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Synthesis of Pyridazine Derivatives. XVII. Some Reactions on 2-Phenylimidazo(1,2-*b*)pyridazines

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The behavior of 2-phenylimidazo(1,2-*b*)pyridazines in some electrophilic and nucleophilic substitution reactions has been examined. It has been found that besides the expected electrophilic substitution at position 3 of the imidazo-(1,2-*b*)pyridazine ring, upon nitration a second nitro group enters the phenyl group on *para* position as evident from an examination of the NMR spectrum. Hydrazinolysis of a 3,6-dihalo derivative proceeded preferentially at position 6.

The ready accessibility of imidazo(1,2-*b*)pyridazines[1–3] enabled us to investigate electrophilic substitution reactions in this ring system. Our present study is confined to some of these reactions as well as to some other reactions on 2-phenylimidazo(1,2-*b*)pyridazines. Comparing π-electron densities of some imidazo(1,2-*a*)pyridines[4,5] with those of imidazo(1,2-*b*)pyridazine* we concluded that in both cases the position 3 in the imidazole ring is most susceptible for electrophilic attack. Furthermore, it can be also anticipated that electrophilic substitutions on the six-membered ring of imidazo(1,2-*b*)pyridazines should not take place under normal conditions and in all reactions so far investigated, we could establish only the formation of 3-substituted products.[1]

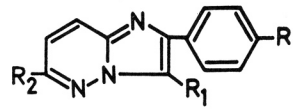
However, if a phenyl group is attached to this polyazaheterocycle, the possibility of an electrophilic attack on the phenyl ring cannot be excluded. This seemed to be of particular interest in view of the known examples of preferential electrophilic substitution on the phenyl group as observed with several phenylimidazoles[6–9] and 2-phenylimidazo(1,2-*a*)pyrimidines.[10] Compounds, which were now investigated, are presented in Table I.

6-Chloro-2-phenylimidazo(1,2-*b*)pyridazine (II) when nitrated with limited amount of nitric acid in sulfuric acid at low temperature, afforded the 3-nitro derivative (III). With an execess of nitric acid a second nitro group could be introduced under practically the same reaction conditions to give compounds IV and V. The location of the second nitro group follows from an examination of the NMR spectrum. The H_7 and H_8 protons appear as an AB pattern with the coupling constant, $J_{7,8} = 9.4$ cps, and the doublet for H_7 is centered at $\tau = 2.07$ and that for H_8 at $\tau = 1.43$. The four phenyl protons appear as a multiplet centered at $\tau = 1.68$. The pattern is characteristic for the *para* disubstituted benzene derivatives and accordingly the following coupling con-

* HMO calculations on imidazo(1,2-*b*) pyridazine were performed by Dr. Pollak and from these it is evident that the preferred position for electrophilic attack is position 3 (unpublished results).

TABLE I

Imidazo(1,2-b)pyridazines



Compound	R	R_1	R_2
I	H	H	H
II	H	H	Cl
III	H	NO_2	Cl
IV	NO_2	NO_2	Cl
V	NO_2	NO_2	H
VI	H	Br	Cl
VII	H	Br	H_2NNH
VIII	H	Br	C_6H_5—CH=N—NH
IX	H	Br	C_6H_5—NH—CS—NH—NH
X	H	Br	C_6H_5—C(Br)=N—NH
XI	H	H	C_6H_5—CH=N—NH
XII	H	Br	H
XIII	Br	H	Cl
XIV	Br	Br	Cl

stants were established: $J_{AB} = J_{A'B'} = 8.5$ cps, $J_{AA'} = J_{BB'} = 2.5$ cps, and $J_{AB'} = J_{A'B} = \pm 0.5$ cps. From these data it appears unambiguously that the phenyl group is substituted in *para* position.

Bromination with bromine in glacial acetic acid of the same two starting compounds proceeded relatively easily, but afforded always only the 3-bromo derivative (VI, XII) even if the reaction was performed in the presence of promotors (Fe or $AlCl_3$). A similar case is known for bromination of 4(5)--phenylimidazole with bromine in chloroform, the phenyl group remaining unaltered.[11] Evidence that substitution has not occurred on the phenyl group was obtained from an unambiguous synthesis of the 2-(*p*-bromophenyl) analog (XIII) from 3-amino-6-chloropyridazine and *p*-bromophenacyl bromide. The product, upon bromination afforded an addition complex, analyzing for four bromine atoms. This compound could be converted by the addition of hot ethanol to the 3-bromo derivative (XIV). It seems most likely, that a 1 : 1 complex with bromine was formed as an intermediate, since this had properties which were observed also with some imidazo(1,2-*b*)pyridazines, prepared earlier,[1] and which have been observed also with several other azaheterocycles.[12]

Although it has been observed that aminolysis of 6-chloro-2-phenylimidazo(1,2-*b*)pyridazine does not proceed even under drastic reaction conditions,[1] hydrazinolysis was successful and this holds also for VI, thus demonstrating an easier displacement of the halogen at position 6 than that at position 3.

Bromination of the corresponding benzylidene derivative XI afforded a product X, where halogen was introduced into the methine group, a reaction experienced earlier with similar derivatives.[2]

EXPERIMENTAL

All melting points were taken on a Kofler apparatus. NMR spectrum was recorded on a Varian HA-100 proton resonance spectrometer with tetramethylsilane as internal standard. Tetramethylurea was used as solvent.

2-Phenylimidazo(1,2-b)pyridazine (I)

a) A solution of 2-phenyl-6-chloroimidazo(1,2-*b*)pyridazine (II, 1.0 g.)[3] in pure dioxane (70 ml.) was hydrogenated under atmospheric pressure in the presence of triethylamine (6.6 ml.) and palladized charcoal (0.5 g., 5% Pd.) After absorption of hydrogen has ceased, water (70 ml.) was added and the solution acidified with hydrochloric acid (1 : 1) to *p*H 3, and the catalyst removed by filtration. The solution was evaporated to 1/5 of its original volume, made alkaline with 10% sodium hydroxide and extracted with chloroform. The chloroform layer was separated, dried, and evaporated to dryness. The residue was crystallized from ethanol—water (1 : 1), m. p. 121°. Yield 0.5 g. (42%).

Anal. $C_{12}H_9N_3$ (195.22) calc'd.: C 73.83; H 4.65; N 21.53%
found: C 73.62; H 4.97; N 21.65%

b) A solution of II (1.85 g.)[3] in glacial acetic acid (60 ml.) was hydrogenated in the presence of palladized charcoal (0.5 g., 5% Pd) until an uptake of about 175 ml. of hydrogen. The catalyst was removed by filtration, the solvent evaporated *in vacuo* and the crude hydrochloride crystallized from a small quantity of ethanol (cca 10 ml.). Yield 1.2 g. (65%); m. p. 230—232°.

Anal. $C_{12}H_{10}ClN_3$ (231.68) calc'd.: C 62.01; H 4.35; N 18.13%
found: C 62.33; H 4.64; N 17.92%

The free base was obtained by dissolving 0.1 g. of the hydrochloride in water (5 ml.) at 70° and adding dropwise a saturated solution of $NaHCO_3$ until no more carbon dioxide is evolved. Upon cooling, the free base separated (40 mg.) and was identical with the compound prepared under *a.*

6-Chloro-3-nitro-2-phenylimidazo(1,2-b)pyridazine (III)

Compound II (2.3 g.) was added under stirring to concentrated sulfuric acid (8 ml.) and the mixture was cooled to —10°. Stirring was continued and during 5 min. nitric acid (0.65 ml., d = 1.5) was added dropwise. The reaction mixture was then stirred at room temperature for 10 min. and poured onto crushed ice (40 g.). The separated product was filtered and recrystallized from *N,N*-dimethylformamide. Yield 1.95 g. (71%); m. p. 280°.

Anal. $C_{12}H_7ClN_4O_2$ (274.67) calc'd.: C 52.47; H 2.57; N 20.40%
found: C 52.57; H 2.79; N 20.32%

6-Chloro-3-nitro-2-(4′-nitrophenyl)imidazo(1,2-b)pyridazine (IV)

The same procedure as above was followed, except for the quantities employed: 1.2 g. of II, 4 ml. concentrated sulfuric acid and 1.2 ml. of nitric acid (d = 1.5). The crude product was purified by crystallization from *N,N*-dimethylformamide and finally washed with ethanol. Yield 73%, m. p. 235—237°.

Anal. $C_{12}H_6ClN_5O_4$ (319.67) calc'd.: C 45.07; H 1.89; N 21.92%
found: C 45.34; H 2.01; N 22.06%

NMR spectrum in tetramethylurea showed a doublet centered at $\tau = 2.07$ (H_7), another one at $\tau = 1.43$ (H_8), and a multiplet centered at $\tau = 1.68$ (phenyl protons).

Bromination of the corresponding benzylidene derivative XI afforded a product X, where halogen was introduced into the methine group, a reaction experienced earlier with similar derivatives.[2]

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a) A solution of 2-phenyl-6-chloroimidazo(1,2-*b*)pyridazine (II, 1.0 g.)[3] in pure dioxane (70 ml.) was hydrogenated under atmospheric pressure in the presence of triethylamine (6.6 ml.) and palladized charcoal (0.5 g., 5% Pd.) After absorption of hydrogen has ceased, water (70 ml.) was added and the solution acidified with hydrochloric acid (1 : 1) to *p*H 3, and the catalyst removed by filtration. The solution was evaporated to 1/5 of its original volume, made alkaline with 10% sodium hydroxide and extracted with chloroform. The chloroform layer was separated, dried, and evaporated to dryness. The residue was crystallized from ethanol—water (1 : 1), m. p. 121°. Yield 0.5 g. (42%).

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6-Chloro-3-nitro-2-phenylimidazo(1,2-b)pyridazine (III)

Compound II (2.3 g.) was added under stirring to concentrated sulfuric acid (8 ml.) and the mixture was cooled to —10°. Stirring was continued and during 5 min. nitric acid (0.65 ml., d = 1.5) was added dropwise. The reaction mixture was then stirred at room temperature for 10 min. and poured onto crushed ice (40 g.). The separated product was filtered and recrystallized from *N,N*-dimethylformamide. Yield 1.95 g. (71%); m. p. 280°.

Anal. $C_{12}H_7ClN_4O_2$ (274.67) calc'd.: C 52.47; H 2.57; N 20.40%
found: C 52.57; H 2.79; N 20.32%

6-Chloro-3-nitro-2-(4′-nitrophenyl)imidazo(1,2-b)pyridazine (IV)

The same procedure as above was followed, except for the quantities employed: 1.2 g. of II, 4 ml. concentrated sulfuric acid and 1.2 ml. of nitric acid (d = 1.5). The crude product was purified by crystallization from *N,N*-dimethylformamide and finally washed with ethanol. Yield 73%, m. p. 235—237°.

Anal. $C_{12}H_6ClN_5O_4$ (319.67) calc'd.: C 45.07; H 1.89; N 21.92%
found: C 45.34; H 2.01; N 22.06%

NMR spectrum in tetramethylurea showed a doublet centered at $\tau = 2.07$ (H_7), another one at $\tau = 1.43$ (H_8), and a multiplet centered at $\tau = 1.68$ (phenyl protons).

3-Nitro-2-(4′-nitrophenyl)imidazo(1,2-b)pyridazine (V)

To a solution of 2-phenylimidazo(1,2-b)pyridazine (0.194 g.) in concentrated sulfuric acid (1 ml.), cooled to — 5°, during 5 min. nitric acid (0.3 ml., d = 1.5) was added dropwise. The reaction mixture was left aside at room temperature for 20 min. and thereafter poured onto ice (5 g.). The separated product was filtered and crystallized from glacial acetic acid. Yield 0.12 g. (42%); m. p. 239—240°.

Anal. $C_{12}H_7N_5O_4$ (285.22) calc'd.: C 50.53; H 2.47; N 24.56%
found: C 50.55; H 2.72; N 24.90%

3-Bromo-6-chloro-2-phenylimidazo(1,2-b)pyridazine (VI)

2.3 g. of II were dissolved in glacial acetic acid (15 ml.) with gentle heating and to this solution excess of bromine (about 2.5 ml.) in a small amount of glacial acetic acid was added dropwise. Upon cooling the precipitate was filtered, washed with glacial acetic acid and upon sublimation at 200—220°/0.1 mm an addition complex was obtained which analyzed for one additional atom of bromine. The complex had m. p. 255—257° and liberated iodine from a solution of potassium iodide. When crystallized from hot ethanol, the pure bromo compound, m. p. 190° was obtained in 74% yield.

Anal. $C_{12}H_7BrClN_3$ (308.57) calc'd.: C 46.70; H 2.29; N 13.62%
found: C 46.44; H 2.34; N 13.80%

3-Bromo-6-hydrazino-2-phenylimidazo(1,2-b)pyridazine (VII)

A suspension of the above bromo compound (3.09 g.) in hydrazine hydrate (10 ml. of 80%) was heated under reflux for 10 min. The starting material dissolved and the new formed precipitate was collected upon cooling. Crystallization from ethanol afforded the pure compound, m. p. 204—205°, in 78% yield.

Anal. $C_{12}H_{10}BrN_5$ (304.16) calc'd.: C 47.39; H 3.31; N 23.02%
found: C 47.59; H 3.29; N 23.02%

The dihydrochloride salt had m. p. over 320° (from ethanol).

Anal. $C_{12}H_{12}BrCl_2N_5$ (377.09) calc'd.: C 38.22; H 3.21; N 18.58%
found: C 38.50; H 3.52; N 18.72%

The benzylidene derivative (VIII) was prepared in the usual way and was crystallized from *N,N*-dimethylformamide, m. p. 236—238°.

Anal. $C_{19}H_{14}BrN_5$ (392.26) calc'd.: C 58.19; H 3.60; N 17.85%
found: C 57.90; H 3.69; N 17.88%

3-Bromo-2-phenyl-6-(4′-phenylthiosemicarbazido)imidazo(1,2-b)pyridazine (IX)

The hydrazino compound VII (3.04 g.) was dissolved in *N,N*-dimethylformamide (10 ml.) with gentle warming and the resulting solution was treated with phenyl isothiocyanate (1.35 g.). Upon cooling, water (10 ml.) was added and the product which separated was filtered off and washed with water. Yield 39%, m. p. 193—194°.

Anal. $C_{19}H_{15}BrN_6S$ (439.34) calc'd.: C 51.94; H 3.44; N 20.40%
found: C 51.64; H 3.82; N 20.21%

N-α-Bromobenzylidene-N′-(3-bromo-2-phenylimidazo[1,2-b]pyridazinyl-6) hydrazine (X)

To a stirred suspension of the benzylidene derivative of 6-hydrazino-2-phenylimidazo(1,2-*b*)pyridazine (XI, 3.12 g.)[3] in glacial acetic acid (20 ml.) excess of bromine (1 ml. of bromine for 1 g. of the hydrazone) was added dropwise at room temperature. After the addition was complete, stirring was continued for 30 min. The obtained product was filtered off and washed with glacial acetic acid. For purification it was crystallized from *N,N*-dimethylformamide and washed with ethanol. Yield 75%, m. p. 220—221°.

Anal. $C_{19}H_{13}Br_2N_5$ (471.16) calc'd.: C 48.43; H 2.78; N 14.86%
found: C 48.63; H 3.02; N 15.17%

3-Bromo-2-phenylimidazo(1,2-b)pyridazine hydrobromide salt (XII. HBr.)

A solution of I (0.97 g.) in glacial acetic acid (8 ml.) was treated with a solution of bromine (2 g.) in glacial acetic acid (6 ml.) at 50—60°. Upon cooling the separated product was filtered off and purified by crystallization from glacial acetic acid or ethanol. Yield 1.3 g. (74%); m. p. 250—252°.

Anal. $C_{12}H_9Br_2N_3$ (345.05) calc'd.: C 40.60; H 2.56; N 11.84%
found: C 40.79; H 2.73; N 11.83%

2-(4'-Bromophenyl)-6-chloroimidazo(1,2-b)pyridazine (XIII)

To a suspension of 3-amino-6-chloropyridazine (2.59 g.) in ethanol (30 ml.) *p*-bromophenacyl bromide (5.56 g.) was added and the mixture heated under reflux for 1 hr. The crude product was collected and crystallized from ethanol. Yield 4.9 g. (78%); m. p. 228—230°.

Anal. $C_{12}H_7BrClN_3$ (308.57) calc'd.: C 46.54; H 2.28; N 13.60%
found: C 46.35; H 2.46; N 13.90%

3-Bromo-2-(4'-bromophenyl)-6-chloroimidazo(1,2-b)pyridazine (XIV)

The above compound (XIII, 3.09 g.) was dissolved in glacial acetic acid (20. ml.) at about 40° and a solution of bromine in glacial acetic acid (1 g. in 2 ml.) was added dropwise until the solution remained colored from unreacted bromine. Upon cooling the separated complex with bromine (4.7 g., 84%) was collected and crystallized from glacial acetic acid. It melted as the 3-bromo derivative, since the complex decomposes upon heating.

Anal. $C_{12}H_6Br_4ClN_3$ (547.31) calc'd.: C 26.33; H 1.11; N 7.68%
found: C 25.67; H 1.52; N 7.33%

If the complex is crystallized from ethanol (about 20 ml.) the pure 3-bromo compound (XIV) is obtained in 56% yield. M. p. 200—201°.

Anal. $C_{12}H_6Br_2ClN_3$ (387.48) calc'd.: C 37.18; H 1.56; N 10.84%
found: C 36.92; H 1.73; N 11.12%

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IZVLEČEK

Sinteze piridazinovih derivatov. XVII. Nekatere reakcije z 2-fenilimidazo(1,2-*b*)piridazini

B. Stanovnik in M. Tišler

Opisane so raziskave elektrofilne in nukleofilne substitucije 2-fenilimidazol (1,2-*b*) piridazinov. Poleg pričakovane elektrofilne substitucije na položaju 3, vstopa pri nitraciji lahko druga nitro skupina na *para* položaj fenilne skupine, kar je mogoče ugotoviti z NMR spektroskopijo. Hidrazinoliza 3,6-dihalogenskega derivata poteka predvsem na položaju 6.

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