Pyridazines, LVII[1]:

Synthesis and Cyclocondensation Reactions of (2-Aminophenyl)-(4-pyridazinyl)-ketone, a New Diaza Isoster of 2-Aminobenzophenone[+)]

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Received January 21, 1991

A convenient approach to the new 2-aminobenzophenone analogue **4** is reported. Condensation reactions of **4** with ortho esters or amide acetals, respectively, followed by intramolecular cyclisations were found to provide smooth access to (4-pyridazinyl)-substituted quinolines **10**, **13a,b**, and the quinazoline derivative **15**.

Pyridazine, 57. Mitt.[1)]: Synthese und Cyclokondensationsreaktionen von (2-Aminophenyl)(4-pyridazinyl)keton, einem neuen Diaza-Isoster des 2-Aminobenzophenons

Ein bequemer Zugang zu dem neuen 2-Aminobenzophenon-Analogon **4** wird beschrieben. Kondensationsreaktionen von **4** mit Orthoestern bzw. Amidacetalen, gefolgt von intramolekularer Cyclisierung, führen glatt zu den (4-Pyridazinyl)-substituierten Chinolinen **10**, **13a,b** sowie zum Chinazolin-Derivat **15**.

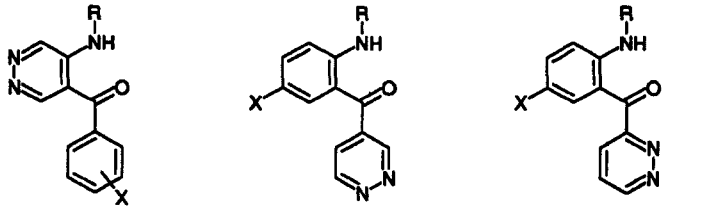
Whereas various 1,2-diazine analogues of the 2-aminobenzophenone system (namely compounds of type A-H) recently have been investigated in some detail[3-7)], so far only one example [*i.e.* (5-amino-4-pyridazinyl)phenyl ketone A] out of the five possible (unsubstituted) parent systems is known[3)].

In extension of our efforts to develop efficient routes to synthetic building blocks of this type, we here report on the first synthesis of the diaza-2-aminobenzophenone **4**, which may be considered an attractive educt for the construction of various pyridazine analogues of drug molecules such as 2-(4-alkyl-1-piperazinyl)-4-phenylquinolines (see below) or 1,4-benzodiazepines. For some recent reports on the improvement of the profile of bio-active compounds achieved by the incorporation of two adjacent nitrogen atoms into an aromatic/heteroaromatic six-membered ring system compare refs.[8-10)]; for an access to congeners of **4** bearing substituents at the amino group and/or at the benzene ring see refs.[6,7)].

The convenient availability of (2-fluorophenyl)(4-pyridazinyl)ketone **1**[6)] together with its smooth transformation into the benzylamino ketone **3**[6)] initially prompted us to search for a route to the primary amine **4** *via* hydrogenolytic debenzylation (Pd/C) of compound **3**. Though this approach failed (as did attempts to convert **1** directly into **4** by treatment with ammonia under various conditions), an efficient synthesis of **4** could be elaborated *via* the 2,1-benzisoxazole **2**. Upon reaction of **1** with sodium azide in dimethylformamide at 120°C, the fluoro substituent was found to be readily replaced by an azido function to give, after spontaneous loss of N_2[11)], the anthranil **2**. Reductive cleavage (H_2/Pd/C)[13)] of the isoxazole ring in the latter compound then turned out to afford the target amino ketone **4** smoothly. Thus, **4** became available in an overall yield (based on **1**) of 67%. On the other hand, treatment of compound **2** with sodium borohydride attacked the pyridazine ring, leading to the 1,4-dihydropyridazine derivative **5**[19)].

In order to evaluate the synthetic potential of the title compound **4**, several derivatisations were studied with the main aim of finding an access to pyridazine congeners of 2-(4-alkyl-1-piperazinyl)-4-phenylquinolines which represent a novel class of potent anti-ulcer agents[21,22)]. For compounds of this type, additional activities (antidepressant, antiinflammatory, and diuretic) had been claimed[23)].

In the reported synthesis[21)] of the above-mentioned drug molecules, 4-phenyl-2-(1*H*)-quinolone (prepared from 2-acetylaminobenzophenone) represents a key intermediate. Accordingly, we directed our initial efforts to the preparation of the diazine analogue **11**. When **4** was refluxed with

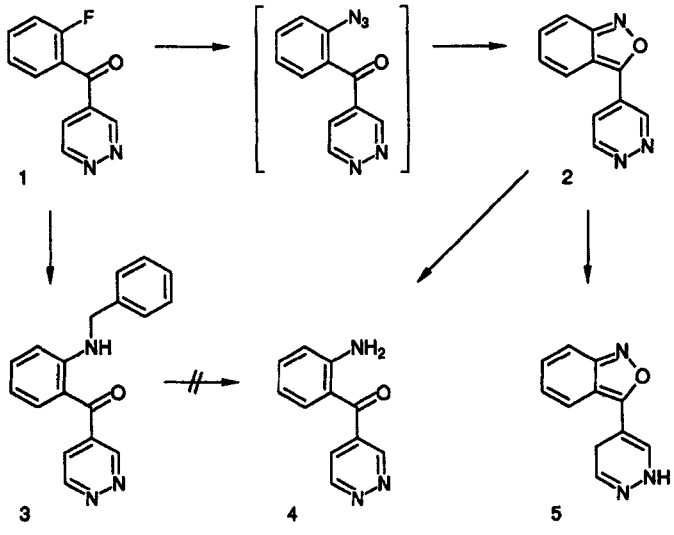


A R = H, X = H
B R = H, X = Hal
C R = Alkyl, X = Hal
D R = Alkyl, X = H
E R = Alkyl, X = Hal
F R = H, X = Hal
G R = Alkyl, X = H
H R = Alkyl, X = Hal

Scheme 1

[+)] Dedicated with best wishes to Prof. Dr. *W. Fleischhacker* on the occasion of his 60th anniversary.

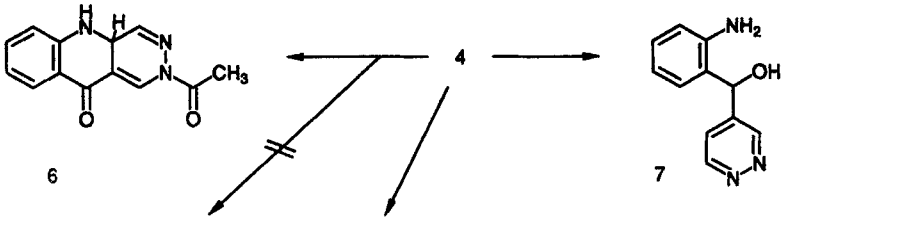
  0365-6233/92/0202-0119 $ 3.50 + .25/0

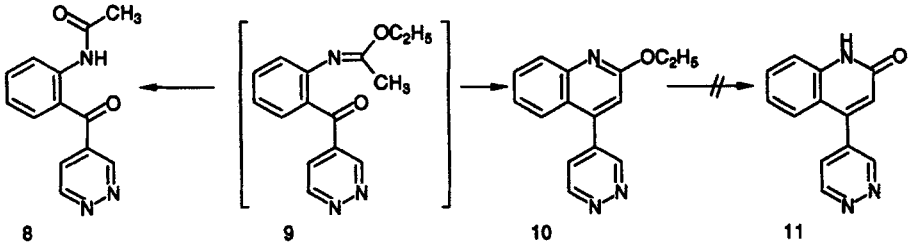


Scheme 2

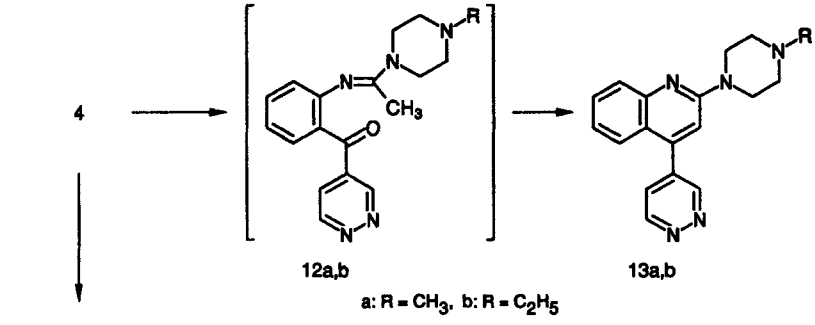
acetic anhydride, we did not obtain the acetamide derivative **8** but - in accordance with findings with (2-alkylaminophenyl)(4-pyridazinyl)-ketones[6] - an intramolecular cyclisation occurred, leading to the dihydro-diazaacridone **6**, the structure of which unambiguously follows from the close resemblance of its ^{1}H-NMR spectrum to the spectra of the corresponding 5-alkyl derivatives[6]. Moreover, attempted acetylation of the conveniently available (sodium borohydride reduction of **4**) amino alcohol **7** only gave complex reaction mixtures.

The primary amino group in **4** smoothly underwent condensation with triethyl orthoacetate yielding an imido ester intermediate **9**. The latter then could be hydrolysed to the amide **8**, albeit in only moderate yield. More interestingly, **9** provides an efficient access to the 2-ethoxy-4-(4-pyridazinyl)quinoline **10** *via* base-induced cyclocondensation (yield: 75%, referred to **4**). However unexpectedly, the ether function in **10** was found to withstand hydrolytic cleavage even on prolonged refluxing in conc. HCl.

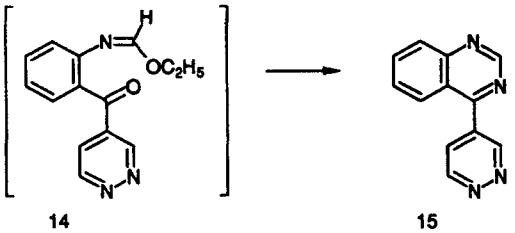




Scheme 3



a: R = CH_3, b: R = C_2H_5



Scheme 4

In view of these findings, we investigated the reactivity of the amino ketone **4** towards appropriate amide acetals (derived from *N'*-alkyl-*N*-acetylpiperazines) bearing in mind the reported utility of such reagents in syntheses of 2-dialkylaminoquinolines[24] and 2-dialkylaminopyrido[2,3-*d*]pyridazines[5]. As shown in the one-pot conversions **4** → **13a,b**, the target pyridazinyl-substituted 2-piperazinylquinolines indeed could be easily prepared *via* the corresponding amidines **12** in satisfactory overall yields.

The amino ketone **4** also provides a convenient access to the novel pyridazinyl-substituted quinazoline **15**. Similar to the transformation **4** → **9**, reaction of **4** with triethyl orthoformate gave an imido ester **14** which - without isolation - could be cyclised to **15** by action of methanolic ammonia.

The results so far obtained indicate that the new amino ketone **4** may well serve as a versatile building block for the construction of (4-pyridazinyl)-substituted benzo-heteroarenes. On the other hand, it became evident that - from the point of view of reactivity - compound **4** [like (5-amino-4-pyridazinyl)aryl ketones[4]] should not be considered merely as a simple analogue of 2-aminobenzophenone.

Experimental Part

Melting points: uncorrected, Reichert-Kofler hot-stage microscope.- IR spectra (KBr; cm^{-1}): Jasco IRA-1.- ^{1}H-NMR spectra: Varian EM 390 (90 MHz), Bruker AM 400 (400 MHz), TMS as internal standard, chemical shifts in δ ppm.- Mass spectra: Hewlett-Packard 5890A/5970B-GC/MSD.- High-resolution mass spectrum: Finnigan MAT 8230 (Institute of General Chemistry, Technical University of Vienna, Ing. *J. Dolezal*).- Column chromatography (cc): Merck Kieselgel 60, 0.063-0.200 mm.- Microanalyses: Institute of Physical Chemistry, University of Vienna, Mag. *J. Theiner*.

3-(4-Pyridazinyl)-[2,1]-benzisoxazole (**2**)

A mixture of 1.01 g (5 mmol) of (2-fluorophenyl)(4-pyridazinyl)ketone[6] (**1**) and 390 mg (6 mmol) of NaN_3 in DMF (50 ml) was stirred at 120°C for 15 h. After evaporation, water (50 ml) was added, the precipitate was filtered off and washed thoroughly with water. The filtrate was extracted exhaustively with dichloromethane; the org. layer was dried over Na_2SO_4 and evaporated. Recrystallisation of the combined materials from ethanol afforded 830 mg (84%) of **2** as colourless needles, m.p. 187°C.- $C_{11}H_7N_3O$ (197.2) clac. C 67.0 H 3.58 N 21.3 found C 67.1 H 3.33 N 21.4.- ^{1}H-NMR ($CDCl_3$): 7.20-7.95 (m, 4H, H-4 - H-7), 8.05 (dd, J_{5-6} = 6 Hz, J_{3-5} = 2 Hz, pyridazine H-5), 9.45 (d, J = 6 Hz, 1H, pyridazine H-6), 9.85 (d, J = 2 Hz, 1H, pyridazine H-3).- MS: m/z = 197 (100%, M^+), 114 (50), 51 (50).

(2-Aminophenyl)(4-pyridazinyl)ketone (**4**)

A solution of 995 mg (5 mmol) of **2** in ethyl acetate (100 ml) was hydrogenated using 10% Pd/C. After filtration, the solvent was evaporated and the residue was purified by cc (ethyl acetate). Recrystallisation from ethanol afforded 800 mg (80%) of **4** as yellow crystals, m.p. 173-177°C.- $C_{11}H_9N_3O$ (199.2) calc. C 66.3 H 4.55 N 21.1 found C 66.3 H 4.62 N 21.2.- IR: 3430; 3300; 3170 (N-H); 1610 (C=O).- ^{1}H-NMR ($CDCl_3$): 6.4 (s br, 2H, NH), 6.5-7.5 (m, 4H, aniline-H), 7.60 (dd, J_{3-5} = 2 Hz, J_{5-6} = 6 Hz, 1H, pyridazine H-5), 9.35-9.50 (m, 2H, pyridazine H-3, H-6).- MS: m/z = 199 (48%, M^+), 170 (54), 120 (100).

3-[4-(2,5-Dihydropyridazinyl)]-[2,1]-benzisoxazole (**5**)

A mixture of 394 mg (2 mmol) of **2** and 300 mg (7.9 mmol) of $NaBH_4$ in ethanol (80 ml) was stirred at room temp. for 15 h. After decomposition of excess $NaBH_4$ with 1% aqueous NaH_2PO_4 (100 ml), the solution was repeatedly extracted with dichloromethane. The combined extracts were washed with water, dried over Na_2SO_4 and evaporated. Recrystallisation from methanol/water afforded 360 mg (90%) of **5** as orange-red needles, m.p. 163-167°C.- $C_{11}H_9N_3O$ (199.2) calc. C 66.3 H 4.55 N 21.1 found C 66.6 H 4.59 N 21.3.- IR: 3280 (N-H).- ^{1}H-NMR ([D_6]DMSO): 3.40 (d, J = 3 Hz, 2H, pyridazine H-5), 6.85 (t, J = 3 Hz, 1H, pyridazine H-6), 6.90 (dd, J_{4-5} = 9 Hz, J_{5-6} = 6 Hz, 1H, H-5), 7.33 (dd, J_{6-7} = 9 Hz, J_{5-6} = 6 Hz, 1H, H-6), 7.45 (d, J = 4 Hz, 1H, pyridazine H-3), 7.47 (d, J = 9 Hz, 1H, H-4), 7.77 (d, J = 9 Hz, 1H, H-7), 9.95 (d, J = 4 Hz, 1H, NH).- MS: m/z = 199 (100%, M^+), 120 (77).

2-Acetyl-2,4a-dihydropyridazino[4,5-b]quinolin-10(5H)-one (**6**)

A solution of 199 mg (1 mmol) of **4** in acetic anhydride (20 ml) was refluxed for 1 h. The oily residue obtained after evaporation was subjected to cc (dichloromethane/methanol 19:1) to afford 97 mg (40%) of **6** as bright yellow crystals, m.p. 168-170°C ($CHCl_3$).- $C_{13}H_{11}N_3O_2$ (241.3) calc. C 64.7 H 4.60 N 17.4 found C 64.5 H 4.57 N 17.1.- IR: 3340 (N-H); 1680 (C=O); 1660 (C=O).- ^{1}H-NMR ($CDCl_3$): 2.40 (s, 3H, $COCH_3$), 4.95 (dd, J_{1-4a} = 3 Hz, J_{4-4a} = 9 Hz, 1H, H-4a), 5.45 (br, 1H, NH), 6.60 (d, J = 3 Hz, 1H, H-1), 6.80-7.10 (m, 2H, H-6, H-8), 7.40-7.75 (m, 2H, H-7, H-9), 7.80 (d, J = 9 Hz, 1H, H-4).- MS: m/z = 241 (15%, M^+), 170 (100).

(2-Aminophenyl)(4-pyridazinyl)methanol (**7**)

A mixture of 199 mg (1 mmol) of **4** and 100 mg (2.6 mmol) of $NaBH_4$ in methanol (20 ml) was stirred at room temp. for 10 min. After decomposition of excess $NaBH_4$ with 1% aqueous NaH_2PO_4 (50 ml), the solution was extracted exhaustively with dichloromethane. The extract was dried over Na_2SO_4 and evaporated. Recrystallisation from ethyl acetate gave 110 mg (55%) of **7** as colourless crystals, m.p. 117°C.- $C_{11}H_{11}N_3O$ (201.2) calc. C 65.7 H 5.51 N 20.9 found C 65.5 H 5.36 N 20.7.- ^{1}H-NMR ($CDCl_3$): 3.8-4.5 (br, 3H, NH, OH), 6.90 (s, 1H, C<u>H</u>-OH), 6.6-7.4 (m, 4H, aniline-H), 7.55 (dd, J_{5-6} = 6 Hz, J_{3-5} = 2 Hz, 1H, pyridazine H-5), 9.05 (d, J = 6 Hz, 1H, pyridazine H-6), 9.20 (d, unresolved, 1H, pyridazine H-3).- MS m/z = 201 (100%, M^+), 129 (77), 51 (78).

(2-Acetylaminophenyl)(4-pyridazinyl)ketone (**8**)

A mixture of 199 mg (1 mmol) of **4** and 6 ml of triethyl orthoacetate was stirred at 160°C for 6 h. To the oily residue obtained after evaporation, 50% ethanol (20 ml) was added and the solution was refluxed for 3 h. After removal of ethanol under reduced pressure, the aqueous solution was extracted repeatedly with dichloromethane. The org. layer was dried over Na_2SO_4 and evaporated. The residue was purified by cc (dichloromethane/methanol 95:5) to afford 100 mg (42%) of **8** as pale yellow crystals, m.p. 158-159°C (ethyl acetate).- $C_{13}H_{11}N_3O_2$ (241.3) calc. C 64.7 H 4.60 N 17.4 found C 64.7 H 4.47 N 17.3.- IR: 1670 (C=O).- ^{1}H-NMR ($CDCl_3$): 2.26 (s, 3H, CH_3), 7.1-7.8 (m, 4H, aniline H-3, H-4, H-5, pyridazine H-5), 8.75 (d, J = 9 Hz, aniline H-6), 9.4-9.6 (m, 2H, pyridazine H-3, H-6), 10.90 (br, 1H, NH).- MS: m/z = 241 (48%, M^+), 199 (56), 170 (100), 120 (91).

2-Ethoxy-4-(4-pyridazinyl)quinoline (**10**)

A mixture of 199 mg (1 mmol) of **4** and 6 ml of triethyl orthoacetate was stirred at 160°C for 6 h. To the oily residue obtained after evaporation, 138 mg (1 mmol) of K_2CO_3 and 10 ml of DMF were added and the mixture was stirred at 120°C for 6 h. After removal of the solvent, water (20 ml) was added and the solution was extracted several times with dichloromethane. The residue left on evaporation was purified by cc (dichloromethane/methanol 95:5) to afford 186 mg (75%) of **10** as colourless crystals, m.p. 136-137°C (ethanol/diisopropyl ether).- $C_{15}H_{13}N_3O$ (251.3) calc. C 71.7 H 5.21 N 16.7 found C 71.7 H 5.05 N 16.7.- ^{1}H-NMR

($CDCl_3$): 1.45 (t, J = 7 Hz, 3H, $CH_2\underline{CH_3}$), 4.60 (q, J = 7 Hz, 2H, $\underline{CH_2}CH_3$), 6.85 (s, 1H, H-3), 7.3-8.1 (m, 5H, H-5, H-6, H-7, H-8, pyridazine H-5), 9.3-9.5 (m, 2H, pyridazine H-3, H-6).- MS: m/z = 251 (35%, M^+), 236 (100), 223 (61).

2-Piperazinyl-4-(4-pyridazinyl)quinolines **13a,b**

A mixture of 1.33 g (10 mmol) of dimethylacetamide dimethyl acetal (DMADMA) and 20 mmol of dry 1-methylpiperazine or 1-ethylpiperazine was heated to 190°C for 5 h. A slow stream of dry argon was continuously bubbled through the solution to remove the liberated dimethylamine[5,24]. After cooling, 199 mg (1 mmol) of **4** were added and the mixture was heated to 130°C for 15 h. Evaporation *in vacuo*, followed by cc (ethyl acetate/methanol, gradient technique) gave the pure products.

2-(4-Methyl-1-piperazinyl)-4-(4-pyridazinyl)quinoline (**13a**)

Yield 140 mg (46%); pale yellow crystals, m.p. 154°C (ethyl acetate).- $C_{18}H_{19}N_5$ (305.4) calc. C 70.8 H 6.27 N 22.9 found C 70.6 H 6.18 N 22.9.- ^{1}H-NMR ($CDCl_3$): 2.35 (s, 3H, CH_3), 2.45-2.65 (m, 4H, CH_2), 3.75-3.95 (m, 4H, CH_2), 6.90 (s, 1H, H-3), 7.15-7.95 (m, 5H, H-5, H-6, H-7, H-8, pyridazine H-5), 9.3-9.5 (m, 2H, pyridazine H-3, H-6).

2-(4-Ethyl-1-piperazinyl)-4-(4-pyridazinyl)quinoline (**13b**)

Yield 137 mg (43%); pale yellow crystals, m.p. 113-116°C (cyclohexane).- $C_{19}H_{21}N_5 \cdot 1/4\ C_6H_{12}$ (340.5)[25] calc. C 72.3 H 7.13 N 20.5 found C 72.3 H 7.11 N 20.6.- ^{1}H-NMR ($CDCl_3$): 1.10 (t, J = 7 Hz, 3H, $CH_2\underline{CH_3}$), 2.47 (q, J = 7 Hz, 2H, $\underline{CH_2}CH_3$), 2.5-2.7 (m, 4H, CH_2), 3.7-3.9 (m, 4H, CH_2), 6.90 (s, 1H, H-3), 7.1-7.9 (m, 5H, H-5, H-6, H-7, H-8, pyridazine H-5), 9.3-9.4 (m, 2H, pyridazine H-3, H-6).- MS: m/z = 319 (14%, M^+), 235 (80), 97 (65), 84 (100).- HRMS: calc. 319.1797 found 319.1806.

4-(4-Pyridazinyl)quinazoline (**15**)

A mixture of 199 mg (1 mmol) of **4** and 6 ml of triethyl orthoformate was stirred at 160°C for 6 h. To the oily residue obtained after evaporation, a saturated solution of NH_3 in methanol (20 ml) was added and the mixture was stirred at room temp. for 15 h. After removal of the solvent, purification of the residue by cc (dichloromethane/methanol 95:5) afforded 127 mg (61%) of **15** as colourless crystals, m.p. 213-214°C (ethyl acetate).- $C_{12}H_8N_4$ (208.2) calc. C 69.2 H 3.87 N 26.9 found C 68.9 H 4.06 N 26.6.- ^{1}H-NMR ($CDCl_3$): 7.6-8.3 (m, 5H, H-5, H-6, H-7, H-8, pyridazine H-5), 9.4-9.6 (m, 2H, pyridazine H-3, H-6), 9.7 (s, 1H, H-2).- MS: m/z = 208 (100%, M^+), 180 (85).

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