CONVENIENT SYNTHESIS OF CYCLOALKENE-FUSED PHTHALAZINONES[1]

Norbert Haider

Institute of Pharmaceutical Chemistry, University of Vienna
Althanstraße 14, A-1090 Vienna, Austria

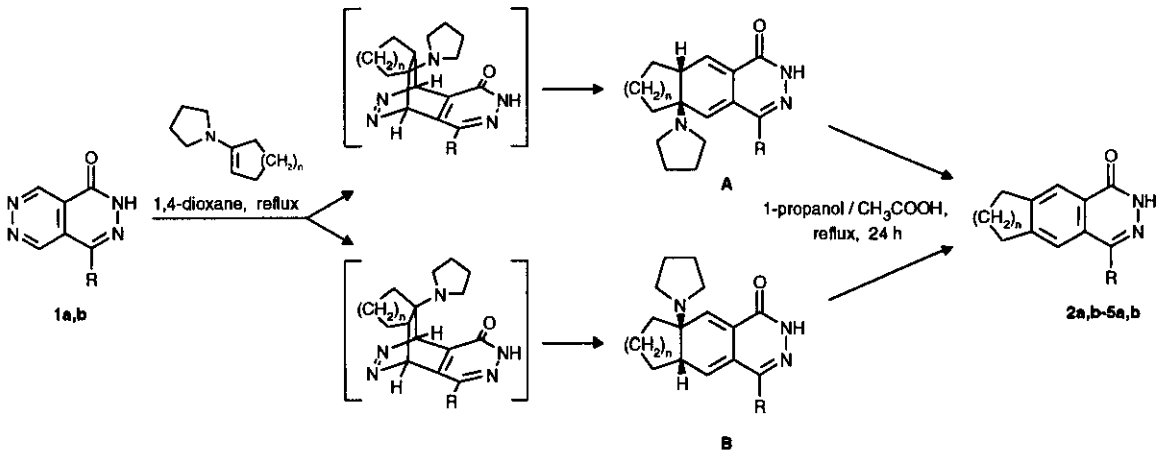
Abstract - A series of cycloalkene-annelated phthalazin-1(2*H*)-ones (**2-5**) was prepared in high yields by a one-pot procedure, employing pyridazino[4,5-*d*]pyridazin-1(2*H*)-ones (**1**) as azadienes and cyclic enamines as dienophiles in an inverse-electron-demand Diels-Alder reaction, followed by acid-catalyzed aromatization.

Phthalazin-1(2*H*)-ones bearing a substituent at C-4 represent key intermediates in the synthesis of various compounds with highly interesting pharmacological properties, such as the blood platelet aggregation inhibitor MY-5445[2] [1-(3-chloroanilino)-4-phenylphthalazine] which has been found to be also a selective phosphodiesterase V_A inhibitor[3] or the thromboxane A_2 synthetase inhibitor and bronchodilator, 2-[2-(1-imidazolyl)ethyl]-4-(3-pyridyl)phthalazin-1(2*H*)-one.[4] Moreover, a number of established drug molecules like *Hydralazine*,[5] *Budralazine*,[6] *Azelastine*,[7] *Ponalrestat*,[8] or *Zopolrestat*[9] are accessible starting from the corresponding phthalazinones. In general, most of the structural modifications of the parent system which have been carried out in order to optimize the biological activity of phthalazine-derived drugs can be seen as a variation of the substitution pattern at positions 1, 2, and 4, i. e. the substitution pattern of the 1,2-diazine part of the bicyclic system. Considerably less effort has been devoted to the modification of the benzene part of the phthalazine skeleton.[10] In the course of a program aimed at the study of structure-activity relationships of various types of phthalazine-derived bio-active molecules by a systematic, gradual variation of the lipophilic and steric properties of the benzene part of the condensed system (without significant alteration of its electronic properties), the need arose to find a suitable access to a series of cycloalka[*g*]phthalazin-1(2*H*)-ones of variable cycloalkene ring size (five-, six-, seven-, and eight-membered). Here we wish to describe an efficient and simple synthesis of such compounds, employing an inverse-electron-demand ($LUMO_{diene}$-controlled) Diels-Alder reaction of a condensed pyridazine as the key step.[11]

We have previously demonstrated that 1,4-disubstituted pyridazino[4,5-*d*]pyridazines can be successfully employed as azadienes in inter- and intramolecular [4+2] cycloaddition reactions with a variety of electron-rich dienophiles.[12,13] Although the calculated LUMO energies for pyridazino[4,5-*d*]pyridazin-1(2*H*)-ones of type (**1**) (which are conveniently accessible, starting from 4-pyridazinecarboxylic acid[14,15]) are somewhat higher than that of the parent system,[16] it was considered worthwhile to attempt the synthesis of cycloalka[*g*]phthalazin-1(2*H*)-ones *via* thermally induced inverse-electron-demand Diels-Alder reactions of such azadienes with simple enamines, derived from cyclic ketones, as dienophiles.

When the pyridazino[4,5-*d*]pyridazin-1(2*H*)-one (**1a**) (R = ethyl) was heated with a fourfold excess of 1-pyrrolidino-1-cyclopentene in 1,4-dioxane at reflux temperature, immediate gas evolution was observed which obviously results from elimination of N_2 from an initially formed, highly strained cycloadduct. After one hour, the starting material was completely consumed, and the resulting mixture contained - according to ^{1}H-nmr - the target phthalazinone (**2a**) as well as smaller amounts of dihydrophthalazinone intermediates of types (**A**) and (**B**), respectively (cf. Scheme 1). Acid-catalyzed elimination of pyrrolidine from the latter compounds smoothly afforded **2a**, this step is most conveniently performed in a one-pot manner by refluxing the crude cycloaddition product mixture in 1-propanol in the presence of acetic acid. Analogous reaction of the 4-phenyl-substituted azadiene (**1b**) with the five-membered enamine, followed by acid treatment gave the corresponding phthalazinone (**2b**) in 84% overall yield. This transformation of the azadienes (**1a,b**) into *g*-annelated phthalazinones gives good yields with six-, seven-, and eight-membered cyclic enamines as well, although considerably longer reaction times (48 hours and 72 hours, respectively) are required in the case of 1-pyrrolidino-1-cyclohexene as a dienophile; this observation is in agreement with previous findings.[12,19,20]

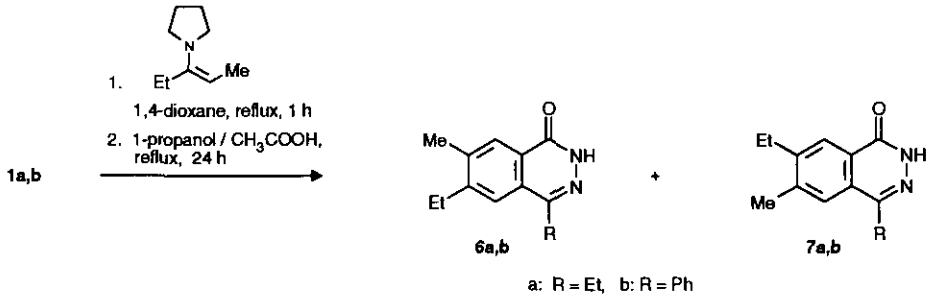
Scheme 1



2-5: n = 1-4 **a**: R = Et **b**: R = Ph

As both intermediates (**A** and **B**) eventually lead to an identical final product of type (**2-5**), an additional experiment was undertaken in order to investigate the regiochemistry of this [4+2] cycloaddition reaction. For this purpose, compounds (**1**) were treated with the "unsymmetrical" enamine, 3-pyrrolidino-2-pentene, under the conditions described above (Scheme 2). Expectedly, mixtures of two isomers were obtained after acidic work-up, in the case of the 4-alkyl as well as of the 4-aryl substituted products. The isomer ratio for **6a** : **7a** was determined as 2.3 : 1 by ^{1}H-nmr spectroscopy. Structure assignment was done by means of nuclear Overhauser enhancement (nOe) difference spectroscopy with the product mixture, taking advantage of the well-separated H-5 signals: only the H-5 singlet of the minor isomer (**7a**) (δ = 7.74 ppm) shows an nOe on saturation of the methyl resonance at 2.46-2.48 ppm. Analogously, a similar ratio of **6b** : **7b** = 2.1 : 1 was found for the 4-phenyl congeners. Thus, the preferred relative orientation of diene and dienophile in the cycloaddition step is that which is characterized by C-C bond formation between C-8 of the azadiene and the more electron-rich of the two sp^2 carbon atoms of the enamine (C-2, in this case).

Scheme 2



In summary, the synthesis described above provides a simple and convenient access to cycloalkene-fused phthalazin-1(2*H*)-ones.

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage microscope and are uncorrected. Ir spectra were taken on a Perkin-Elmer 1605 FT-IR spectrophotometer for KBr pellets; ^{1}H-nmr spectra were recorded on a Bruker AC 80 (80 MHz) or on a Varian Unity*plus* 300 (300 MHz) spectrometer, using TMS as internal reference. Microanalyses were performed at the Institute of Physical Chemistry (Microanalytical Laboratory), University of Vienna. Enamines were prepared according to literature procedures[21,22] and were distilled prior to use. All cycloaddition reactions were carried out under an atmosphere of dry argon.

General Procedure for the Preparation of 4-Substituted Cycloalka[*g*]phthalazin-1(2*H*)-ones (**2-5**)

To a solution of 4-ethylpyridazino[4,5-*d*]pyridazin-1(2*H*)-one[14] (**1a**) (176 mg, 1 mmol) or 4-phenylpyridazino[4,5-*d*]pyridazin-1(2*H*)-one[14,23] (**1b**) (224 mg, 1 mmol), respectively, in dry 1,4-dioxane (10 ml) was added the cycloalkanone enamine (4 mmol) in one portion, and the mixture was refluxed for 1 h (**2a,b**, **4a,b**, and **5a,b**), 48 h (**3a**), or 72 h (**3b**). The solvent and excess reagent were removed under reduced pressure, then the residue was taken up in a mixture of 1-propanol (10 ml) and acetic acid (0.5 ml). The solution was refluxed for 24 h, cooled, and evaporated to dryness. Recrystallization from ethanol/water gave the pure products as colorless crystals.

4-Ethyl-7,8-dihydro-6*H*-cyclopenta[*g*]phthalazin-1(2*H*)-one (**2a**)

Yield: 180 mg (84%), mp 236-237°C. *Anal.* Calcd for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.07. Found: C, 72.86; H, 6.51; N, 13.11. Ir (cm^{-1}): 3155, 3030, 2930, 1656, 1388, 772. ^{1}H-Nmr (80 MHz, DMSO-d_6) δ: 12.26 (br s, 1 H, NH), 8.05 (s, 1 H, H-9), 7.77 (s, 1 H, H-5), 3.12-2.77 (m, 6 H, Ar-CH_2), 2.07 (quint, J = 7.2 Hz, 2 H, CH_2-C$\underline{H}_2$-CH_2), 1.23 (t, J = 7.4 Hz, 3 H, CH_3).

7,8-Dihydro-4-phenyl-6*H*-cyclopenta[*g*]phthalazin-1(2*H*)-one (**2b**)

Yield: 220 mg (84%), mp 247-249°C. *Anal.* Calcd for $C_{17}H_{14}N_2O$: C, 77.84; H, 5.38; N, 10.68. Found: C, 77.54; H, 5.75; N, 11.06. Ir (cm^{-1}): 3158, 3032, 2954, 1650, 1380, 768, 700. ^{1}H-Nmr (300 MHz, DMSO-d_6) δ: 12.68 (br s, 1 H, NH), 8.17 (s, 1 H, H-9), 7.60-7.50 (m, 5 H, C_6H_5), 7.46 (s, 1 H, H-5), 3.06 (t, J = 7.5 Hz, 2 H, Ar-CH_2), 2.98 (t, J = 7.5 Hz, 2 H, Ar-CH_2), 2.07 (quint, J = 7.5 Hz, 2 H, CH_2-C$\underline{H}_2$-CH_2).

4-Ethyl-6,7,8,9-tetrahydrobenzo[*g*]phthalazin-1(2*H*)-one (**3a**)

Yield: 123 mg (54%), mp 242-243°C. *Anal.* Calcd for $C_{14}H_{16}N_2O$: C, 73.66; H, 7.06; N, 12.27. Found: C, 73.64; H, 7.12; N, 12.18. Ir (cm^{-1}): 3156, 3028, 2936, 1650, 1616, 928, 768. ^{1}H-Nmr (80 MHz, DMSO-d_6) δ: 12.20 (br s, 1 H, NH), 7.90 (s, 1 H, H-10), 7.59 (s, 1 H, H-5), 3.00-2.70 (m, 6 H, Ar-CH_2), 1.90-1.70 (m, 4 H, CH_2-C$\underline{H}_2$-CH_2), 1.21 (t, J = 7.4 Hz, 3 H, CH_3).

6,7,8,9-Tetrahydro-4-phenylbenzo[*g*]phthalazin-1(2*H*)-one (**3b**)

Yield: 240 mg (87%), mp 249-250°C. *Anal.* Calcd for $C_{18}H_{16}N_2O$: C, 78.24; H, 5.84; N, 10.14. Found: C, 77.95; H, 5.79; N, 9.99. Ir (cm^{-1}): 3164, 3028, 2930, 1666, 1616, 1330, 928, 766, 700. ^{1}H-Nmr (80 MHz, DMSO-d_6) δ: 12.61 (br s, 1 H, NH), 8.01 (s, 1 H, H-10), 7.60-7.50 (m, 5 H, C_6H_5), 7.31 (s, 1 H, H-5), 3.10-2.70 (m, 4 H, Ar-CH_2), 1.90-1.60 (m, 4 H, CH_2-C$\underline{H}_2$-CH_2), .

4-Ethyl-7,8,9,10-tetrahydro-6*H*-cyclohepta[*g*]phthalazin-1(2*H*)-one (**4a**)

Yield: 196 mg (81%), mp 203-204°C. *Anal.* Calcd for $C_{15}H_{18}N_2O$: C, 74.35; H, 7.49; N, 11.56. Found: C, 74.00; H, 7.60; N, 11.82. Ir (cm^{-1}): 3154, 3030, 2976, 2928, 1650, 1616, 914, 768. ^{1}H-Nmr (80 MHz, DMSO-d_6) δ: 12.28 (br s, 1 H, NH), 7.96 (s, 1 H, H-11), 7.70 (s, 1 H, H-5), 3.05-2.75 (m, 6 H, Ar-CH_2), 2.00-1.40 (m, 6 H, CH_2-C$\underline{H}_2$-CH_2), 1.23 (t, J = 7.4 Hz, 3 H, CH_3).

7,8,9,10-Tetrahydro-4-phenyl-6*H*-cyclohepta[*g*]phthalazin-1(2*H*)-one (**4b**)

Yield: 260 mg (87%), mp 265-266°C. *Anal.* Calcd for $C_{19}H_{18}N_2O \cdot 0.5\ H_2O$: C, 76.23; H, 6.40; N, 9.36. Found: C, 76.61; H, 6.25; N, 9.40. Ir (cm^{-1}): 3162, 3024, 2910, 1666, 1616, 1372, 960, 758, 706. ^{1}H-Nmr (80 MHz, DMSO-d_6) δ: 12.69 (br s, 1 H, NH), 8.07 (s, 1 H, H-11), 7.60-7.50 (m, 5 H, C_6H_5), 7.38 (s, 1 H, H-5), 3.20-2.70 (m, 4 H, Ar-CH_2), 2.00-1.40 (m, 6 H, CH_2-CH_2-CH_2).

4-Ethyl-6,7,8,9,10,11-hexahydrocycloocta[*g*]phthalazin-1(2*H*)-one (**5a**)

Yield: 210 mg (82%), mp 244-245°C. *Anal.* Calcd for $C_{16}H_{20}N_2O$: C, 74.97; H, 7.86; N, 10.93. Found: C, 74.81; H, 7.82; N, 10.83. Ir (cm^{-1}): 3162, 3030, 2928, 1646, 1616, 1356, 882, 780, 760. ^{1}H-Nmr (300 MHz, DMSO-d_6) δ: 12.26 (br s, 1 H, NH), 7.99 (s, 1 H, H-12), 7.71 (s, 1 H, H-5), 2.98-2.88 (m, 6 H, Ar-CH_2), 1.74-1.62 (m, 4 H, CH_2-CH_2-CH_2), 1.33-1.26 (m, 4 H, CH_2-CH_2-CH_2), 1.24 (t, J = 7.5 Hz, 3 H, CH_3).

6,7,8,9,10,11-Hexahydro-4-phenylcycloocta[*g*]phthalazin-1(2*H*)-one (**5b**)

Yield: 240 mg (79%), mp 245-247°C. *Anal.* Calcd for $C_{20}H_{20}N_2O$: C, 78.92; H, 6.62; N, 9.20. Found: C, 78.67; H, 6.84; N, 9.28. Ir (cm^{-1}): 3158, 3026, 2922, 1650, 1614, 1352, 750, 698. ^{1}H-Nmr (300 MHz, DMSO-d_6) δ: 12.68 (br s, 1 H, NH), 8.09 (s, 1 H, H-12), 7.61-7.51 (m, 5 H, C_6H_5), 7.41 (s, 1 H, H-5), 2.99-2.91 (m, 2 H, Ar-CH_2), 2.88-2.80 (m, 2 H, Ar-CH_2), 1.75-1.55 (m, 4 H, CH_2-CH_2-CH_2), 1.35-1.25 (m, 4 H, CH_2-CH_2-CH_2).

Cycloaddition Reaction of 4-Ethylpyridazino[4,5-*d*]pyridazin-1(2*H*)-one (**1a**) with 3-Pyrrolidino-2-pentene

To a solution of 4-ethylpyridazino[4,5-*d*]pyridazin-1(2*H*)-one[14] (**1a**) (176 mg, 1 mmol) in dry 1,4-dioxane (10 ml) was added 3-pyrrolidino-2-pentene (556 mg, 4 mmol) in one portion, and the mixture was refluxed for 1 h. The solvent and excess reagent were removed under reduced pressure, then the residue was taken up in a mixture of 1-propanol (10 ml) and acetic acid (0.5 ml). The solution was refluxed for 24 h, cooled, and evaporated to dryness. Recrystallization from ethanol/water gave a mixture (2.3 : 1, according to ^{1}H-nmr) of 4,6-diethyl-7-methylphthalazin-1(2*H*)-one (**6a**) and 4,7-diethyl-6-methylphthalazin-1(2*H*)-one (**7a**) as colorless crystals (163 mg, 74%), mp 194-202°C. Repeated recrystallization did not change the isomer ratio. *Anal.* Calcd for $C_{13}H_{16}N_2O \cdot 0.25\ H_2O$: C, 70.72; H, 7.53; N, 12.69. Found: C, 70.84; H, 7.42; N, 12.73. Ir (cm^{-1}): 3158, 3026, 2970, 1648, 1618, 1376, 914, 886, 788, 760. ^{1}H-Nmr (300 MHz, DMSO-d_6) δ: 12.26 [br s, 1 H, NH (**6a** and **7a**)], 8.01 [s, 1 H, H-8 (**6a** and **7a**); shows nOe on irradiation at 2.48-2.46 ppm], 7.74 [s, 1 H, H-5 (**7a**); shows nOe on irradiation at 2.48-2.46 ppm], 7.69 [s, 1 H, H-5 (**6a**)], 2.97-2.87 [m, 2 H, CH_2 (**6a** and **7a**)], 2.83-2.73 [m, 2 H, CH_2 (**6a** and **7a**)], 2.48 [s, 3 H, Ar-CH_3 (**7a**)], 2.46 [s, 3 H, Ar-CH_3 (**6a**)], 1.28-1.20 [m, 3 H, CH_3 (**6a** and **7a**)].

Cycloaddition Reaction of 4-Phenylpyridazino[4,5-*d*]pyridazin-1(2*H*)-one (**1b**) with 3-Pyrrolidino-2-pentene

To a solution of 4-phenylpyridazino[4,5-*d*]pyridazin-1(2*H*)-one[14,23] (**1b**) (224 mg, 1 mmol) in dry 1,4-dioxane (10 ml) was added 3-pyrrolidino-2-pentene (556 mg, 4 mmol) in one portion, and the mixture

was refluxed for 1 h. The solvent and excess reagent were removed under reduced pressure, then the residue was taken up in a mixture of 1-propanol (10 ml) and acetic acid (0.5 ml). The solution was refluxed for 24 h, cooled, and evaporated to dryness. The residue was triturated with 70% ethanol, filtered off, and dried to give a mixture (2.1 : 1, according to ^{1}H-nmr[24]) of 6-ethyl-4-phenyl-7-methylphthalazin-1(2*H*)-one (**6b**) and 7-ethyl-4-phenyl-6-methylphthalazin-1(2*H*)-one (**7b**) as colorless crystals (160 mg, 61%). A sample of pure **6b** was obtained by repeated recrystallization from ethanol/water as colorless crystals, mp 221-224°C. *Anal.* Calcd for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10; N, 10.60. Found: C, 77.30; H, 5.80; N, 10.68. Ir (cm^{-1}): 3160, 3032, 2966, 2920, 1674, 1618, 1364, 766, 700. ^{1}H-Nmr (300 MHz, DMSO-d_6) δ: 12.69 (br s, 1 H, NH), 8.12 (s, 1 H, H-8), 7.62-7.52 (m, 5 H, C_6H_5), 7.44 (s, 1 H, H-5), 2.72 (q, J = 7.2 Hz, 2 H, CH_2), 2.49 (s, 3 H, CH_3; shows nOe on irradiation at 8.12 ppm), 1.13 (t, J = 7.2 Hz, 3 H, CH_3).

ACKNOWLEDGEMENT

Support of this work by the Austrian "Fonds zur Förderung der wissenschaftlichen Forschung" (project no. P10540-CHE) is gratefully acknowledged.

REFERENCES AND NOTES

1. Counts as Part 8 of the series *"Inverse-Electron-Demand Diels-Alder Reactions of Condensed Pyridazines"*; for Part 7 cf. N. Haider, K. Mereiter, and R. Wanko, *Heterocycles*, 1995, **41**, 1445 (1995).
2. M. Hagiwara, T. Endo, T. Kanayama, and H. Hidaka, *J. Pharmacol. Exp. Ther.*, 1984, **228**, 467; *Chem. Abstr.*, 1984, **100**, 150783.
3. K. J. Murray, *Drug News and Perspectives*, 1993, **6**, 150, and references cited therein.
4. M. Yamaguchi, K. Kamei, T. Koga, M. Akima, T. Kuroki, and N. Ohi, *J. Med. Chem.*, 1993, **36**, 4052.
5. A. Kleemann and J. Engel, *"Pharmazeutische Wirkstoffe - Synthesen - Patente - Anwendungen"*, Vol. 5, Thieme, Stuttgart, 1982.
6. K. Ueno, R. Moroi, M. Kitagawa, K. Asano, and S. Miyazaki, *Chem. Pharm. Bull.*, 1976, **24**, 1068.
7. G. Scheffler, J. Engel, B. Kutscher, W. S. Sheldrick, and P. Bell, *Arch. Pharm.*, 1988, **321**, 205.
8. *Drugs of the Future*, 1987, **12**, 347, and references cited therein.
9. *Drug Data Report*, 1991, **13**, 495, and references cited therein.
10. For instance, cf. Y. Eguchi, F. Sasaki, Y. Takashima, M. Nakajima, and M. Ishikawa, *Chem. Pharm. Bull.*, 1991, **39**, 795; A. Sugimoto, S. Ito, Y. Eguchi, H. Tanaka, Y. Takashima, and M. Ishikawa, *Eur. J. Med. Chem.*, 1984, **19**, 223; A. Sugimoto, H. Tanaka, Y. Eguchi, S. Ito, Y. Takashima, and M. Ishikawa, *J. Med. Chem.*, 1984, **27**, 1300; S. Cherkez, J. Herzig, and H. Yellin, *J. Med. Chem.*, 1986, **29**, 947.

11. It is of interest to note that phthalazin-1(2*H*)-one derivatives have also been obtained by Diels-Alder reactions of electron-deficient pyridazin-1(2*H*)-ones as dienophiles with 2,3-dimethyl-1,3-butadiene as a diene: P. Mátyus, K. Fuji, and K. Tanaka, *Heterocycles*, 1993, **36**, 1975; V. Dal Piaz, M. P. Giovannoni, G. Ciciani, D. Giomi, and R. Nesi, *Tetrahedron Lett.*, 1993, **34**, 161.
12. N. Haider, *Tetrahedron*, 1991, **47**, 3959.
13. N. Haider and C. Loll, *J. Heterocycl. Chem.*, 1994, **31**, 357.
14. G. Heinisch and I. Kirchner, *Monatsh. Chem.*, 1979, **110**, 365.
15. For an efficient method for the preparation of the intermediate 5-aroyl-4-pyridazinecarboxylic acids, cf. G. Heinisch, I. Kirchner, I. Kurzmann, G. Lötsch, and R. Waglechner, *Arch. Pharm.*, 1983, **316**, 508.
16. The calculated LUMO energy for pyridazino[4,5-*d*]pyridazine is -1.591 eV. For the hydroxy tautomers of the pyridazino[4,5-*d*]pyridazin-1(2*H*)-ones (**1**), the LUMO energies are -1.445 eV (**1a**) and -1.510 eV (**1b**), respectively; in the case of the oxo tautomers, the LUMO+1 orbitals are the relevant ones (-1.061 eV for **1a**, -1.069 eV for **1b**), as indicated by the corresponding orbital coefficients at C-5 and C-8. All semiempirical calculations were performed using the AM1 Hamiltonian[17] as implemented in the AMPAC program package.[18]
17. M. J. S. Dewar, E. G. Zoebisch, E. F. Healy, and J. J. P. Stewart, *J. Am. Chem. Soc.*, 1985, **107**, 3902.
18. AMPAC 5.0, © 1994 Semichem, 7128 Summit, Shawnee, KS 66216, USA.
19. N. Haider, *Tetrahedron*, 1992, **48**, 7173.
20. D. L. Boger and J. S. Panek, *J. Org. Chem.*, 1981, **46**, 2179.
21. M. E. Kuehne, *J. Am. Chem. Soc.*, 1959, **81**, 5400.
22. G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Am. Chem. Soc.*, 1963, **85**, 207.
23. S. Chimichi and R. Nesi, *J. Chem. Soc., Perkin Trans. 1*, 1979, 2215.
24. The following ^{1}H-nmr signals of **7b** are sufficiently separated from those of the isomer (**6b**) (300 MHz, DMSO-d_6) δ: 7.43 (*s*, 1 H, H-5), 2.80 (*q*, J = 7.5 Hz, 2 H, CH_2), 1.26 (*t*, J = 7.5 Hz, 3 H, CH_3).

Received, 16th June, 1995