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Original Scientific Paper

Synthesis of Pyridazine Derivatives. IX. Formation of Pyridazines in the Reaction of Some Acid Anhydrides with Hydrazines*

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Reaction between 4-cyclohexene-1,2-dicarboxylic acid anhydride and hydrazine hydrate was investigated. There were obtained different products depending on reaction conditions but no pyridazines were formed. The reaction between hydrazino pyridazines and different acid anhydrides was also investigated and only monohydrazides were obtained. Finally, a ring contraction of a pyridazine derivative into a pyrazole derivative has been established.

Although reactions of hydrazines with dicarboxylic acids or esters to give pyridazines or other derivatives are well known, analogous reactions with acid anhydrides, except with maleic and phthalic anhydride, appear to have been studied to a lesser extent. The object of the present work was to investigate the reactions of hydrazine or substituted hydrazines with some acid anhydrides for the preparation of compounds containing the pyridazine nucleus.

Aliphatic dicarboxylic acids or derivatives and hydrazines usually form hydrazides, but with succinic acid also a pyridazo-(1,2-*a*)-pyridazine was obtained[1]. Heterocyclic 1,2-diesters and hydrazine react in two ways. The formation of pyridazines has been observed in the case of diesters derived from azines, diazines and thiophene[2-5] whereas diesters of other five-membered heterocycles gave dihydrazides, but the substituted ones formed also pyridazines[2,6]. With ethyl-α,α'-diacetosuccinate, however, a pyridazine or a pyrrole derivative were formed[7-9]. In the case of maleic or phthalic anhydride the formation of pyridazines proceeds smoothly, but *N*-aminophthalimide is known to be the product which is formed first. Many factors are influencing the reaction course and as a rule excess hydrazine, higher temperatures and prolonged reaction time favour the formation of phthalylhydrazides[10,11]. On the other hand 3,6-diphenyl-phthalic anhydride is an exception and only *N*-aminophthalimide derivative is formed[12].

In an attempt to prepare condensed pyridazines by treating *cis*-4-cyclohexene-1,2-dicarboxylic acid anhydride (I) with hydrazine hydrate we have discovered that several products are formed, depending upon the reaction conditions. If the reaction conditions which are usually employed for the formation of pyridazines were followed, *e. g.* when I was heated with hydrazine hydrate in glacial acetic acid, or if the reaction was conducted under pressure, no pyridazines were formed. The structure of the obtained *N*-amino-4-cyclo-

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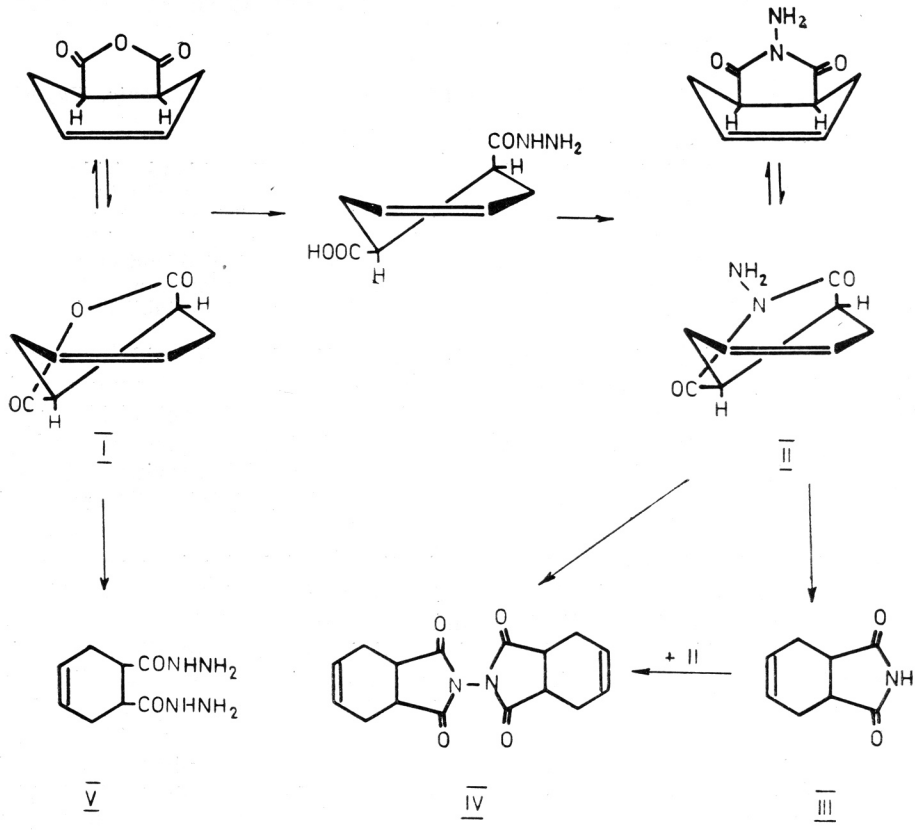
hexene-1,2-dicarboximide (II) was confirmed through its conversion into the known 4-cyclohexene-1,2-dicarboximide (III) or through the following reaction. Heating (II) in dilute hydrochloric acid afforded IV and this compound is formed also in the reaction between II and III. If, however, hydrazine hydrate was used in excess and reacted with I, the dihydrazide (V) was formed and this, under conditions which were employed for the formation of pyridazines from dihydrazides[2], remained unchanged.



The most logical explanation for the failure of obtaining pyridazines in the above reaction appears to be on steric grounds. In the case of cyclohexene itself the half-chair conformation is calculated to be approximately 2.7 kcal/ /mole more stable than the corresponding half-boat conformation[13]. In the case of I, however, the half-boat conformation would be most probably more favoured than the half-chair form since the fused rings would be less strained[14]. If we assume that in the first step hydrazinolysis of the anhydride affords a monohydrazide, the favoured conformation of this compound would be the half-chair conformation as in the case of the non-cyclic derivatives of tetrahydrophthalic acids[13], the functional groups being as far apart as possible[15]. Now, taking into consideration the steric grounds and bond angles (in the case of pyridazine formation from heterocyclic 1,2-diesters or phthalic esters bond

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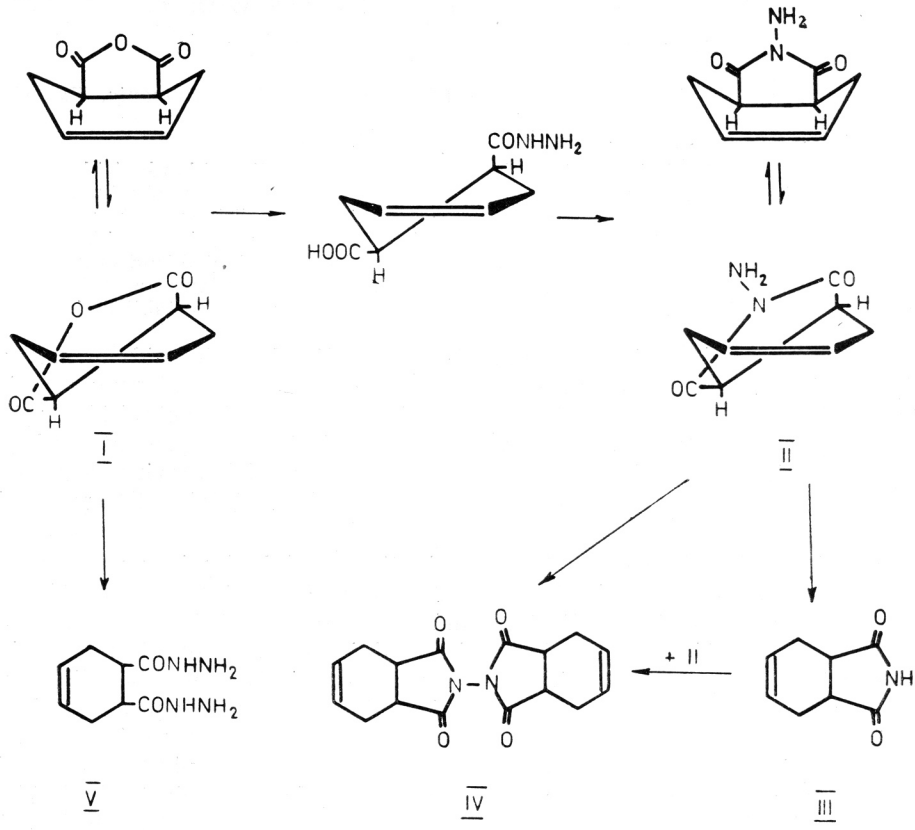

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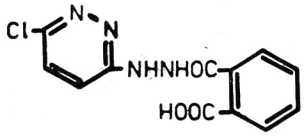
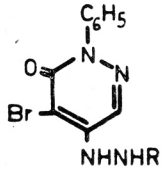
angles are in the range of 118—127° wheras in the case of cyclohexane this is 109°), the subsequent formation of a hydrazine bridge leading to a pyridazine derivative is not favoured because of the spatial arrangements of both functional groups and so the less strained five-membered ring is formed.

VI



VII



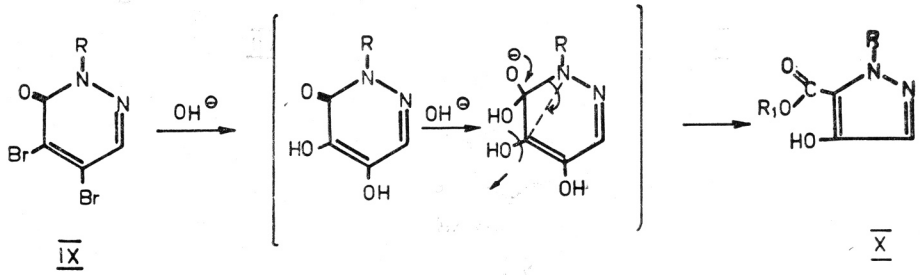
VIII

Furthermore, it was of interest to investigate if hydrazino-pyridazines can be employed as the starting hydrazino compounds for the formation of another pyridazine ring. 3-Hydrazino-6-chloropyridazine reacted with maleic anhydride to give only the uncyclized product (VI, R = H). The failure of forming the pyridazine nucleus as a result of the possible isomerization to the *trans* form is rejected on grounds that the *cis* form is preserved as evident from IR spectra of VI ($R = C_2H_5$) and VIII (R = COCH=CHCOOH). The carbonyl frequency was in both cases very close to such frequency of maleic acid itself which is known to be by 25 $cm.^{-1}$ higher than that of fumaric acid[16]. A similar uncyclized product (VII) was obtained from the reaction with phthalic anhydride and such a reaction course can be most adequately explained in following terms. The reactivity of the hydrazino group, being adjacent to a sp^2-hybridized ring nitrogen, is reduced similarly as with amino groups in such systems[17] and a reduced reactivity is observed also with arylhydrazines as compared with hydrazine[18]. However, greater chemical reactivity of an amino and hydrazino group is usually observed at the 4 position of the pyridazine ring and electronic effects reflect also on the basicity (4-amino derivatives of azines are always more basic than their *ortho* amino analogs[19]). For these reasons we have investigated also the reaction with some 4-hydrazino derivatives.

1-Phenyl-4,5-dibromo-6(1 *H*)-pyridazone was synthesized first by Bistrzycki[20] and since ethanol was used as solvent, besides the cyclic product obtained in low yield also the uncyclized product was obtained. By employing acetic acid as solvent we could obtain only the pyridazine derivative in good yield and this holds also in the case when other arylhydrazines were employed. With such 4,5-dibromo compounds nucleophilic displacement usually takes place at the position 4[21-23] and with hydrazine hydrate we were able to obtain the 4-hydrazino derivative (VIII, R = H). This reacted with maleic anhydride

just in the same way as the above 3-hydrazino compound giving rise to the uncyclized product (VIII, R = — COCH=CHCOOH) only.

Although the above attempts to prepare a new pyridazine ring failed, the 3-hydrazino group is able to form a pyrazolone ring in the reaction with acetoacetic ester or thiosemicarbazides with *iso*-thiocyanates. The reaction between 3-hydrazino-6-chloropyridazine and acetoacetic ester was already described by Druey *et al.*[24] but only an uncyclized product was obtained. We have found that initial cooling was necessary and under such conditions the pyrazolone ring was formed.



IX X

Finally, an interesting reaction was observed during an attempt te hydrolize 1-phenyl-4,5-dibromo-6(1 *H*)-pyridazone. When heating it with aqueous alkali, rearrangement with ring contraction occured and a pyrazole derivative, *e. g.* 1-phenyl-4-hydroxy-pyrazole-5-carboxylic acid (X, R = C_6H_5 —, R_1 = H) was formed. The assignement of this structure is secured upon spectroscopic evidence and transformation of the acid into the corresponding ester (X, R = C_6H_5 —, R_1 = CH_3 —) with diazomethane or methanolic HCl. There are known some cases of ring contractions of cyclic amides[25] and in the pyridazine field only one case of similar ring contraction into a pyrazole derivative was recorded[26-28]. In this case an intermediate dihydro derivative was postulated, yet with our compound a benzilic type of rearrangement, as indicated, seems to be more likely.

EXPERIMENTAL

Melting points were determined on a Kofler heating microscope. UV spectra were recorded with a Beckman Model DU Spectrophotometer. IR spectra were recorded with Perkin-Elmer Model 21 Spectrophotometer as KBr discs or Nujol mulls.

N-*Amino-4-cyclohexene-1,2-dicarboximide (II)*

To *cis*-4-cyclohexene-1,2-dicarboxylic acid anhydride (1.52 g.) hydrazine hydrate (0.6 g. of 80%) were added during stirring. After the exothermic reaction has subsided the reaction mixture was left aside to cool down at room temperature and thereafter the product was collected and crystallized three times from ethanol-water (4 : 1) to give 1.5 g. (90%) of colourless crystals, m. p. 103—104°.

Anal. $C_8H_{10}N_2O_2$ (166.18) calc'd.: C 57.82; H 6.07; N 16.86%
found: C 57.96; H 5.83; N 16.86%

4-Cyclohexene-1,2-dicarboximide (III)

a) From the *N*-amino derivative.

The above *N*-amino derivative (1.66 g.) was dissolved in 0.4 *N* hydrochloric acid (50 ml.) the solution cooled so that during the reaction the temperature did not rise over 5° and an aqueous solution of sodium nitrite (4.14 g. in 10 ml. water) was added

slowly. After the evolution of gases ceased the mixture was left at room temperature for 1/2 hr. and then the precipitate collected. After repeated crystallizations from ethanol-water (3 : 1) the compound had m. p. 140—141°, yield 1.2 g. (79%). (Lit.[29-32] gives m. p. 139—140°, 136.5—137.5°, 136° or 136—138°).

Anal. $C_8H_9NO_2$ (151.16) calc'd.: C 63.56; H 6.00; N 9.27%
found: C 63.29; H 6.16; N 9.15%

b) From 4-cyclohexene-1,2-dicarboxylic acid anhydride and urea.

A mixture of I (1.52 g.) and urea (0.3 g.) was heated for 1/2 hr at 140° and then 2 hrs. at 165°. The residue was repeatedly crystallized from a mixture of ethanol and water (4 : 1) with the addition of charcoal. M. p. 140—141° and mixed m. p. was undepressed with the compound prepared as under a). Yield 1.24 g. (82%).

N,N′-*bis-(4-Cyclohexene-1,2-dicarboximide) (IV)*

a) To a solution of II (1.66 g.) in benzene (30 ml.) I (1.52 g.) was added and the mixture was heated under reflux on water bath for 1 hr. After standing overnight at room temperature the precipitate was collected and crystallized three times from a methanol-water mixture (3 : 1). Yield 1.9 g. (63%), m. p. 177—178°.

Anal. $C_{16}H_{16}N_2O_4$ (300.30) calc'd.: C 63.99; H 5.37; N 9.33%
found: C 64.18; H 5.47; N 9.85%

b) A solution of II (1.66 g.) in 5% hydrochloric acid (15 ml.) was heated under reflux for 1 hr. Upon cooling the colourless crystals which separated were filtered and recrystallized, giving rise to colourless crystals, m. p 177—178°. Yield 0.9 g. (60%). Mixed m. p. with the compound prepared under a) was undepressed and IR spectra were identical.

4-Cyclohexene-1,2-dicarboxylic Acid Dihydrazide (V)

Compound I (1.52 g.) was treated with excess hydrazine hydrate (6 g. of 80%) and after the exothermic reaction has subsided the mixture was heated under reflux for 10 min. at 160°. The product which was obtained was recrystallized from ethanol-water (5 : 1) giving rise to colourless crystals, m. p. 219—220°. Yield 1.8 g. (90%).

Anal. $C_8H_{14}N_4O_2$ (198.22) calc'd.: C 48.47; H 7.12; N 28.27%
found: C 48.33; H 7.00; N 28.48%

N_2-*(6′-Chloropyridazinyl-3′)-monohydrazide* of *Maleic Acid* (*VI*, R = H)

To a solution of 3-hydrazino-6-chloropyridazine (1.45 g.) in glacial acetic acid (10 ml.) maleic anhydride (0.98 g.) was added and the mixture heated to reflux for 3 hrs. The solvent was evaporated in *vacuo* to 1/3 of the original volume and the residue was diluted with water (10 ml.). After standing overnight on ice, crystals separated which were collected and crystallized from ethanol-water, m. p. 188—190°. Yield 56%. UV (ethanol) λ_{max} 3280 Å, ε 8.640.

Anal. $C_8H_7ClN_4O_3$ (242.63) calc'd.: N 23.10%
found: N 22.93%

N_2-*(6′-Chloropyridazinyl-3′)-monohydrazide* of *Maleic Acid Ethyl Ester* (*VI*, *R* = C_2H_5)

The above acid (2.43 g.) was dissolved in absolute ethanol (50 ml.) and dry hydrogen chloride was introduced to saturation. The mixture was heated under reflux for 1/2 hr., the solvent evaporated to half of its initial volume and after cooling colourless crystals separated. Recrystallization from ethanol afforded the pure compound, m. p. 179—180°. Yield 2.0 g. (74%). UV spectrum (ethanol): λ_{max} 3020 Å, ε 3.940. The IR spectrum exhibited a band at 1706 $cm.^{-1}$ assignable to CO group.

Anal. $C_{10}H_{11}ClN_4O_3$ (270.68) calc'd.: C 44.37; H 4.97; N 20.70%
found: C 44.53; H 5.02; N 20.57%

N_2-(6′-Chloropyridazinyl-3′)-monohydrazide of Phthalic Acid (VII)

To a solution of 3-hydrazino-6-chloropyridazine (1.45 g.) in glacial acetic acid (10 ml.) phthalic anhydride (2.22 g.) was added. The reaction mixture, after the initial exothermic reaction, was left aside for two days at room temperature. The colourless precipitate was filtered and recrystallized from much ethanol to yield (1.11 g., 38%) of colourless crystals, m. p. 200°. UV spectrum (*N,N*-dimethylformamide): λ_{max} 3020 Å, ε 3.810.

Anal. $C_{12}H_9ClN_4O_3$ (292.68) calc'd.: C 49.23; H 3.10; N 19.14%
found: C 48.83; H 3.32; N 19.56%

N_2-(6′-Chloropyridazinyl-3′)-monohydrazide of Formic Acid Ethyl Ester

To a suspension of 3-hydrazino-6-chloropyridazine (7.23 g.) in ethanol (50 ml.) a solution of sodium acetate (5 g.) in water (25 ml.) was added and ethyl chloroformate (7.02 g.) added dropwise. The exothermic reaction caused a complete solution and the reaction mixture was heated to reflux on a water bath for 1/2 hr. The solvent was evaporated in *vacuo* to 1/3 of the original volume and the cooled residue poured onto crushed ice (100 g.). The crude product was separated and crystallized twice from ethanol-water (2 : 1), m. p. 157—158°. Yield 5.0 g. (46%). UV spectrum (ethanol): λ_{max} 2380 and 3080 Å, ε 7.890 and 1.120.

Anal. $C_7H_9ClN_4O_2$ (216.63) calc'd.: C 38.87; H 4.19; N 25.90%
found: C 38.80; H 4.34; N 25.76%

1-Phenyl-4-hydrazino-5-bromo-6(1 H)-pyridazone (VIII, R = H)

To a solution of 1-phenyl-4,5-dibromo-6(1*H*)-pyridazone (IX, R = C_6H_5—) (3.3 g.) in pyridine (15 ml.) hydrazine hydrate (0.6 g. of 80%) was added. A few min. after the exothermic reaction has subsided the product started to separate from the solution. The obtained product was crystallized from ethanol and the colourless crystals had m. p. 161—162°. Yield 2.0 g. (71%). UV spectrum (tetrahydrofurane): λ_{max} 3020 Å. ε 10.840.

Anal. $C_{10}H_9BrN_4O$ (281.12) calc'd.: C 42.75; H 3.23; N 19.94%
found: C 43.01; H 2.93; N 19.93%

N_2-(1′-Phenyl-5′-bromo-6′(1′ H)-pyridazonyl-4′)-monohydrazide of Maleic Acid (VIII, R = — COCH=CHCOOH)

To a solution of hydrazino compound (VIII, R = H, 1.41 g.) in glacial acetic acid (40 ml.) maleic anhydride (0.49 g.) was added and the mixture was heated under reflux for 1 hr. The brownish red solution was evaporated in *vacuo* to about 10 ml. and the residue diluted with water. For purification the crude product was dissolved in an aqueous solution of sodium bicarbonate, filtered and precipitated with hydrochloric acid. After repeated crystallizations from ethanol the compound melted at 126—127°. Yield 0.54 g. (30%). UV spectrum (ethanol): λ_{max} 2920 Å, ε 10.840. The IR spectrum exhibited a band at 1718 $cm.^{-1}$ assignable to CO group.

Anal. $C_{14}H_{11}BrN_4O_4$ (379.18) calc'd.: C 44.34; H 2.92; N 14.78%
found: C 44.61; H 3.02; N 14.94%

1-(6′-Chloropyridazinyl-3′)-3-methyl-5-pyrazolone

Into a cooled solution of 3-hydrazino-6-chloropyridazine (1.44 g.) in an ethanol--water mixture (2 : 1) acetoacetic ester (1.3 g.) was added dropwise. After the addition was complete and the initial exothermic reaction has subsided the mixture was heated under reflux on water bath for 2 hrs. The solution was left overnight, the precipitate filtered and purified by sublimation in *vacuo* at 13 mm. Hg and finally crystallized from a small quantity of dioxane. M. p. of colourless needles 232—233°, yield 0.3 g. (14%). UV spectrum (ethanol): λ_{max} 2460 Å, ε 16.040.

Anal. $C_8H_7ClN_4O$ (210.63) calc'd.: C 45.64; H 3.35; N 26.61%
found: C 46.01; H 3.50; N 26.28%

1-Phenyl-(4′-phenylthiosemicarbazido-1′)-5-bromo-6(1 H)-pyridazone (VIII, R = — $CSNHC_6H_5$)

A mixture of VIII (R = H) (1.41 g.), ethanol (100 ml.) and phenyl *iso*-thiocyanate (0.68 g.) was heated under reflux for 1 hr., the solvent evaporated in *vacuo* and the residue treated with water (100 ml.). The colloidal solution was treated with some sodium chloride and left aside overnight. The precipitate was then filtered, washed with water and repeatedly crystallized from *N,N*-dimethylformamide-water (1 : 4), m. p. 175—176°.

Anal. $C_{17}H_{14}BrN_5OS$ (416.30) calc'd.: C 49.05; H 3.24; N 16.82; S 7.70%
found: C 48.71; H 3.54; N 16.83; S 8.38%

1-(6′-Chloropyridazinyl-3′)-4-ethylthiosemicarbazide

3-Hidrazino-6-chloropyridazine (1.45 g.), ethanol (30 ml.) and ethyl *iso*-thiocyanate (0.87 g.) were mixed together and the mixture heated to reflux for 1/2 hr. The pale yellow precipitate was collected and crystallized from ethanol, m. p. 197—198°. Yield 1.7 g. (74%).

Anal. $C_7H_{10}ClN_5S$ (231.71) calc'd.: C 36.29; H 4.35; N 30.23; S 13.84%
found: C 36.72; H 4.73; N 30.10; S 13.86%

1-Phenyl-4,5-dibromo-6(1 H)-pyridazone (IX, R = C_6H_5 —)

Mucobromic acid (25.8 g.) was dissolved at 50° in a mixture of water and glacial acetic acid (2 : 1; 250 ml.) and phenylhydrazine hydrochloride (14.5 g.) was added portionwise under stirring. The stirred reaction mixture was heated 1 hr. at 95°, the separated crystals were collected and crystallized from ethanol, m. p. 144—145° (Lit.[20] gives m. p. 145°). In essentially the same way other 1-aryl-4,5-dibromo-6(1*H*)-pyridazones were prepared.

(i) 1-(*p*-Chlorophenyl)-4,5-dibromo-6(1*H*)-pyridazone (IX, R = *p*-Cl-C_6H_4-), obtained in 80% yield, m. p. 183—184°. UV spectrum (ethanol): λ_{max} 2680 and 3240 Å, ε 6.020 and 6.930.

Anal. $C_{10}H_5Br_2ClN_2O$ (364.44) calc'd.: C 32.96; H 1.38; N 7.69%
found: C 33.15; H 1.53; N 8.15%

(ii) 1-(*p*-Nitrophenyl)-4,5-dibromo-6(1*H*)-pyridazone (IX, R = *p*-NO_2-C_6H_4-), m. p. 233—235° (from 2-ethoxyethanol). UV spectrum (ethanol): λ_{max} 4040 Å, ε 41.800.

Anal. $C_{10}H_5Br_2N_3O_3$ (374.98) calc'd.: C 32.03; H 1.34; N 11.20%
found: C 32.42; H 1.69; N 11.12%

(iii) 1-(*p*-Tolyl)-4,5-dibromo-6(1*H*)-pyridazone (IX, R = *p*-CH_3-C_6H_4-), m.p. 129—130° (from ethanol-water, 4 : 1). UV spectrum (ethanol): λ_{max} 2680 and 3220 Å, ε 5.040 and 6.060.

Anal. $C_{11}H_8Br_2N_2O$ (344.02) calc'd.: C 38.40; H 2.34; N 8.14%
found: C 38.08; H 2.65; N 8.21%

(iv) 1-(1′-Naphthyl)-4,5-dibromo-6(1*H*)-pyridazone (IX, R = $C_{10}H_7$-(1)-), m. p. 226—228° (2-ethoxyethanol).

Anal. $C_{14}H_8Br_2N_2O$ (380.05) calc'd.: C 44.24; H 2.12; N 7.37%
found: C 44.51; H 2.29; N 7.23%

(v) 1-(2′-Naphthyl)-4,5-dibromo-6(1*H*)-pyridazone (IX, R = $C_{10}H_7$-(2)-), m. p. 189—190° (ethanol). UV spectrum (ethanol): λ_{max} 2680 and 3260 Å, ε 10.790 and 7.840.

Anal. $C_{14}H_8Br_2N_2O$ (380.05) calc'd.: C 44.24; H 2.12; N 7.37%
found: C 44.06; H 2.35; N 7.82%

1-Phenyl-4-hydroxy-pyrazole-5-carboxylic Acid (X, R = C_6H_5 —, R_1 = H)

A suspension of IX (R = C_6H_5-) (1.65 g.) in aqueous KOH (40 ml. of 10%) was heated under reflux for 1 hr. The hot solution was filtered, concentrated in *vacuo*

to 1/3 of its original volume and acidified with 2 *N* hydrochloric acid to *p*H 4. The obtained product was crystallized from ethanol-water (3 : 1), m. p. 257—258°. Yield 0.6 g. (58%). UV spectrum (ethanol): λ_{max} 2780 Å, ε 7.030. The IR spectrum exhibited the following important bands: at 3160 cm.$^{-1}$ (OH), 2500 cm.$^{-1}$ (bonded OH) and 1690 cm.$^{-1}$ (CO).

Anal. $C_{10}H_8N_2O_3$ (204.18) calc'd.: C 58.82; H 3.95; N 13.72%
found: C 58.69; H 4.34; N 13.78%

1-Phenyl-4-hydroxy-pyrazole-5-carboxylic Acid Methyl Ester (*X*, R = C_6H_5 —, R_1 = CH_3)

a) A suspension of the above acid (X, R = C_6H_5-,R_1 = H) (0.51 g.) in diethyl ether (5 ml.) was treated with an ethereal solution of diazomethane (prepared from 2.06 g. of *N*-nitrosomethylurea[33]). The addition was discontinued after evolution of nitrogen has subsided and the solution remained pale yellow coloured. The precipitate thus formed was filtered and crystallized three times from ethanol to give colourless crystals, m. p. 224—225°.

Anal. $C_{11}H_{10}N_2O_3$ (218.21) calc'd.: C 60.54; H 4.62; N 12.84%
found: C 60.63; H 5.03; N 12.69%

b) A solution of the above acid (0.51 g.) in absolute methanol (20 ml.) was heated under reflux for 1 hr. During this time hydrogen chloride was slowly bubbled into the solution. At the end of the reaction methanol was distilled off and the residue was crystallized from methanol, m. p. 223°. Mixed m. p. with the ester, obtained as under a), was undepressed.

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IZVLEČEK

Sinteze piridazinovih derivatov. IX. Tvorba piridazinov v reakciji med nekaterimi anhidridi kislin in hidrazini.

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Raziskovali smo reakcijo med anhidridom 4-cikloheksen-1,2-dikarboksilne kisline in hidrazinovim hidratom. V odvisnosti od reakcijskih pogojev nastanejo različne spojine, vendar ne derivati piridazina. Raziskovali smo tudi reakcijo med hidrazino piridazini in različnimi anhidridi kislin pri čemer so nastali le monohidrazidi. Končno smo ugotovili tudi, da poteče pri nekaterih derivatih piridazina skrčitev obroča ter nastane derivat pirazola.

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