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Pyridazines with Hetero-Atom Substituents in Position 3 and 5, Part VII [1]. Halogenation of 2-Aryl-5-hydroxy-pyridazin-3(2*H*)-ones in Position 4

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Summary. The reaction of 2-aryl-5-hydroxy-3(2 *H*)-pyridazinones (**1 a, b**) with bromine yields the 4-bromo derivatives **2 a, b** and with sulfuryl chloride the chloro compounds **3 a, b** are obtained. However, with an excess of chlorine or sulfuryl chloride the 4,4-dichloro-pyridazine-dione **4** is produced. Hydrolysis of **4** leads to **5**, and in a similar manner the open chain hydrazone **8** is obtained from the carboxylic acid **6**.

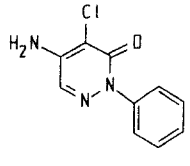
Keywords. Halogenation; 3(2*H*)-Pyridazinones; Ring opening of pyridazinones.

Pyridazine mit Heteroatom-Substituenten in Stellung 3 und 5, 7. Mitt. [1]. Halogenierung von 2-Aryl-5-hydroxy-pyridazin-3(2*H*)-onen in 4-Stellung

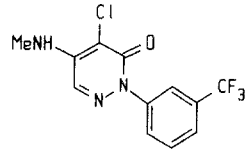
Zusammenfassung. Die Reaktion von 2-Aryl-5-hydroxy-pyridazin-3(2*H*)-onen (**1 a, b**) mit Brom liefert die 4-Bromderivate **2 a, b**, während mit Sulfurylchlorid **3 a, b** erhalten werden. Ein Überschuß von Sulfurychlorid oder Chlorgas gibt jedoch das 4,4-Dichlor-pyridazin-dion **4**. Die Hydrolyse von **4** führt unter Ringöffnung und Decarboxylierung zu **5**. In analoger Weise gibt die freie Carbonsäure **6** das Hydrazon **8**.

Introduction

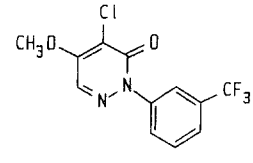
Derivatives of 2-aryl-pyridazin-3(2*H*)-ones containing a chloro substituent in position 4 have been of great interest as herbicidal agents, e.g. Chloridazon [3, 4] and BAS 44521 [5] manufactured by BASF, and Norflurazon [6, 7] manufactured by Sandoz AG. Therefore the present work deals with halogenation reactions at 2-aryl-5-hydroxy-6-methoxycarbonyl-pyridazin-3(2*H*)-ones. Other aspects of this class of compounds have been investigated in previous papers [1, 8].



CHLORIDAZON



NORFLURAZON

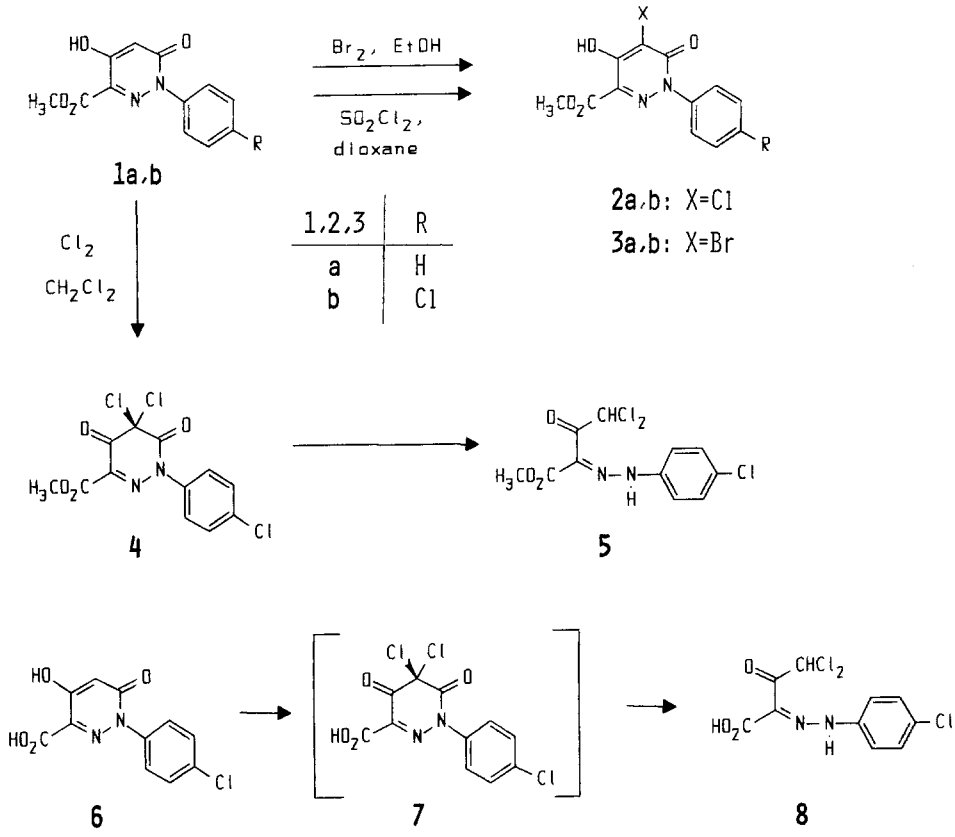


BAS 44521

Results and Discussion

Six-membered heterocyclic malonyl systems, such as 4-hydroxy-2(1*H*)-quinolones [9] and 4-hydroxy-2(1*H*)-pyridones [10] are readily chlorinated with sulfuryl chloride or brominated with bromine [11] to yield dihalogenomalonyl derivatives. The halogenation of N-unsubstituted and N-substituted 5-hydroxy-6-phenyl-3(2*H*)-pyridazinones has already been studied [12, 13], and in these cases stable 4,4-dihalogenated pyridazine-3,5-diones were obtained.

The N-arylpyridazinones **1a, b** show a different behaviour. While mono-bromination to **2a, b** with bromine and monochlorination with sulfuryl chloride to **3a, b** is easily achieved in 80–90% yield, the dichlorination of **1b** to **4** can be accomplished only by using an excess of chlorine gas in dichloromethane. Utilization



of an excess of sulfuryl chloride on **1b** affords to a mixture of **4** (max. 90%) and **3b** only. Employment of **1a** in these reactions leads to a number of compounds because chlorination takes place at the phenyl substituent too. The formation of a 4,4-dibromo derivative could not be observed even if bromine itself was used as solvent.

In an attempt to separate **3b** and **4** by column chromatography on silica gel a conversion of **4** to **5** was observed. This reaction involves a hydrolytic ringopening and decarboxylation of the intermediate β-keto acid. A similar ringopening reaction of a 3,3-dichloro-2,4-dioxo-1,2,3,4-tetrahydro-pyridine has previously been described [10]; however, the column material employed was aluminum oxide. At-

tempts to achieve the reaction of **4** to **5** by using aqueous hydrolysis conditions at different *pH* values were unsuccessful (as in the case described previously [10]). Therefore the catalysis of the reaction with silica gel is (so far) the only method for obtaining the hydrazone **5**. The quite general ringopening reaction of dichloromalonyl heterocycles to dichloroacetyl systems has already been discussed earlier [14]. The conversion of **4** to **5** depends of course on the presence of water. If the necessary quantity of water is not present on the adsorption material or in the solvents (which is usually the case) it must be added.

Interestingly, the chlorination of the free carboxylic acid **6** with an excess of sulfuryl chloride without solvent, and aqeuous work up resulted in the formation of the hydrazone **8**. The intermediate **7** could not be isolated.

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Experimental

Melting points were determined on a Gallenkamp Melting Point Apparatus Mod. MFB-595. ^{1}H-NMR spectra were obtained on a Varian EM 360 (*TMS* as internal standard), ^{13}C-NMR spectra on a Varian XL 200, IR spectra on a Perkin Elmer 298 (KBr pellets), mass spectra on a Finnegan mass spectrometer 4500 (EI: 70 eV, CI: 120 eV, methane) and elemental analyses on a C,H,N automat Carlo Erba 1106.

4-Bromo-5-hydroxy-6-methoxycarbonyl-2-phenyl-pyridazin-3(2H)-one (**2a**)

5-Hydroxy-6-methoxycarbonyl-2-phenyl-pyridazin-3(2*H*)-one [8] (**1a**, 1.23 g, 0.005 mol) was dissolved in 20 ml ethanol and treated with bromine (0.93 g, 0.058 mol). Within five minutes the product precipitated. Yield: 1.38 g (85%), m.p. 162–163 °C from ethanol. IR: 3350–3000 w, b, 2960 w, 1700 sh, 1670 s, 1600 w, 1590 w, 1490 w cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ = 4.1 (s, CH_3), 7.4–7.7 (m, 5 aromat. H), 11.1 (s, OH). $C_{12}H_9BrN_2O_4$ (325.1): calcd. C 44.33, H 2.79, N 8.62; found C 44.09, H 2.85, N 8.50.

4-Bromo-2-(4-chlorophenyl)-5-hydroxy-6-methoxycarbonyl-pyridazin-3(2H)-one (**2b**)

2-(4-Chlorophenyl)-5-hydroxy-6-methoxycarbonyl-pyridazin-3(2*H*)-one (**1b** [8], 2.12 g, 0.0075 mol) was dissolved in 30 ml of ethanol and treated with bromine (1.40 g, 0.0088 mol). The product precipitated immediately. Yield: 2.29 g (85%), m.p. 190–193 °C from ethanol. IR: 3100 w, 3060 sh, 3040 w, 2980 sh, 2960 w, 1690 s, 1680 s, 1670 s, 1610 w, 1590 sh, 1510 sh, 1490 m cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ = 4.0 (s, CH_3), 7.5 (s, 4 aromat. H), 11.0 (s, OH). $C_{12}H_6BrClN_2O_4$ (356.6): calcd. C 40.08, H 2.24, N 7.79; found C 40.32, H 2.40, N 7.78.

4-Chloro-5-hydroxy-6-methoxycarbonyl-2-phenyl-pyridazin-3(2H)-one (**3a**)

A solution of the pyridazinone **1a** [8] (2.46 g, 10 mmol) in 30 ml of dioxane was warmed up to 50 °C. Sulfuryl chloride (1.66 g, 0.12 mol) was added, the temperature rose to 65 °C and the solution was stirred for ten further minutes, then poured into 200 ml of ice water. The precipitate was filtered and dried. Yield: 2.16 g (77%), m.p. 137–138 °C toluene/hexane. IR: 3380–3080 w, b, 2960 w, 1700 s, 1675 sh, 1670 s, 1650 sh, 1645 sh, 1635 sh, 1605 w, 1590 w, 1500 sh, 1490 w cm^{-1}. ^{1}H-NMR

($CDCl_3$): δ = 4.1 (s, CH_3), 7.5 (s, 5 aromat. H). $C_{12}H_9ClN_2O_4$ (280.7): calcd. C 51.35, H 3.23, N 9.98; found C 51.72, H 3.42, N 10.02.

4-Chloro-2-.(4-chlorophenyl)-5-hydroxy-6-methoxycarbonyl-pyridazin-3(2H)-one (**3b**)

The pyridazinone **1b** [8] (1.41 g, 5 mmol) was suspended in 20 ml of dioxane and treated with sulfuryl chloride (1.32 g, 0.01 mol). The solid phase was dissolved by stirring at 50 °C for ten minutes. The solution was cooled to room temperature and poured into 100 ml of ice water to precipitate **3b**. Yield: 1.44 g (91%), m.p. 196–199 °C. IR: 3 100 w, 3 060–3 020 w, b, 1 690 s. 1 670 s, 1 610 w, 1 590 sh, 1 510 w, 1 490 m cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ = 4.0 (s, CH_3), 7.4 (s, 4 aromat. H), 10.9 (s, OH). $C_{12}H_8Cl_2N_2O_4$ (315.1): calcd. C 45.74, H 2.56, N 8.89; found: C 45.78, H 2.59, N 8.75.

4,4-Dichloro-2-(4-chlorophenyl)-6-methoxycarbonyl-pyridazin-3,5(2H,4H)-dione (**4**)

The pyridazinone **1b** [8] (3.0 g, 10.7 mmol) was dissolved in 50 mol of chichloromethane. This solution was treated with an excess of chlorine at room temperature within 30 minutes. The solvent was removed under reduced pressure and the residue recrystallized from ethanol/water. Yield: 3.36 g (90%), m.p. 116–118 °C. IR: 2 960 w, 1 760 s, 1 730 s, 1 710 m, 1 590 w, 1 560 m, 1 540 sh, 1 490 m cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ = 4.0 (s, CH_3), 7.5 (s, 4 aromat. H). MS (EI): **m**/e (%) = 354 (4, M^+, 3 ^{37}Cl), 352 (29, M^+), 1 ^{37}Cl + 2 ^{35}Cl), 351 (15), 350 (97, M^+, 1 ^{37}Cl + 2 ^{35}Cl), 349 (16) 348 (100, M^+ 1, 3 ^{35}Cl), 324 (19), 322 (61), 321 (12), 320 (63), 319 (10), 318 (10), 317 (18), 316 (55), 315 (15), 314 (84), 284 (14), 282 (20), 256 (18), 254 (27), 212 (14), 210 (43), 202 (11), 200 (17), 174 (19), 172 (29), 155 (18), 153 (45), 149 (10), 139 (19), 128 (15), 127 (45), 126 (43), 125 (51), 113 (26), 111 (85). $C_{12}H_7Cl_3N_2O_4$ (349.6): calcd. C 41.23, H 2.03, N 8.02; found: C 41.64, H 2.48, N 7.78.

Methyl 3,3-Dichloro-1-(4-chlorophenylhydrazono)-2-oxo-propane-1-carboxylate (**5**)

Silica gel 60 (5.0 g, Merck) was added to a solution of the dichloro pyridazine **4** (1.0 g, 29 mmol) in 10 ml of toluene, 3 ml of acetone and 3 drops of water. This mixture was transferred on top of a 2 × 25 cm column of silica gel, and after standing overnight chromatographed with toluene/acetone 9 : 1. Yield: 0.50 g (54%), m.p. 132–134 °C from cyclohexane. IR: 3 180–3 140 w, b, 2 950 w, 2 920 w, 2 840 w, 1 695 s, 1 690 s, 1 590 s, 1 520 s, 1 490 m cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ = 3.9 (s, CH_3), 7.1 (s, H at C−3), 7.4 (s, 4 ArH), 13.2 (s, NH). ^{13}C-NMR ($CDCl_3$, decoupled): δ = 52.9 (C of CH_3), 67.1 (C-HCl_2), 117.1 (C−2 and C−6 of phenyl), 121.6 (C−4 of phenyl), 130.0 (C−3 and C−5 of phenyl), 138.8 (C−1 of phenyl), 163.7 (C = N), 181.4 (181.4) (C of carboxylic acid), 190.8 (C = 0). MS (EI): *m*/e (%) = 326 (9), 324 (26), 322 (M^+, 3 ^{35}Cl, 28), 264 (8), 262 (8), 257 (6), 255 (9), 241 (26), 240 (11), 239 (94), 149 (14), 128 (31), 127 (21), 126 (100), 125 (30), 113 (12), 111 (30). $C_{11}H_9Cl_2N_2O_3$ (323.6): calcd. C 40.83, H 2.80, N 8.66; found: C 41.23, H 3.13, N 8.44.

3,3-Dichloro-1-(4-chlorophenylhydrazono)-2-oxo-propane-1-carboxylic acid (**8**)

2-(4-Chlorophenyl)-5-hydroxy-3-oxo-2,3-dihydro-pyridazine-6-carboxylic acid [8] (**6**, 0.5 g, 0.002 mol) was refluxed in 20 ml of sulfuryl chloride for two hours. The hot solution was poured into 200 ml of water, the precipitate was filtered and dried. Yield: 0.45 g (72%). IR: 3 160–3 040 w, b, 3 000 w, 1 710 s, 1 655 sh, 1 650 sh, 1 640 m, 1 590 m, 1 540 sh, 1 520 s, 1 510 sh cm^{-1}. ^{1}H-NMR (*DMSO-d_6*): δ = 7.3–7.8 (m, 4 aromat. H and H at C−3), 12.3–13.1 (b, COOH and NH). MS (EI): *m*/e (%) = 312 (8), 310 (17), 308 (M^+, ^{35}Cl, 20), 264 (7), 262 (10), 228 (17), 226 (60), 129 (35), 128 (26), 127 (100), 114 (13), 112 (44), 101 (22), 100 (67), 76 (35). $C_{10}H_7Cl_3N_2O_3$ (309.6): calcd. C 38.80, H 2.28, N 9.05; found C 38.84, H 2.42, N 8.55.

References

[1] Part VI: Schober B. D., Megyeri G., Kappe T. (1990) J. Heterocyl. Chem. **27**: 471; for Part V see: Stadlbauer W., Pfaffenschlager A., Kappe T. (1989) Synthesis: 781
[2] Schober B. D. (1988) Dissertation. Univ. Graz
[3] Rapos P., Winternitz P. (1965) French Patent 1,461,373; (1967) Chem. Abstr. **67**: 90824 g
[4] Rapos P., Winternitz P. (1963) Czech Patent 120,858; (1968) Chem. Abstr. **68**: 78303 z
[5] Badische Anilin- und Soda-Fabrik AG (1969) French Patent Appl 2,001,700; (1970) Chem. Abstr. **72**: 111494 v
[6] Sandoz AG (Ebner C., Schuler M., Inv.) (1970) Swiss Patent 482,684; (1970) Chem. Abstr. **72**: 121567 k
[7] Sandoz AG (Ebner C., Schuler M., Inv.) (1969) French Patent 1,575,643; (1970) Chem. Abstr. **73**: 35389 t
[8] Schober B. D., Megyeri G., Kappe T. (1989) J. Heterocycl. Chem. **26**: 169
[9] Ziegler E., Salvador R., Kappe T. (1962) Monatsh. Chem. **93**: 1376; Ziegler E., Kappe T. (1963) Monatsh. Chem. **94**, 447
[10] Kappe T., Baxevanidis G., Ziegler E. (1969) Monatsh. Chem. **100**: 1715
[11] Ziegler E., Salvador R., Kappe T. (1963) Monatsh. Chem. **94**: 941
[12] Zengerer S. (1985) Dissertation. Univ. Graz
[13] Pfaffenschlager A. (1987) Dissertation. Univ. Graz
[14] Kappe T., Ziegler E. (1963) Monatsh. Chem. **94**: 935

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