PYRIDAZINE DERIVATIVES, IX. SYNTHESIS OF 2H-PYRIDAZIN-3-ONES WITH AROYLPIPERAZINYL GROUPS

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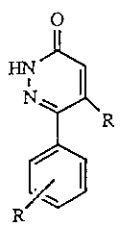
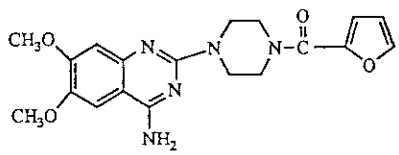
Abstract -Several 2H-pyridazin-3-ones with phenyl- or 2-furoylpiperazinyl group, have been prepared. 6-Phenyl-5-(N^4-aroyl-N^1-piperazinyl)-2H-pyridazin-3-ones were obtained by nucleophilic substitution of the chlorine atom of 6-phenyl-5-chloro-2H-pyridazin-3-one or alternatively, by aroylation of N^1-piperazinyl-2H-pyridazin-3-one. Also, 6-phenyl-5-(N^4-aroyl-N^1-piperazinylmethyl)-2H-pyridazin-3-ones were prepared by displacement of the bromine in 6-phenyl-5-bromomethyl-2H-pyridazin-3-one.

It is known that a series of 2H-pyridazin-3-ones of general formula I have antihypertensive properties[1,2] experiments with a relatively large number of structural variations have shown that the substitution at position 5 (e.g. 5-CH_3) is favourable to these properties.[1] It has also been noted that there is an N-aroylpiperazine moiety in several drugs acting on the cardiovascular system including the α_1-adrenergic blocker prazosin (II), and its benzothiadiazine analogue[3] (III), losulazine[4] (IV), and vesnarinone[5] (V).



I



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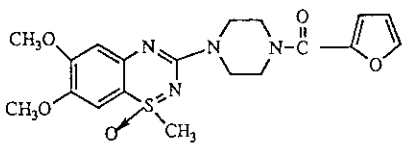

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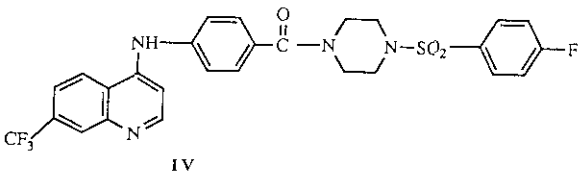

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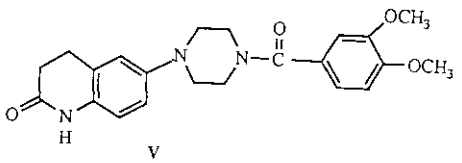
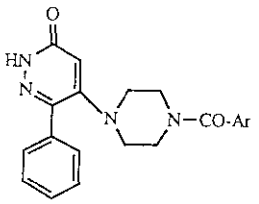
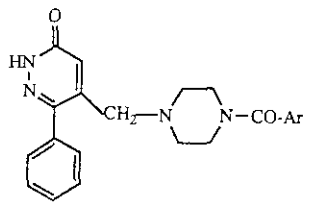


V

As a continuation of our previous papers[6] on the chemistry and pharmacology of pyridazines we describe here the synthesis of **VIa,b** and **VIIa,b** which have this pharmacophore.



VIa,b



VIIa,b

a: Ar= 

b: Ar= 

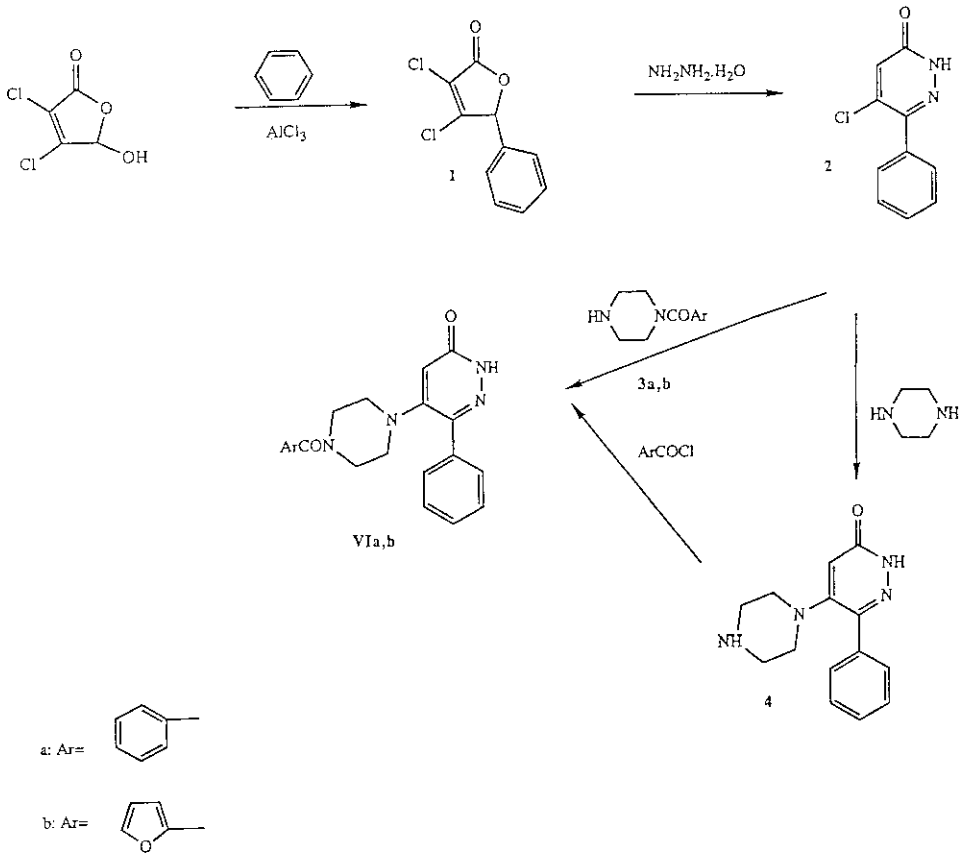
6-Phenyl-5-(N^4-aroyl-N^1-piperazinyl)-2H-pyridazin-3-ones (**VI**) were prepared following the Scheme I. Alkylation of benzene with mucochloric acid by a Friedel-Crafts reaction according to Ettel et al.[7] gave γ-phenyl-α,ß-dichloro-$\Delta^{\alpha,\beta}$-crotonolactone (1), which upon treatment with hydrazine afforded 6-phenyl-5-chloro-2H-pyridazin-3-one[8] (2). Nucleophilic substitution of the halogen atom in **2** with benzoyl- and furoylpiperazines produced the final products (**VIa,b**), but only in yields of less than 15% (method A). However yields of 50% were achieved by aroylation of N^1-piperazinyl-2H-pyridazin-3-one (**4**), obtained by nucleophilic displacement of **2** with a large excess of piperazine.

6-Phenyl-5-(N^4-aroyl-N^1-piperazinylmethyl)-2H-pyridazin-3-ones (**VIIa,b**) were likewise prepared from ß-benzoylpropionic acid as shown in Scheme II.

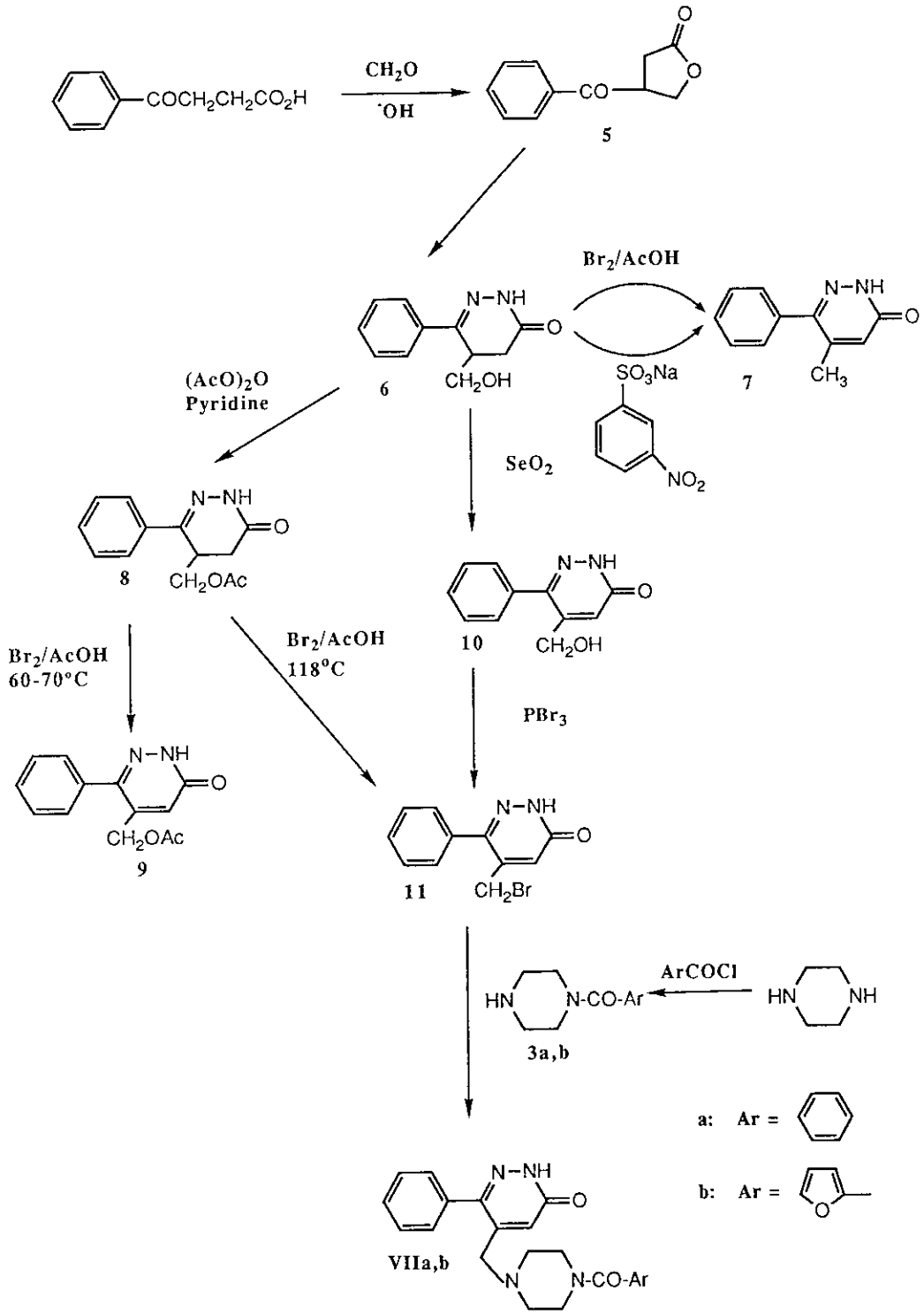
Treatment of ß-benzoyl-γ-butyrolactone[9] with a large excess of hydrazine hydrate gave 6-phenyl-5-hydroxymethyl-4,5-dihydro-2H-pyridazin-3-one[10] (**6**). Attempted dehydrogenation of this compound with bromine in acetic acid or with the sodium salt of m-nitrobenzenesulphonic acid invariably afforded the methyl derivative (**7**). However, the acetyl derivative (**8**) on treatment with bromine acetic acid at 60-70°C gave the derivative (**9**); if the temperature of the reaction was raised to 118°C the compound obtained was the bromomethylpyridazinone (**11**), which was also obtained by dehydrogenation of **6** with selenium dioxide and subsequent phosphorus tribromide treatment of the resulting hydroxymethyl-2H-pyridazin-3-one (**10**). The structure of **10** was confirmed from the analytical and spectral data. The ^{1}H-nmr spectrum of **10** ($CDCl_3$/TFA) exhibits a doublet at δ 7.69 (1H, J=1.3 Hz, CH-CO), a multiplet at δ 7.56-7.53 (3H, m- and p-Ph), a multiplet at δ 7.40-7.36 (2H, o-Ph) and a doublet at δ 4.71 (2H, J=1.3 Hz, CH_2OH).

Finally, replacement of the bromine atom in 11 with benzoyl- and furoylpiperazines gave the final products (VIIa,b) in good yield (94 and 87%, respectively).

Scheme I



Scheme II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CH2O
·OH
CO
O
5
Br2/AcOH
N–NH
O
CH2OH
6
SO3Na
NO2
7
CH3
(AcO)2O
Pyridine
SeO2
8
CH2OAc
10
Br2/AcOH
60-70°C
Br2/AcOH
118°C
PBr3
9
11
CH2Br
ArCOCl
HN
N-CO-Ar
NH
3a,b
a: Ar =
b: Ar =
VIIa,b

EXPERIMENTAL PART

Melting points were measured on a Gallemkamp melting point apparatus and are uncorrected. The ir spectra were recorded on a Perkin-Elmer 681 spectrophotometer (KBr discs and NaCl film, ν max in cm^{-1}). The ^{1}H-nmr spectra were obtained with a Brucker WM (250 MHz) spectrometer using TMS as internal standard (chemical shifts in δ values, J in Hz). Microanalyses were determined with a Perkin-Elmer 240B instrument (C, H, N).

N^1-Furoyl- and N^1-benzoylpiperazine were prepared by acylation of anhydrous piperazine following the procedures described by Althuis et al.[11] and Desai et al.,[12] respectively.

α,ß-Dichloro-γ-phenyl-Δ^{α,ß}-crotonolactone (1)

Mucochloric acid (66 g, 0.40 mol) was slowly added with stirring to a mixture of 320 ml (3.6 mol) of benzene and 80 g (0.06 mol) of $AlCl_3$. After the addition was completed, the stirring was continued for 3 h at room temperature. After addition of 606 g of ice and 128 ml of conc. HCl, the resulting mixture was extracted with benzene. The extract was dried (Na_2SO_4) and concentrated in vacuo to afford a crystalline solid which was filtered out and recrystallized from methanol, mp 79-81°C, lit.[7] mp 80°C, yield 65 g (73%). Ir: 1760 (CO lactonic); 1600 (C=C aromatics). ^{1}H-Nmr (DMSO): 7.45 (m, 5H, Ph); 6.38 (s, 1H, Ar-CH-).

5-Chloro-6-phenyl-2H-pyridazin-3-one (2)

This compound was prepared according to Dury[8] by reaction of 1 (23.3 g, 0.10 mol) with 80% hydrazine hydrate (8.13 ml, 0.16 mol), yield 14 g (67%), mp 230-231°C, lit.[8] 230°C. Ir (KBr): 3200-3000 (NH); 1700-1680 (CO). ^{1}H-Nmr (DMSO): 7.39 (m, 5H, Ph); 7.29 (s, 1H, H^4 pyridazinone); 8.31 (br s,1H, NH deuterium oxide exchangeable). Anal. Calcd for $C_{10}H_7N_2OCl$: C 58.11; H 3.39; N 13.56. Found: C 58.01; H 3.32; N 13.37.

6-Phenyl-5(N^1-piperazinyl)-2H-pyridazin-3-one (4)

A suspension of 3.76 g (0.018 mol) of 2 and 9.29 (0.11 mol) of anhydrous piperazine in 16 ml of butanol was refluxed for 16 h and then cooled to obtain a solid which was filtered out, washed with water, and recrystallized from isopropanol to give 4, mp 264-267°C. The filtrate was evaporated and the resulting was solid washed with water, giving a second crop of 4. Total 2.9 g (63%). Ir (KBr): 3240 (NH amine); 1660 (CO pyridazinone); 1590 (C=C aromatics). ^{1}H-Nmr ($CDCl_3$/TFA): 7.60 (m, 5H, Ph); 6.86 (s, 1H, pyridazine); 3.36 (m, 8H, $(CH_2)_2$-NH, $(CH_2)_2$-N). Anal. Calcd for $C_{14}H_{16}N_4O$: C 65.60; H 6.29; N 21.88. Found: C 65.30; H 6.39; N 22.12.

6-Phenyl-5-(N^4-benzoyl-N^1-piperazinyl)-2H-pyridazin-3-one (VIa)

Method A

A solution of 3.13 g (0.015 mol) of 2 in 12 ml of butanol was added to 5.7 g (0.03 mol) of 3a in 25 ml of butanol, and the resulting solution was refluxed for 33 h. After cooling, the precipitate formed was filtered out, washed with water and purified by silica gel column chromatography with ethyl acetate as eluent to give a yellow solid that was recrystallized from ethanol-ethyl acetate, mp 248-250°C. A small second crop was obtained by concentration of the filtrate and subsequent purification as above. Yield, 3 g (16%). Ir (KBr): 1670 (CO pyridazinone); 1600 (C=C aromatics). ^{1}H-Nmr ($CDCl_3$): 11.47 (s, 1H, NH deuterium oxide exchangeable); 7.67 (m, 2H, *o*-Ph-C=N-); 7.41 (m, 8H, Ph-CO, *m*, *p*-Ph-C=N-); 6.26 (s, 1H, pyridazine); 3.80-3.30 (2 m, 4H, $(CH_2)_2$-N-CO); 3.05-2.70 (m, 4H, $(CH_2)_2$-N-C=CH-). Anal. Calcd for $C_{21}H_{20}N_4O_2$: C 69.98; H 5.59; N 15.55. Found: C 69.75; H 5.73; N 15.23.

Method B

To a solution of 0.44 g (1.7 mmol) of 4 and 0.27 ml (0.2 g, 2 mmol) of triethylamine in 12 ml of DMF was slowly added under stirring, 0.23 ml (0.28 g, 2 mmol) of benzoyl chloride. After the addition was completed, the resulting solution was heated at 140°C for 3 h. After cooling, the triethylamine hydrochloride was filtered out and the filtrate was evaporated under reduced presure to give 0.38 g (62%) of VIa, mp 245-247°C (isopropanol).

6-Phenyl-5-(N^4-(2-furoyl)-N^1-piperazinyl)-2H-pyridazin-3-one (VIb)

This compound was obtained by the similar procedures as VIa in 14% (method A) and 65% (method B) yield, mp 141-143°C. Ir (KBr): 1640 (CO pyridazinone); 1620 (CO amide); 1590 (C=C aromatics). ^{1}H-Nmr ($CDCl_3$): 9.02 (s, 1H, NH deuterium oxide exchangeable); 7.69 (m, 2H, *o*-Ph-C=N); 7.45 (m, 4H, H^5 furan, *m*, *p*-Ph-C=N-); 7.03 (dd, J=3.5 and 0.5 Hz, 1H, H^3 furan); 6.47 (dd, J=3.5 and 1.8 Hz, 1H, H^4 furan); 6.25 (s, 1H, =CH-CO); 3.73 (m, 4H, $(CH_2)_2$-N-CO); 2.95 (m, 4H, $(CH_2)_2$-N-C=CH). Anal. Calcd for $C_{19}H_{18}N_4O_3$: C 65.13; H 5.15; N 15,99. Found: C 65.28; H 5.01; N 16,24.

6-Phenyl-5-hydroxymethyl-4,5-dihydro-2H-pyridazin-3-one (6)

This compound was prepared by reaction of ß-benzoyl-γ-butyrolactone[9] with hydrazine hydrate according to a previously described procedure,[10] mp 166-168°C, lit.[10] 160-163°C. Ir (KBr): 3180-3050 (NH); 1650 (CO). ^{1}H-Nmr ($CDCl_3$/TFA): 7.73 (m, 2H, o-Ph); 7.48 (m, 3H, p-, m-Ph); 3.88 (m, 2H, CH_2-OH); 3.62 (m, 1H, CH); 2.95 (m, 2H, CH_2-CO).

6-Phenyl-5-methyl-2H-pyridazin-3-one (7)

A solution of 1.04 ml (18 mmol) of bromine in 10 ml of glacial acetic acid was dropped into 3.67 g (18 mmol) of 6 in 25 ml of the same solvent and the mixture was warmed for 3 h at 60-70°C. After cooling the reaction mixture was poured into ice-water. The white precipitated solid was filtered out and treated with 25% ammonium hydroxide to give 7 (yield 2.3 g, 70%), mp 218-219°C, lit.[13] 218-220°C. Ir (KBr): 3150-2900 (NH); 1650 (CO); 1570-1510 (C=C aromatics). ^{1}H-Nmr ($CDCl_3$): 8.40 (br s, 1H, NH deuterium oxide exchangeable); 7.40 (m, 5H, Ph); 6.86 (d, J=1.2 Hz, 1H, CH-CO); 2.19 (d, J=1.2 Hz, 3H, CH_3).

6-Phenyl-5-hydroxymethyl-4,5-dihydro-2H-pyridazin-3-one acetate (8)

To a solution of 3.64 g (18 mmol) of 6 in 10 ml of dry pyridine was added 3.4 ml (36 mmol) of acetic anhydride. The resulting mixture was left at room temperature for 12 h and then poured into ice-water (50 g). The white precipitate formed was filtered out and recrystallized from ethanol. Quantitative yield (4.42 g), mp 126-128°C. Ir (KBr): 3200-2900 (NH); 1720 (CO ester); 1660 (CO pyridazinone). ^{1}H-Nmr ($CDCl_3$): 8.86 (br s, 1H, NH deuterium oxide exchangeable); 7.82-7.77 (m, 2H, o-Ph); 7.46-7.44 (m, 3H, p-, m-Ph); 4.33 (dd, J=11.3 and 5.3 Hz, 1H, HCH-O-Ac); 4.06 (dd, J=11.3 and 8.5 Hz, 1H, HCH-O-Ac); 3.75-3.61 (m, 1H, CH); 2.85 (m, 2H, CH_2-CO-NH); 2.02 (s, 3H, CH_3). Anal. Calcd for $C_{13}H_{14}N_2O$: C 63.39; H 5.73; N 11.36. Found: C 63.70; H 5.49; N 11.12.

6-Phenyl-5-hydroxymethyl-2H-pyridazin-3-one acetate (9)

This was prepared from 8 by dehydrogenation with bromine in glacial acetic acid following a procedure similar to that described for 7. Yield 75%, mp 129-132°C (isopropanol). Ir (KBr): 1720 (CO ester); 1660 (CO pyridazinone); 1580 (C=C aromatics). ^{1}H-Nmr ($CDCl_3$): 7.49-7.39 (m, 5H, Ph); 7.06 (d, J=1.2 Hz, 1H, CH-CO); 4.91 (d, J=1.2 Hz, 2H, CH_2-OAc); 2.12 (s, 3H, CH_3). Anal. Calcd for $C_{13}H_{12}N_2O_3$: C 63.92; H 4.95; N 11.47. Found: C 63.38; H 5.01; N 11.37.

6-Phenyl-5-hydroxymethyl-2H-pyridazin-3-one, (10)

A suspension of 1.02 g (5 mmol) of 6 and 1.76 g (15 mmol) of selenium dioxide in 30 ml of ethanol was refluxed with stirring for 1 h. After cooling, the black precipitate formed was removed by

filtration and the filtrate was evaporated in vacuo. The oily residue obtained was treated with 20% potassium carbonate to give a 1:3 mixture of 7 and 10. Recrystallization from isopropanol yielded 0.58 g (57%) of 10, mp 198-201°C. Ir (KBr): 3200-2900 (NH); 1650 (CO); 1590 (C=C aromatics). ^{1}H-Nmr ($CDCl_3$/TFA): 7.69 (d, J=1.3 Hz, 1H, CH-CO); 7.56-7.53 (m, 3H, p-, m-Ph); 7.40-7.36 (m, 2H, o-Ph); 4.71 (d, J=1.3 Hz, 2H, CH_2-OH); Anal. Calcd for $C_{11}H_{10}N_2O_2$: C 63.33; H 4.98; N 13.86. Found: C 63.68; H 5.04; N 13.98.

6-Phenyl-5-bromomethyl-2H-pyridazin-3-one (11)

To an ice cooled solution of 2.02 g (10 mmol) of 6-phenyl-5-hydroxymethyl-2H-pyridazin-3-one (10) in 50 ml of dry ether was slowly added 3.25 g (12 mmol) of phosphorous tribromide in 50 ml of dry ether. After stirring for 2 h at room temperature, the resulting mixture was poured into ice and made alkalin with diluted ammonium hydroxide under stirring. The ether layer was washed with water and dried (Na_2SO_4), and the solvent was evaporated in vacuo to afford 2.1 g (80%) of a white solid, mp 181-184°C (isopropanol). Ir (KBr): 2850 (NH); 1660 (CO); 1600 (C=C aromáticos). ^{1}H-Nmr ($CDCl_3$): 7.58-7.48 (m, 6H, aromatics); 4.29 (s, 2H, CH_2-Ar); Anal. Calcd for $C_{11}H_9N_2OBr$: C 49.80; H 3.39; N 10.56. Found: C 50.22; H 3.35; N 10.64.

11 was also abtained from 8 by aromatization with bromine in glacial acetic acid at 118°C for 5 h using a procedure similar to that described above for the preparation of 9 (yield 38%), mp 182-185°C.

6-Phenyl-5(N^4-benzoyl-N^1-piperazinylmethyl)-2H-pyridazin-3-one (VIIa)

To a solution of 1.3 g (6.8 mmol) of N-benzoylpiperazine in 10 ml of methanol was added 0.9 g (3.4 mmol) of 11 in 10 ml of methanol. After stirring for 12 h at room temperature, the solvent was evaporated in vacuo and the white solid residue was treated with water under stirring. The resulting mixture was extracted twice with dichloromethane, and the organic extracts were dried (Na_2SO_4) and the solvent was evaporated in vacuo to give 1.2 g (94%) of VIIa as an oily residue which crystallize on standing mp 190-192°C (EtOH). Ir (NaCl): 3150-2900 (NH); 1660 (CO pyridazinone); 1620 (CO benzoylpiperazine); 1600 (C=C aromatics). ^{1}H-Nmr ($CDCl_3$): 7.42 (m, 5H, Ph); 7.37 (m, 5H, Ph-CO); 7.18 (s, 1H, pyridazine); 3.72 (m, 2H, $(H_{eq}CH)_2NCO$); 3.37 (m, 2H, $(HCH_{ax})_2NCO$); 3.30 (s, 2H, CH_2-pyridazine); 2.40 (m, 4H, $(CH_2)_2NCH_2$). Chlorohydrate mp 185-187°C (ethanol/ether), Anal. Calcd for $C_{22}H_{23}N_4O_2Cl$: C 64.31; H 5.60; N 13.64. Found: C 64.10; H 5.78; N 13.80.

Picrate mp 153-153°C (ethanol).

6-Phenyl-5(N^4-(2-furoyl)-N^1-piperazinylmethyl)-2H-pyridazin-3-one (VIIb) was prepared similarly. Yield 87%, picrate, mp 80-83°C (ethanol). Chlorohydrate mp 191-193°C (recrystallized from ethanol/ether). ^{1}H-Nmr ($CDCl_3$): 7.48 (m, 1H, H^5 furan); 7.40 (m, 5H, Ph); 7.18 (s, 1H, pyridazine); 6.68 (m, 1H, H^3 furan); 6.49 (m, 1H, H^4 furan); 3.75 (m, 4H, $(CH_2)_2$-N-CO); 3.28 (s, 2H, CH_2-pyridazine); 2.42 (m, 4H, $(CH_2)_2$-N-CH_2); Anal. Calcd for $C_{20}H_{21}N_4O_3Cl$: C 59.92; H 5.24; N 13.98. Found: C 59.71; H 5.51; N 13.69.

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