube. After cooling, 50 ml 15% HCl was added to the reaction products, and the whole extracted 5 times with ether. The ether extracts were dried over K_2CO_3, evaporated, and the residue distilled under reduced pressure, the following 2 cuts being taken: 1) bp 140-143° (14 mm), 2, 6-dichloro-3-vinyl-4-methylpyridine, yield, 0.6 g (16.6%); 2) bp 174-177° (14 mm), trichlorocollidine II, yield 2 g (23%). The HCl solution was made alkaline with 50% K_2CO_3 solution, then extracted with ether, the ether extract dried over K_2CO_3, and distilled, to give 2.7 g (30.7%) I, bp 147-148° (1 mm), n_D^{20} 1.5508 [7], a colorless oily compound, readily soluble in the usual organic solvents, sparingly soluble in water. Found: C 64.24; H 7.85; N 12.13; Cl 15.45, 15.53%. Calculated for $C_{12}H_{17}ClN_2$: C 64.14; H 7.57; N 12.48; Cl 15.81%.

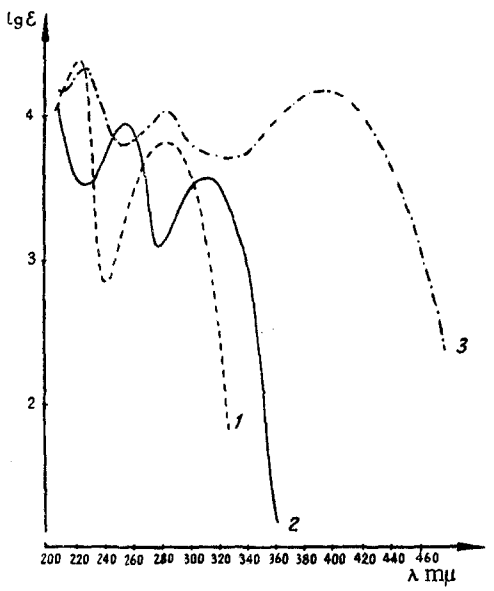


Fig. 1. UV spectra: 1) 1-butyl-4-methyl-7-azaindole (IV); 2) 1-butyl-4-methyl-7-azaindoline; 3) 1-butyl-3-(β-nitrovinyl)-4-methyl-7-azaindole (VIII).

1-Butyl-4-methyl-7-azagramine (V). 0.65 g (8 mmole) dimethylamine hydrochloride and 0.25 g (2.8 mmole) paraform were added to a solution of 1.4 g (7.4 mmole) 1-butyl-4-methyl-7-azaindole (IV) [8] in 26 ml n-butanol. The reaction mixture was refluxed for 30 min, the butanol distilled off under reduced pressure, 10 ml 5% HCl added to the residue, and the whole extracted with ether. The water layer was made alkaline to phenolphthalein with 50% K_2CO_3 solution, extracted with ether, the ethereal extract dried over K_2CO_3, and evaporated under reduced pressure, to give a residue (1 g) which was converted into the hydrochloride; yield of this hydrochloride V, 1.15 g (63.6%). It formed colorless crystals mp 163.5-164° (ex Me_2CO), readily soluble in water, ethanol, and $CHCl_3$, insoluble in ether, benzene, and toluene. Found: C 63.97; H 8.45; N 14.87; Cl 12.80%. Calculated for $C_{15}H_{23}N_3 \cdot HCl$: C 63.94; H 8.52; N 14.92; Cl 12.61%.

1-Butyl-3-formyl-4-methyl-7-azaindole (VI). a) 0.35 g $POCl_3$ was added dropwise to 1.1 g (15 mmole) distilled dimethylformamide cooled to 10°, then at room temperature was added a solution of 0.8 g (4.3 mmole) IV in 1.1 g (15 mmole) dimethylformamide. The reaction mixture was held at 35° for 45 min, poured onto ice, and then made alkaline to phenolphthalein with a 40% NaOH solution. The suspension formed was heated to boiling, cooled to room temperature, and extracted with ether, the ether extract dried over $MgSO_4$, and then evaporated, to give a residue which was distilled under reduced pressure. Yield of VI, 0.44 g (48%); pale yellow oily compound, readily soluble in ordinary organic solvents, sparingly soluble in water, bp 150-153° (0.5 mm), n_D^{20} 1.5758. IR spectrum* (Fig. 2): 1680 cm^{-1} (CHO). Found: C 72.04; H 7.68; N 12.61%. Calculated for $C_{13}H_{16}N_2O$: C 72.23; H 7.40; 12.96%.

The yield of compound VI was not increased by doubling the amount of $POCl_3$ or increasing the reaction time from 45 min to 3 hr.

b) A solution of 1 g (4 mmole) V and 0.2 g (1.4 mmole) urotropine in 3 ml propionic acid was added over 15 min to a boiling solution of 0.2 g (1.4 mmole) urotropine in 1 ml propionic acid. Refluxing was continued for 2 hr more, then 50% K_2CO_3 solution added until the mixture was alkaline to phenolphthalein, and the whole extracted with ether. The ethereal extract was dried over $MgSO_4$, and evaporated under reduced pressure. The residue was distilled, to give a cut bp 150-153° (0.5 mm), n_D^{20} 1.5765, yield of VI, 0.2 g (25%).

*The IR spectrum was obtained with a UR-10 spectrophotometer, and a paste in vaseline.

The oxime formed colorless crystals, mp 126-127° (ex benzene). It was soluble in $CHCl_3$, EtOH, dioxane, sparingly soluble in benzene, insoluble in petrol ether and water. Found: C 67.20; H 7.12; N 17.96%. Calculated for: $C_{13}H_{17}N_3O$: C 67.53; H 7.36; N 18.18%.

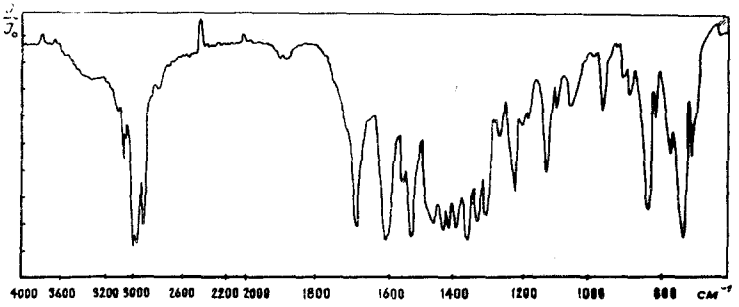


Fig. 2. IR spectrum of 1-butyl-3-formyl-4-methyl-7-azaindole (VI).

1-Butyl-3-aminomethyl-4-methyl-7-azaindole (VII). 12 g Zn dust was added at room temperature, and in portions, to a stirred solution of 2.2 g (9.5 mmole) of the oxime of 1-butyl-3-formyl-4-methyl-7-azaindole in 125 ml 17% HCl, after which stirring was continued for a further 1 hr, excess 50% KOH solution added, and the mixture extracted with ether, the ether solution dried over K_2CO_3, and evaporated, to give a residue (1.6 g), which was dissolved in absolute EtOH and alcoholic HCl added. The colorless crystals of dihydrochloride of VII which separated were filtered off, yield, 1.1 g (63%), mp 191-192° (ex dry ethanol). The compound was readily soluble in water and aqueous EtOH, insoluble in ether, benzene, Me_2CO, and $CHCl_3$. Found: C 53.83; H 7.25; N 14.40; Cl 24.03%. Calculated for $C_{13}H_9N_3 \cdot 2HCl$: C 53.79; H 7.24; N 14.50; Cl 24.45%.

1-Butyl-3-(β-nitrovinyl)-4-methyl-7-azaindole (VIII). A mixture of 0.5 g (2.3 mmole) VI, 0.18 g (2.3 mmole) NH_4OAc, and 2 ml nitromethane was heated on a boiling water bath for 1 hr. On cooling a yellow precipitate VIII separated out from the reaction products, yield 0.2 g (33.3%). Yellow crystals mp 113-114° (ex petrol ether). The compound was soluble in ether, benzene, $CHCl_3$ and EtOH, insoluble in water and petrol ether. UV spectrum λ_{max} (lg ε): 246 (4.34), 285 (4.04), 395 mμ (4.19). Found: C 64.66; H 6.74; N 15.84%. Calculated for $C_{14}H_{17}N_3O_2$: C 64.86; H 6.56; N 16.22%.

1-Butyl-4-methyl-7-azatryptamine (IX). 1.6 g (6.2 mmole) VIII was added to a suspension of 1.17 g (31 mmole) $LiAlH_4$ in 30 ml dry tetrahydrofuran, the reaction mixture refluxed for 6 hr, 3 ml water added, the mixed Li and Al hydroxides filtered off, and carefully washed with ether. The bulked ether-tetrahydrofuran solutions were dried over K_2CO_3, and evaporated under reduced pressure, to give a residue which was converted to the hydrochloride, yield 1.3 g (77.8%) colorless crystals mp 199-200° (decomp). The compound was readily soluble in water and alcohols, insoluble in Me_2CO, benzene, $CHCl_3$, and ether. Found: C 63.05, 63.17; H 8.29, 8.04; Cl 13.36, 13.38; N 15.66, 15.35%. Calculated for $C_{14}H_{21}N_3 \cdot HCl$: C 62.83; H 8.22; Cl 13.27; N 15.70%.

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