Pyridazines. L. Methylations and Methyl Group Migrations of Some Imidazo[1,2-b]pyridazines

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Methylation studies on different imidazo[1,2-b]pyridazines have been conducted and at elevated temperatures the methylated compounds undergo methyl group migrations. The methyl groups can be transposed from oxygen at C_6 to N_5 or N_1 and demethylation at N_1 or N_5 has been observed.

Our previous observation that quaternized *s*-triazolo[4,3-*b*]pyridazines may undergo methyl group transposition in the five-membered ring[1] prompted us to investigate this phenomenon in the imidazo[1,2-*b*]-pyridazine series.

It has been reported[2] that methylation of 2-phenylimidazo[1,2-*b*]pyridazin-6(5*H*)-one with methyl iodide afforded the corresponding 5-methyl derivative **3**. We have repeated this experiment and have found that the product is in fact a mixture of the 6-methoxy compound **2** (40%) and the 5-methyl compound **3** (52%) accompanied by a small amount of the starting material (8%).

On the other hand, 6-chloro-1-methyl-2-phenylimidazo[1,2-*b*]pyridazin-4-ium iodide (**4**), when treated with sodium methylate, afforded **5**. In a similar experiment with aqueous potassium hydroxide, however, the anhydro salt **6** was formed. Upon methylation, this anhydro salt was transformed into a mixture of the 1,5-dimethyl derivative **7** and the 6-methoxy compound **5** in a ratio of about 1:5. Moreover, compound **7** is formed also from **2** at 150–155° under pressure, and here again an almost equal amount of **5** was formed. Pure **7** could be obtained by thermal rearrangement of **5** when this compound was heated over its melting point (203°) or by quaternization of compound **3** with methyl iodide at about 160°. Although the 1,5-dimethyl derivative **7** on hand of these experiments appears to be the thermodynamically most stable compound, heating under high vacuum at 240° for 2 hr caused some demethylation to give **3** and a small amount of the anhydro salt **6** accompanying the unchanged starting material.

Migration of the methyl group from the methoxy compound **2** could be observed upon heating this compound at 240°, whereupon a mixture of three compounds could be separated by chromatography. There were present the starting compound, the *N*-methyl derivative **3**, and the anhydro salt **6** in the ratio of about 25:61:14. Evidently, this process involved migration not only to the neighboring N atom (N_5), but in considerable extent also to the nitrogen in the five-membered ring (N_1). In order to obtain evidence as to whether in the case of the above-mentioned transformation of **5** into **7** only methyl group migration from the methoxy group occurred or whether also the N_1-methyl group may participate in this process, the deuterated compound **8** was used as starting material. Nmr spectral evidence, which allowed distinction between the N_1-methyl and N_5-methyl groups in **7**, showed that the rearranged product **9** retained the CD_3 group at the N_5 atom and that no interchange of methyl groups was detected. As with other related systems, the migration of the methyl group is most probably intermolecular.[3] The driving force for these OMe → NMe rearrangements is certainly the greater stability of the amido structures, a feature which has been observed with several monocyclic heterocycles and which we have recently observed also in the *s*-triazolo[4,3-*a*]-1,3,5-triazine series.[4] On the other hand, it is well known that such rearrangements are promoted in the presence of small amounts of an alkyl halide.[3]

Except for an isolated example which we have described before,[5] the formation of anhydro salts of the type **6** represents the first case in this series. There are, however, several examples of anhydro salt formation with other heterocycles, in particular with cinnolines[6,7] and phthalazines.[8,9] The formation of **10** could be therefore accomplished similarly from 6-chloro-1-methylimidazo[1,2-*b*]pyridazin-4-ium iodide, and this undergoes also a smooth displacement of the chlorine atom with hydrazine hydrate to give **11**.

Experimental Section

Melting points were taken on a Kofler micro hot stage. Infrared spectra were recorded on a Perkin-Elmer 137 Infracord as KBr disks, nmr spectra were taken on a JEOL JNM-C-60HL spectrometer (tetramethylsilane as internal standard), and mass spectra were obtained on a CEC 21-110C instrument.

Methylation of 2-Phenylimidazo[1,2-*b*]pyridazin-6(5*H*)-one.—A solution of **1**,[2] 0.65 g, nmr (DMSO-d_6) τ 1.66 (s, H_3), 3.36 (d, H_7), 2.25 (d, H_8), 2.75, 2.20 (m, Ph), $J_{7,8}$ = 9.5 Hz, in methanolic KOH (0.21 g of KOH in 20 ml of MeOH) was treated with MeI (1.03 g) and the mixture was heated under reflux for 2 hr. The solvent was evaporated, the residue was treated with water (5 ml), and the precipitate was filtered off. Upon recrystallization from 65% EtOH the crystals (0.7 g) had mp 120–123°; 30 mg was separated by tlc (DC Fertigplatten Kieselgel F-254, Merck) with a mixture of $CHCl_3$ and MeOH (30:1). Each of the separated three spots was eluted with MeOH. There were obtained 10 mg of **2** [R_f 0.81; nmr (DMSO-d_6, 93°) τ 1.70 (d, H_3), 3.31 (d, H_7), 2.21 (dd, H_8), 2.75, 2.20 (m, Ph), 6.06 (s, OMe), $J_{3,8}$ = 0.6, $J_{7,8}$ = 9.5 Hz; mass spectrum *m/e* 225 (M^+). *Anal.* Calcd for $C_{13}H_{11}N_3O$: C, 69.32; H, 4.92; N, 18.66. Found: C, 69.64; H, 4.87; N, 18.32.], 13 mg of **3** [mp 153°; R_f 0.52; mass spectrum *m/e* 225 (M^+); nmr ($CDCl_3$) τ 2.40 (d, H_3), 3.42 (d, H_7), 2.24 (dd, H_8), 2.7, 2.3 (m, Ph), 6.20 (s, NMe), $J_{3,8}$ = 0.6, $J_{7,8}$ = 9.5 Hz; ir (KBr) 1656 cm^{-1} (CO). *Anal.* Calcd for $C_{13}H_{11}N_3O$: C, 69.32; H, 4.92; N, 18.66. Found: C, 69.54; H, 5.21; N, 19.00.], and the starting compound **1** (2 mg, R_f 0.23).

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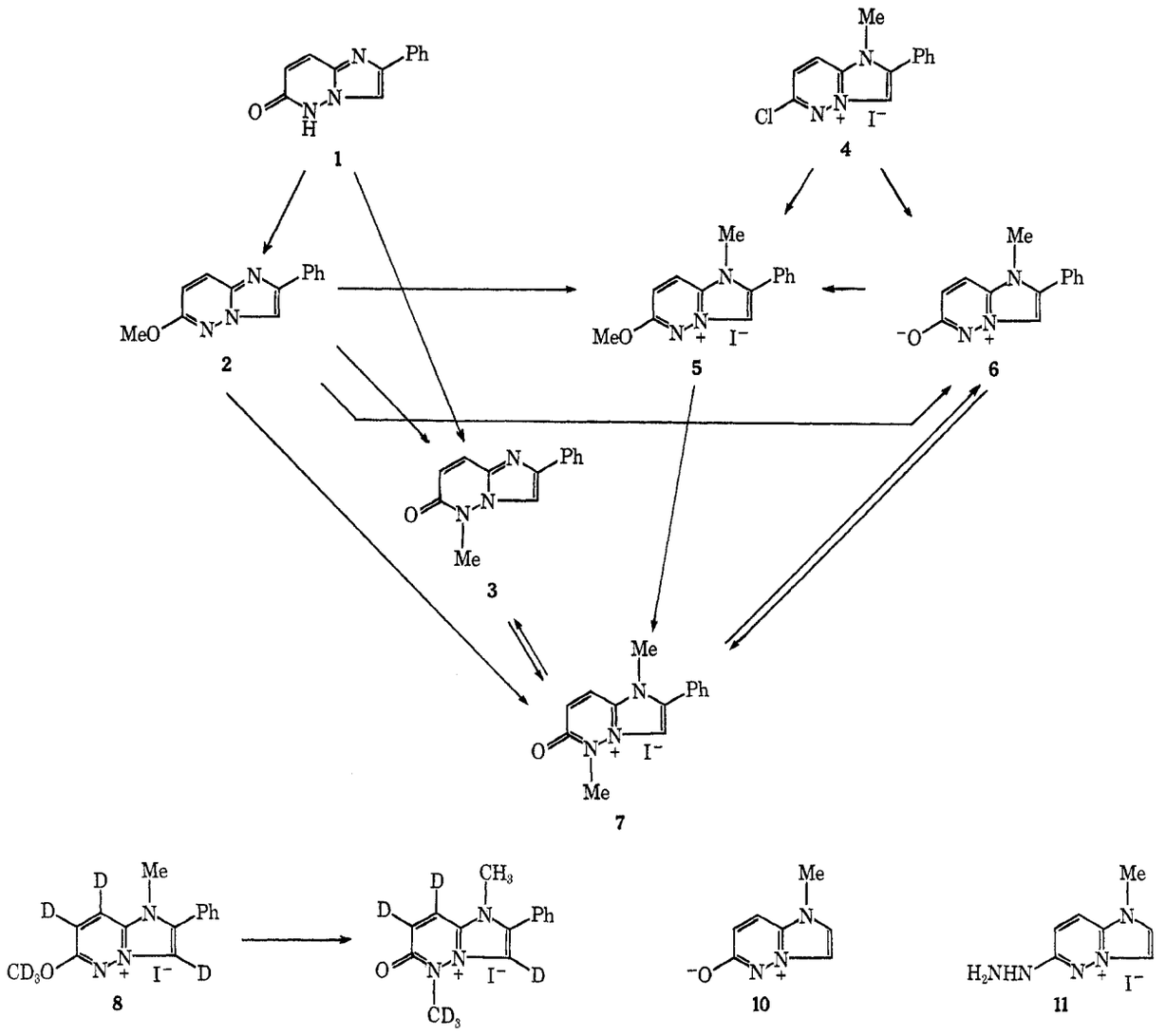

6-Chloro-1-methyl-2-phenylimidazo[1,2-*b*]pyridazin-4-ium Iodide (4).—A suspension of 6-chloro-2-phenylimidazo[1,2-*b*]-pyridazine[10] [2.30 g; nmr ($CDCl_3$) τ 1.92 (d, H_3), 3.11 (d, H_7), 2.25 (dd, H_8), 2.75, 2.20 (m, Ph), $J_{3,8}$ = 0.6, $J_{7,8}$ = 9.3 Hz] in EtOH (80 ml) was treated with MeI (2.84 g) and the mixture was heated in an autoclave at 160° for 5 hr. The separated product was filtered off (2.9 g, 78%) and upon recrystallization from EtOH it had mp 260–262°; nmr (DMSO-d_6) τ 1.10 (d, H_3), 1.96 (d, H_7), 1.12 (dd, H_8), 2.40 (m, Ph), 5.93 (s, Me), $J_{3,8}$ = 0.6, $J_{7,8}$ = 9.6 Hz.

Anal. Calcd for $C_{13}H_{11}ClIN_3$: C, 42.01; H, 2.98; N, 11.31. Found: C, 42.22; H, 3.44; N, 11.26.

6-Methoxy-1-methyl-2-phenylimidazo[1,2-*b*]pyridazin-4-ium Iodide (5).—A suspension of 4 (1.86 g) in a solution of sodium methylate in MeOH (prepared from 0.12 g of sodium in 20 ml of MeOH) was heated under reflux for 2 hr. The solvent was evaporated to dryness, ice water (5 ml) was added, and the residue was filtered off and crystallized from EtOH (1.1 g, 60%): the product melted at 203°; the melt solidified at about 205° and melted again at 249–250°; mass spectrum *m/e* 225 (M^+ − MeI); nmr ($CDCl_3$) τ 2.16 (d, H_3), 2.80 (d, H_7), 1.18 (dd, H_8), 5.98 (s, OMe), 5.85 (s, NMe), 2.53 (m, Ph), $J_{3,8}$ = 0.6, $J_{7,8}$ = 9.6 Hz.

Anal. Calcd for $C_{14}H_{14}IN_3O$: C, 45.80; H, 3.85; N, 11.45. Found: C, 45.60; H, 3.90; N, 11.46.

6-Trideuteriomethoxy-1-methyl-2-phenyl-3,7,8-trideuterioimidazo[1,2-*b*]pyridazin-4-ium iodide (8) was prepared in the same manner as **5**, but using CD_3OD: mp 203°; mass spectrum 231 (M^+ − MeI); nmr ($CDCl_3$) τ 5.85 (s, NMe), 2.52 (m, Ph).

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6-Hydroxy-1-methyl-2-phenylimidazo[1,2-*b*]pyridazin-4-ium Anhydro Salt (6).—A suspension of 4 (3.72 g) in aqueous KOH (20 ml of 10% solution) was heated under reflux for 10 min. Upon cooling the separated product was filtered off, washed with ice water until neutral, and crystallized from EtOH (1.77 g, 78%): mp 272–273°; mass spectrum *m/e* 225 (M^+); nmr (DMSO-d_6) τ 2.30 (s, H_3), 3.40 (d, H_7), 2.40 (d, H_8), 2.48 (m, Ph), 6.28 (s, NMe), $J_{7,8}$ = 9.6 Hz.

Anal. Calcd for $C_{13}H_{11}N_3O$: C, 69.32; H, 4.92; N, 18.66. Found: C, 68.99; H, 4.62; N, 18.58.

Methylation of 6-Hydroxy-1-methyl-2-phenylimidazo[1,2-*b*]-pyridazin-4-ium Anhydro Salt.—A solution of the anhydro salt **6** (0.9 g) in EtOH (10 ml) was treated with MeI (1 g) and the mixture was heated under reflux for 1 hr. Upon complete evaporation to dryness, $CHCl_3$ (5 ml) was added and after thorough mixing the solid was filtered off. The residue was crystallized from EtOH and had mp 249–250° (0.2 g). The compound was identified as 1,5-dimethyl-2-phenylimidazo[1,2-*b*]-pyridazin-6(5*H*)-on-4-ium iodide (**7**), mixture melting point undepressed with an authentic specimen prepared from **3**. The filtrate was evaporated to dryness and crystallized from EtOH to give 6-methoxy-1-methyl-2-phenylimidazo[1,2-*b*]pyridazin-4-ium iodide (**5**, 1.0 g), mp 203° (after solidification of the melt, mp 249–250°) and mixture melting point with an authentic specimen undepressed.

Methylation of 6-Methoxy-2-phenylimidazo[1,2-*b*]pyridazine.—A mixture of **2** (1.12 g), MeI (2.0 g), and MeOH (80 ml) was heated in an autoclave at 150–155° for 3 hr. Upon evaporation to dryness, $CHCl_3$ (20 ml) was added and the residue was filtered off. Crystallization from EtOH gave the pure **7** (0.4 g), mp 249–250°. The filtrate was evaporated and the residue was crystallized from EtOH to give **5** (0.31 g), mp 203°.

1,5-Dimethyl-2-phenylimidazo[1,2-*b*]pyridazin-6(5*H*)-on-4-ium Iodide (7). A.—Compound **5** (50 mg) was heated just above its melting point in a sublimation tube for 5 min. Thereafter the tube was connected to vacuum (0.1 mm) and the temperature was raised to 240° to sublime off traces of the demethylated products. The residue (46 mg) was pure **7**: mp 249–250°; mass spectrum *m/e* 225 (M^+ − MeI); ir (KBr) 1672 cm^{-1} (CO); nmr (DMSO-d_6) τ 1.26 (s, H_3), 2.94 (d, H_7), 1.68 (d, H_8), 2.46 (m, Ph), 6.04 (s, 1-Me), 6.22 (s, 5-Me), $J_{7,8}$ = 9.9 Hz.

Anal. Calcd for $C_{14}H_{14}IN_3O$: C, 45.80; H, 3.85; N, 11.45. Found: C, 45.65; H, 3.81; N, 11.80.

B.—A mixture of **3** (0.45 g), MeOH (30 ml), and MeI (0.5 g) was heated in an autoclave at 160° for 3 hr. The solvent was evaporated and the residue was crystallized from EtOH (0.35 g, 48%), mp 249–250°. The compound was identical with the product obtained as described under A.

1-Methyl-2-phenyl-5-trideuteriomethyl-3,7,8-trideuterioimidazo[1,2-*b*]pyridazin-6(5*H*)-on-4-ium iodide (9) was obtained from **8** in the same manner as described for the nondeuterated compound **7** under A: mp 249–250°; mass spectrum *m/e* 231 (M^+ − MeI), 228 (M^+ − CD_3I); nmr (DMSO-d_6) τ 6.03 (s, 1-Me), 2.44 (m, Ph).

Demethylation of 1,5-Dimethyl-2-phenylimidazo[1,2-*b*]pyridazin-6(5*H*)-on-4-ium Iodide.—The compound **7** (183 mg) was heated in a sublimation tube at 240° (0.1 mm) for 2 hr. The sublimate (28 mg) was identified as 5-methyl-2-phenylimidazo-[1,2-*b*]pyridazin-6(5*H*)-one (**3**). The residue was composed of the starting material as the main component and a small amount of 6-hydroxy-1-methyl-2-phenylimidazo[1,2-*b*]pyridazin-4-ium anhydro salt (**6**) as shown by thin layer chromatography (DC Fertigplatten Kieselgel F-254, Merck, MeOH as solvent).

Rearrangement of 6-Methoxy-2-phenylimidazo[1,2-*b*]pyridazine.—The methoxy compound **2** (225 mg) was heated in a sealed tube at 240° for 2 hr. The dark residue was treated with MeOH (5 ml) and purified by column chromatography (column diameter 18 mm, length 10 cm, filled with alumina type 507 C Fluka, for elution MeOH was used). The purified solution was evaporated to dryness and the residue (150 mg) was a mixture of three compounds.

A solution of this mixture (30 mg) in MeOH (2 ml) was submitted to tlc (PSC Fertigplatten Kieselgel F-254, MeOH and $CHCl_3$, 1:30, as solvent) and the spots were separated and eluted with MeOH. Upon evaporation of each solution there were obtained the starting compound **2** (7 mg) and 5-methyl-2-phenylimidazo[1,2-*b*]pyridazin-6(5*H*)-one (**3**) (17 mg).

When the same tlc procedure was applied, but MeOH was used as solvent, the spot with R_f 0.48 afforded after elution with MeOH pure 6-hydroxy-1-methyl-2-phenylimidazo[1,2-*b*]pyridazin-4-ium anhydro salt (**6**) (4 mg), identified by its melting point and ir spectrum when they were compared with those of an authentic specimen.

6-Hydroxy-1-methylimidazo[1,2-*b*]pyridazin-4-ium Anhydro Salt (10).—A suspension of 6-chloro-1-methylimidazo[1,2-*b*]-pyridazin-4-ium iodide[1] [1.95 g; nmr (DMSO-d_6) τ 1.32 (d, H_2), 1.08 (dd, H_8), 1.73 (d, H_7), 0.92 (dd, H_8), 5.75 (s, NMe), $J_{2,3}$ = 2.1, $J_{3,8}$ = 0.6 $J_{7,8}$ = 9.6 Hz] in aqueous KOH (1.12 g of KOH in 7 ml of water) was heated under reflux for about 10 min until a complete dissolution was achieved. After cooling, neutralization with concentrated hydrochloric acid, and evaporation to dryness, the residue was sublimed at 220° (0.1 mm) (0.7 g, 47%): mp 125–127°; mass spectrum *m/e* 149 (M^+); nmr (DMSO-d_6) τ 2.25 (d, H_2), 2.06 (dd, H_3), 3.53 (d, H_7), 2.30 (dd, H_8), 6.30 (s, NMe), $J_{2,3}$ = 2.0, $J_{3,8}$ = 0.6, $J_{7,8}$ = 9.5 Hz.

Anal. Calcd for $C_7H_7N_3O$: C, 56.37; H, 4.73; N, 28.18. Found: C, 56.43; H, 4.85; N, 27.87.

6-Hydrazino-1-methylimidazo[1,2-*b*]pyridazin-4-ium Iodide (11).—A mixture of 6-chloro-1-methylimidazo[1,2-*b*]pyridazin-4-ium iodide[1] (1.48 g) and hydrazine hydrate (5 ml, 80%) was heated under reflux for 10 min. Upon cooling the separated product was filtered off, washed with water, and crystallized from EtOH (0.8 g, 54%), mp 260°.

Anal. Calcd for $C_7H_{10}IN_5$: C, 28.88; H, 3.46; N, 24.07. Found: C, 28.87; H, 3.70; N, 24.51.

Registry No.—**1**, 34876-76-1; **2**, 1844-61-7; **3**, 1845-04-1; **4**, 34876-79-4; **5**, 34876-80-7; **6**, 34876-81-8; **7**, 34876-82-9; **8**, 34876-83-0; **9**, 34876-84-1; **10**, 34876-85-2; **11**, 34876-86-3.

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Ion Radicals. XXV. The Reactions of Thianthrene and Phenothiazine Perchlorates with Nitrite Ion, Pyridine, and Other Nucleophiles[1]

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Reaction of thianthrene perchlorate (**1**) with sodium nitrite in nitromethane solution gave thianthrene 5-oxide (**2**) and nitric oxide, each in greater than 90% yield. Reaction with ^{18}O-labeled nitrite ion showed that the oxygen in **2** came from the nitrite ion. Reaction of **1** with sodium nitrate gave **2** (92, 98%) and nitrogen dioxide (71, 75%). Reaction of **1** with pyridine in nitromethane solution gave 73% of *N*-(2-thianthrenyl)pyridinium perchlorate (**3**) and 90% of thianthrene (**4**), the yields being calculated after compensation for the reaction of **1** with residual water in the pyridine. Reaction of solid **1** with neat pyridine was violent and was accompanied by explosion and flame unless carried out with small amounts of **1**, in which case the products were again **3** and **4**. Attempts to prepare **3** directly by the oxidation of **4** with iodine and silver perchlorate in the presence of pyridine failed. Reaction of phenothiazine perchlorate (**5**) with nitrite ion gave 3-nitrophenothiazine (96%) and phenothiazine (**6**) (100%). Oxidation of **6** with iodine and silver nitrite in acetonitrile solution gave 3-nitrophenothiazine in 70% yield. Reaction of **5** with pyridine gave *N*-(3-phenothiazinyl)pyridinium perchlorate (**7**) (78, 84%), **6** (72, 80%), and 3,10′-biphenothiazine (**8**) (2.1, 9%). Attempts to prepare **7** directly by the oxidation of **6** with iodine and silver perchlorate in the presence of pyridine gave mixtures of **7** and unidentified green solids whose separation was too difficult to achieve. Reaction of **5** with chloride and bromide ion gave the 3- and 3,7-dihalogenophenothiazines in approximately 75 and 8% yields, respectively, and, in each case, **6** in 85–90% yield. Reaction of **5** with fluoride ion gave only **6** (38%), **8** (17%), and an unidentified green solid.

In earlier publications, we have described the reactions of thianthrene perchlorate (**1**) with water,[4] electron-rich aromatics,[5] and dry ammonia.[1a] In each of these reactions the nucleophile attacked the thianthrene ring at sulfur (the 5 position) to form a 5-sub-

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