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AZACARBAZOLES
II. Alkylation of 5H-Pyridazino [4, 5-b] Indole*

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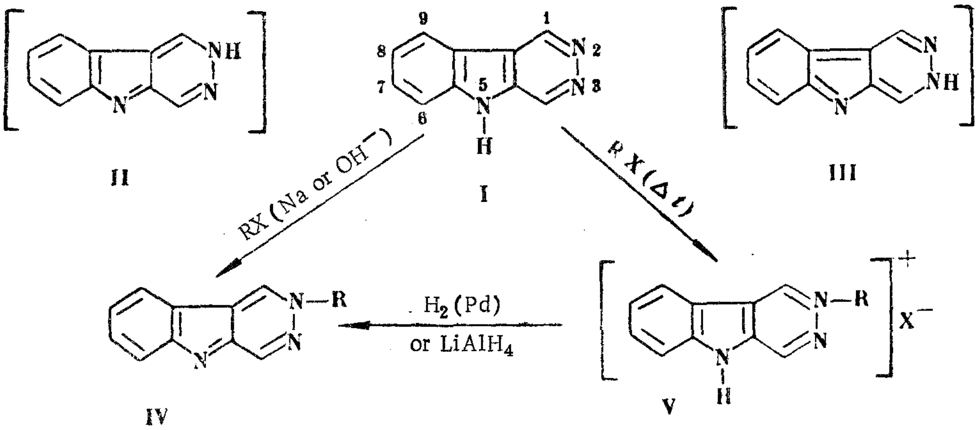
Alkylation of 5H-pyridazino [4, 5-b] indole with halogen compounds or dimethyl sulfate in the presence of alkaline reagents gives 2-alkyl-2H-pyridazino [4, 5-b] indoles. Reduction of the methiodide or chlorobenzylate of 5H-pyridazino [4, 5-b] indole also gives 2-alkyl derivatives. $LiAlH_4$ reduction of 3-alkyl-3H-pyridazino [4, 5-b] indolones-4 gives 3-alkyl-3H-pyridazino [4, 5-b] indoles.

5H-Pyridazino [4, 5-b] indole was previously synthesized by some of the present authors, and shown to have an indole (I) and not an indolenine (II or III) structure [1].

Methyl iodide or dimethyl sulfate methylation in alkaline solution, or benzylation of the Na derivative of I with benzyl chloride in ethylcellosolve or liquid ammonia gives compounds which are isomeric with the previously synthesized 5-methyl-(XI, R=Me), and 5-benzyl-(XI, R=$PhCH_2$) - 5H-pyridazino [4, 5-b] indoles. From the UV spectra (displacement of maxima towards the longwave region, Fig. 1, curves 1 and 2) it can be assumed that the alkylation products have a type II or III indolenine structure.



The corresponding 3-alkyl derivatives of the indolenine form III were synthesized to establish the structures. Reaction of methyl- and benzylhydrazines with 2-carboethoxyindole-3-aldehyde (VI) gave the corresponding indolones, and the accordance of their IR and UV spectra with those for 5H-pyridazino [4, 5-b] indolone-4 (IX), and their insolubility in alkalies, showed them to have structure VII and not VIII. Reduction of VII (R=Me or $PhCH_2$) with lithium aluminum hydride gave 3-methyl- and 3-benzyl-3H-pyridazino-[4, 5-b] indoles (X, R=Me or $PhCH_2$, respectively), which differed from those of the corresponding alkylation products IV. They also differed from the previously prepared substances of type XI (Fig. 2). So the alkylation products must be 2-methyl- and 2-benzyl-2H-pyridazino [4, 5-b] indoles (IV, R=Me and $PhCH_2$ respectively). It is assumed that their formation in alkylation of I is due to an A. N. Mesmeyanov migration of the reaction center.

Methyl iodide methylation of the Na derivative of I in ethylcellosolve gives 5-methyl-5H-pyridazino [4, 5-b] indole methiodide (XII), whose physical properties and UV spectrum are identical with the methiodide of XI (R=Me), and differ from those of the methiodide of IV (R=Me) (Fig. 3). Evidently here the methiodide V (R=Me) is first formed, and this is then further normally alkylated at position 5.

Similar transformations were recently noted for β-carboline compounds [2]. The fact that reduction of the methiodide or benzochloride of 5H-pyridazino [4, 5-b] indole gives its alkyl derivatives IV (R=Me and $PhCH_2$ respectively) makes it possible to assign structure V to these quaternary compounds.

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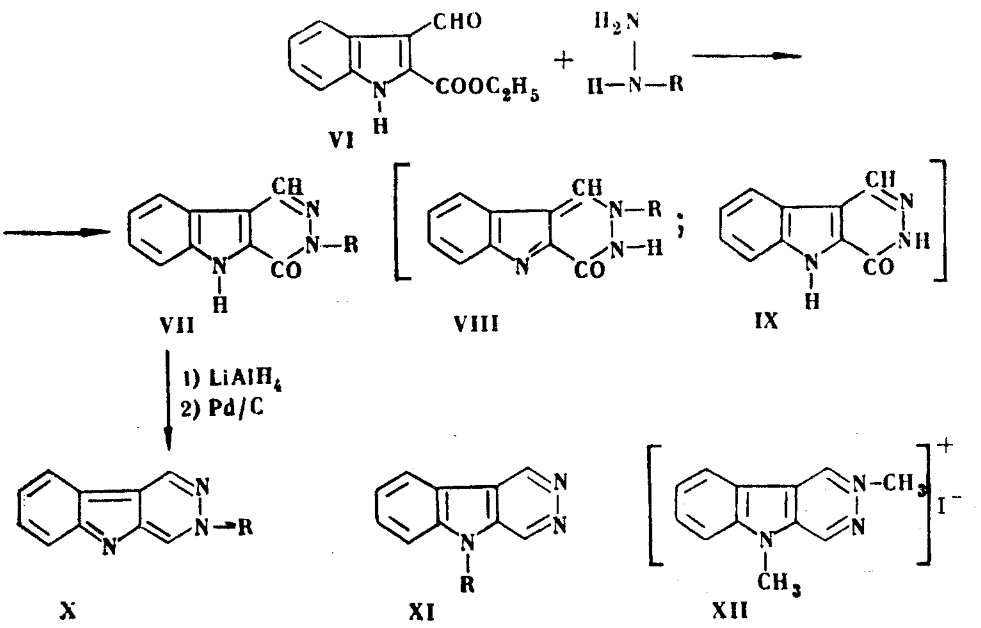
*For Part I see [1]. The main results of the research were reported at the Conference on Heterocyclic Rings in Organic Synthesis, Kiev, June 1964.



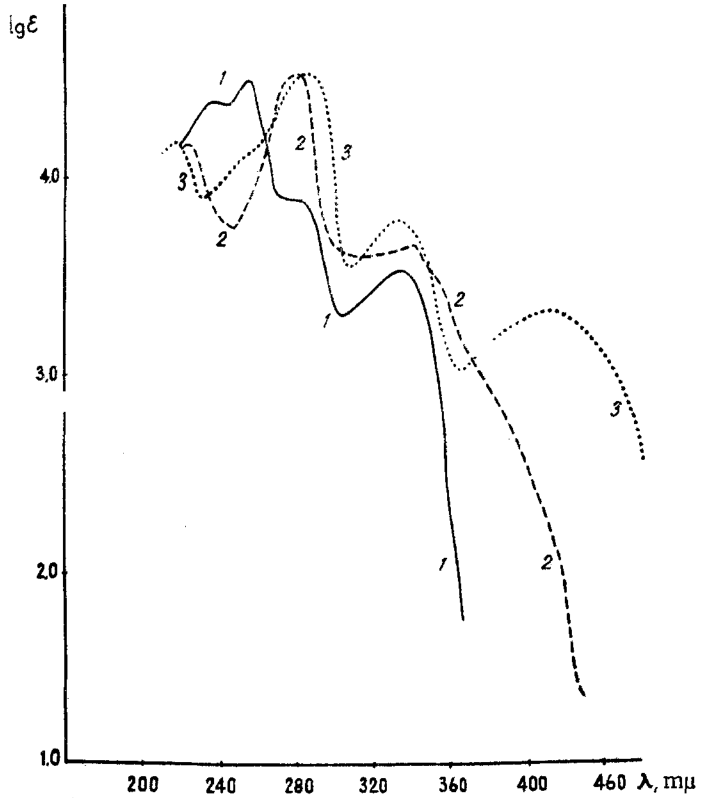


Fig. 1. UV absorption spectra: 1) 5-methyl-5H-pyridazino [4, 5-b] indole; 2) 2-methyl-2H-pyridazino-[4, 5-b] indole; 3) 3-methyl-3H-pyridazino [4, 5-b] indole.

Experimental

IR spectra were measured with a UR-10 instrument, with the crystalline compounds made into a paste with vaseline. UV spectra were measured with a SF-4 spectrophotometer, in ethanol solution.

Methylation of 5H-pyridazino [4, 5-b] indole (I). a) 0.9 ml (9.5 mmole) dimethyl sulfate was added dropwise over a period of 5 min to a solution of 0.5 g (3 mmole) I in 175 ml 10% aqueous NaOH solution at room temperature.

The solution became more and more yellow as addition proceeded, and a precipitate was formed. The yellow precipitate formed was filtered off, mp 197.5-198° (ex EtOH-H_2O 1:1), yield of 2-methyl-2H-pyridazino [4, 5-b] indole (IV, R=Me) 0.14 g (25.9%). Found: 71.99; H 5.13; N 23.24, 22.24%. Calculated for $C_{11}H_9N_3$: 72.11; 4.95; N 22.94%.

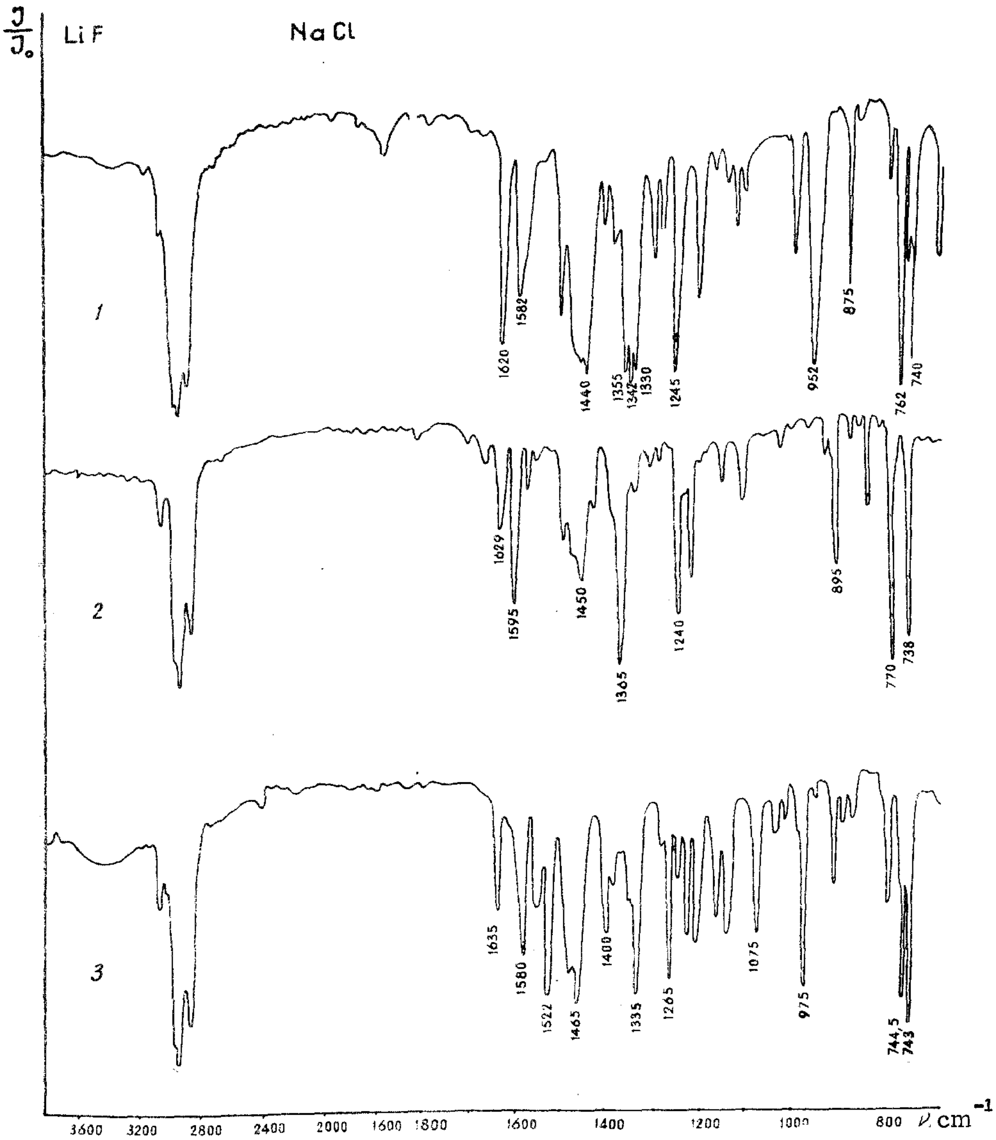


Fig. 2. IR absorption spectra of 5H-pyridazino [4, 5-b] indole alkylation products: 1) 3-methyl-3H-pyridazino [4, 5-b] indole; 2) 2-methyl-2H-pyridazino-[4, 5-b] indole; 3) 5-methyl-5H-pyridazino [4, 5-b] indole.

b) 0.38 g methyl iodide in 15 ml tetrahydrofuran was added dropwise over a period of 2 hr 30 min to 0.5 g (3 mmole) I dissolved in 175 ml 10% aqueous NaOH solution. The lemon-colored precipitate was filtered off, yield 0.11 g (31.4%), mp 202.5-203.5° (ex EtOH-H_2O 1:1). The compound obtained was completely identical with compound IV prepared in (a) above.

Picrate (yellow crystals) mp 297-297.5° (decomp). Found: C 49.22, 49.38; H 3.08, 3.10; N 20.26%. Calculated for $C_{11}H_9N_3 \cdot C_6H_3N_3O_7$: C 49.52; H 2.93; N 20.39% .

Methiodide, mp 305.5-307° (decomp). Found: C 43.70, 43.67; H 3.86, 3.50: I 39.80, N 13.03% . Calculated for $C_{12}H_{12}IN_3$, C 44.31; H 3.72; I 39.03, N 12.92%.

3-Methyl-3H-pyridazino [4, 5-b] indolone-4 (VII, R=Me). 0.68 g (3.1 mmole) 2-carboethoxyindolyl-3-aldehyde in 13.6 ml ethylcellosolve was added to an aqueous solution of methylhydrazine (prepared from 6.19 g methylhydrazine sulfate), and the whole refluxed in a stream of N_2 for 3 hr. The white crystalline precipitate formed was filtered off, and washed with ethylcellosolve and dry ether, mp 282-282.5° (ex ethylcellosolve), yield 0.62 g (99.5%). Found: C 66.75, 66.89; H 4.36, 4.58; N 20.66, 20.81%. Calculated for $C_{11}H_9N_3O$: C 66.40; H 4.52; N 21.10%.

3-Methyl-3H-pyridazino [4, 5-b] indole (X, R=Me). 0.94 g (4.7 mmole) indolone VII (R=Me) in 100 ml tetrahydrofuran was added to 0.47 g (12 mmole) lithium aluminum hydride in 51 ml tetrahydrofuran, and the mixture heated in a stream of nitrogen for 3 hr in a bath at 80°. After decomposing the reaction products with water, and evaporating off the solvent, 0.63 g residue was obtained. To dehydrogenate possible further reduction products, 0.63 g of this substance was dissolved in 61.7 ml dry xylene, 0.63 g Pd/C added, and the whole heated in a stream of nitrogen for 3 hr. The catalyst was filtered off from the hot solvent. The precipitate formed was filtered off, washed with cooled xylene and dry ether, mp 186-186.5° (ex benzene), yield of X (R=Me) 0.26 g (41.8%). Found: C 72.21, 72.26; H 5.15, 5.08; N 22.79, 22.90%. Calculated for $C_{11}H_9N_3$: C 72.11; H 4.95; N 22.94%.

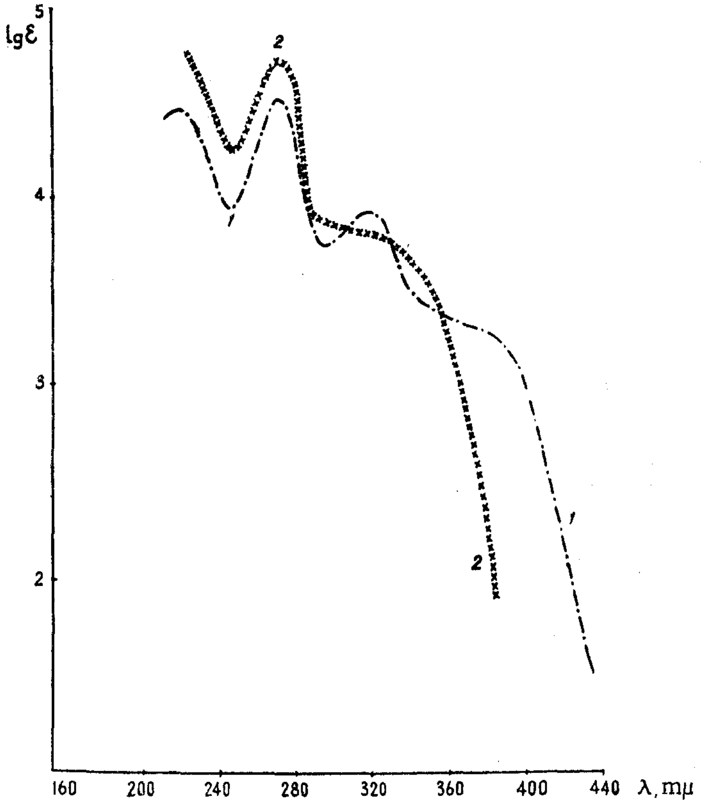


Fig. 3. UV absorption spectra: 1) 5-methyl-5H-pyridazino [4, 5-b] indole methiodide; 2) 2-methyl-2H-pyridazino [4, 5-b] indole methiodide.

Unlike 5-methyl-5H-pyridazino- and 2-methyl-2H-pyridazino [4, 5-b]-indoles, its IR spectrum lacks N—H bond bands (see Fig. 2). Both the compound and its derivatives give depressed mixed melting points with the corresponding compounds mentioned.

Picrate (yellow crystalline compound), mp 292° (decomp). Found: C 49.39; H 3.00; N 20.40%. Calculated for $C_{11}H_9N_3 \cdot C_6H_3N_3O_7$: C 49.52; H 2.93; N 20.39%.

5-Methyl-5H-pyridazino [4, 5-b] indole methiodide (XII). 0.5 g (3 mmole) I was added, in a stream of nitrogen, and at room temperature to a solution of 0.07 g (0.003 g at) sodium metal in 20 ml ethylcellosolve, followed by 0.38 ml methyl iodide over a period of 1 hr. When addition was complete, the reaction mixture was refluxed for 3 hr, the precipitate which separated from the hot solution was filtered off, washed with hot ethylcellosolve, and then with dry ether. Yield 0.41 g (42.6%), mp 298.5-299.5° (darkening). Found: C 44.21; H 4.40; I 38.81; N 12.93, 13.07%. Calculated for $C_{12}H_{12}IN_3$: C 44.31; H 3.72; I 39.03; N 12.92%. Mixed mp with a specimen of 5-methyl-5H-pyridazino [4, 5-b] indole methiodide, prepared from the authentic 5-methyl derivative (XI, R=Me), undepressed.

Benzylation of 5H-pyridazino [4, 5-b] indole (I). a) 0.5 g (3 mmole) I was added to 0.07 g (0.003 g at) sodium metal in 20 ml ethylcellosolve at room temperature, in a current of nitrogen, then 0.34 ml benzyl chloride was dropped in over a period of 1 hr. When addition was complete, the reactants were refluxed for 3 hr. The precipitate of sodium chloride formed (0.17 g, theory 0.173 g) was filtered off from the hot solution, washed with hot ethylcellosolve, and then with dry ether.

The mother liquor was evaporated to dryness under reduced pressure. The residue was a yellow crystalline material, mp 231-233° (decomp). (ex ethanol). Yield of 2-benzyl-2H-pyridazino- [4, 5-b] indole (IV, R=$PhCH_2$) 0.23 g (30%).

It gave a depressed mixed mp with 5-benzyl-5H-pyridazino [4, 5-b] indole. Their IR spectra differed. Found: C 78.71; H 5.20; N 16.02%. Calculated for $C_{17}H_{13}N_3$: C 78.74; H 5.05; N 16.21%. Picrate (yellow crystalline compound), mp 269-269.5° (decomp). Found: C 56.56; H 3.17; N 16.95, 17.50%. Calculated for $C_{17}H_{13}N_3 \cdot C_6H_3N_3O_7$: C 56.56; H 3.30; N 17.21%. Methiodide, mp 240.5°. Found: C 53.94, 53.43; H 3.82, 4.40; I 31.86; N 10.45%. Calculated for $C_{18}H_{16}IN_3$: C 53.87; H 4.01; I 31.63; N 10.45%.

b) 0.07 g (0.003 g at) sodium metal was dissolved in 100 ml liquid ammonia, and 0.5 g (3 mmole) I added immediately. When the solution had become colorless, 0.34 ml benzyl chloride was added, and the mixture stirred for 8 hr, then left overnight. After evaporating off the ammonia, a yellow residue remained, mp 227-228° (decomp) (ex ethanol). The benzylation product was identical with that obtained in (a) above.

3-Benzyl-3H-pyridazino [4, 5-b] indolone-4 (VII, R=$PhCH_2$). 2.78 g (13 mmole) 2-carboethoxy-3-indolaldehyde (VI) in 55.6 ml ethylcellosolve, and 1.72 g (14 mmole) benzylhydrazine were refluxed together in a stream of nitrogen for 3 hr. The products were cooled, the solvent distilled off in a current of N_2 to incipient crystalization, mp 293-294° (ex ethylcellosolve), yield 1.12 g (31.8%). Found: C 74.01; H 4.58; N 15.26, 15.03%. Calculated for $C_{17}H_{13}N_3O$: C 74.16; H 4.75; N 15.26%.

3-Benzyl-3H-pyridazino [4, 5-b] indole (X, R=$PhCH_2$). 1.12 g (4 mmole) VII (R=$PhCH_2$) in 150 ml tetrahydrofuran was added to a solution of 0.56 g (15 mmole) lithium aluminum hydride in 50 ml tetrahydrofuran while a stream of N_2 was passed, and the whole then heated for 3 hr in a bath at 80°. After cooling, 1.12 ml distilled water was added. The precipitate formed was filtered off, washed with 40 ml tetrahydrofuran, and the solvent distilled off from the filtrate in a current of N_2 until dryness. The residue, 0.94 g yellow crystalline material, was rubbed with 25 ml dry ether, and recrystallized from ethanol. To dehydrogenate possible further reduction products, 0.53 g of this material was dissolved in 55 ml hot dry xylene, the solution cooled, and 0.53 g Pd/C added, after which the mixture was refluxed for 3 hr in a current of N_2. The catalyst was filtered off from the hot solution, the solution then cooled. Mp 228-229° (decomp), yield 0.13 g (24.4%). Found: C 78.44, 78.50; H 5.52, 5.31; N 16.10, 15.98%. Calculated for $C_{17}H_{13}N_3$: C 78.74; H 5.05; N 16.21%. Picrate (yellow crystalline compound) mp 271° (decomp). Found: C 57.33, 57.50; H 3.51, 3.57; N 17.39%. Calculated for $C_{17}H_{13}N_3 \cdot C_6H_3N_3O_7$: C 56.56; H 3.30; N 17.21%.

Methiodide, mp 226-226.5°, Found: C 53.58; H 4.31; I 30.40; N 10.45%. Calculated for $C_{18}H_{16}IN_3$: C 53.87; H 4.01; I 31.63; N 10.45%.

The IR spectrum of VII (R=$PhCH_2$, lacks N—H bonds bands) differs from those of 5-benzyl-5H-pyridazino- and 2-benzyl-2H-pyridazino- [4, 5-b] indoles. Both the compound and its derivatives give depressed mixed mps with corresponding preparations of the compounds mentioned.

2-Methyl-2H-pyridazino [4, 5-b] indole (IV, R=Me). 2.67 g (8.5 mmole) methiodide V (R=Me) in 400 ml distilled water and 100 ml ethanol, was hydrogenated with 2.67 g Pd/C at room temperature and 20 atm. The catalyst was then filtered off, and washed with ethanol. The ethanol was distilled off under reduced pressure in a stream of nitrogen to incipient crystallization. 0.74 g of the resultant hydriodide was dissolved in 100 ml distilled water, and 20 ml aqueous ammonia added. Yellow crystals separated. Air was passed through the solution. The precipitate was filtered off, mp 197.5-198°. Found: C 72.36; H 4.77; N 22.94%. Calculated for $C_{11}H_9N_3$: C 72.11; H 4.95; N 22.94%. The compound was the same as that obtained by methylating 5H-pyridazino [4, 5-b] indole. Methiodide, mp 308-309.5° (decomp). Found: C 44.59; H 3.93; I 39.27%. Calculated for $C_{12}H_{12}IN_3$: C 44.31; H 3.72; I 39.03%. Picrate, mp 297.5-298° (decomp). Found: C 49.66; H 3.00; N 20.08%. Calculated for $C_{11}H_9N_3 \cdot C_6H_3N_3O_7$: C 49.52; H 2.93; N 20.39%.

3-Chlorobenzylate of 5H-pyridazino [4, 5-b] indole (V, R=$PhCH_2$). 0.58 g (3.4 mmole) 5H-pyridazino [4, 5-b] indole in 30 ml ethylcellosolve and 0.4 ml benzylchloride was refluxed for 1 hr in a current of N_2. At the end of the reaction the products were cooled, and the solvent distilled off in a current of N_2. The residue (1.77 g oil) was triturated with 20 ml dry ether, when the oil crystallized. The solid was filtered off, and washed with dry ether, mp 246-247° (ex ethanol). Found: Cl 11.89; N 13.85%. Calculated for $C_{17}H_{14}ClN_3$: Cl 12.00; N 14.21%.

2-Benzyl-2H-pyridazino [4, 5-b] indole (IV, R=$PhCH_2$). 0.25 g (6.6 mmole) lithium aluminum hydride in 15 ml tetrahydrofuran was stirred at its boiling point for 1 hr, in a current of nitrogen. Then 0.4 g (1.4 mmole) V (R=$PhCH_2$) was added, and the whole heated for 3 hr. When reaction was complete, the products were cooled, and a solution of 1.056 g NaOH in 4.23 ml water added. Mp 232-233.5° (decomp) (ex ethanol). Found: C 78.50; H 5.20; N 16.37%. Calculated for $C_{17}H_{13}N_3$: C 78.74; H 5.05; N 16.21%. The compound was identical with the product of benzylating 5H-pyridazino [4, 5-b] indole. Picrate, mp 269° (decomp). Found: C 56.47; H 3.37; N 16.87%. Calculated for $C_{17}H_{13}N_3 \cdot C_6H_3N_3O_7$: C 56.56; H 3.30; N 17.21%.

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