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Syntheses in the Pyridazine Series. XXIX. Reactions between 3-Amino-6-chloropyridazine and α, ω-Dihaloalkanes, α- and β-Halo Esters and α- and β-Halo Acylchlorides

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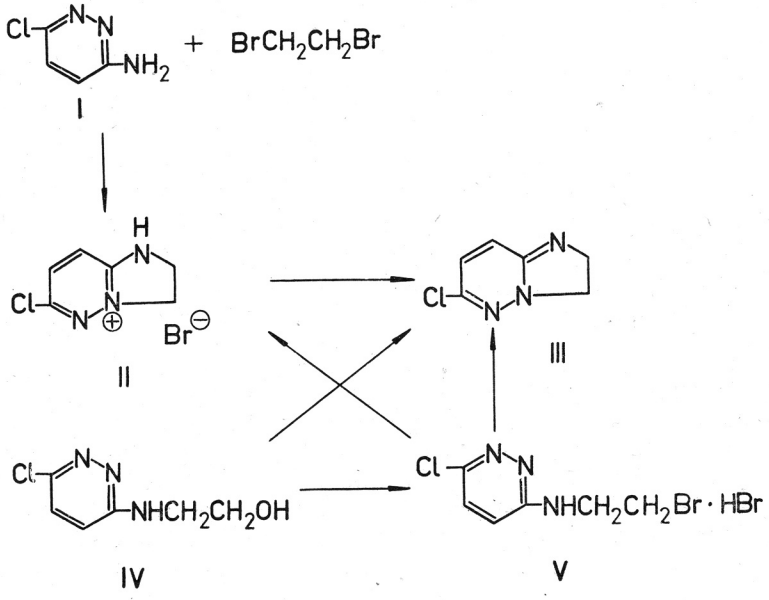
Reactions between 3-amino-6-chloropyridazine and different dihalogenides, halo esters and halo acylhalides have been investigated. In some cases it was possible to obtain the bicyclic products, such as derivatives of imidazo(1,2-b)pyridazine or pyrimido(1,2-b)-pyridazine.

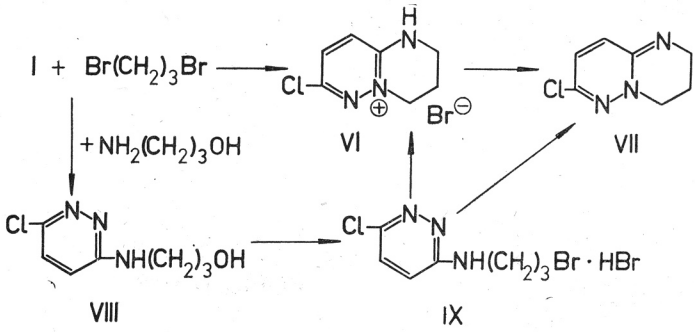
The reaction between 3-aminopyridazines and α-halocarbonyl compounds was intensively investigated in connection with syntheses of imidazo (1,2-b)-pyridazines[1-8] and their polycyclic analogs[9,10]. It was therefore of interest to extend this synthetic approach by employing other bifunctional compounds as starting material. The work to be described was undertaken to examine the possibilities of forming a fused five-or six-membered ring to the pyridazine skeleton. The pyrimido(1,2-b)pyridazine system, in particular, was considered of interest because of its novelty.

As an easily accessible aminopyridazine, 3-amino-6-chloropyridazine was chosen as starting model compound. It reacted with 1,2-dibromoethane, but even



after prolonged reaction time it afforded in low yield a product, identified as the bicycle II, which could be easily transformed into the free base III. The structure assigned to this product is compatible with its elemental analysis and its NMR spectrum which revealed two doublets at $\tau = 1.91$ and 1.71 assigned to the AB-system of protons H_7 and H_8, and two multiplets centered at $\tau = 5.37$ and $\tau = 4.65$ for the 2-CH_2- and 3-CH_2-groups. In addition, an independent synthesis, starting with 3-(2′-hydroxyethylamino)-6-chloropyridazine (IV) afforded further evidence. The last mentioned compound, after treatment with phosphorus tribromide in acetonitrile, was converted into the corresponding bromide (V) and this in hot ethanol easily cyclized to II, or in the presence of potassium carbonate to III, in good overall yield. An attempt of direct conversion of the alcohol IV into the bicycle II by means of thionyl chloride was less successful. Compound II could be obtained only in low yield in contrast to the much better synthesis of the related 2,3-dihydroimidazo(1,2-*b*)pyridazinium chloride (2,3-dihydro-1,3*a*,4-triazaindenium chloride)[11]. We feel that the structure of the hydrobromide salt of III is best represented with the structure II since molecular orbital calculations indicate N_1 to be the most basic nitrogen in the molecule of imidazo(1,2-*b*)pyridazine[12] and hence, by analogy, protonation of the partially reduced system should occur at the same heteroatom.

The same reaction pattern as above was followed in another series of experiments which afforded, by employing 1,3-dibromopropane, the pyrimido (1,2-*b*)pyridazine VI in low yield. We have announced the discovery of this new ring system only recently[13] and the as yet unknown parent aromatic pyrimido(1,2-*b*)pyridazinium cation poses an interesting challenge. Again, a better approach to this bicycle has been found to proceed from the hydroxypropylamino derivative VIII *via* the bromide IX to the hydrobromide salt of the bicycle (VI) or to the free base VII. The proposed structure is in full accord with the recorded NMR data. Two doublets at $\tau = 2.01$—2.35 and 2.18—2.62 (in different solvents) correspond to the aromatic protons H_8 and H_9, forming an



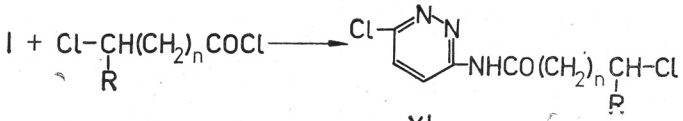
AB-system. The multiplets corresponding to 3-CH_2- or 4-CH_2-groups of compounds III and VII are deshielded in comparison with the chemical shifts for the terminal -CH_2Br group in the noncyclic counterparts V and IX. Here, the difference in chemical shifts for the terminal CH_2-groups and the CH_2-group, adjacent to the side-chain NH-group, is smaller than that between the chemical shifts of the 2-CH_2- and 3-CH_2-groups in compound III or the 2-CH_2-

and 4-CH_2-groups in compound VII. This can be of diagnostic value for differentiation between the uncyclized and cyclized products.

In a further investigation of the above sequence of reactions by employing the next homolog, 1,4-dibromobutane, no cyclic product could be obtained. Only the quaternized pyridazine X could be isolated in low yield. Quaternization is considered to proceed at N_2 on the basis of theoretical considerations and from analogy of related quaternization studies[14]. Although quaternizations of pyridazines have been reviewed and discussed[15], recent investigations with application of NMR techniques[14] gave better insight in the quaternization processes. Thus, the composition of the mixture resulting from quaternization is determined mainly by inductive and pronounced steric effects, although other effects may be also operating to some extent. Moreover, the formation of products is kinetically controlled. The site of quaternization of 3-amino-6-chloropyridazine indicates that basic centre is N_2, which is obviously more basic than N_1 on account of the strong electron donor properties of the amino group.

Further experiments were performed with α- and β-halo acyl chlorides and as expected, acylamino compounds of the type XI were formed in good yield. In no case was the formation of bicyclic products observed.

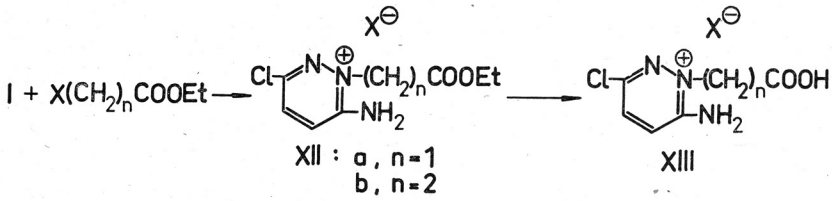
X



XI

3-Amino-6-chloropyridazine reacted with α- and β-halo esters to form quaternized products of the type XII. Quaternization of pyridazine or its 3,6-dimethyl analog with ethyl bromoacetate is known to proceed very easily[16] and introduction of a reactive functional group, such as amino, at position 3 was expected to provide a multiplicity of reacting centers and allow eventually subsequent cyclization. On the other hand, it follows from tosylation and methylation studies on 4-aminopyridazines and -pyridazinones that the amino group is attacked only to a small extent, if at all[17–19].

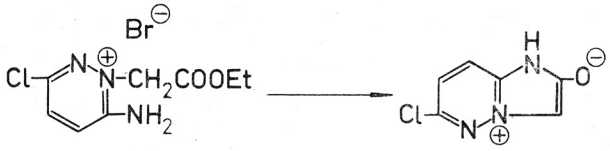
On the basis of NMR spectra examinations we could conclude that quaternization with halo esters afforded only one of the two possible isomeric quaternized pyridazines. The site of quaternization being at N_2 followed from the conversion of the carbethoxymethyl derivative XIIa into the bicycle XIV and likewise from the conversion of the carbethoxyethyl derivative XIIb into the pyrimido(1,2-*b*)pyridazine derivative (XV). The quaternized compound of the type XII are decomposed under the influence of alkali and the starting pyridazine was regenerated. However, when treated with hydrochloric acid



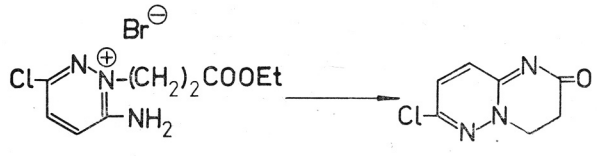
XII : a, n=1
b, n=2

(approx. 15%) at room temperature these esters were converted into the corresponding acids (XIII).

The bicyclic products XIV and XV could be obtained by cyclizing the appropriate ester with the aid of polyphosphoric acid at elevated temperature. Whereas the product XV revealed in its IR spectrum a typical carbonyl absorption band, the IR spectrum of the bicycle XIV was completely free from carbonyl absorption, but strong hydrogen bonding (broad band at about 3.9 μ)



XIIa XIV



XIIb XV

was discernible. Since immonium bands at 4.5—5.5 μ[20] were lacking, it seems that the bicycle is best represented with a formula such as XIV. On the other hand, the structure of XV as an unenolized compound is evident from its NMR spectrum which is in accord with the formulated structure (τ = 2.74 (s, H_7, H_4) τ = 7.19 (t, 3-CH_2) and 5.55 (t, 4-CH_2).

EXPERIMENTAL

Melting points were taken on a Kofler micro hot stage and are corrected. NMR spectra were recorded with a Varian A—60 spectrometer using $CDCl_3$, DMSO-d_6, $(CF_3CO)_2O$, or D_2O solutions and TMS or sodium trimethylsilylpropane sulfonate as internal or external standards. The infrared spectra were determined on a Infracord Model 137 spectrophotometer as mulls in Nujol or KBr discs.

3-(2′-Hydroxyethylamino)-6-chloropyridazine, 3-amino-6-chloropyridazine, and 3,6-dichloropyridazine were prepared according to known procedures.[21,22]

3-(2′-Bromoethylamino)-6-chloropyridazine hydrobromide (V)

3-(2′-Hydroxyethylamino)-6-chloropyridazine (IV) (13 g., 0.075 mole) was dissolved in hot acetonitrile (80 ml.). The solution was cooled to room temperature and during stirring phosphorus tribromide (10 ml.) was added portionwise during 20 min. After the addition was complete, the reaction mixture was heated under reflux for

2 hrs. and filtered still hot. Upon cooling the product which separated was filtered off and washed with some acetonitrile. The colourless crystals had m. p. 133—138°, yield 17 g. (71%). Only freshly prepared samples showed relatively sharp m. p. whereas upon standing the sample melted in a broad temperature interval up to 250° on account of the cyclic product present. NMR (CF_3COOD, TMS as internal standard): $\tau = 0.95$ (d, H_4), 1.56 (d, H_5), 4.57 (m, $-NHC\mathbf{H}_2-CH_2Br$), 4.98 (m, $-NHCH_2C\mathbf{H}_2Br$); $J_{4,5} = 9.5$ cps.

Anal. $C_6H_8Br_2ClN_3$ (317.44) calc'd.: C 22.70; H 2.54; N 13.25%
found: C 23.10; H 2.73; N 13.01%

6-Chloro-1H,2,3-dihydroimidazo(1,2-b)pyridazin-4-ium bromide (II)

a) The above compound V (3.17 g., 0.01 mole) in abs. ethanol (50 ml.) was heated under reflux for 30 min. Upon cooling the separated crystals were collected and crystallized from ethanol. Yield 2.3 g. (97%); m. p. 242—245°. IR (KBr): 6.04μ (C = N).

Anal. $C_6H_7BrClN_3$ (236.53) calc'd.: C 30.49; H 2.98; N 17.77%
found: C 30.53; H 3.06; N 17.49%

b) 3-Amino-6-chloropyridazine (I) (6.0 g., 0.046 mole), 1,2-dibromoethane (5.8 ml.) and abs. ethanol (25 ml.) were heated under reflux for 20 hrs. Upon cooling the precipitate was filtered off and the filtrate evaporated *in vacuo* to dryness. The residue was dissolved in water (30 ml.) and treated with dilute aqueous sodium hydroxide until *p*H 10. The precipitated product (about 4.0 g. of unreacted starting pyridazine) was filtered off and the aqueous solution extracted with ethyl acetate. The combined extracts (100 ml.) were dried over anhydrous $MgSO_4$, filtered and the solvent evaporated to dryness. The residue was then dissolved in diethyl ether and under cooling hydrogen bromide gas was introduced. The separated crystals were filtered off and crystallized from abs. ethanol. Yield 0.2 g. (1.8%), m. p. 239—242°. On hand of analytical data and IR spectra comparison the compound was found to be identical with the sample obtained as described under *a*).

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

a) The hydrobromide salt II (2.0 g., 0.0085 mole) was dissolved in water (15 ml.) and the solution made alkaline with dilute aqueous sodium hydroxide until *p*H 10. The solution was extracted with diethyl ether (4 × 50 ml.), the separated ethereal layer dried over anhydrous $MgSO_4$ and upon filtration the filtrate was evaporated to a small volume. Upon standing on ice yellowish needles separated and they were crystallized from diethyl ether with the addition of some petrolether. Yield 0.5 g. (38%); m. p. 113—115°. NMR (in D_2SO_4, TMS as external standard): $\tau = 1.91$ (d, H_7), 1.71 (d, H_8), 5.37 (m, 2-CH_2), 4.65 (m, 3-CH_2); $J_{7,8} = 9.5$ cps.

Anal. $C_6H_6ClN_3$ (155.61) calc'd.: C 46.31; H 3.85; N 27.01%
found: C 46.09; H 3.72; N 27.05%

b) 3-(2′-Bromoethylamino)-6-chloropyridazine hydrobromide (V) (1.6 g., 0.005 mole) was dissolved in abs. ethanol (40 ml.) and the solution treated with aqueous potassium carbonate (2.1 g. in 50 ml. of water). The mixture was heated under reflux for 2 hrs, ethanol was removed by distillation and the mixture cooled. Upon extraction with diethyl ether (three times with 30 ml.) and drying the extracts over magnesium sulfate, the ethereal solution was concentrated and upon standing on ice yellow needles separated. Yield 0.5 g. (65%). M. p. 112—115° upon crystallization from diethyl ether and some petrolether. The product was identical in all respects with the compound prepared as described under *a*).

c) 3-(2′-Hydroxyethylamino)-6-chloropyridazine (IV) (7.0 g., 0.04 mole) was added portionwise to thionyl chloride (25 ml.), previously cooled to 0°. After the addition was complete the reaction mixture was stirred and cooled with ice during 2 hrs and thereafter the mixture was left to stand at room temperature overnight. Chloroform (40 ml.) was then added and the mixture evaporated to dryness. The residue was dissolved in abs. ethanol (200 ml.) and this solution was poured into a stirred aqueous potassium carbonate solution (14 g. in 150 ml. of water). The mixture was stirred at room temperature for 30 min. and then heated under reflux for 2 hrs. Ethanol was then distilled off and the aqueous solution extracted with diethyl ether. The combined

ethereal extracts (90 ml.) were dried over anhydrous magnesium sulfate, filtered and the solvent was evaporated to a small volume. Upon standing on ice yellow crystals were obtained (1.5 g., 24%) which proved to be identical in all respects with the products obtained as described under *a*) or *b*).

3-(3′-Hydroxypropylamino)-6-chloropyridazine (VIII)

3,6-Dichloropyridazine (30 g., 0.208 mole), 3-amino-1-propanol (25 g., 0.33 mole) and ethanol (150 ml.) were heated under reflux for 5 hrs. Upon cooling the separated crystals were filtered off (27 g., 72% yield) and for analysis a sample was crystallized from ethanol, m. p. 132.5—133°. NMR (DMSO-d_6): $\tau = 2.14$ (d, H_4), 3.08 (d, H_5), 6.50 (m, -NHC**H**$_2$CH$_2$C**H**$_2$OH), 8.22 (m, -NHCH$_2$C**H**$_2$CH$_2$OH), 5.42 (broad, NH, OH); $J_{4,5} = 9.5$.

Anal. $C_7H_{10}ClN_3O$ (187.63) calc'd.: C 44.82; H 5.37; N 22.39%
found: C 44.77; H 5.26; N 22.81%

3-(3′-Bromopropylamino)-6-chloropyridazine hydrobromide (IX)

The above compound VIII (13.8 g., 0.0737 mole) was dissolved in hot acetonitrile (100 ml.). The solution was then cooled to room temperature and during stirring phosphorus tribromide (9 ml.) was added portionwise during 20 min. After the addition was complete the reaction mixture was heated under reflux for 2 hrs. and filtered still hot. Upon cooling the separated product was filtered off and washed with some acetonitrile, yield 18.9 g. (75%). The colourless crystals had m. p. 135—141° when freshly prepared, otherwise m. p. up to 210° was observed on account of the formation of the cyclic product. NMR (D_2O, TMSPS-Na as internal standard): $\tau = 2.16$ (d, H_4), 2.41 (d, H_5), 6.33 (t, -NHC**H**$_2$CH$_2$CH$_2$Br), 7.93 (t, -NHCH$_2$C**H**$_2$CH$_2$Br), 6.36 (t, -NHCH$_2$CH$_2$C**H**$_2$Br); $J_{4,5} = 9.5$; $J_{CH_2,CH_2} = 6.5$ cps).

Anal. $C_7H_{10}Br_2ClN_3$ (331.46) calc'd.: C 25.36; H 3.04; N 12.68%
found: C 25.22; H 3.37; N 12.79%

*7-Chloro-1,2,3,4-tetrahydropyrimido(1,2-*b*)pyridazin-5-ium bromide* (VI)

a) The above compound IX (1.0 g., 0.003 mole) and abs. ethanol (50 ml.) were heated under reflux for 30 min. Upon cooling the separated crystals were filtered off and crystallized from ethanol. M. p. 210—211°; yield 0.62 g. (80%). NMR (DMSO-d_6): $\tau = 2.0$ (d, H_9), 2.18 (d, H_8), 6.47 (m, 2-CH_2), 7.83 (m, 3-CH_2), 5.64 (m, 4-CH_2), 0.33 (broad, NH); $J_{8,9} = 9.5$ cps. In CF_3COOD (TMS as external standard): $\tau = 2.29$ (s, H_8, H_9), 6.27 (m, 2-CH_2), 7.57 (m, 3-CH_2), 5.50 (m, 4-CH_2); in $(CF_3CO)_2O$ (TMS as external standard): $\tau = 2.28$ (d, H_9), 2.50 (d, H_8); 6.27 (m, 2-CH_2), 7.61 (m, 3-CH_2), 5.50 (m, 4-CH_2); $J_{8,9} = 9.5$ cps.

Anal. $C_7H_9BrClN_3$ (250.54) calc'd.: C 33.56; H 3.61; N 16.77%
found: C 33.31; H 3.51; N 16.89%

b) A mixture of 3-amino-6-chloropyridazine (I) (8.75 g., 0.0676 mole), 1,3-dibromopropane (17 ml.) and absol. ethanol (75 ml.) was heated under reflux for 8 hrs. The solvent and unreacted 1,3-dibromopropane were distilled off *in vacuo* and the residue was treated with some water and aqueous sodium hydroxide until *p*H 9—10 was reached. The unreacted starting pyridazine derivative (3.8 g.) was separated by filtration and the aqueous solution was extracted with diethyl ether. The dried ethereal extracts (90 ml) were evaporated to a small volume and hydrogen bromide gas was introduced. The collected crystals were crystallized from absol. ethanol and the pure compound (0.5 g., 2.9% yield) had m. p. 210—212°. On hand of mixed m. p. and IR spectra correlation the compound was found to be identical with the product obtained as described under *a*).

*7-Chloro-4*H*,2,3-dihydropyrimido(1,2-*b*)pyridazine* (VII)

a) The hydrobromide salt VI (1.1 g., 0.0043 mole) was dissolved in water (15 ml.) and treated with dilute aqueous sodium hydroxide until *p*H 10. The solution was extracted with diethyl ether (three portions of 30 ml), the ethereal extracts dried over anhydrous magnesium sulfate and upon filtration the filtrate was concentrated *in vacuo* to a small volume. Upon standing on ice, the separated yellow crystals were filtered off (0.3 g., 40%) and were purified by crystallization from diethyl ether and

petrolether. The free base, m. p. 76—79° is not stable and upon exposure on air after several hours darkens. NMR (DMSO-d_6): $\tau = 2.35$ (d, H_9), 2.62 (d, H_8), 6.52 (m, 2-CH_2), 7.87 (m, 3-CH_2), 5.75 (m, 4-CH_2); $J_{8,9} = 9.5$ cps.

Anal. $C_7H_8ClN_3$ (169.62) calc'd.: C 49.56; H 4.75; N 24.77%
found: C 49.43; H 4.90; N 24.88%

b) The bromopropylamino compound IX (1.1 g., 0.0033 mole), dissolved in abs. ethanol (40 ml.) was treated with an aqueous solution of potassium carbonate (2.1 g. in 50 ml. of water). The reaction mixture was then heated under reflux for 2 hrs, ethanol was removed *in vacuo* and the cooled aqueous residue was extracted with diethyl ether. The dried ethereal extracts (90 ml) were concentrated to a small volume and upon standing on ice the yellow needles which separated were filtered off (0.2 g., 35%). For analytical purposes the compound was crystallized from diethyl ether and petrolether, m. p. 76—79°. The compound was found to be identical with the product obtained as described under *a*).

3-Amino-2-(4′-bromobutyl)-6-chloropyridazinium bromide (X)

A mixture of 3-amino-6-chloropyridazine (5.2 g., 0.004 mole), 1,4-dibromobutane (12 ml.) and abs. ethanol (80 ml.) was heated under reflux for 8 hrs. Ethanol and excess 1,4-dibromobutane were distilled off *in vacuo* and the residue was treated with water and dilute sodium hydroxide until *p*H 10. The mixture was extracted with diethyl ether and from the dried extracts (90 ml.) the solvent was completely removed by distillation. The residue was dissolved in abs. ethanol and hydrogen bromide was introduced. The separated product (0.8 g., 5.7%) was repeatedly crystallized from abs. ethanol to yield colourless crystals with m. p. 202—208°.

Anal. $C_8H_{12}Br_2ClN_3$ (345.49) calc'd.: C 27.81; H 3.51; N 12.17%
found: C 28.02; H 3.60; N 12.32%

6-Chloro-3-chloroacetylaminopyridazine (XI, R = H, n = 0)

To a cold stirred suspension of 3-amino-6-chloropyridazine (7.8 g., 0.06 mole) in toluene (70 ml.) chloroacetylchloride (8 ml.) was added portionwise. After the addition was complete the mixture was heated under reflux for 1 hr. Hydrogen chloride was evolved from the reaction mixture. Upon cooling the separated product was filtered off (11.2 g., 90%) and was crystallized from ethanol to give colourless crystals of m. p. 181—184°. UV (ethanol): $\lambda_{max.}$ 244 mμ, $\varepsilon = 19250$. IR: 3.15, 3.21 (NH), 5.89μ (C = O). NMR $(CF_3CO)_2O$: $\tau = 1.21$ (d, H_4), 1.75 (d, H_5), 5.53 (s, CH_2); $J_{4,5} = 9.5$ cps.

Anal. $C_6H_5Cl_2N_3O$ (206.04) calc'd.: C 34.97; H 2.44; N 20.40%
found: C 34.94; H 2.71; N 20.40%

6-Chloro-3-(3′-chloropropionylamino)-pyridazine (XI, R = H, n = 1)

The compound was prepared in essentially the same way as described for the chloroacetylamino analog from 3-amino-6-chloropyridazine (7.8 g., 0.06 mole), 3-chloropropionyl chloride (8 ml.) and toluene (70 ml.). The crude product (11.7 g., 88%) was crystallized from ethanol to give colourless needles, m. p. 150—155°. NMR (DMSO-d_6): $\tau = 1.55$ (d, H_4), 2.11 (d, H_5), 6.08 (t. -$COCH_2CH_2Cl$), 6.97 (t, -$COCH_2CH_2Cl$), —1.22 (broad, NH); $J_{4,5} = 9.5$, $J_{CH_2,CH_2} = 7$ cps.

Anal. $C_7H_7Cl_2N_3O$ (220.06) calc'd.: C 38.20; H 3.21; N 19.09%
found: C 37.85; H 3.43; N 18.89%

6-Chloro-3-(2′-chloropropionylamino)-pyridazine (XI, R = CH_3, n = 1)

The compound was prepared in essentially the same way as described for the chloroacetylamino analog. The following quantities of reactants were employed: 3-amino-6-chloropyridazine (3.9 g, 0.03 moles), 2-chloropropionyl chloride (8 ml.) and toluene (40 ml.). The crude product (5.7 g., 86%) was crystallized from ethanol and had m. p. 149—152°. UV (Ethanol): $\lambda_{max.}$ 246 mμ, $\varepsilon = 19090$. IR (KBr): 3.11 (NH), 5.85 μ (C = O).

Anal. $C_7H_7Cl_2N_3O$ (220.06) calc'd.: C 38.20; H 3.21; N 19.09%
found: C 38.02; H 3.40; N 19.17%

3-Amino-2-carbethoxymethyl-6-chloropyridazinium bromide (XIIa, X = Br)

A mixture of 3-amino-6-chloropyridazine (I) (12.9 g., 0.1 mole), ethyl bromoacetate (6 ml.) and abs. ethanol (80 ml.) was heated under reflux for 4 hrs. Excess of ethyl bromoacetate and ethanol was removed by distillation *in vacuo* and the residue was crystallized from ethanol. The colourless crystals had m. p. 203—205°. Yield 17 g. (57%). IR: 3.01, 3.20 (NH_2), 5.71 μ (C = O). NMR (D_2O, TMSPS-Na as int. standard): τ = 2.16 (d, H_4), 2.41 (d, H_5), 4.82 (s, CH_2COOEt), 5.75 (q, $COOCH_2CH_3$), 8.80 (t, CH_3); $J_{4,5}$ = 9.5 cps.

Anal. $C_8H_{11}BrClN_3O_2$ (296.56) calc'd.: C 32.40; H 3.74; N 14.16%
found: C 32.22; H 3.90; N 14.15%

In essentially the same way the following compounds were prepared:

i) 3-Amino-2-carbethoxyethyl-6-chloropyridazinium bromide (XIIb, X = Br)

Obtained from 3-amino-6-chloropyridazine (12.9 g.), ethyl 3-bromopropionate (15 ml.) and ethanol (80 ml.) in 32% yield. M. p. 185—188° (from ethanol). NMR (DMSO-d_6): τ = 1.92 (d, H_4), 2.17 (d, H_5), —0.4 (broad, NH), 5.54 (t, CH_2CH_2COOEt), 7.05 (t, CH_2CH_2COOEt), 5.90 (q, $COOCH_2CH_3$), 8.82 (t, CH_3); $J_{4,5}$ = 10 cps, J_{CH_2,CH_2} = = 6.5 cps, J_{CH_2,CH_3} = 7 cps,

Anal. $C_9H_{13}BrClN_3O_2$ (310.59) calc'd.: C 34.80; H 4.22; N 13.53%
found: C 34.61; H 4.18; N 13.68%

ii) 3-Amino-2-carbethoxyethyl-6-chloropyridazinium chloride (XIIb X = Cl)

The compound was obtained from 3-amino-6-chloropyridazine (3 g.) and ethyl 3-chloropropionate (16 ml.) in abs. ethanol (20 ml.). 1.9 g. of the starting pyridazine were recovered and the product was obtained in 4.8% yield, m. p. 198—203° (from ethanol and diethyl ether).

Anal. $C_9H_{13}Cl_2N_3O_2$ (266.13) calc'd.: C 40.62; H 4.93; N 15.79%
found: C 40.66; H 4.77; N 15.34%

iii) 3-Amino-2-carbethoxymethyl-6-chloropyridazinium chloride (XIIa, X = Cl)

The reaction mixture, consisting of 3-amino-6-chloropyridazine (3 g.), ethyl chloroacetate (10 ml.) and abs. ethanol (30 ml.) was heated under reflux for 10 hrs. Upon cooling the unreacted pyridazine (0.7 g.) was separated and the filtrate evaporated *in vacuo* to dryness. The residue was crystallized from ethanol and diethyl ether, m. p. 190—195°.

Anal. $C_8H_{11}Cl_2N_3O_2$ (252.11) calc'd.: C 38.11; H 4.40; N 16.67%
found: C 38.31; H 4.45; N 16.82%

3-Amino-2-carboxymethyl-6-chloropyridazinium chloride (XIII, n = 1, X = Cl)

The corresponding ester (XIIa, n = 1, X = Cl) (3.0 g., 0.01 mole) was dissolved in cold hydrochloric acid (prepared from 8 ml. of the acid with d = 1.19 and 12 ml. of water). The solution was left to stand at room temperature for 24 hrs. The separated crystals (1.25 g., 55%) were collected and a sample crystallized from ethanol, m. p. 185—187°. IR: 3.08 (NH_2), 5.66 μ (C = O). NMR (D_2O, TMSPS-Na as int. standard): τ = 2.16 (d, H_4), 2.41 (d, H_5), 4.90 (s, CH_2); $J_{4,5}$ = 9.5 cps.

Anal. $C_6H_7Cl_2N_3O_2$ (224.05) calc'd.: C 32.16; H 3.14; N 18.75%
found: C 32.03; H 3.25; N 18.90%

3-Amino-2-carboxyethyl-6-chloropyridazinium chloride (XIII, n = 2, X = Cl)

The above procedure was applied to the ester XIIb (n = 2, X = Cl) (2.9 g.). The acid was obtained in 54% yield as colourless crystals, m. p. 189—192°. IR: 5.83 (C = O), 3.10 μ (NH_2). NMR (DMSO-d_6): τ = 1.98 (s, H_4,H_5), 5.55 (t, CH_2CH_2COOH), 7.10 (t, CH_2CH_2COOH), —0.30 (broad, NH, COOH).

Anal. $C_7H_9Cl_2N_3O_2$ (238.08) calc'd.: C 35.31; H 3.81; N 17.65%
found: C 35.18; H 3.53; N 17.42%

6-Chloro-2-hydroxyimidazo(1,2-b)pyridazine (XIV)

3-Amino-2-carbethoxymethyl-6-chloropyridazinium bromide (2.96 g., 0.01 mole) and polyphosphoric acid (20 g.) were heated for 10 min. at 40—45°. In this time the evolution of hydrogen bromide has ceased and the temperature was raised up to 135—140°. After about 1 hr. at this temperature when foaming was no more percieved the reaction mixture was cooled on ice and crushed ice (70 g.) was added. Portionwise solid sodium bicarbonate was added until *p*H 4. The separated product was filtered off, washed with iced water and dried. Yield 1.19 g. (71%). Upon crystallization from 50% ethanol or sublimation at 175—180°/1 mm. the pure compound had m. p. 230—231°. IR: 3.9 μ (broad, H-bonding). NMR (DMSO-d_6): τ = 2.38 (s, H_3), 2.80 (d, H_7), 2.05 (d, H_8), 4.40 (very broad, NH); $J_{7,8}$ = 9 cps.

Anal. $C_6H_4ClN_3O$ (169.57) calc'd.: C 42.49; H 2.38; N 24.78%
found: C 42.59; H 2.55; N 24.90%

7-Chloro-3,4-dihydropyrimido(1,2-b)pyridazin-2-one (XV)

Starting from the ester (XIIb, n = 2, X = Br) (1.55 g., 0.005 mole) and polyphosphoric acid (20 g.) the same procedure as above was applied, except that the reaction mixture was heated at 165—175° for 2 hrs. The product (0.57 g., 62%) was crystallized from ethanol and had m. p. 203—205°. IR (KBr): 6.01 μ (C = O). NMR ($CDCl_3$): τ = 2.74 (s, H_7, H_8), 7.19 (t, 3-CH_2), 5.55 (t, 4-CH_2); $J_{3\text{-}CH_2\ 4\text{-}CH_2}$ = 8.0 cps.

Anal. $C_7H_6ClN_3O$ (183.60) calc'd.: C 45.79; H 3.29; N 22.89%
found: C 45.79; H 3.48; N 22.49%

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IZVLEČEK

Sinteze v vrsti piridazinov. XXIX. Reakcije 3-amino-6-klorpiridazina z α, ω-dihalogeniranimi alkani, α- in β-halogeniranimi estri ter z α- in β-halogeniranimi acilhalogenidi

S. Ostroveršnik, B. Stanovnik in M. Tišler

Raziskovali smo reakcije med 3-amino-6-klorpiridazinom in različnimi dihalogenskimi spojinami, halogeniranimi estri in halogeniranimi acilhalogenidi. V nekaterih primerih je bilo mogoče pripraviti biciklične produkte, derivate imidazo (1,2-b) piridazina in pirimido (1,2-b)piridazina.

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