Pyridazino[3,4-*b*]quinoxalines and Their Reduced Derivatives. Preparation and Structure

Joseph Armand, Yvette Armand and Line Boulares

Laboratoire de Physicochimie des Solutions, E.N.S.C.P.,
11 Rue Pierre et Marie Curie, 75231 Paris Cedex 05, France

Christian Bellec

Laboratoire de Chimie des Hétérocycles, Université Pierre et Marie Curie,
4, Place Jussieu, 75230 Paris Cedex 05, France

Jean Pinson

Laboratoire d'Electrochimie, Université Paris VII,
2, Place Jussieu, 75231 Paris Cedex 05, France

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The reaction of *o*-phenylenediamine with a β-ketoacid, leads in most cases to quinoxalinones. Their structure has been determined as well as that of their corresponding hydrazones. The reaction of hydrazine with these quinoxalinones gives dihydropyridazino[3,4-*b*]quinoxalines, the structure of which has been ascertained. It has been shown that among the six possible formulas, the only 1,2-dihydro structure fits with the spectroscopic data. On the contrary, *N*-substituted *o*-phenylenediamines lead to 2,10-dihydro derivatives. The electrochemical behavior of the 2,10-dihydro-10-methyl-3-phenylpyridazino[3,4-*b*]quinoxaline has been investigated. It has also been shown that the 3,4,6-trichloropyridazine reacts with *o*-phenylenediamines to give 5,10-dihydropyridazino[3,4-*b*]quinoxalines. These compounds can be oxidized to give the new heterocycle pyridazino[3,4-*b*]quinoxaline.

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Although no pyridazino[3,4-*b*]quinoxaline has ever been described, the dihydropyridazino[3,4-*b*]quinoxalines which evidence a tuberculostatic activity have been dealt with in several papers [1-7]. The aim of the authors is to find a riboflavin antagonist. Riboflavin is a major growth material for many microorganisms. Worthwhile routes for the synthesis of these antagonists are both synthesis in which the geometry of the riboflavin molecule is maximally retained and ways by which the molecule is deeply changed for example by substitution of the pyrimidine ring by a pyridazine ring. This corresponds to pyridazino-[3,4-*b*]quinoxalines.

The structure of the dihydro compounds has not been established with certainty, although it is clearly of some importance in relation to the interesting pharmacological activity of these derivatives. This paper aims at determining the structure of the different dihydro compounds and describes the preparation of pyridazino[3,4-*b*]quinoxalines.

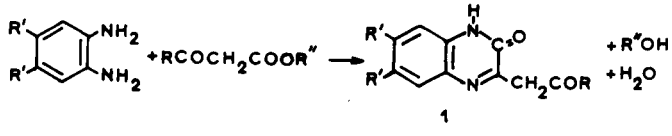
1,2-Dihydropyridazino[3,4-*b*]quinoxalines (**3**).

The first dihydropyidazino[3,4-*b*]quinoxaline has been prepared by Bodforss [1] by reaction of 2-phenacylquinoxalin-3-one (**1a**) with hydrazine. The same procedure has been applied later on to other quinoxalinones [2,3,4].

In order to obtain more characteristic nmr spectra, quinoxalinones with methyl groups on the 6- and 7-positions have been utilized. The cyclization with hydrazine leads to dihydropyridazino[3,4-*b*]quinoxalines with methyl groups on the 7- and 8-positions as in the case of flavins.

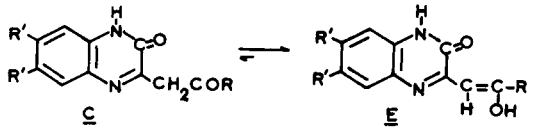
Structure of Quinoxalinones **1**.

The general preparation of these compounds involves the condensation of an *o*-phenylenediamine with a β-ketoacid or with a β-ketoester [1,2,3] and references therein.



1

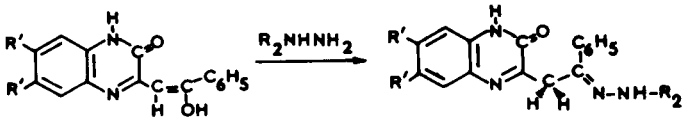
In solution, these quinoxalinones overwhelmingly exist in the enol form **E** (no ketonic form can be detected).



Thus, for **1a** and **1b**, no signal is observed for -CH_2-CO- between 3.5 and 4.5 ppm, while a one proton singlet is observed at 6.80 ppm (**1a**) and 5.98 ppm (**1b**) for -C*H*=C(OH)- (Table 1).

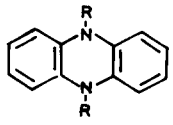
Hydrazones.

In ethanol, the reaction of hydrazines R_2NH-NH_2 with quinoxalinones leads to an hydrazone **2** as shown below in the case of **1a** with hydrazine and **1c** with methylhydrazine.

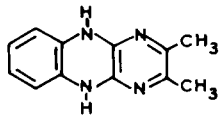


1a : R' = H
1c : R' = CH_3

2a : R' = R_2 = H
2c : R' = R_2 = CH_3



R = alkyl 4



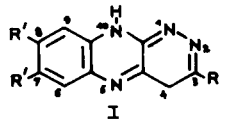
5

The nmr spectra of **2a** and **2c** show that, in solution, these compounds exist as hydrazone (the ene-hydrazine form cannot be detected). Besides, the two protons of the methylene group are non-equivalent. Two doublets are observed which could be due to a restricted rotation of the side chain.

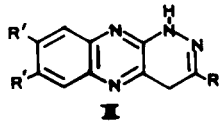
Structure of Dihydropyridazino[3,4-*b*]quinoxalines (**3**).

The reaction of hydrazine with quinoxalinones **1** in ethanol-acetic acid solution (or in acetic acid for **2**) leads to dihydropyridazino[3,4-*b*]quinoxalines **3** for which different structures have been proposed, although no really convincing argument has ever been given.

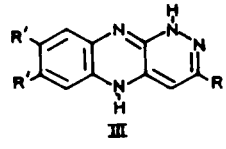
In view of the many isomers of the dihydrogenated nitrogen heterocycles dihydroquinoxalines [8], dihydropyrido[2,3-*b*]pyrazines [9], dihydropyridotriazines [10], the following structures can be anticipated:



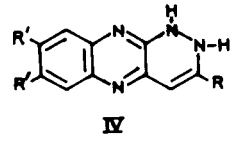
I



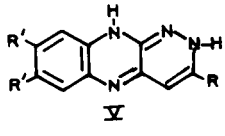
II



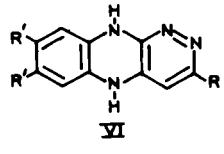
III



IV



V



VI

Let us first consider compound **3d** (R = R' = CH_3) the nmr spectrum of which is given in Table 2. A -CH_2- group would give a singlet between δ = 3 and 4 ppm; after addition of deuterium oxide no signal can be observed in this part of the spectrum, thus structures I and II can be excluded. Furthermore, the H_6 and H_9 protons being equivalent, structures III and V can be excluded. In order to discriminate between structures IV and VI, it must be remarked that IV has a quinoxaline structure while VI is similar to **4** and **5**. In the latter both of these compounds the aromatic protons give an AA'BB' pattern, between 6.06 and 6.70 ppm for **4** and between 6.1 and 6.5 ppm for **5** [11]. The values of these chemical shifts are noticeably lower than that of the protons of benzene (δ = 7.23 ppm). Indeed, in these compounds the structure of the benzene ring is similar to that of an *N,N'*-disubstituted *o*-phenylenediamine; it is well known that in a benzene ring the electronic effects of the amino groups on the *ortho* and *meta* protons amount to a shielding of several tenth of ppm, thus, the protons of *o*-phenylenediamine present a singlet at 6.70 ppm. Thus, if **3d** had structure VI it should present for H_6 and H_9 a singlet between 6 and 7 ppm; besides similar chemical shifts should be observed for H_4, H_6 and H_9 which is not the case. The benzene protons of quinoxalines lie between 7 and 8.2 ppm, the exact value depending on the nature of the substituents on the pyrazine ring. As the chemical shift of H_6 and H_9 is δ = 7.22 ppm, one can conclude that the only structure IV is in agreement with the nmr spectrum. This conclusion is reinforced by the chemical shift of the H_6 and H_9 protons of **8b** (δ = 6.24 ppm) (R = Cl, R' = CH_3) which, as we will see later on, posseses structure VI.

The same conclusion can be reached with **3b**: the benzene protons present an AA'BB' pattern with a chemical shift larger than 7 ppm and the chemical shift of H_4 is close to that of the same proton in **3d**. In the same way the benzene protons of **3a** and **3c** are situated at positions higher than 7 ppm. Thereof, it appears from the above results that the reaction of hydrazine with quinoxalinones leads most generally to 1,2-dihydro derivatives.

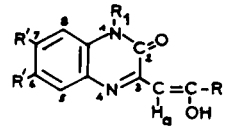
The reaction of monosubstituted hydrazines with quinoxalinones **1** leads to dihydropyridazino[3,4-*b*]quinoxalines substituted on nitrogen N_1 [6]. The authors [6] have assigned structure III to the product they obtain. We have reacted methylhydrazine with quinoxalinone **1c**. The nmr spectrum of **3f** obtained in this reaction (Table 2) is very similar to that of **3c**. In view of the similarity of the spectra and the preparations of **3c** and **3f** we propose for **3f** as for **3c** a structure of type IV. Besides, would the structure of **3f** be that given in [6] one should observe for H_6 a signal with δ < 7 ppm-in the case of quinoxalinone **1c**, H_8 close to the sp^3 hybridized N_1 presents a signal at δ < 7 ppm while H_5 close to the sp^2 hybridized N_4 is observed at δ = 7.27 ppm.

2,10-Dihydropyridazino[3,4-*b*]quinoxalines (**6**).

The reaction of an *N*-substituted *o*-phenylenediamine with a β-ketoacid or a β-ketoester leads to *N*-substituted

Table 1

NMR Data for **1a-1e**
(Solvent DMSO-d_6)

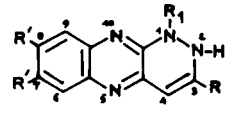


Compound	R	R′	R_1	H_a	5-H	8-H	R′	R	N-R_1	O-*H* [a]
1a	C_6H_5	H	H	6.80 (s)		7.0-8.15 (m)			11.85 [a]	13.81
1b	CH_3	H	H	5.98 (s)		6.6-7.4 (m)		2.17 (s)	11.75 [a]	12.83
1c	C_6H_5	CH_3	H	6.78 (s)	7.27 (s)	6.92 (s)	2.21 (s)	7.4-8.1 (m)	11.90 [a]	13.83
1d	CH_3	CH_3	H	5.93 (s)	7.04 (s)	6.77 (s)	2.14 (s)	2.16 (s)	11.67 [a]	12.98
1e	C_6H_5	H	CH_3	6.85 (s)		7.15-8.20 (m)			3.60 (s)	13.87

[a] Exchanged with deuterium oxide.

Table 2

NMR Data for **3a-3f**
(solvent DMSO-d_6)

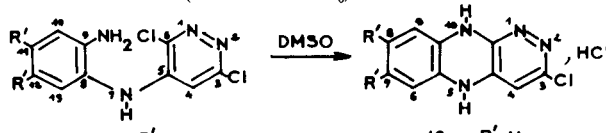


Compound	R	R′	R_1	N_1-R_1 N_2-H [a]	R	R′	6-H 9-H	4-H
3a	C_6H_5	H	H	4.1 br s (2H)		7.2-8.1 m (9H)		
3b	CH_3	H	H	4.0 br s (2H)	2.32 s (3H)	7.0-7.6 AA′BB′ pattern (4H)		6.60 s (1H)
3c	C_6H_5	CH_3	H	4.2 br s (2H)	7.2-8.1 m	2.32 s (6H)	7.2-8.1 m	
3d	CH_3	CH_3	H	4.0 br s (2H)	2.3 s (9H)		7.22 s (2H)	6.52 s (1H)
3f	C_6H_5	CH_3	CH_3	12.65 br s (1H) 4.34 s (3H)	7.2-8.0 m	2.32 s (6H)	7.2-8.0 m	

[a] Exchanged with deuterium oxide.

Table 3

NMR Data for **9a**, **9b**, **10a** and **10b**
(Solvent DMSO-d_6)



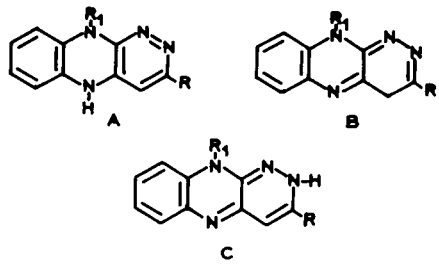
9a: R′ = H
9b: R′ = CH_3

10a: R′ = H
10b: R′ = CH_3

Compound	4-H	10-H 13-H	R′	N_7-H* [a]	NH_2* [a]	Compound	4-H	6-H 9-H	R′	N_5-H [a] N_{10}-H
9a	6.08 s (1H)	6.4-7.3 m (4H)		8.83 br s (1H)	5.2 br s (2H)	**10a**	6.05 s (1H)	6.66 s (4H)		8.01 br s (2H)
9b	6.10 s (1H)	6.68 s (1H) 6.81 s (1H)	2.10 s (3H) 2.15 s (3H)	8.67 br s (1H)	4.8 br s (2H)	**10b**	5.95 s (1H)	6.38 s (2H)	1.97 s (6H)	11.6 br s (2H)

[a] Exchanged with deuterium oxide.

quinoxalinones which react with hydrazine to give dihydropyridazino[3,4-*b*]quinoxalines, the structure of which has not yet been proved [2]. Among the three possible structures, the authors have considered **A** as the most likely on the basis of the obtention of a monoacetylated derivative, the uv spectrum and the colour.



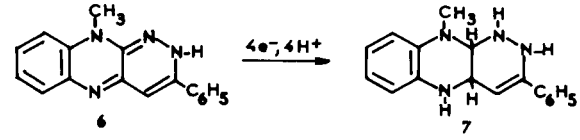
Structure.

We have prepared compound **6** and recorded its nmr spectrum. It allows us to exclude unambiguously structures **A** and **B**. Indeed, after addition of deuterium oxide, no signal can be observed between 3 and 4 ppm indicating the absence of a CH_2 group in the 4-position which rules out structure **B**. As concerns structure **A** it would be similar to that of a 5,10-dihydrophenazine with hydrogens or alkyl groups on the 5- and 10-positions. For such compounds the nmr spectrum of the benzene protons appear as a multiplet, the chemical shifts of which are always between 6 and 7 ppm. For example 5,10-bis-*n*-propyl-5,10-dihydrophenazine presents an AA'BB' pattern between 6.06 and 6.70 ppm. If **6** had structure **A** one should observe a multiplet between 6 and 7 ppm for the H_6, H_7, H_8 and H_9 protons while no signal is observed below 7.15 ppm.

Thus, only structure **C** can account for the nmr spectrum and **6** must be a 2,10-dihydro compound.

Electrochemical Reduction of 2,10-Dihydro-10-methyl-3-phenylpyridazino[3,4-*b*]quinoxaline (**6**).

In hydroorganic medium the 1,2-dihydro derivatives cannot be reduced. But **6** presents between *p*H 0 and 8 (dimethylformamide 30%) a polarographic wave which is *p*H dependent: $E_{1/2}$ (v) = −1.05-0.058 *p*H. The height of this wave is close to 4F/mole between *p*H 0 and 4; at *p*H higher than 4 this wave decreases and disappears at *p*H > 8. A preparative electrolysis at *p*H 1.60 furnishes the 1,2,4a,5,10,10a-hexahydro-10-methyl-3-phenylpyridazino-[3,4-*b*]quinoxaline (**7**).

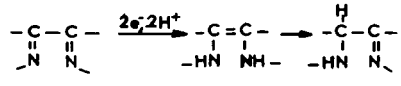


The structure of **6** is similar to that of flavines; these compounds give rise to a redox system with the 1,5-dihydrogenated compound [12]. The flavines are easily reduced, as an example the two electrons wave of riboflavin is observed at $E_{1/2}$ = −0.45 V at *p*H 7 [12].

In the case of **6** two reduction mechanisms can be thought of: either the successive reduction of two C=N double bonds, or a reduction similar to that of flavines followed by a transposition and a second reduction.

The first hypothesis is unlikely since a single polarographic wave is observed it would imply that the product obtained after reduction of the first C=N double bond be more easily reduced than the starting compound.

In the second case, the first step is analogous to the reduction of flavines, it is followed by a transposition as already observed in the case of many compounds with a -N=C-C=N- group [8,9,12] and references therein.

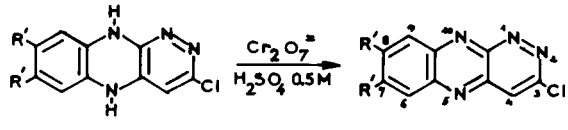


The transposed compound is then reduced to **7**. Two different transpositions are possible either a −1,5 → −1,10a or a 1,5 → −4a,5 isomerization. The first possibility is more likely as the transposed compound present a C=N double bond conjugated with a C=C double bond which is not the case of the second possible transposition.

Thereof we propose the following mechanism:

Table 4

NMR Data for **8a**, **8b**, **11a** and **11b**



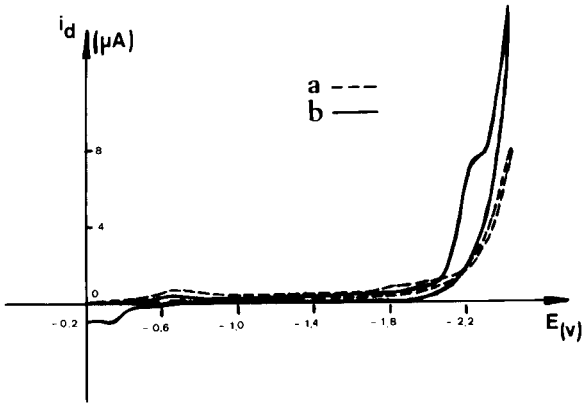
8a: R' = H
8b: R' = CH_3

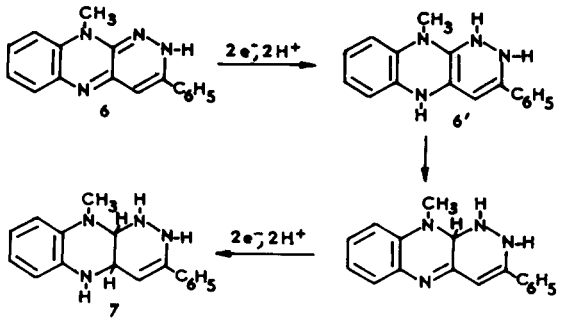
11a: R' = H
11b: R' = CH_3

Compound		4-H	6-H 9-H	R'	N_5-H N_{10}-H [c]	Compound	4-H	6-H 9-H	R'
8a	[a]	5.72 s (1H)	6.2-6.75 s (4H)		9.2 s (2H)	**11a**	8.36 s (1H)	7.6-8.3 m (4H)	
8b	[a]	5.83 s (1H)	6.24 s (2H)	1.95 s (6H)	9.9 s (2H)	**11b** [b]	8.34 s (1H)	7.98 s (1H) 8.15 s (1H)	2.63 s (6H)

[a] Solvent DMSO-d_6. [b] Solvent deuteriochloroform. [c] Exchanged with deuterium oxide.

Figure 1

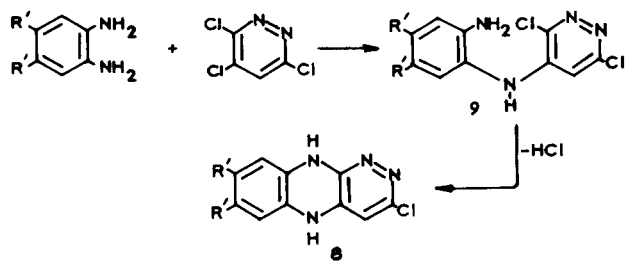




The voltammogram of **6** (Figure 1) supports this mechanism. In dimethylformamide, in the presence of phenol a voltammogram of **6** between −0,2 V and −2,4 V shows a cathodic peak at −2.20 V and an anodic peak at −0.36 V on the reverse scan. This is an agreement with the structure of **6'** similar to that of the easily oxidized 1,5-dihydrogenated flavines.

5,10-Dihydropyridazino[3,4-*b*]quinoxalines (**8**).

The reaction of 3,4,6-trichloropyridazine with *o*-phenylenediamine furnishes a dihydropyridazino[3,4-*b*]quinoxaline [5,6,7] of unproved structure. For the same reasons as above we used 4,5-dimethyl-*o*-phenylenediamine as a starting material.



The nmr spectrum of the compound obtained in this way **8b** (Table 4) clearly shows that it is a 5,10-dihydro derivative *i.e.* a structure of type VI. Indeed, H_6 and H_9 are equivalent and the chemical shift of the singlet lies between 6 and 7 ppm.

During the preparation of **8** an intermediate **9** is isolated; its structure [5] is in agreement with the nmr spectrum (Table 3). In dimethylsulfoxide this intermediate undergoes a quantitative cyclization to give **10**, the hydrochloride of **8**. This observation allows us to improve the yield of **8** starting from 3,4,6-trichloropyridazine.

Preparation of Pyridazino[3,4-*b*]quinoxalines.

We tried, without success, to oxidize the 1,2-dihydropyridazino[3,4-*b*]quinoxalines **3** either by reaction of manganese oxide in hot dimethylsulfoxide or by potassium dichromate in hot acetic acid. Negative results were also obtained by Bodforss [1] using hydrogen peroxide or potassium persulfate in order to oxidize **3c**.

On the contrary, 5,10-dihydro[3,4-*b*]quinoxalines **8** are easily oxidized into the corresponding pyridazino[3,4-*b*]-quinoxalines **11**. However, these compounds are not very stable in solution and some care must be taken during their preparation. Thus, the oxidation by manganese oxide in dichloromethane followed by filtration and evaporation of the solvent furnishes partially decomposed **11**. This last compound can be obtained through the oxidation of a suspension of **8** in sulfuric acid 0.5 *N* by sodium dichromate as described in the experimental section.

The nmr spectra of **11a** and **11b** are in agreement with the structures proposed (Table 4). In the case of **11b** the width of the singlet at 8.34 ppm is smaller than that of the singlets at 7.98 and 8.15 ppm. The irradiation of the methyl groups decreases the width of these last two singlets and the three singlets reach the same height. This shows that H_6 and H_9 undergo a long range coupling with the methyl groups and the low field signal can be assigned to H_4.

To our knowledge **11a** and **11b** are the first pyridazino-[3,4-*b*]quinoxalines to be described.

In order to obtain other more stable pyridazino[3,4-*b*]-quinoxalines we have tried but without success to replace the chlorine atom in derivatives **8**. The catalytic hydrogenation does not allow to substitute Cl by H and the reaction of phenylmagnesium bromide in the presence of $NiCl_2Ph_2P(CH_2)_3PPh_2$ does not permit to replace Cl by C_6H_5 although this method leads to an easy substitution with many halogenated heterocycles [13].

EXPERIMENTAL

Melting points are uncorrected. The ^{1}H-nmr spectra were recorded on a Bruker WH 80, a Varian A 60 and a Bruker 250 MHz spectrometer, using tetramethylsilane (TMS) as internal standard. The apparatus and techniques used for the electrochemical studies and *p*H measurements have been described previously [9]. All the potentials are referred to the

saturated calomel electrode (sce); the temperature of the solutions was 20°. The microanalyses were performed by the "Service de Microanalyse, Université Pierre et Marie Curie". The following abbreviations are used in reporting nmr results: s = singlet, d = doublet, t = triplet, q = quadruplet, m = multiplet. All the compounds described gave correct elemental analyses.

Preparation of Quinoxalinones **1**.

The quinoxalinones **1a, 1b** and **1e** were prepared by condensation of *o*-phenylenediamine or *N*-methyl-*o*-phenylenediamine in the case of **1e** with benzoylpyruvic acid or methyl acetylpyruvate according to [1] [2] and [3].

1c.

To 7.9 g of benzoylpyruvic acid in 100 ml of ethanol was added 5.6 g of 4,5-dimethyl-*o*-phenylenediamine in 100 ml of ethanol. After stirring for three hours the precipitate which appeared was filtered, washed with ethanol and ether, yield, 11.2 g (93%) mp 220° dec.

Anal. Calcd. for $C_{18}H_{16}N_2O_2$: C, 73.95; H, 5.52; N, 9.58. Found: C, 73.90; H, 5.65; N, 9.52.

1d.

To 8.5 g of methyl acetylpyruvate in 40 ml of ethanol was added 7.5 g of 4,5-dimethyl-*o*-phenylenediamine in 40 ml of ethanol. The solution was refluxed during one hour, cooled and the precipitate was filtered and washed with ethanol, 5.1 g (40%) mp 250° dec.

Anal. Calcd. for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.86; H, 6.05; N, 12.12.

Preparation of Hydrazones **2**.

The hydrazone **2a** was prepared according to [6]; ^{1}H nmr (dimethylsulfoxide-d_6): δ 3.02-3.95 (two d, CH_2, 2 × 1H, J = 18 Hz), 6.8-8.1 (m, H-5 + H-6 + H-7 + H-8 + C_6H_5, 9H), 5.05 (broad s, H-4 + NH_2, 3H).

2c.

To a suspension of 2 g of **1c** in 50 ml of ethanol were added 16 ml of methylhydrazine. The mixture was refluxed overnight. The precipitate was filtered, washed with water, ethanol and ether, 2 g (91%) mp 230°; ^{1}H nmr (dimethylsulfoxide-d_6): δ 2.06 (s, CH_3-6 + CH_3-7, 6H), 2.60 (s, CH_3-NH, 3H), 3.1 and 4.01 (2 singlets, CH_2, 2 × 1H, J = 18 Hz), 6.55 and 6.62 (2 singlets H-5 + H-8, 2 × 1H), 7.25-7.75 (m, C_6H_5, 5H), 10.7 (broad s, NH, 1H).

Anal. Calcd. for $C_{19}H_{20}N_4O$: C, 71.22; H, 6.29; N, 17.49. Found: C, 71.13; H, 6.15; N, 17.54.

Preparation of 1,2-Dihydropyridazino[3,4-*b*]quinoxalines (**3**).

The procedure used was similar to that employed by [1] and [2].

3a.

A mixture of **1a** (10 g), ethanol (140 ml), 98% hydrazine hydrate (11 g) and acetic acid (20 ml) was refluxed overnight. The mixture was then poured into 400 ml of water and the precipitate was filtered, washed with water and dried, 9.7 g (90%).

With the same procedure **1c** (11.2 g) leads to **3c**, 8.5 g (77%) mp 260° dec.

Anal. Calcd. for $C_{18}H_{16}N_4$: C, 74.97; H, 5.59; N, 19.43. Found: C, 75.06; H, 5.63; N, 19.34.

Preparation of **3b** and **3d**.

A mixture of **1b** (2.9 g), ethanol (100 ml), 98% hydrazine hydrate (4.3 ml) and acetic acid (6.8 ml) was refluxed for 18 hours. After driving off the solvent the residue was filtered, washed with 300 ml of water. Sodium bicarbonate (10 g) was added in the filtrate. The solid which precipitated was filtered, washed with cold water and dried, 900 mg (30%) mp 308°.

With the same procedure 3.3 g of **1d** gives **3d**, 1.2 g (37%), mp 290-295° dec.

Anal. Calcd. for $C_{13}H_{14}N_4$: C, 69.00; H, 6.24; N, 24.76. Found: C, 69.10; H, 6.40; N, 24.69.

Preparation of **3f**.

A mixture of the hydrazone **2c** (2 g) and 10 ml of acetic acid was refluxed for two hours and then poured into 100 ml of cold water. The precipitate was filtered, washed with water and dried, 1.6 g (85%), mp 144°.

Anal. Calcd. for $C_{14}H_{16}N_4$: C, 69.97; H, 6.71; N, 23.32. Found: C, 69.93; H, 6.84; N, 23.35.

Preparation of 2,10-Dihydro-10-methyl-3-phenylpyridazino[3,4-*b*]quinoxaline (**6**).

Compound **6** was obtained by reaction of quinoxalinone **1e** with hydrazine according to [2]; ^{1}H nmr (dimethylsulfoxide-d_6): δ 3.5 (broad s, N*H*, 1H), 4.2 (s, N-CH_3, 3H), 7.15-8.15 (m, H-4 + H-6 + H-7 + H-8 + H-9 + C_6H_5, 10H).

Electrolysis of **6**. Preparation of **7**.

An electrolysis was carried out at *p*H = 1.60 and E = −1.25 V (sce). The cathodic compartment contained 548 mg (2 × 10^{-3} mole) of **6** in 200 ml of solution (dimethylformamide 30%). After consumption of about 7 F per mole, the electrolysis was stopped. The solution was made alkaline with a solution of sodium hydroxide unto *p*H = 12 and extracted three times with 60 ml of chloroform. The organic layer was washed with water, dried over sodium sulfate and evaporated to give 210 mg (38%) of 1,2,4a,5,10,10a-hexahydro-10-methyl-3-phenylpyridazino[3,4-*b*]quinoxaline (**7**), mp 125-130° dec; ^{1}H-nmr (deuteriochloroform): δ 3.25-4.30 (m, H-1 + H-2 + H-4a + H-5 + H-10a, 5H, 3H exchanged with deuterium oxide), 4.14 (s, N-CH_3, 3H), 4.85-5.10 (m, H-4, 1H), 6.80-8.0 (m, C_6H_5 + H-6 + H-7 + H-8 + H-9, 9H).

Anal. Calcd. for $C_{17}H_{18}N_4$: C, 73.35; H, 6.52; N, 20.13. Found: C, 73.30; H, 6.65; N, 20.08.

Preparation of 5,10-Dihydropyrazino[3,4-*b*]quinoxalines **8**.

Preparation of 3,6-Dichloro-5-(*o*-aminophenylamino)pyridazine (**9a**) and of **9b**.

Compound **9a** was obtained by condensation of *o*-phenylenediamine with 3,4,6-trichloropyridazine according to [4]. Compound **9b** was similarly prepared with 15 g of 4,5-dimethyl- *o*-phenylenediamine, 20 g of 3,4,6-trichloropyridazine, 12 g of anhydrous sodium acetate and 250 ml of ethanol. We obtained 17 g (55%) of **9b**, mp 195-200° dec.

Anal. Calcd. for $C_{12}H_{12}Cl_2N_4$: C, 50.88; H, 4.24; N, 19.78; Cl, 25.09. Found: C, 50.93; H, 4.35; N, 19.83; Cl, 25.03.

Preparation of **8a** and **8b**.

One g of **9a** or **9b** was stirred in 10 ml of dimethylsulfoxide during 48 hours. The mixture was poured into a cold solution of 1 g of potassium hydrogen carbonate in 70 ml of water. The precipitate was filtered, washed with water and dried 48 hours in a stove at 80°. Compounds **8a** and **8b** were obtained in quantitative yield; **8b**: mp 270° dec.

Anal. Calcd. for $C_{12}H_{11}N_4Cl$: C, 58.42; H, 4.46; N, 22.72; Cl, 14.40. Found: C, 58.48; H, 4.61; N, 22.65; Cl, 14.47.

Preparation of Pyridazino[3,4-*b*]quinoxalines **11a** and **11b**.

A mixture of 132 mg of **8a** in fine powder and 100 mg of sodium dichromate dihydrate in 10 ml of sulfuric acid 0.5 *M* was vigorously stirred during three hours and then filtered. The solid was washed with a solution of sodium hydrogen carbonate and then with water and dried. The solid obtained was stirred with 25 ml of chloroform. The solution was filtered and the filtrate was rapidly evaporated to give 39 mg (30%) of **11a**, mp 190° dec.

Anal. Calcd. for $C_{10}H_5ClN_4$: C, 55.43; H, 2.31; N, 25.87; Cl, 16.40. Found: C, 55.39; H, 2.42; N, 25.81; Cl, 16.36.

With a same procedure 150 mg of **8b** gave 60 mg of **11b** (40%), mp 175-180° dec.

Anal. Calcd. for $C_{12}N_5ClN_4$: C, 58.89; H, 3.68; N, 22.90; Cl, 14.52. Found: C, 58.83; H, 3.80; N, 22.94; Cl, 14.61.

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