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7-AZAINDOLE DERIVATIVES

XII. Synthesis of 2, 6-Dichloro-3-(β-chloroethyl)-5-cyanopyridine and its Conversion to 1-Phenyl-5-cyano-7-azaindole*

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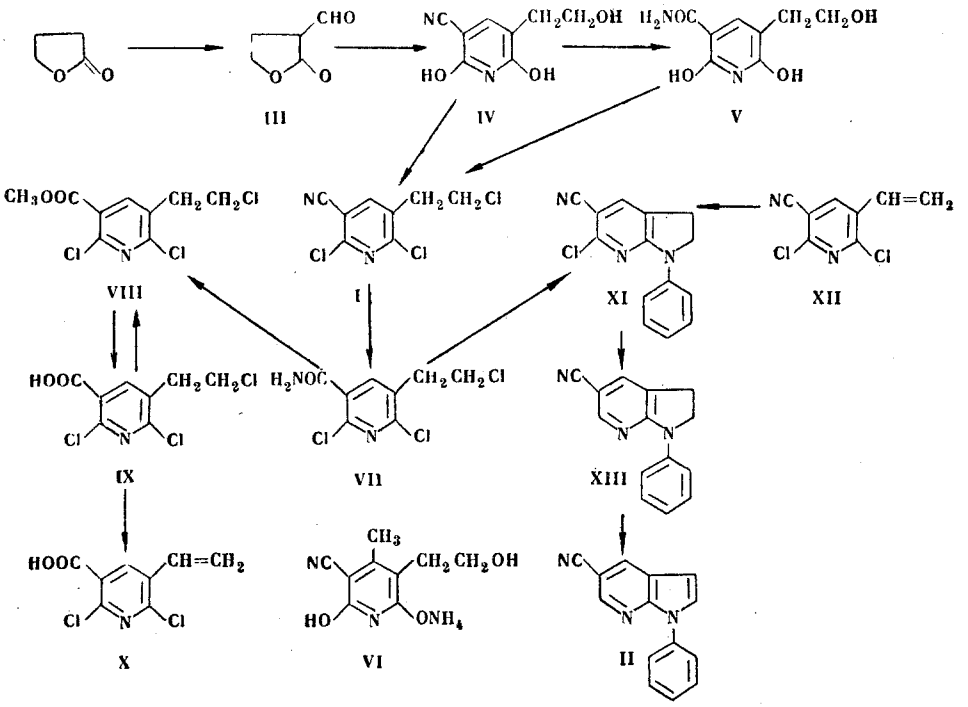
To extend the field of application of a previously discovered reaction of secondary amines and substituted 2-chloro-3-(β-chloroethyl) pyridines, giving 7-azaindole derivatives, 2, 6-dichloro-3-(β-chloroethyl)-5-cyanopyridine is synthesized, and converted into 1-phenyl-5-cyano-7-azaindole, and other compounds.

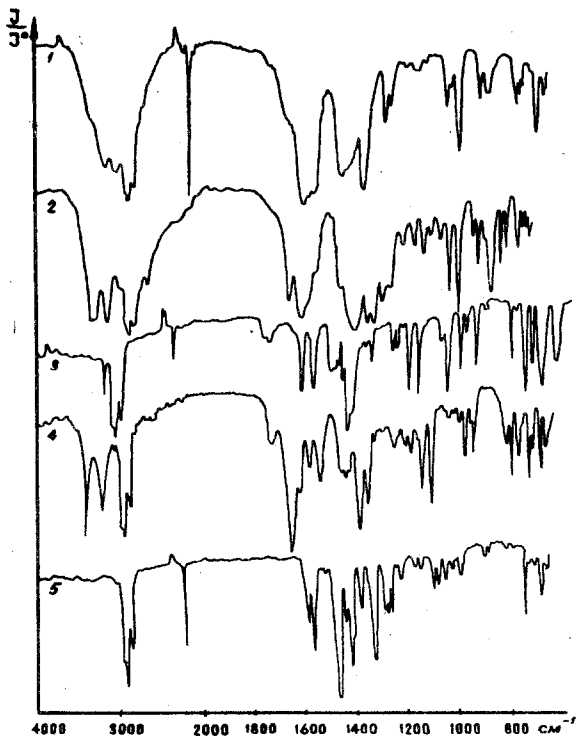
Previous papers have described the synthesis of 7-azaindole derivatives from various secondary amines and substituted 2-chloro-3-(β-chloroethyl) pyridines. Pyridine derivatives used were 2, 6-dichloro-3-(β-chloroethyl)-4-methylpyridine [1-3], 2-chloro-3-(β-chloroethyl)-4-methylpyridine [1, 4], and 2, 4, 6-trichloro-3-(β-chloroethyl) pyridine [5]. With a view to extending the field of application of the reaction discovered, we have synthesized 2, 6-dichloro-3-(β-chloroethyl)-5-cyanopyridine (I), and converted it to 1-phenyl-5-cyano-7-azaindole (II). These transformations reveal the possibility of preparing various 7-azaindole derivatives, substituted at position 5.



The starting compound for synthesizing I was γ-butyrolactone, converted by condensation with ethyl formate into α-formyl-γ-butyrolactone (III) [6, 7]. Compound III is unstable, so it was not isolated pure, but the technical product was treated with cyanoacetamide in aqueous ammonia, which gave the ammonium salt of 2, 6-dihydroxy-3-(β-hydroxyethyl)-5-cyanopyridine (IV). The presence of bands, in the IR spectrum, belonging to the —CONH— group (1630, 3080 cm^{-1}) showed that compound IV exists in the pyridone form (Fig.). However, we did not succeed in locating the position of the carbonyl group (whether at position 2 or 6), so that formulas IV and V are in the hydroxy form. It is of interest to note that the cyclic amide link in IV is significantly less well-defined than in the homolog of that compound, the ammonium salt of 2, 6-dihydroxy-3-(β-hydroxyethyl)-4-methyl-5-cyanopyridine (VI), previously synthesized by Stevens and coworkers [8] along the same lines. While the cyano group of VI is readily hydrolyzed with simultaneous decarboxylation, by heating with concentrated sulfuric acid at 150° [8], or by boiling with 70% sulfuric acid, to give 4-methyl-6-hydroxydihydrofurano [2, 3-b] pyridine, under the same conditions the pyridine ring of IV is decomposed, and the compound resinified. Under milder conditions, half an hour's refluxing with concentrated hydrochloric acid, or thirty hours' refluxing with 10% aqueous potassium hydroxide, the nitrile group in IV is saponified only as far as an amide group. With 2, 6-dihydroxy-3-(β-hydroxyethyl) pyridine-5-carboxamide (V), which also

*For Part XI see [1].

exists as the carbonyl form [IR spectrum (figure): 1639 cm^{-1} (−CONH−), 1687 cm^{-1} ($-CONH_2$)], the primary amide group at position 5 and the secondary amide group in the pyridine ring are evidently equally readily saponified, so that selective saponification is excluded.



IR spectra:
1) ammonium salt of 2, 5-dihydroxy-3-(β-hydroxyethyl)-5-cyanopyridine (IV); 2) 2, 6-dihydroxy-3-(β-hydroxyethyl) pyridine-5-carboxamide (V); 3) 2, 6-dichloro-3-(β-chloroethyl)-5-cyanopyridine (I); 4) 2, 6-dichloro-3-(β-chloroethyl) pyridine-5-carboxamide (VII); 5) 1-phenyl-5-cyano-6-chloro-7-azaindoline (XI).

Treatment of the ammonium salt of 2, 6-dihydroxy-3-(β-hydroxyethyl)-5-cyanopyridine (IV) with phosphorus oxychloride at 180° for 5 hr gave 2, 6-dichloro-3-(β-chloroethyl)-5-cyanopyridine (I) in approximately 27% yield. Raising the reaction temperature to 200° cut the yield of I to 9%. Lowering the reaction temperature also cut the yield of I (e.g., it was 16.8% at 160° for 5 hr). In all cases reaction was accompanied by considerable resinification. The literature contains statements about considerable resinification when there is a nitrile group in the pyridine ring and chlorine derivatives of phosphorus are used to replace hydroxyls [9]. I was also prepared by treating 2, 6-dihydroxy-3-(β-hydroxyethyl)-pyridine-5-carboxamide (V) with phosphorus oxychloride. There replacement of the hydroxyl group by chlorine was accompanied by dehydration of the amide group at position 5 in the pyridine ring.

Methanolic hydrogen chloride at room temperature readily converts the nitrile group of I into amide, but further alcoholysis of the amide group of VII to give VIII takes place only to the extent of 20-25% even on refluxing for many hours. At the same time methyl 2, 6-dichloro-3-(β-chloroethyl) pyridine-5-carboxylate (VIII) is very easily saponified, even by the moisture of the air.

Heating 2, 6-dichloro-3-(β-chloroethyl)-5-cyanopyridine (I) or 2, 6-dichloro-3-(β-chloroethyl) pyridine-5-carboxamide (VII) with N-methylaniline or N-ethylaniline at 140° gave one and the same product, 1-phenyl-5-cyano-6-chloro-7-azaindole (XI). Apparently with VII formation of the 1-phenyl-7-azaindole derivative was accompanied by dehydration of the amide group. Pyrroline ring closure under the action of N-alkylanilines took place, with I and VII, quite analogously to reactions with other 2-chloro-3-(β-chloroethyl) derivatives of pyridine [2-4], but introduction of a nitrile group at position 5 activated chlorine atoms not only in the pyridine ring, but also in the β-chloroethyl group. There, reaction took place at a much lower temperature (140° instead of 190°), and was accompanied by formation of a side product, 2, 6-dichloro-3-vinyl-5-cyanopuridine (XII) through dehydrohalogenation, not observed in reactions of N-alkylanilines with other 2-chloro-3-(β-chloroethyl) pyridine.

Further dehalogenation of XI in the presence of a palladium catalyst, and subsequent dehydrogenation of XIII with chloranil, made it possible to pass to a 5-substituted 1-phenyl-7-azaindole, viz. 1-phenyl-5-cyano-7-azaindole (II).

Experimental

Ammonium salt of 2, 6-dihydroxy-3-(β-hydroxyethyl)-5-cyanopyridine (IV). 92 g Na was brought into a fine state of division in dry xylene (700 ml), the xylene poured off, 1 *l* dry benzene added, the mixture stirred, and 185 ml dry ethanol plus 200 ml benzene added dropwise in 2 hr, the temperature being held at 60-65°. Stirring was continued for another 6 hr at the same temperature, and the reaction products left overnight, at room temperature. The resultant suspension of NaOEt in benzene was cooled to −5°, and a mixture of 344 g freshly distilled γ-butyrolactone and 296 g purified ethyl formate added gradually, the temperature being held not above 10°. Then the whole was stirred for a further 6 hr at 10°, and the products left for 48 hr at 20-25°. The crystalline sodium derivative of α-hydroxymethylene-γ-butyrolactone which separated was filtered off, dissolved in 2 *l* of a saturated aqueous solution of K_2SO_4, and the resultant solution extracted with benzene. The aqueous layer was separated off and acidified to pH 2.5 with a saturated aqueous solution of $NaHSO_4$. The oily α-formyl-γ-butyrolactone (290 g) was separated off, and without further purification mixed with 214 g cyanoacetamide and 640 ml 26% aqueous ammonia. The reaction mixture was cooled with ice water, stirred for 20 min, saturated for 3 hr with ammonia gas, and left for 72 hr in a refrigerator at −5°, after which IV was filtered off. Yield 326 g 41.4% on the γ-butyrolactone), colorless crystals, mp 257-258° (decomp, ex

water). The substance had low solubility in the usual organic solvents and cold water, good solubility in hot water. IR spectrum,* cm^{-1} : 2202 (C≡N) 1580, (pyridine ring), 3230 (associated hydroxyl group); 1630, 3080 (−CONH−) (Fig.). Found: C 48.63; H 5.55; N 21.23%. Calculated for $C_8H_7N_2O_3 \cdot NH_4$: C 48.73; H 5.58; N 21.32%.

2, 6-Dihydroxy-3-(β-hydroxyethyl) pyridine-5-carboxamide (II). a) A mixture of 15 g IV and 75 ml concentrated HCl was refluxed for 1 hr 30 min. The resultant solution was diluted with an equal volume of water, and left overnight at −5°. The crystals which separated were filtered off. Yield of V 9.76 g (64.96%), colorless crystals, readily soluble in hot water. IR spectrum, cm^{-1}: 1579 (pyridine ring), 1639 (−CONH−), 1687 ($-CONH_2$) (figure). Found: C 48.74; H 5.15; N 13.86%. Calculated for $C_8H_{10}N_2O_4$: C 48.48; H 5.05; N 14.14%.

b) 5 g IV was refluxed for 30 hr with 10% aqueous KOH. The reaction products were made acid to congo red with concentrated HCl, and then left overnight in a refrigerator at −5°. 1.5 g crystalline V was isolated. By evaporating the mother liquor to half volume, a further 0.25 g V was obtained; yield 31.9%.

2, 6-Dichloro-3-(β-chloroethyl)-5-cyanopyridine (I). a) 10 g IV and 16 ml $POCl_3$ were heated together for 5 hr at 180°in a stainless steel autoclave, volume 120 ml. The contents were poured onto ice, and the dark precipitate formed was filtered off, and extracted with ether in a Soxhlet. The aqueous layer was also extracted with ether. The bulked ether solutions were evaporated under reduced pressure, and the residue distilled at 140-141° (0.35 mm). Yield of I 3; 3.2 g (26.9%), colorless crystals mp 57-58° (ex petrol ether). The compound was readily soluble in ether, benzene, chloroform, and acetone, less soluble in alcohols and petrol ether, insoluble in water. IR spectrum, cm^{-1}: 2250 (C≡N), 1586 (pyridine ring) (figure). Found: C 40.93; H 1.95; N 11.70; Cl 45.63%. Calculated for $C_8H_5Cl_3N_2$: C 40.76; H 2.12; N 11.89; Cl 45.23%.

In a similar run at 200 the yield of I was 9%, and at 160° it was 16.9%.

b) A mixture of 5 g V and 20 ml $POCl_3$ was heated in a sealed glass tube for 5 hr at 180°. The product was worked up as described in experiment a). Yield of I, 1.5 g (25.2%).

2, 6-Dichloro-3-(β-chloroethyl) pyridine-5-carboxamide (VII). HCl gas was passed for 5 hr into a solution of 0.5 g I in 10 ml methanol at room temperature. The reaction products were evaporated under reduced pressure, the residue made alkaline with 50% potash solution, and extracted with benzene. The extract was dried over potash, and evaporated under reduced pressure. The residue (0.45 g) was washed twice with 1 ml ether each time. 0.35 g (65%) VII was obtained. Colorless crystals, mp 128-129°, bp 160-162° (1.5 mm). Readily soluble in alcohols, $CHCl_3$, Me_2CO. AcOEt, low solubility in ether, insoluble in water. IR spectrum, cm^{-1}: 1665, 3200, 3400 ($-CONH_2$) (figure). Found: C 37.57; H 3.03; N 11.06; Cl 42.08%. Calculated for $C_8H_7Cl_3N_2O$: C 37.87; H 2.76; N 11.04; Cl 42.01%.

Evaporation of the ethereal mother liquor gave 0.1 g oily material bp 148° (0.5 mm), n_D^{20} 1.5630, identified as methyl 2, 6-dichloro-3-(β-chloroethyl) pyridine-5-carboxylate (VIII), yield, 17.5%.

2, 6-Dichloro-3-(β-chloroethyl) pyridine-5-carboxylic acid (IX). A reaction mixture comprising 65 g I and 100 ml MeOH was refluxed for 12 hr, HCl gas being bubbled in, and the reaction products were distilled under reduced pressure. The mixture of amide and methyl ester of 2, 6-dichloro-3-(β-chloroethyl) pyridine-5-carboxylic acid thus obtained was refluxed with a mixture of 60 ml AcOH plus 25 ml hydrochloric acid for 6 hr, then evaporated under reduced pressure. The residue was made alkaline with 50% potash solution, and extracted with benzene. The extract was dried over potash, and evaporated under reduced pressure, when it gave 45 g 2, 6-dichloro-3-(β-chloroethyl)- pyridine-5-carboxamide (VIII), mp 128-129°. The aqueous alkaline solution was made acid to congo red with concentrated HCL and then extracted with ether. The ether extract was dried over $MgSO_4$ and evaporated under reduced pressure, to give 16.1 g IX. Amide VII isolated was submitted to alcoholysis, and then saponified under the conditions described above, to give an additional 10.6 g IX, 19.6 g (28%) amide VII being recovered. Total yield of IX, 26.7 g (37.8%). Colorless crystals, mp 129-130° (ex benzene). The compound readily dissolved in alcohols and $CHCl_3$, less readily in benzene, and was insoluble in water. IR spectrum, cm^{-1}: 1715 (COOH). Found: C 37.68; H 2.40; N 5.50, 5.61; Cl 41.44%. Calculated for $C_8H_6Cl_3NO_3$: C 37.72; H 2.36; N 5.50; Cl 41.85%.

Methyl 2, 6-dichloro-3-(β-chloroethyl) pyridine-5-carboxylate (VIII). 100 ml of an ethereal solution of diazomethane was prepared from 10 g nitrosomethylurea, and added to 0.5 g IX, and the whole then stirred and kept at room temperature for 30 min, after which it was evaporated to give 0.52 g (100%) VIII, colorless oily substance, readily soluble in the usual organic solvents, insoluble in water, bp 157° (0.8 mm), n_D^{20} 1.5630. Found: C 40.47; H 3.15; N 5.25, 5.35; Cl 39.60%. Calculated for $C_9H_8Cl_3NO_2$: C 40.29; H 2.98; N 5.22; Cl 39.66%.

2, 6-Dichloro-3-vinylpyridine-5-carboxylic acid (X). 0.5 g IX was refluxed for 8 hr with a solution of 0.24 g KOH in 15 ml dry ethanol. The reaction products were evaporated under reduced pressure, 5 ml 10% HCl added to the residue, and X extracted with ether. The ether solution was dried over $MgSO_4$, and evaporated under reduced pressure,

* All IR spectra were determined in vaseline, using a UR-10 spectrophotometer.

the residue was then crystallized from benzene, to give 0.38 g (89%) X, colorless crystals, mp 152°, readily soluble in ether, alcohols, and Me_2CO, less soluble in benzene and $CHCl_3$, insoluble in water. Found: C 43.86; H 2.46; N 6.79; Cl 32.27%. Calculated for $C_8H_5Cl_2NO_2$: C 44.00; H 2.29; N 6.42; Cl 32.57%.

1-Phenyl-5-cyano-6-chloro-7-azaindoline (XI). a) 5 g I and 5 ml ethylaniline were heated together for 7 hr at 140°. There was marked resinification of the reaction mixture. 20 ml 50% aqueous potash solution plus 20 ml ether were added, the precipitate filtered off; 1.85 g XI was obtained, mp 189° (ex ethanol). The substance had a low solubility in benzene, ethanol, Me_2CO and $CHCl_3$, and it was insoluble in water and ether. IR spectrum, cm^{-1}: 2235 (C ≡ N) (figure). Found: C 65.66; H 4.08; N 16.56; Cl 13.92%. Calculated for $C_{14}H_{10}ClN_3$: C 65.75; H 3.91; N 16.44; Cl 13.90%.

After removing XI, the ether layer was separated off from the filtrate and dried over potash. The ether and N-ethylaniline were distilled off under reduced pressure, and the residue distilled, 2 cuts being taken: 1st bp 75° (3 mm), 0.4 g; 2nd, bp 162-165° (3 mm), 0.6 g. The latter was XI, total yield, 2.45 g (49%). The 1st cut was 2, 6-dichloro-3-vinyl-5-cyanopyridine (XII), yield, 13.8%, colorless crystals mp 92.5-93° (ex ethanol). Soluble in ether, benzene, $CHCl_3$ and Me_2CO, sparingly soluble in ethanol, insoluble in water. Found: C 48.58; H 2.22; N 14.46; Cl 35.41%. Calculated for $C_8H_4Cl_2N_2$: C 48.24; H 2.01; N 14.07; Cl 35.68%.

Similar results were obtained in the reaction with I, when N-methylaniline was used instead of N-ethylaniline.

b) 5 g VII and 5 ml N-ethylaniline were heated together for 7 hr at 140°, 10 ml 50% potash solution and 10 ml ether added. The XI which separated was filtered off, yield 2.3 g; the ether solution was evaporated and distilled under reduced pressure, a cut bp 150-155° (1.7 mm) being taken, when a further 1 g XI was obtained, total yield 3.3 g (66%).

1-Phenyl-5-cyano-7-azaindoline (XIII). 3 g palladium chloride dissolved in 15 ml 18% HCl, was added to a solution of 2.8 g XI in 300 ml AcOH. Hydrogenation was carried out at room temperature and using 20-30 cm water excess pressure. The catalyst was filtered off, the filtrate evaporated under reduced pressure, the residue made alkaline with 50% potash solution, and extracted with ether. The ether extract was dried with potash, and evaporated under reduced pressure, to give 0.8 g (34.8%) 1-phenyl-5-cyano-7-azaindoline (XIII), which was converted to hydrochloride mp 230-231° (ex ethanol). The compound was slightly soluble in alcohols, Me_2CO, and water. Found: C 65.14; H 4.95; N 16.20; Cl 14.12%. Calculated for $C_{14}H_{11}N_3 \cdot HCl$: C 65.24; H 4.66; N 16.31; Cl 13.79%.

1-Phenyl-5-cyano-7-azaindole (II). 0.75 g XIII and 0.75 g chloranil were refluxed together for 1 hr 30 min in 10 ml dry xylene. 3 ml 40% NaOH solution was added to the reaction mixture. II was extracted from the mixture with benzene-xylene (1:1), the extract dried over potash and evaporated, to give 0.37 g (50%) II, converted to its hydrochloride mp 184° (ex ethanol). The compound was readily soluble in Me_2CO, sparingly soluble in EtOH and water, insoluble in ether. IR spectrum cm^{-1}: 2230 (C≡N). Found: C 65.39; H 3.94; N 16.17; Cl 14.18%. Calculated for $C_{14}H_9N_3 \cdot HCl$: C 65.75; H 3.91; N 16.44; Cl 13.90%.

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