New Synthesis of 11-Acyl-5,11-dihydro-6*H*-pyrido[2,3-*b*][1,4]-benzodiazepin-6-ones and Related Studies

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New synthesis of 11-acyl-5,11-dihydro-6*H*-pyrido[2,3-*b*][1,4]benzodiazepin-6-ones (**42-44**) is reported. The crucial steps (Scheme VI) represented *N*-oxydation of **1** (**1A**) to **35** (**35A**), facilitated ring-closure of **36** into **37**, its subsequent *N*-α-chloroacetylation to **38**, aminolysis to **39-41** (involving *N-O* anchimeric assistance as depicted in **38A**) and deoxygenation to **42-44** (Scheme VII). The central intermediate **37** is also obtained on oxygenation of **2**, a new synthesis of which was reported in the previous paper of this series [3]. Other attempts of cyclisation "from the top" or "from the bottom" (Scheme I) are described. Thus, interaction of **1** with acetamide afforded **3** and **4** instead of the expected **2A**. Compound **5** cyclised into 3-pyridoquinazolone **6** while its 2-(4'-methylpiperazin-1'-yl analogue **9** was observed to be unstable for the attempted ring-opening and reclosure to **42**. "From the bottom" cyclisations of **10A-10C**, *via* intermediary amines **11A-11C** failed and pyridoquinazolinone **13** was isolated (Scheme V). The attempted oxidative cyclisation of the compounds **15** and **18** into **2** and **42**, respectively, **13** afforded imidazolo[5,4-*b*]pyridine derivative (**18** → **19**), while **15** remained unchanged. 3-Acylamino-2-arylaminopyridines (**21-24**), cyclised into imidazolopyridines **29-30**. Model compounds **45-50** were prepared to study selective aminolysis of the chlorine atoms in 2-chloro-3-(2'-chlorobenzoyl)aminopyridine **1**, and its *N*-oxide **35**.

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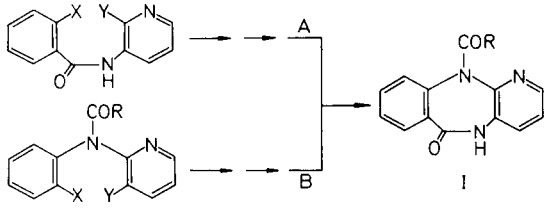
Introduction.

In the preceeding papers we described synthesis and pharmacological screening of some new 11-substituted-5,11-dihydro-6*H*-pyrido[2,3-*b*][1,4]benzodiazepin-6-ones [2] and the new synthesis of its basic tricyclic system [3]. In this paper we report the studies that resulted in another efficient synthesis of the 11-substituted derivatives.

Results and Discussion.

We examined two general variants of the 7-member ring closure in the title compounds as outlined in the Scheme I.

SCHEME I



I

We shall call the closure according to the pathway A "from the top", and the closure according to B "from the bottom"; X and Y represent any functionality that could be transformed into a diarylamino subunit already acylated or unacylated (case A) or to amide linkage or its synthetic precursor (case B).

Approach A.

The first approach was the attempted conversion of compound **1** to the *N*-11-acetyl derivative of the tricyclic compound **2A** by reacting acetamide with the two chlorinated positions of **1** (Scheme II).

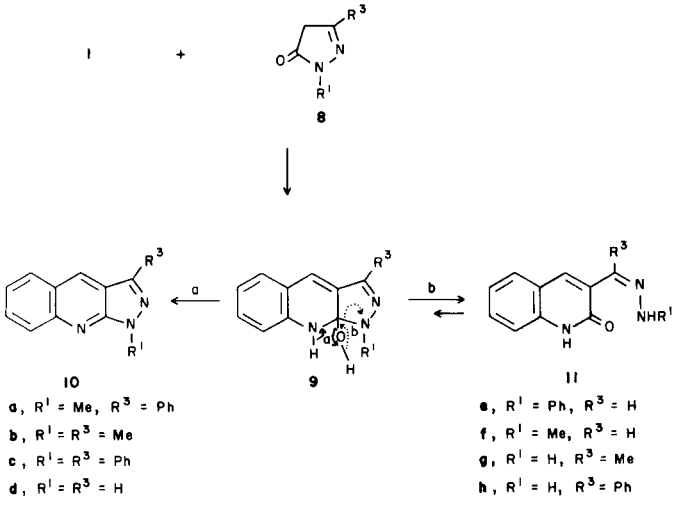
Two main products, **3** and **4** were isolated while the formation of **2A** was not observed. The reaction mixtures were monitored by tlc using pure **2A** (prepared *via* an alternate synthesis [2]) as a standard. A mechanism for the production of **3** and **4** is proposed in Scheme II.

These results revealed easy hydrolysis and amidolysis of the chlorine in the 2 position on the pyridine ring in **1**. Therefore, compound **5** was prepared which is a proposed intermediate in Scheme II and care was taken in the attempted cyclization to avoid hydrolysis of the chlorine on the pyridine ring. However, the only product observed in the cyclization reactions of **5** was the quinazolone compound **6** (Scheme III), which opened reversibly to **5** upon brief heating in hexamethylphosphoric acid triamide/potassium hydroxide. This type of ring closure of *N*-acylaminoanthranilic acid arylamides to 2-alkyl-3-arylquinazolon-4-ones is well known [4-6]. Therefore to avoid this type of ring closure (as in Scheme III) and to promote 7-member ring formation, it was decided to introduce a bulky substituent such as the *N*-acyl group which would sterically impair attack on the *N*-acyl carbonyl. To this end compound **9** was prepared *via* the intermediate compounds **7** or **8** (Scheme IV).

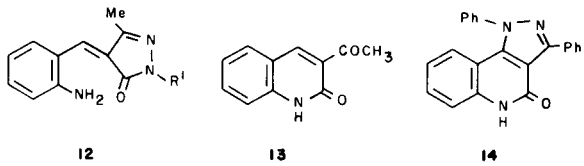
When the hydrolytic ring opening of **9** (analogous to the ring opening of **6** in Scheme III) was conducted, only decomposition products were observed. Therefore, it was not possible to ring open **9** and recyclize to form the 7-membered ring which would have given compound **42** (shown later in Scheme VII).

On the other hand, when 1-methyl-3-phenylpyrazolin-5-one (**8a**) was used the only product formed at 150° (98% yield) was 1-methyl-3-phenyl-1*H*-pyrazolo[3,4-*b*]quinoline (**10a**). No visible reaction took place between **1** and **8a** in boiling benzene. Thus, the intermediate **9** either loses water (to give **10**) (pathway *a*, Scheme 1) or undergoes ring opening (to give **11**) (pathway *b*, Scheme 1) based largely on the nature of the substituents in **8**. One would expect that

SCHEME 1



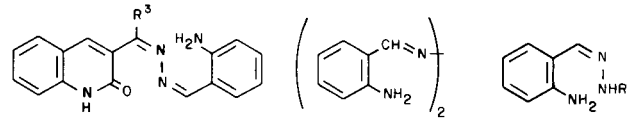
substituents on N_1 of the pyrazole ring that can delocalize a pair of electrons would favor ring opening (path *b*), while those that do not would favor dehydration (path *a*) and, to that extent, compounds **2** (N_1-Ph) and **8a** (N_1-Me) behave predictably. The substituent at C_3 of the pyrazole does play a key role, however, as indicated by the behavior of **8b** ($R^1 = R^3 = Me$) and **8c** ($R^1 = R^3 = Ph$). Thus, when **8b** ($R^1 = R^3 = Me$) and **1** were heated at 150° a good yield (70%) of the benzylidene derivative (**12**) ($R^1 = Me$) was obtained, together with a small amount (8%) of 3-acetylcarbostyril (**13**). The latter could arise from **11** ($R^1 = R^3 = Me$) during the purification process. At 260°, both paths *a* and *b* seem to be followed to about the same extent, with **10b** ($R^1 = R^3 = CH_3$) and **4** being obtained in 20% yield each. When **12** ($R^1 = Me$) was heated to 260° a quantitative yield of **10b** was formed. The substituents are thus influencing not only the rate of attack of the carbonyl group by the amino function but also the subsequent steps (paths *a* or *b*--Scheme 1). It would appear from these results as though a 3-methyl group facilitates ring-opening (path *b*) while a 3-phenyl group (as in **8a**) facilitates dehydration (path *a*), though the balance between the



substituents effects from N_1 and C_3 is not clear at all. Indeed, our subsequent experiments (particularly when $R^1 = H$ and $R^3 = Me$ *or* Ph in **8**) cast serious doubt on such a generalization.

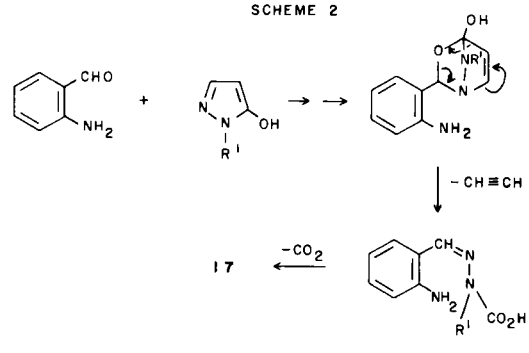
When 1,3-diphenylpyrazolin-5-one (**8c**) is heated with **1** at 200° the main product (68%) is **10c** ($R^1 = R^3 = Ph$), suggesting that the 3-Ph group is exerting the dominant electronic effect in this case. The phenylhydrazine **11c** ($R^1 = R^3 = Ph$) is obtained in only 5-7% yield and some 1,3-diphenyl-2*H*-pyrazolo[4,3-*c*]-1*H*-quinolin-2-one (**14**) (15%) was also formed. On the other hand, when the reaction is carried out at 150° only traces of **10c** were detected, the main product being **11c** (79%), together with **14** (15%). Phenylhydrazone **11c** is stable to atmospheric oxygen at room temperature for several months and at its melting point for several hours. A possible explanation for the formation of **14** is that the oxidative cyclization of **11c** (and, presumably, of **3**–**5**) is mediated by excess *o*-aminobenzaldehyde. Thus, when **11c** was heated with boiling nitrobenzene it gave **14** (82%).

1*H*-Pyrazolinone (**8d**) itself gave no pyrazolo[3,4-*b*]quinoline. Instead, *o*-aminobenzaldazine (**15a**) (10%) and 2,2'-diaminobenzaldazine (**16**) (40%) were obtained. Compound **15a** undoubtedly arises from reaction of **11d** ($R^1 = R^3 = H$) (formed by path *b*) with unchanged *o*-aminobenzaldehyde (**1**) while **16** appears to be formed from *o*-aminobenzaldehyde hydrazone (**17a**) (see below). Compound **8e**



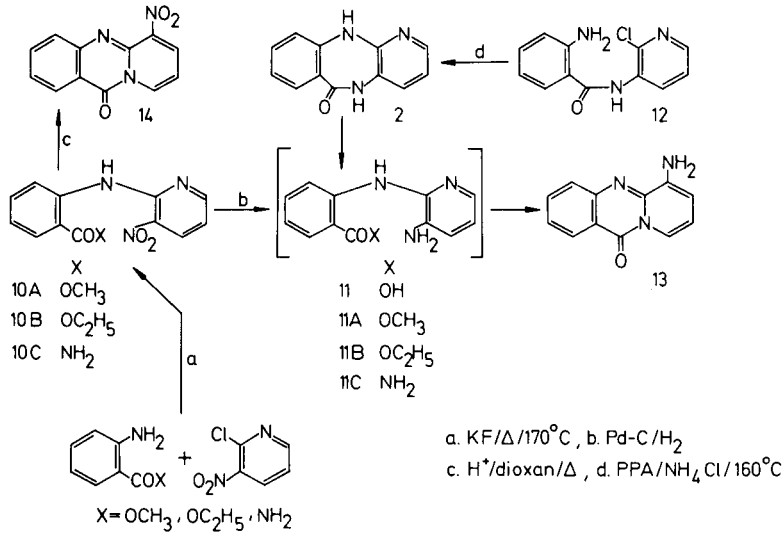
($R^1 = Ph$, $R^3 = H$), on the other hand, gave a virtually quantitative yield of *o*-aminobenzaldehyde phenylhydrazone (**17b**). Acetylene was also formed in this reaction and trapped as copper acetylide. A possible mode of formation of **17** is shown in Scheme 2 (formation of the proposed bridged (4 + 2) adduct may well be a stepwise process).

SCHEME 2



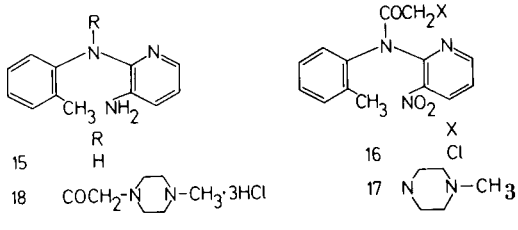
The reaction of **8f** took yet a different path, yielding a dimer of 4-*o*-aminobenzylidene-1-methylpyrazolin-5-one

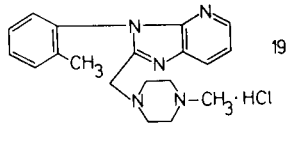
SCHEME V



compound **15** was prepared, and the cyclization was attempted into the azomethine derivative by treatment of **15** with elemental sulfur, according to a procedure by Yutilov [10]. Attempts to cyclize **15** using the Yutilov procedure at various temperatures failed. Since Yutilov succeeded in an intermolecular version of this reaction, *i.e.*, condensation of 2,3-diaminopyridine with 2,6-lutidine to give 2-(pyridyl-2')imidazo[5,4-*b*]pyridine, the failure to cyclize **15** may be due to the lower acidity of the methyl group protons in **15** compared with the methyl group protons of 2,6-lutidine.

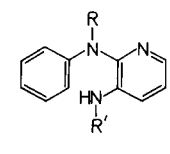
To increase the acidity of the methyl group protons of **15**, the acylated compound **18** was prepared *via* **16** and **17**. When compound **18** was heated with sulfur only the imidazopyridine derivative **19** resulted and there was no evidence of the 7-membered azomethine **42**.



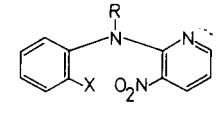


In another approach to I compounds **21** and **24** were prepared, as well as their *N*(1)-acetylated derivatives **22** and **23**. Friedel-Crafts reactions using polyphosphoric acid, boron trifluoride etherate in chloroform, aluminum trichloride, or a mixture of phosphoric acid/phosphoroxychloride were conducted. All of these reagents yielded imidazopyridine derivatives **29-31** as the main products.

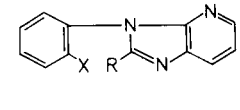
When compounds **20** and **22** were reacted with phosgene in methylene chloride, ethyl acetate, or nitromethane in the presence of aluminum chloride, intermediate isocyanates were detected on tlc analysis of the reaction mixtures. However, upon work up these isocyanates were presumed to have cyclized to **30** which was the major product of the reaction or to have decomposed into starting materials. Compound **30** was also formed by treating **24** with polyphosphoric acid.



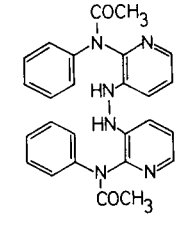
	R	R'
20	H	H
21	H	$COOC_2H_5$
22	$COCH_3$	H
23	$COCH_3$	$COOC_2H_5$
24	H	CHO



	R	X
25	H	H
26	$COCH_3$	H
27	H	Br
28	$COCH_3$	Br



	R	X
29	H	H
30	OH	H
31	CH_3	H
32	CH_3	Br



When the nitro group on compound **28** was catalytically hydrogenated, cyclization occurred and compound **32** was isolated. When the catalytic hydrogenation of **26** was conducted, the cyclization product **31** was observed, accompanied by 50% of the uncyclized compound **22** and a third product **33** which was produced in a 28% yield. The intermediate **20** was prepared by an alternate method by reacting aniline and 2-chloro-3-aminopyridine in diethylene glycol and aqueous hydrobromic acid. Compound **20** was produced in 85% yield, an improvement over the previous known method [11]. The intermediate **25** was produced in 90% yield by the method described by Bishop [12].

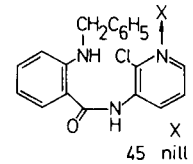
Another attempt to conduct a cyclization "from the bottom" involved compound **34** which was prepared from **27**. To close the 7-membered ring carbon monoxide was to be inserted by catalysis with palladium salt in the presence of triphenyl/*n*-tributylamine. This method was used by Ban *et al.* to cyclize 2-bromo-ω-aminoalkylbenzene [13]. However, the cyclization of **34** to give compound **2** was not observed.

It was discovered that by reacting compound **35** with aqueous ammonia/copper(I) chloride in saturated sodium chloride only the chlorine on the benzene ring was displaced to yield **36**. We employed this method in the synthesis of **12** from compound **1** in 70% yield. The sodium chloride solution seems to increase nucleophilicity of the ammonium by reducing the ammonias solvation. Previous methods explored to synthesize **12** involved the reaction of anthranilic acid and 2-chloro-3-aminopyridine. Various media (fusion above 160° without solvent, trichlorobenzene, polyphosphoric acid, polyphosphoric acid/diethylene glycol, polyphosphoric acid/40% hydrobromic acid) and a broad range of temperatures were explored. However, the highest yield (40-45%) was obtained in polyphosphoric acid at 120-140°.

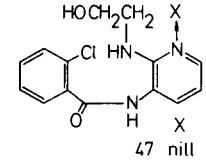
To avoid the cyclization reactions outlined in Scheme V, it was decided that the pyridine nitrogen should be protected as the *N*-oxide (Scheme VI). This approach was discovered to be the most convenient method to produce the title compound.

The *N*-oxide **35** was obtained in over 90% yield from **1**, whereby ammonolysis of the chlorine atom on the benzene ring of **35** was successfully performed in aqueous ammonia, as previously described, producing **36**. Compound **36** was then cyclized in the desired manner upon heating in the presence of acid in diethylene glycol monomethyl ether producing **37** almost quantitatively.

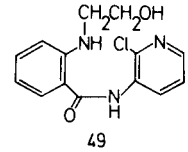
A comparative study was conducted between compounds **1** and **35** to determine their relative reactivity and selectivity to amines when copper(I) chloride is used as a catalyst. Compounds **1** and **35** react with benzylamine in the presence of copper(I) chloride to yield **45** and **46** in 74% and 82% respectively. These compounds were less reactive to cyclization. Low conversion was observed to the benzyl derivatives of **2** and **37**. In the absence of copper(I) ions, β-hydroxyethylamine reacted at 170-180° with **1** and **35** affording in both cases the 2-β-hydroxyethylaminopyridine derivatives **47** and **48**, accompanied by small quantities of the side products **49** and **50**.



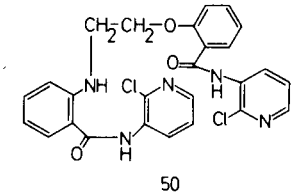
45 nill
46 O



47 nill
48 O

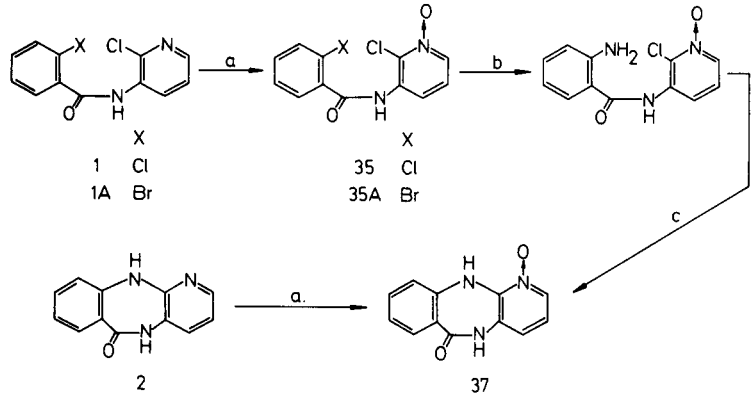


49



50

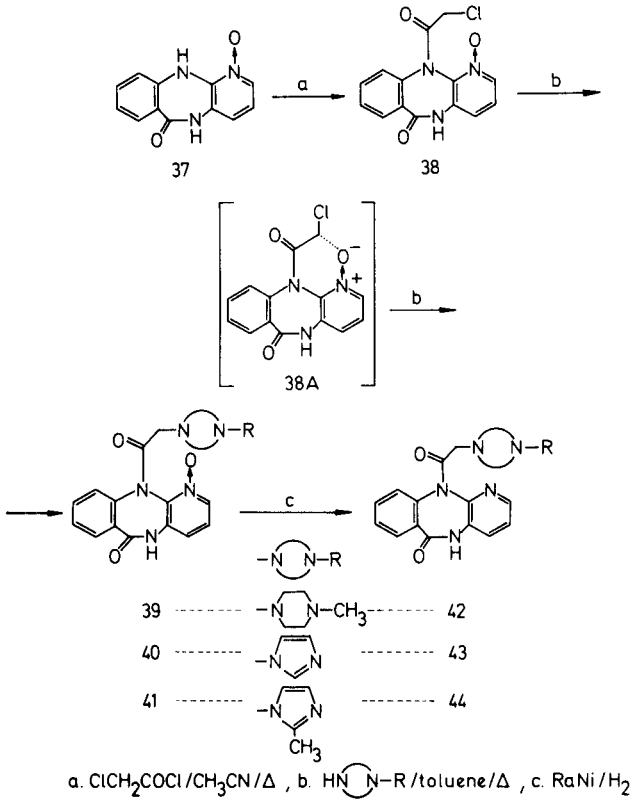
SCHEME VI



a. 40% / H_2O_2 / AcOH , b. CuCl / NH_3 conc. / NaCl / 80°, c. DEG – MM / H^+ / 100°

Compounds **37** and **38** underwent subsequent reaction steps (Scheme VII) more readily than their *N*-deoxy congeners did in the original synthesis of pirenzepin and its analogs [14]. This finding prompted the preparation of **37** by *N*-oxygenation of **2** (Scheme VI). The preparation of **2** is described in the previous paper [3]. Compound **37** was more easily acylated than compound **2** was, which may be due to perturbance of the amidinic system of **37** by the *N*-oxide moiety.

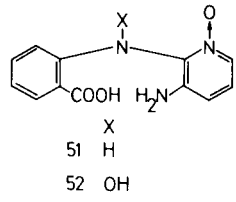
SCHEME VII

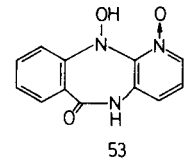


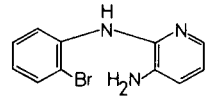
Faster aminolysis of the α-chlorine atom in **38**, than the chlorine in the compound without the *N*-oxide, which affords the α-aminoacyl derivative, is due to participation of the *N*-oxide in the reaction *via* intermediate **38A**. A closely similar finding of anchimeric assistance of an oxygen semipolar bond has recently been documented [15]. In the final step Raney-Nickel catalyzed deoxygenation of **39-41** afforded pirenzepin **42**, as well as the imidazo congeners **43** and **44**, which were studied for their anti-secretory activity [2].

Tricyclic *N*-oxides exhibit interesting behaviour under hydrolytic conditions. On heating in a biphasic system consisting of 50% aqueous potassium hydroxide and toluene the parent compound **37** gave **51**. The *N*-acylated compound **39** afforded its *N*-hydroxy congener **52**, along with the cyclic analog **53**. The latter compound is stable and easily available [16].

The structure of **53** was determined by elemental analysis, the presence of a large band at 3330-3370 cm^{-1} in the ir spectrum, additional bands at 1668 and 1606 cm^{-1} and singlets in the nmr spectrum at δ 8.88 and 10.0, respectively. Compound **52** exhibited two signals in the low field region at 8.52 (N-OH), a signal at 12.1 (COOH) and was found to be much more soluble in water and methanol than its deoxy congener **51**.







In conclusion it can be stated that the overall yield of the deoxy compounds **42-44**, according to Schemes V and VII, is about 60% which is significantly more than in the original approach to 11-acylated derivatives of 5,11-dihydro-6*H*-pyrido[2,3-*b*][1,4]benzodiazepin-6-ones. This makes our new approach interesting for large scale production of the title compounds. This paper together with the preparation of the basic tricyclic system described in our previous paper [3], represent a new route to these biologically important compounds.

EXPERIMENTAL

For the general remarks see the second paper in this series [3]. Compound **1**, **1A**, and **2** were prepared as in reference [3], compound **2A** as in reference [2].

Reaction of 3-(2'-Chlorobenzoyl)amino-2-chloropyridine (**1**) With Acetamide (Isolation of the Compounds **3** and **4**).

Compound **1** (2.69 g, 10.0 mmoles), acetamide (1.2 g, 20.0 mmoles), potassium carbonate anhydrous (1.0 g), and freshly activated copper bronze (0.2 g) were slurried in trichlorobenzene (2.0 ml), and the reaction vessel immersed into an oil bath preheated to 190°. After 5-6 minutes stirring under nitrogen, the evolution of gas (carbon dioxide) was initiated, and the reaction mixture turned from green-blue into dark-brown. After 30 minutes complete disappearance of the starting **1** was confirmed by tlc (toluene-ethyl acetate 3:1). The reaction mixture was poured into ice-water (200 ml) and extracted with ethyl acetate (3 × 100 ml). The dried organic extracts were evaporated, and the crude product mixture was fractionated on a silica gel column (250 g) using toluene-ethyl acetate (3:1) as the eluent.

2-Methyl-3-(2'-pyridon-3'-yl)quinazolin-4-one (**3**).

Compound **3** (425 mg, 18%) was obtained in the fractions 60-75 (10 ml per fraction) and crystallized from ether, **3** had mp 158-159°; the halogen test was negative; ir 3050-3300 (broad, 1705, 1635, 1610, 1592, 1530, 1435, 1405, 1370, 1300, 1268, 1242, 1220, 800, 770, 765 cm^{-1}; nmr (deuteriochloroform): 2.34 (s, 3H), 7.1-7.8 (m, 3H), 8.1 (dd, J_1 = 12 Hz, J_2 = 4 Hz, 1H), 8.3-8.6 (m, 2H), 8.88 (dd, J_1 = 10 Hz, J_2 = 2 Hz, 1H), 11.7 (broad s, 1H).

Anal. Calcd. for $C_{14}H_{11}N_3O_2$ (235.25): C, 66.39; H, 4.38; N, 16.59. Found: C, 66.35; H, 4.40; N, 16.15.

2-(2'-Chlorophenyl)imidazolo[5,4-*b*]pyridine (**4**).

In the fractions 95-118, from the same column, compound **4** (310 mg, 15%) was isolated, and was recrystallized from ethanol mp 118-120°); the halogen test was positive; ir: 1615, 1604, 1542, 1470, 1405, 1225, 1020, 915, 800, 765 cm^{-1}; nmr (deuteriochloroform): 7.4-7.9 (m, 4H), 8.0-8.7 (m, 3H).

Anal. Calcd. for $C_{12}H_8ClN_3$ (202.64): C, 62.75; H, 3.51; N, 18.29. Found: C, 62.41; H, 3.28; N, 18.65.

2-Methyl-3-(2'-chloropyrid-3'-yl)quinazolin-4-one (**6**).

2-Methylbenzoxazin-4-one (4.11 g, 30.0 mmoles) which is easily available in quantitative yield on heating of an equimolar mixture of anthranilic acid and acetic anhydride) was melted with 2-chloro-3-aminopyridine (3.58 g, 30.0 mmoles) at 140° for 2 hours. Thereafter the reaction mixture was allowed to cool to ambient temperature, the residue was dissolved in hot methanol, filtered hot with charcoal and evaporated to a small volume. Upon cooling 7.5 g (92%) of the compound **6** was obtained which on recrystallization from 2-propanol had mp 179-180°; ir: 3060, 3010, 1685, 1608, 1568, 1475, 1447, 1425, 1410, 1380, 1340, 1323, 1280, 1120, 1080, 780, 747, 700 cm^{-1}; nmr (deuteriochloroform): 2.22 (d, 3H), 7.3-8.7 (m, 7H).

Anal. Calcd. for $C_{14}H_{10}ClN_3O$ (271.71): C, 61.88; H, 3.71; N, 15.47. Found: C, 61.65; H, 3.52; N, 15.09.

3-(2'-Acetylaminobenzoyl)amino-2-chloropyridine (**5**).

To a mixture of the finely pulverized potassium hydroxide (0.88 g, 15.7 mmoles) in hexamethylphosphoric acid triamide (18 ml), preheated to 135° was added 2.09 (7.35 mmoles) of compound **6**. After 20 minutes stirring under nitrogen the reaction went to completion (the only visible spot on tlc at $R_f \sim 0.50$; ethyl acetate-light petroleum 8:2 as eluent). To the cooled reaction mixture water (200 ml) was added and extracted with methylene chloride (3 × 100 ml). The combined organic extracts were washed with water (2 × 50 ml), dried and evaporated. The crude **5** obtained was purified on a silica gel column (140 g) using the above solvent mixture. Pure **5** was obtained, 0.335 g (15%), mp 163-164° (from ethanol); ir: 3285, 1682, 1650, 1605, 1577, 1530, 1490, 1305, 810, 750, 712, 700 cm^{-1}; nmr (deuteriochloroform): 2.22 (s, 3H), 7.0-9.0 (m, 7H), 11.6 (broad s, 2H, 2NH).

Anal. Calcd. for $C_{14}H_{12}ClN_3O_2$ (289.72): C, 58.03; H, 4.17; N, 14.51. Found: C, 57.95; H, 4.03; N, 14.20.

The structure of the compound **5** was confirmed by acetylation of **12** with a mixture of acetyl chloride/triethlamine in dioxane, the yield of **5** was 94% mp 162-163° cyclisation of **5** into **6**.

Compound **5** (0.145 g, 0.5 mmole) was heated at 200° for 5 minutes under the atmosphere of dry nitrogen. The resulting melt was dissolved in hot methanol, filtered hot with charcoal and evaporated to dryness. Crude **6** thus obtained was recrystallized from 2-propanol (0.12 g), mp 178-180°. The ir and nmr spectra were identical with those obtained for the specimen of **6** prepared as described above.

2-Chloro-3-(2'-chloropyrid-3'-yl)quinazolin-4-one (**7**).

N-Chloroacetylanthranilic acid (2.0 g, 9.5 mmoles) and 2-chloro-3-aminopyridine (1.2 g, 9.3 mmoles) were dissolved in polyphosphoric acid (30 g) and heated at 140° under stirring for 2 hours. The reaction mixture was allowed to cool to ambient temperature, added and the resulting slurry was stirred for 2 hours. The crystals that separated were collected on a filter, washed with water and dried affording 2.8 g (93%) of crude **7**, which on recrystallization from acetone had mp of 184-185°; ir: 1685, 1605, 1568, 1440, 1345, 1290, 770, 732 cm^{-1}; nmr (deuteriochloroform): 4.32 (q, J = 6 Hz, 2H), 7.3-8.4 (m, 6H), 8.68 (dd, J_1 = 6 Hz, J_2 = 2 Hz, 1H).

Anal. Calcd. for $C_{14}H_9Cl_2N_3O$ (324.16): C, 54.92; H, 2.96; N, 13.73. Found: C, 54.64; H, 3.12; N, 13.43.

2-Bromomethyl-2-(2'-chloropyrid-3'-yl)quinazolin-4-one (**8**).

Compound **6** (0.40 g, 1.48 mmoles), *N*-bromosuccinimide (3.11 g, 1.48 mmoles) and azobisisobutyronitrile (10 mg) in carbon tetrachloride (10 ml) were heated under reflux for 1 hour. The nmr monitoring of the reaction mixture indicated complete disappearance of **6** and formation of a mixture of **8** and its 2-dibromomethyl congener in the ratio of about 7:3. A sample of **8** was purified by column chromatography using ethyl acetate-methanol (9:1); ir: 1680, 1610, 1585, 1575, 1330, 1282, 765 cm^{-1}; nmr (deuteriochloroform): 4.66 (d, 1H), 7.3-8.4 (m, 6H), 8.70 (dd, J_1 = 6 Hz, J_2 = 2 Hz, 1H).

Anal. Calcd. for $C_{14}H_9BrClN_3O$ (350.61): C, 47.94; H, 2.58; N, 11.98. Found: C, 48.08; H, 2.30; N, 11.69.

2-(N^4-Methylpiperazin-N^1-yl)methyl-3-(2'-chloropyrid-3'-yl)quinazolin-4-one (**9**).

Compound **8** (0.40 g, about 1.15 mmoles, calculated as 70% in the mixture obtained in the previously described step) and *N*-methylpiperazine (0.34 g, 3.4 mmoles were refluxed in toluene (20 ml) for 1 hour. After evaporation *in vacuo* to dryness (water bath 100°) the residual mixture was dissolved in acetone (20 ml) and filtered. The filtrate evaporated to leave 0.29 g (90%) of crude **9**. An analytical sample was obtained after chromatographing the crude **9** on a silica gel column (70 g) using ethyl acetate-methanol (8.5:1.5) as the eluent. The resultant oil resisted crystallization attempts; ir: 2990, 2940, 1685, 1610, 1580, 1335, 1290, 1275, 1100, 760, 680 cm^{-1}.

Anal. Calcd. for $C_{19}H_{20}ClN_5O$ (279.85): C, 61.70; H, 5.45; N, 18.94. Found: C, 61.66: H, 5.18; N, 18.71.

Attempted Ring-Opening of Compound **9**.

Compound **9** (0.10 g, 0.35 mmole) was added to a mixture of finely pulverized potassium hydroxide (0.15 g) in hexamethylphosphoric acid triamide (4.0 ml). The resulting slurry was maintained under dry nitrogen and the reaction vessel immersed into an oil-bath preheated to 115-120°. The bath temperature was gradually raised to 160° during 2 hours while the reaction mixture was continuously controlled on tlc (ethyl acetate-light petroleum-methanol 8.0:1.5:0.5 as eluent). From the very beginning, formation of more spots could be verified, while not one of them increased in relative intensity (tlc) as the reaction proceeded.

The same result was obtained when the reaction was performed at lower temperatures (60-110°) at the prolonged time intervals.

2-(2'-Carboxymethylphenyl)amino-3-nitropyridine (**10A**).

Anthranilic acid methyl ester (4.26 g, 28.2 mmoles), 2-chloro-3-nitropyridine (4.0 g, 25.2 mmoles), and potassium fluoride (2.0 g, 34.5 mmoles) were heated and stirred together at 170° for 3 hours. The reaction mixture was allowed to cool to ambient temperature, then hot 2-propanol (about 30 ml) was added. The undissolved material was filtered off, and the filtrate was chilled on ice. Crystalline **10** was collected upon filtration, washed with water and dried affording 3.8 g (65%) of yellow crystals, mp 145-146°; ir: 3270, 1695, 1608, 1495, 1350, 1250, 1098, 845, 750, 715 cm^{-1}; nmr (deuteriochloroform): 4.02 (s, 3H), 6.8-8.8 (m, 7H), 12.3 (broad s, 1H).

Anal. Calcd. for $C_{13}H_{11}N_3O_4$ (273.22): C, 57.14; H, 4.06; N, 15.38. Found: C, 57.47; H, 4.14; N, 15.63.

In the same manner compounds **10B** and **10C** were prepared, starting from anthranilic acid ethyl ester and anthranilic acid amide, respectively.

2-(2'-Carboxyethylphenyl)amino-3-nitropyridine (**10B**).

On recrystallization from 2-propanol, mp 83-84°; ir: 2995, 1700, 1610, 1590, 1565, 1500, 1450, 1255, 1082, 750 cm^{-1}; nmr (deuteriochloroform): 1.45 (t, 3H), 4.50 (q, 2H), 6.9-8.2 (m, 6H), 8.55 (broad s, 1H), 8.60 (dd, 1H).

Anal. Calcd. for $C_{14}H_{13}N_3O_4$ (287.27): C, 58.53; H, 4.56; N, 14.63. Found: C, 58.27; H, 4.53; N, 14.61.

2-(2'-Carboxamidophenyl)amino-3-nitropyridine (**10C**).

On recrystallization from 2-propanol, mp 102-104°; ir: 3410, 3250, 1652, 1604, 1550, 1505, 1425, 1305, 1298, 760 cm^{-1}; nmr (deuteriochloro-

form + DMSO-d_6, about 1:1): 6.9-8.0 (m, 6H), 8.55 (s, 1H), 8.6 (m, 1H), 12.1 (broad s, 2H).

Anal. Calcd. for $C_{12}H_{10}N_4O_3$ (258.23): C, 55.81; H, 3.90; N, 21.69. Found: C, 55.72; H, 3.72; N, 21.44.

6-Amino-11*H*-pyrido[2,1-*b*]quinazolin-11-one (**13**).

Method A.

Compounds **10A-10C** (3.0 mmoles) were dissolved in dioxane (50 ml), and hydrogenated over palladium on carbon (0.2 g) at ambient temperature, and 2 atmospheres hydrogen pressure (Parr's all purpose bomb, magnetic stirring). Disappearance of the starting compound on tlc was accompanied by the formation of two spots, first in the R_f region 0.2-0.3 (toluene-ethyl acetate 2:8), corresponding to the intermediary 3-amino derivatives **11A-11C**, and the second at $R_f \sim 0.8$, corresponding to the final compound **13**. All attempts to isolate **11A-11C** by fast chromatography or crystallization failed. On filtration of the catalyst and evaporation of dioxane, crude product was briefly treated with hot 96% ethanol, then cooled and collected on a filter. The yield was nearly quantitative. On recrystallization from diisopropyl ether, it had mp 212-214°; ir: 3460, 3350, 1670, 1630, 1605, 1595, 1520, 1455, 755, 735, 690 cm^{-1}.

Anal. Calcd. for $C_{12}H_9N_3O$ (211.22): C, 68.23; H, 4.29; N, 19.89. Found: C, 68.01; H, 4.14; N, 19.54.

Method B.

Compound **12** (1.0 g, 4.0 mmoles), and ammonium chloride (5.0 g, 93.5 mmoles) in polyphosphoric acid (13.0 g) were stirred and heated at 160° for 4 hours. The reaction mixture was allowed to cool to ambient temperature, water (100 ml) was added, and the crystals were collected on a filter (0.60 g). On recrystallization from DMF-water 0.48 g (66%) of **2** was obtained, mp 276-279°.

The filtrate was made alkaline with concentrated ammonia, the precipitated product was collected on a filter and purified on a silica gel column using ethyl acetate-2-propanol (1:1) as the eluent. Pure **13** (0.16 g, 19%) was obtained, mp 212-213°.

3-(2'-Aminobenzoyl)-2-chloropyridine (**12**).

Compound **1** (1.33 g, 5.0 mmoles) was added to the suspension of 0.70 g of copper(I) chloride and sodium chloride (10 g), in concentrated aqueous ammonia (25 ml). The reaction mixture was heated in a Parr all-purpose bomb at 80° for 3 hours. The reaction mixture was cooled to 0°, the crude product was collected on a filter, washed with water and dried affording 0.88 g (71%) of product. The solid was recrystallized from 2-propanol affording pure **12** with mp 170-173°; the ir and nmr spectra corresponded to those obtained for the sample prepared according to reference [14].

6-Nitro-11*H*-pyrido[2,1-*b*]quinazolin-11-one (**14**).

Compound **10A** (300 mg, 1.1 mmoles) was dissolved in a mixture of dioxane-glacial acetic acid (2 + 2 ml) and heated at 120-125° for 24 hours. On cooling the crude product crystallized, the solid was collected on a filter, washed with ethanol and dried (251 mg, 88%), mp 250-255° dec; ir: 1715, 1648, 1520, 765, 690 cm^{-1}.

Anal. Calcd. for $C_{12}H_7N_3O_3$ (241.20): C, 59.75; H, 2.92; N, 17.42. Found: C, 59.52; H, 2.90; N, 17.08.

Under similar reaction conditions compounds **10B** and **10C** could be quantitatively converted to **14**.

2-*o*-Toluidino-3-aminopyridine (**15**).

To the solution of *o*-toluidine (5.35 g, 50.0 mmoles) in diethylene glycol (30 ml), 2-chloro-3-aminopyridine (1.28 g, 10.0 mmoles), and 48% aqueous hydrogen bromide (1.25 ml, 10.0 mmoles) were added under nitrogen. The dark yellow solution was heated at 170° for 18 hours, and then 5 hours at 195°. The mixture was allowed to cool to room temperature, then it was poured into an aqueous buffer (*p*H 8-9, 100 ml) and extracted with chloroform (3 × 50 ml). The dark oil, obtained on evaporation of dried organic extracts, was purified on a silica gel column using ether as eluent. Pure **15** was obtained 1.2 g (53%), which on recrystallization from 2-propanol had mp 162-163°; ir: 3365, 3250, 3160, 1640, 1600, 1580, 1480, 1460, 1440, 1300, 1280, 1250, 1235, 1140, 1115 cm^{-1}; nmr (deuteriochloroform): 2.30 (s, 3H), 3.35 (broad s, 2H, NH_2), 6.10 (s, 1H,NH), 6.7-7.4 (m, 6H), 7.8-8.05 (dd, 1H).

Anal. Calcd. for $C_{12}H_{13}N_3$ (199.25): C, 72.30; H, 6.58; N, 21.02. Found: C, 72.22; H, 6.39; N, 21.10.

2-(*N*-Chloroacetyl-*N*-*o*'-toluyl)amino-3-nitropyridine (**16**).

2-*o*-toluidino-3-nitropyridine (2.29 g, 10.0 mmoles) was dissolved in dry dioxane (40 ml), 10 ml of chloroacetyl chloride was added, and the mixture was heated under gentle reflux for 1.5 hours. The solvent and excess reagent were evaported, the residual oil was dissolved in chloroform (150 ml), dried and evaporated. The crude **16** was placed on a column (35 g) of silica gel and eluted with methylene chloride (the column was wrapped with aluminum foil to protect the product from decomposition by light). In the first 20 fractions (about 5 ml per fraction) unreacted starting material (0.44 g) was isolated, while fractions 15-40 contained 2.47 g (81%) of the pure **16**. It resisted numerous attempts at crystallization. An analytical sample was obtained by repeated chromatography and drying at 0.1 mm Hg over phosphorus pentoxide (glassy material); ir: 3020, 1690, 1592, 1535, 1428, 1355, 850 cm^{-1}; nmr (deuteriochloroform): 2.45 (s, 3H), 4.0 (s, 2H), 7.2-7.6 (m, 5H), 8.42 (dd, J_1 = 4 Hz, J_2 = 8 Hz, 1H), 8.63 (dd, J_1 = 4 Hz, J_2 = 8 Hz, 1H).

Anal. Calcd. for $C_{14}H_{12}ClN_3O_3$ (305.72): C, 54.99; H, 3.96; N, 13.74. Found: C, 54.79; H, 3.86; N, 13.39.

2-[*N*-(4'-Methylpiperazin-1'-yl)acetyl-*N*-(*o*-tolyl)]amino-3-nitropyridine (**17**).

Compound **16** (3.05 g, 10.0 mmoles) was dissoloved in dry toluene (50 ml) 4.4 ml (40.0 mmoles) of *N*-methylpiperazine was added and the mixture was heated at 80° (oil bath) for 20 hours. After evaporation of the solvent and excess reagent, the crude product was dissolved in chloroform (300 ml), the solution was washed with water (300 ml), dried and evaporated leaving 4.11 g of a glassy transparent residue. It was purified on a column (30 g) of silica gel using acetone-methanol (5:1) as the eluent. The first 10 fractions (about 5 ml per fraction) contained 0.28 g of the starting **16**, while in the fractions 25-70, 2.11 g (57%) of the pure **17** emerged. It resisted numerous attempts at crystallization, thus an analytical sample was prepared by repeated chromatography and drying at 0.1 mm Hg over phosphorus pentoxide; ir: 1690, 1580, 1530 (broad), 1455, 1410, 1298, 1086, 1055, 808, 730, 720 cm^{-1}; nmr (deuteriochloroform): 2.28 (s, 3H), 2.45 (broad s, 3H + 8H, 11H), 3.1 (s, 2H), 7.2-7.6 (m, 5H), 8.34 (dd, J_1 = 4 Hz, J_2 = 8 Hz, 1H), 8.59 (dd, J_1 = 4 Hz, J_2 = 8 Hz, 1H).

Anal. Calcd. for $C_{19}H_{23}N_5O_3$ (369.41): C, 61.77; H, 6.27; N, 18.96. Found: C, 61.82; H, 6.01; N, 18.90.

2-[*N*-(4'-Methylpiperazin-1'-yl)acetyl-*N*'-(*o*'-tolyl)]-3-diaminopyridine Trihydrochloride (**18**).

Compound **17** (740 mg, 2.0 mmoles) was hydrogenated in 20 ml of 96% ethanol using palladium on carbon (100 mg) as the catalyst in a stream of hydrogen at atmospheric pressure. After 3 hours the reaction was complete, the catalyst was filtered off, 10 ml of 10% ethanolic solution of hydrogen chloride was added and the solvent was evaporated to dryness. The crude product was crystallized from acetone, mp 206-210° dec; ir: 3400, 3260 (broad), 1675, 1595, 1508, 1420, 1365, 1300, 1215, 1050, 760 cm^{-1}.

Anal. Calcd. for $C_{19}H_{28}Cl_3N_5O$ (448.83): C, 50.84; H, 6.29; N, 15.60. Found: C, 50.61; H, 6.18; N, 15.41.

1-(*o*'-Tolyl)-2-(4'-methylpiperazin-1'-yl)methylpyrido[2,3-*d*]imidazole Hydrochloride (**19**).

Compound **18** (600 mg, 1.34 mmoles) was heated in a melt of 5 g of the yellow sulphur, at 250° for 8 hours under nitrogen. The mixture was allowed to cool to ambient temperature, then water (50 ml) and carbon disulphide (50 ml) were added. After brief stirring undissolved material was

collected on a filter, and crystallized from DMF-water. A solid was obtained 220 mg (38%) of pure **19**, mp 224-227°; ir: 2900-3200 (broad), 1605, 1585, 1510, 1480, 1385, 805, 775, 690 cm^{-1}; nmr (pyridine-d_5): 2.60 (s, 6H), 3.25 (s, 3H), 3.5-4.0 (m, 8H), 4.3-7.55 (m, 2H), 7.4-8.1 (m, 7H).

Anal. Calcd. for $C_{19}H_{26}ClN_5$ (430.81): C, 52.97; H, 6.08; N, 15.25. Found: C, 52.63; H, 5.87; N, 15.16.

2-Phenylamino-3-aminopyridine (**20**).

Aniline (0.93 g, 10.0 mmoles) and 2-chloro-3-aminopyridine (1.28 g, 10.0 mmoles) were dissolved in diethylene glycol (15 ml), and 3-4 drops of 40% aqueous hydrogen bromide were added. After 5 hours heating at 170° the reaction mixture was diluted with water (30 ml) and the precipitate was collected on a filter. Recrystallization from 2-propanol afforded 1.57 g (85%) of pure **20**, mp 143-144° (literature [11] mp 142°); ir: 3340, 3240, 3160, 1600, 1510, 1492, 1450, 1350, 1290, 1142, 1070, 920, 880, 750 cm^{-1}; nmr (DMSO-d_6): 5.08 (broad s, 2H), 6.5-7.9 (m, 8H).

2-Anilino-3-ethoxycarbonylaminopyridine (**21**).

To the compound **20** (2.77 g, 15.0 mmoles), was dissolved in dry tetrahydrofuran (60 ml) and cooled to −5°, triethylamine (3.25 ml) and ethyl chloroformate (2.3 ml, 24.0 mmoles) were added dropwise during 30 minutes. The mixture was then allowed to warm to room temperature and was stirred for 12 hours. The precipitate was filtered off and the filtrate was evaporated to dryness. The oily residue was dissolved in ethyl acetate (100 ml), washed with water (2 × 50 ml), the organic phase was dried, evaporated and the residue was crystallized from ether affording 3.6 g (90%) of the pure **21**, mp 104-105°; ir: 3400, 3020, 1700, 1675, 1615, 1590, 1510, 1440, 1240, 1050, 900, 740, 690 cm^{-1}; nmr (DMSO-d_6): 1.28 (t, 3H), 4.22 (q, 2H), 6.7-8.1 (m, 8H), 8.2 (s, 1H), 9.0 (s, 1H).

Anal. Calcd. for $C_{14}H_{15}N_3O_2$ (257.29): C, 65.37; H, 5.87; N, 16.32. Found: C, 65.22; H, 5.66; N, 16.09.

2-(*N*-Acetyl-*N*-phenyl)amino-3-aminopyridine (**22**).

Compound **26** (5.14 g, 20.0 mmoles) was dissolved in ethanol (60 ml), and 0.5 g of palladium on carbon (10%) was added and hydrogenation was performed in the Parr apparatus at 3 atmospheres and 25° for 6 hours. Thereafter the catalyst was filtered off, the solvent was evaporated and the product was purified on a silica gel column using methylene chloride-methanol (8:2) as the eluent. Compound **22** was isolated in 53% yield (2.40 g), mp 174-175° (from ethanol); ir: 3390, 3320, 1675, 1585, 1495, 1445, 1370, 1320, 1000, 790 cm^{-1}; nmr (DMSO-d_6): 1.93 (s, 3H), 5.5 (broad s, 1H), 7.2-7.7 (m, 5H), 7.8-8.0 (m, 3H).

Anal. Calcd. for $C_{13}H_{13}N_3O$ (227.27): C, 68.70; H, 5.77; N, 18.49. Found: C, 68.50; H, 5.55; N, 18.15.

2-(*N*-Acetyl-*N*-phenyl)amino-3-ethoxycarbonylaminopyridine (**23**).

Compound **21** (3.08 g, 12.0 mmoles) and triethylamine (1.3 g, 13.0 mmoles) were dissolved in toluene (60 ml) and the reaction mixture was stirred at room temperature while acetyl chloride (1.02 g, 13.0 mmoles) was added dropwise. Stirring was continued for 8 hours, then the precipitate was filtered off and the filtrate was evaporated to dryness affording an oily residue which resisted numerous attempts of crystallization. After chromatography on a column of silica gel using ethyl acetate as eluent ($R_f \sim 0.4$), 2.69 g (75%) of pure **23** was obtained; ir: 3300, 1730, 1675, 1595, 1510, 1420, 1370, 1300, 1220, 1050, 755, 695 cm^{-1}; nmr (DMSO-d_6): 1.20 (t, 3H), 1.97 (s, 3H), 4.13 (q, 2H), 7.1-7.7 (m, 6H), 8.0-8.5 (m, 2H), 9.35 (s, 1H).

Anal. Calcd. for $C_{16}H_{17}N_3O_3$ (299.33): C, 64.22; H, 5.71; N, 14.04. Found: C, 64.23; H, 5.90; N, 14.10.

2-Phenylamino-3-formylaminopyridine (**24**).

Compound **20** (1.43 g, 7.7 mmoles) was stirred in formic acid (30 ml) at room temperature for 8 hours. Then the excess formic acid was evaporated, the residue was dissolved in ethyl acetate (100 ml), washed with 10% aqueous bicarbonate solution (2 × 50 ml). The solution was dried and the solvent evaporated. Crude **24** was crystallized from ether, affording 1.48 g (90%) of the pure product, mp 100-102°; ir: 3360, 3240, 1650, 1609, 1527, 1495, 1445, 1230, 1390, 900 cm^{-1}; nmr (deuteriochloroform): 6.6-7.8 (m, 6H), 8.0-8.3 (m, 3H), 9.2 (s, 1H).

Anal. Calcd. for $C_{12}H_{13}N_3O$ (215.26): C, 66.97; H, 6.09; N, 19.52. Found: C, 67.01; H, 6.01; N, 19.45.

2-Phenylamino-3-nitropyridine (**25**).

Aniline (8.94 g, 96 mmoles) and 2-chloro-3-nitropyridine (6.34 g, 40 mmoles) were heated under vigorous stirring at 140° for 6 hours. Then the reaction mixture was slurried in water (200 ml), and extracted with chloroform (3 × 150 ml). The dried organic extracts were evaporated and the residue was crystallized from 2-propanol affording 7.63 g (89%) of pure **25**, mp 74-75° (literature [12] mp 75°).

2-*N*-Acetyl-*N*-phenylamino-3-nitropyridine (**26**).

To compound **25** (2.73 g, 12.7 mmoles) dissolved in acetic anhydride (25 ml), two drops of concentrated sulphuric acid were added and the mixture was stirred and heated at 120° for 30 minutes. The solution was allowed to cool to room temperature, then it was poured in ice-water (200 g), and the product was extracted with ethyl acetate (3 × 40 ml). The organic extracts were dried, the solvent was evaporated and the crude product was crystallized from ethanol affording 2.93 g (90%) of **26**, mp 117-118°; ir: 3080, 1680, 1590, 1565, 1520, 1430, 1350, 1305, 850, 700 cm^{-1}; nmr (DMSO-d_6): 2.0 (s, 3H), 7.5-7.7 (m, 5H), 8.5-8.9 (m, 3H).

Anal. Calcd. for $C_{13}H_{11}N_3O_3$ (257.25): C, 60.70; H, 4.31; N, 16.33. Found: C, 60.65; H, 4.37; N, 16.29.

2-(2'-Bromophenylamino)-3-nitropyridine (**27**).

2-Bromoaniline (1.72 g, 10.0 mmoles) and 2-chloro-3-nitropyridine (1.58 g, 10.0 mmoles) were fused under nitrogen at 140° for 4 hours. The mixture was allowed to cool to room temperature. The crude product was extracted into chloroform (2 × 50 ml), the solvent was evaporated and the residual yellow crystals were recrystallized from *n*-heptane affording 2.50 g (85%) of the pure **27**, mp 92-94° (from methanol); ir: 3310; 2850 (weak), 2610, 2580 (both weak), 1600, 1498, 1465, 1435, 1250, 748 cm^{-1}; nmr (deuteriochloroform): 6.8-7.8 (m, 5H), 8.4-8.7 (m, 2H).

Anal. Calcd. for $C_{11}H_8BrN_3O_2$ (294.11): C, 44.92; H, 2.74; N, 14.29. Found: C, 44.85; H, 2.81; N, 14.37.

2-*N*-Acetyl-*N*-2'-bromophenylamino-3-nitropyridine (**28**).

2-(2'-Bromophenyl)amino-3-nitropyridine **27** (2.0 g, 7.17 mmoles) was dissolved in 10 ml of acetic anhydride, 5 drops of concentrated sulphuric acid were added, and reaction mixture was heated under reflux for 1 hour. The mixture was allowed to cool to room temperature, then 60 ml of water was added and the mixture was briefly heated until homogeneous. On chilling in ice the pure **28** precipitated (1.89 g, 82%), which on recrystallization from ethanol-water had mp of 134-135°; ir: 3090, 1700, 1592, 1470, 1450, 1369, 1300, 1255, 1240, 850, 765 cm^{-1}; nmr (deuteriochloroform): 2.08 (s, 3H), 7.0-9.0 (m, 8H).

Anal. Calcd. for $C_{13}H_{10}BrN_3O_3$ (336.16): C, 46.44; H, 3.01; N, 12.50. Found; C, 46.49; H, 3.10; N, 12.60.

1-Phenylimidazolo[5,4-*b*]pyridine (**29**).

Compound **24** (4.26 g, 20 mmoles) was heated in polyphosphoric acid (40 g) at 90-100° for 1 hour. Then the solution was diluted with water (200 ml) and the *p*H was adjusted to 8. Crude product was extracted with methylene chloride and crystallized from ether to give 3.3 g (85%) of the pure compound **29**, mp 108-109°; ir: 3050, 1600, 1505, 1410, 1290, 1235, 800, 770, 685 cm^{-1}; nmr (deuteriochloroform): 7.2-7.9 (m, 5H), 8.1-8.7 (m, 3H), 8.42 (s, 1H).

Anal. Calcd. for $C_{12}H_9N_3$ (195.22): C, 73.82; H, 4.65; N, 21.53. Found: C, 73.71; H, 4.51; N, 21.74.

When compound **24** was heated in nitrobenzene with aluminum trichloride, or in chloroform with boron trifluoride etherate, the formation of **29** as the main product was noticed.

1-Phenyl-2-oxoimidazolo[5,4-*b*]pyridine (**30**).

A solution of compound **21** (2.57 g, 10 mmoles) and potassium hydroxide (0.56 g, 10 mmoles) in ethanol (50 ml) was heated under reflux for 15 minutes. Thereafter the solvent was evaporated and the crude product was crystallized from ethyl acetate to give 2.0 g (95%) of the pure **30**, mp 242-244°; ir: 3130, 1690, 1500, 1445, 1385, 1230, 1065, 885, 765, 697 cm^{-1}; (DMSO-d_6): 7.0-8.2 (m, 9H).

Anal. Calcd. for $C_{12}H_9N_3O$ (211.22): C, 68.23; H, 4.29; N, 19.89. Found: C, 68.20; H, 4.35; N, 20.01.

The same compound (**30**) was isolated when the amine **20** or its monoacetyl derivative **22** (1.5 mmoles) was treated with phosgene, on dissolution in ethyl acetate (15 ml). The analysis (ethyl acetate as eluent) indicated formation of the intermediate isocyanate ($R_f \sim 0.3$) which upon workup, *i.e.*, addition of aqueous bicarbonate, extraction into ethyl acetate, and crystallization afforded **30**.

1-Phenyl-2-methylimidazolo[5,4-*b*]pyridine (**31**).

Compound **23** (3.0 g, 10.0 mmoles) was heated in 50 ml of polyphosphoric acid at 120-130° for 30 minutes. Thereafter the crude product was isolated as described for **29** (2.0 g, 96%). It was purified on a silica gel column using ethyl acetate as the eluent. The oil thus obtained resisted crystallization; ir: 1600, 1500, 1420, 1385, 1300, 1280, 1235, 1008, 800, 774, 695 cm^{-1}; nmr (deuteriochloroform): 2.58 (s, 3H), 7.1-8.5 (m, 8H).

Anal. Calcd. for $C_{13}H_{11}N_3$ (209.25): C, 74.62; H, 5.31; N, 20.07. Found: C, 74.99; H, 5.51; N, 20.43.

In another attempt compound **23** was heated in a mixture of phosphoric acid/phosphorus oxychloride (5:1). The only product that formed, as indicated by tlc, was **31**.

1-*o*'-Bromophenyl-2-methylimidazolo[5,4-*b*]pyridine (**32**).

Compound **17**, (0.61 g, 1.65 mmoles) was dissolved in dry dioxane (10 ml). Raney Nickel (0.35 g) was added and hydrogenation was performed in the Parr all purpose bomb at 2 atmospheres for 2 hours. Thereafter the catalyst was filtered off, the solvent was evaporated and the crude product was purified on a silica gel column using toluene-ethyl acetate (3:2) as the eluent. Pure **32** was obtained 0.19 g (41%) which on crystallization had mp 95-96°; ir: 3055, 1670, 1600, 1585, 1520, 1483, 1440, 1417, 1387, 1300, 1280, 1230, 800, 778, 768 cm^{-1}; nmr (deuteriochloroform): 2.50 (s, 3H), 7.0-8.6 (m, 7H).

Anal. Calcd. for $C_{13}H_{10}BrN_3$ (288.15): C, 54.18; H, 3.51; N, 14.58. Found: C, 53.98; H, 3.42; N, 14.32.

N,N'-Bis-2-(*N*-phenyl-*N*-acetyl)aminopyrid-3-ylhydrazine (**33**).

This compound was isolated as the second product in the previous preparation (0.21 g, 28%), mp 106-107° (from ether); ir: 3300, 3000, 1675, 1610, 1535, 1445, 1305, 1265, 1110, 790 cm^{-1}; nmr (deuteriochloroform): 1.97 (s, 6H), 6.6-7.5 (m, 16H), 8.0-8.2 (m, 2H).

Anal. Calcd. for $C_{26}H_{24}N_6O_2$ (452.47): C, 69.01; H, 5.34; N, 18.56. Found: C, 69.05; H, 5.40; N, 18.45.

2-(2'-Bromophenyl)amino-3-aminopyridine (**34**).

Compound **27** (2.94 g, 10.0 mmoles) was dissolved in a mixture of methanol (60 ml) and concentrated hydrochloric acid (35 ml). To the vigorously stirred solution tin(II) chloride (12.0 g) was added gradually during 1 hour, maintaining a gentle boiling. Then the methanol was evaporated, the mixture was allowed to cool to ambient temperature and made alkaline with 20% aqueous sodium hydroxide. It was extracted with chloroform (3 × 100 ml), the organic extracts were dried, evaporated, and the crude **34** which remained was crystallized from 2-propanol affording 1.78 g (85%) of the pure product, mp 104-105°; ir: 3360, 3150, 1630, 1600, 1580, 1470, 1460, 1440, 1300, 1240, 1140, 1030, 845, 780, 755, 655 cm^{-1}; nmr (deuteriochloroform): 6.8-8.0 (m, 10*H*).

Anal. Calcd. for $C_{11}H_{10}BrN_3$ (264.13): C, 50.01; H, 3.81; N, 15.91. Found: C, 49.62; H, 3.71; N, 15.74.

3-(2'-Chlorobenzoyl)amino-2-chloropyridine 1-Oxide (**35**).

3-(2'-Chlorobenzoyl)amino-2-chloropyridine (4.1 g, 15.3 mmoles) was heated in 50 ml of 40% hydrogen peroxide in acetic acid at 55-60° (oil bath temperature) for 24 hours. According to tlc (methylene chloride-methanol 10:1) the conversion was complete. The pale yellow solution was evaporated. The residual mass was triturated with ethanol (2 × 20 ml) and the ethanol was evaproated. The residual crystalline product was slurried in acetone (20 ml) and filtered affording 3.9 g (90%) of pure **35**, mp 160-161° dec; ir: 3350, 1670, 1590, 1520, 1430, 1415, 1270, 1240, 1110, 1055, 800, 785, 760, 738 cm^{-1}; nmr (DMSO-d_6): 7.4-7.95 (m, 5H), 8.55 (dd, 1H), 10.7 (broad s, 1H).

Anal. Calcd. for $C_{12}H_8Cl_2N_2O_2$ (283.11): C, 50.90; H, 2.84; N, 9.89. Found: C, 51.15; H, 2.73; N, 9.90.

3-(2'-Bromobenzoyl)amino-2-chloropyridine 1-Oxide (**35A**).

Synthesized by the method described for **35** using 3-(2'-bromobenzoyl)amino-2-chloropyridine, compound **35A** was prepared in 90% yield, mp 187-189° dec; ir: 3170, 3100, 1688, 1595, 1530, 1455, 1430, 1400, 1092, 1040, 1020, 780, 770 cm^{-1}; nmr (methanol-d_4): 7.4-7.95 (m, 4H), 8.15 (dd, 1H), 8.50 (dd, 1H).

Anal. Calcd. for $C_{12}H_8BrClN_2O_2$ (327.57): C, 43.99; H, 2.46; N, 8.55. Found: C, 44.16; H, 2.31; N, 8.26.

3-(2'-Aminobenzoyl)amino-2-chloropyridine 1-Oxide (**36**).

Compound **35A** (19.66 g, 60 mmoles), copper(II) sulphate pentahydrate (7.5 g, 30 mmoles) and sodium chloride (30 g) were slurried in 120 ml of concentrated ammonium hydroxide. After 3 hours stirring at 60°, the crude product was separated by filtration, and washed with water. The pink-yellow crystals (14.5 g, 91.5%) could be used in the next step without further purification. On recrystallization from DMF-water (1:3) pure product **36** had mp of 185-187° dec; ir: 3440, 3275, 1668, 1620, 1595, 1570, 1525, 1415, 1255, 1245, 1174, 1120, 1058, 1005, 790, 750, 695, 645 cm^{-1}; nmr (DMSO-d_6): 6.5-7.9 (m, 6H + NH_2), 8.36 (dd, 1H).

Anal. Calcd. for $C_{12}H_{10}ClN_3O_2$ (263.68): C, 54.65; H, 3.82; N, 15.93. Found: C, 54.51; H, 3.72; N, 15.64.

Starting with 11.32 g (40 mmoles) of 3-(2'-chlorobenzoyl)amino-2-chloropyridine 1-oxide (**35**), copper(I) chloride (1.98 g, 20 mmoles), and sodium chloride (70 g), the reaction was performed in 160 ml of concentrated ammonium hydroxide as described above. After 5 hours heating at 80° pure **36** (8.96 g) was isolated, mp 183°.

1-Oxo-5,11-dihydro-6*H*-pyrido[2,3-*b*][1,4]benzodiazepin-6-one (**37**).

Method A.

Compound **36** (2.37 g, 8.98 mmoles) was slurried in diethylene glycol monomethyl ether (18 ml) and 0.2 ml of 5% aqueous hydrochloric acid was added. The reaction mixture was stirred and heated for 1.5 hours at 110° (oil bath temperature). Thereafter crude product, which separated on cooling as fine pink-yellow crystals, was filtered off affording 1.96 g (96%), mp 305-306° strong dec. The tlc (methylene chloride-methanol 10:1 as eluent) of compound **37** demonstrated (uv 254) one yellow spot ($R_f \sim 0.35$). On recrystallization from DMF-methanol (1:20) it had mp of 305-307° strong dec; ir: 2370, 1650, 1615, 1525, 1485, 1370, 1225, 1205, 1162, 955 cm^{-1}; nmr (DMSO-d_6): 6.9-7.6 (m, 6H), 7.7-8.1 (m, 1H), 9.60 (s, 1H), 10.25 (s, NH).

Anal. Calcd. for $C_{12}H_9N_3O_2$ (227.22): C, 63.42; H, 3.99; N, 18.49. Found: C, 63.59; H, 4.07; N, 18.19.

Method B.

Compound **2** (8.44 g, 40 mmoles) was dissolved in glacial acetic acid (350 ml) and 40% aqueous hydrogen peroxide (200 ml) was added. The solution was heated under vigorous stirring for 3 hours at 50°, then for 24 hours at 20-25°. After evaporation of the solvent to dryness the crude product was slurried in 100 ml of cold 96% ethanol, stirred, then deposited on ice. Crystals were collected on a filter, and dried affording 8.64 g (95%) of the pure **37**, mp 305-308° dec.

1-Oxo-11-(2'-chloroacetyl)-5,11-dihydro-6*H*-pyrido[2,3-*b*][1,4]benzodiazepin-6-one (**38**).

1-Oxo-5,11-dihydro-6*H*-pyrido[2,3-*b*][1,4]benzodiazepin-6-one (**37**) (9.08 g, 40 mmoles) was slurried in acetonitrile (150 ml), and chloroacetyl chloride (30 ml, 42.6 g, 377 mmoles) was added. Thereafter the reaction mixture was stirred and heated for 2 hours at 80°. From the solution

crude product slowly precipitated as a white-grey powder, which on tlc (methylene chloride-methanol 10:1) exhibited only one spot ($R_f \sim 0.80$). The yield was 10.93 g (90%), mp 255°. On recrystallization from DMF-ethanol-water compound **38** had a mp of 260°, strong dec; ir: 3190, 3060, 1712, 1665, 1450, 1370, 1338, 1263, 1175, 1115, 845, 790, 722, 655, 625 cm^{-1}; nmr (DMSO-d_6): 4.40 (s, 2H), 7.3-8.0 (m, 7H), 10.9 (broad s, 1H).

Anal. Calcd. for $C_{14}H_{10}ClN_3O_3$ (303.70): C, 55.36; H, 3.31; N, 13.83. Found: C, 55.22; H, 3.20; N, 14.02.

1-Oxo-11,2'-(4''-methylpiperazin-1''-yl)acetyl-5,11-dihydro-6*H*-pyrido-[2,3-*b*][1,4]benzodiazepin-6-one (**39**).

Compound **38** (15.2 g, 50 mmoles) and *N*-methylpiperazine (13.9 ml, 125 mmoles) were slurried in toluene (200 ml). After 5-10 minutes heating and stirring at 85° a clear solution resulted and soon the product started to precipitate. The reaction was continued for 2 hours at 80°, then the reaction mixture was collected on a filter. It was purified first by washing with water, then by crystallization from DMF-water (1:6) or 96% ethanol, 17.45 g (95%), mp 271-272° strong dec; ir: 3190, 3060, 1690, 1650, 1570, 1440, 1370, 1320, 1260, 1170, 1130, 1110, 1010, 900, 830, 760, 700, 620 cm^{-1}; nmr (pyridine-d_5): 1.90 (s, 3H), 1.9-2.3 (m, 8H), 3.06, 3.98 (dd, J = 16 Hz, 2H, $COCH_2$), 7.0-8.4 (m, 6H), 8.8 (s, 1H).

Anal. Calcd. for $C_{19}H_{21}N_5O_3$ (367.41): C, 62.11; H, 5.76; N, 19.06. Found: C, 61.85; H, 5.56; N, 19.14.

1-Oxo-5,11-dihydro-11-imidazol-1'-ylacetyl-6*H*-pyrido[2,3-*b*][1,4]benzodiazepin-6-one (**40**).

Working as described for **39** and using imidazole (8.51 g, 125 mmoles) as the nucleophile, 16.7 g (quantitative) of compound **40** was obtained mp 272-274°, on crystallization from DMF-water (1:6); ir: 3160, 1695, 1665, 1600, 1510, 1450, 1380, 1350, 1300, 1280, 1240, 1080, 920, 830, 810, 750, 700, 660, 630 cm^{-1}; nmr (DMSO-d_6): 5.05 (s, 2H), 6.9 (s, 1H), 7.15 (s, 1H), 7.3-8.1 (m, 8H), 10.95 (s, 1H).

Anal. Calcd. for $C_{17}H_{13}N_5O_3$ (335.33): C, 60.90; H, 3.91; N, 20.89. Found: C, 60.72; H, 4.04; N, 20.66.

1-Oxo-5,11-dihydro-11-(2''-methylimidazol-1''-yl)acetyl-6*H*-pyrido[2,3-*b*]-[1,4]benzodiazepin-6-one (**41**).

Working as described for **39**, and using 2-methylimidazole (10.26 g, 125 mmoles) as the nucleophile, product **41** was obtained 17.4 g (quantitative), mp 278-280° upon crystallization from DMF-water (1:6); ir: 3200, 1700, 1665, 1600, 1450, 1360, 1310, 1290, 1240, 1130, 960, 815, 750, 735, 670, 645, 605 cm^{-1}; nmr (DMSO-d_6): 2.2 (s, 3H), 4.95 (s, 2H), 6.76 (s, 1H), 7.05 (s, 1H), 7.3-8.1 (m, 7H), 11.05 (s, 1H).

Anal. Calcd. for $C_{18}H_{15}N_5O_3$ (349.35): C, 61.89; H, 4.33; N, 20.05. Found: C, 61.63; H, 4.28; N, 20.01.

5,11-Dihydro-11-(4'-methylpiperazin-1'-yl)acetyl-6*H*-pyrido[2,3-*b*][1,4]-benzodiazepin-6-one (**42**).

Compound **39** (36.7 g, 0.1 mole) was dissolved in diethylene glycol dimethyl ether (400 ml) and was hydrogenated with Raney Nickel (5.0 g) in a stream of hydrogen. After 16 hours of hydrogenation under vigorous stirring and heating at 50°, the reaction mixture was cooled, the catalyst was filtered off, and the filtrate was evaporated to dryness affording 35.0 g (quantitative) of the pure product. The product was slurried in methanol (700 ml), and then 25% hydrogen chloride in ethanol (105 ml) was added. After 1 hour stirring at room temperature pure dihydrochloride was obtained, mp 240-243°; ir: 3560, 3220, 2700-2400, 1710, 1670, 1600, 1480, 1430, 1360, 1140, 970, 780, 760, 610 cm^{-1}; nmr (deuterium oxide): 3.2 (s, 3H), 3.6-4.05 (m, 8H), 4.2-4.6 (m, 2H), 7.45-8.0 (m, 6H), 8.35-8.6 (m, 1H).

Anal. Calcd. for $C_{19}H_{20}N_5O_2 \cdot 2HCl$ (424.43): C, 53.77; H, 5.47; N, 16.51. Found: C, 53.82; H, 5.23; N, 16.60.

5,11-Dihydro-11-imidazol-1'-ylacetyl-6*H*-pyrido[2,3-*b*][1,4]benzodiazepin-6-one (**43**).

Compound **40** (16.7 g, 50 mmoles) was dissolved in 96% ethanol (250 ml) and Raney Nickel (2.0 g) was added. A stream of hydrogen has passed through the vigorously stirred solution during 8 hours at 60°. The catalyst was filtered off, evaporated to dryness, and crude **43**, 15.8 g (quantitative) was slurried in methanol (50 ml) and then 25% hydrogen chloride in ethanol (75 ml) was added. After 2 hours stirring at room temperature the pure hydrochloride was obtained mp 273-276°; ir: 3500-3000, 1715, 1675, 1622, 1600, 1550, 1445, 1390, 1265 cm^{-1}; nmr (DMSO-d_6): 5.40 (dd, 2H), 7.2-8.15 (m, 8H), 8.3-8.55 (m, 1H), 9.2 (m, 1H), 11.10 (s, 1H).

Anal. Calcd. for $C_{17}H_{13}N_5O_2 \cdot HCl$ (355.78): C, 57.38; H, 3.96; N, 19.68. Found: C, 57.13; H, 3.86; N, 19.42.

5,11-Dihydro-11-(2'-methylimidazol-1'-yl)acetyl-6*H*-pyrido[2,3-*b*][1,4]-benzodiazepin-6-one (**44**).

Compound **41** (3.49 g, 10.0 mmoles) was dissolved in diethylene glycol monomethyl ether (160 ml) and was hydrogenated over Raney Nickel, as described for **42**. Compound **44** was isolated 3.55 g (96%) as the pure hydrochloride, mp 286-289°; ir: 3200, 2800, 1692, 1660, 1610, 1460, 1425, 1375, 1320, 1290, 805 cm^{-1}; nmr (DMSO-d_6): 2.58 (s, 3H), 5.28 (dd, 2H), 7.4-8.1 (m, 8H), 8.3-8.6 (m, 1H), 11.8 (broad s, 1H).

Anal. Calcd. for $C_{18}H_{15}N_5O_2 \cdot HCl$ (369.80): C, 58.46; H, 4.36; N, 18.94. Found: C, 58.24; H, 4.28; N, 18.68.

3-(2'-Benzylaminobenzoyl)amino-2-chloropyridine (**45**).

3-(2'-Bromobenzoyl)amino-2-chloropyridine (prepared as described in reference [2]; 2.0 g, 5.35 mmoles), benzylamine (2.0 ml, 1.96 g, 18.3 mmoles), and copper(I) chloride (0.15 g) were mixed and stirred for 15 minutes at room temperature. A strong exothermic reaction took place, then the mixture was allowed to cool to ambient temperature, diluted with aqueous ammonia (50 ml), and after briefly stirring, the precipitate was filtered off. The precipitate was washed with water, dried (1.9 g, 64%), and recrystallized from acetone, mp 104-105°; ir: 3420, 3330, 1650, 1510, 1390, 1305, 1220, 805 cm^{-1}; nmr (deuteriochloroform): 4.45 (d, 2H), 6.5-8.6 (m, 12H), 8.9 (broad s, 2H).

Anal. Calcd. for $C_9H_{16}ClN_3O$ (337.80): C, 67.55; H, 4.77; N, 12.44. Found: C, 67.57; H, 4.81; N, 12.68.

3-(2'-Benzylaminobenzoyl)amino-2-chloropyridine *N*-Oxide (**46**).

Compound **35** (2.0 g, 7.06 mmoles), benzylamine (4.0 ml, 3.92 g, 36.6 mmoles) and copper(I) chloride (0.15 g) were mixed with stirring. After the initial exothermic reaction ceased, the mixture was stirred 1 hour at ambient temperature, the mixture was then diluted with aqueous ammonia (100 ml), and the crude product was extracted with ethyl acetate (3 × 50 ml). The dried extracts were evaporated and crude **46** (1.3 g, 52%) was crystallized from acetone affording pure product, mp 180-182°; ir: 3380, 1655, 1445, 1070, 985, 745 cm^{-1}; nmr (deuteriochloroform): 4.42 (d, 2H), 6.4-8.6 (m, 12H).

Anal. Calcd. for $C_{19}H_{16}ClN_3O_2$ (353.80): C, 64.50; H, 4.56; N, 11.88. Found: C, 64.55; H, 4.42; N, 11.88.

3-(2'-Chlorobenzoyl)amino-2-(2'-hydroxyethyl)aminopyridine (**47**).

3-(2'-Chlorobenzoyl)amino-2-chloropyridine (2.32 g, 10.0 mmoles) and ethanolamine (6 ml) were heated at reflux for 2 hours. Then the solution was diluted with water and extracted with ethyl acetate (50 ml). Evaporation of dried organic phase gave 1.3 g (45%) of the compound **47** (oil). An analytical sample was obtained by column chromatography (acetonitrile-acetone 9:1); ir (neat): 3300, 1650, 1460, 1390, 1285, 1235, 1070, 800, 770 cm^{-1}; nmr (deuteriochloroform): 4.0 (d, 2H), 4.25 (d, 2H), 7.3-7.7 (m, 4H), 7.85 (m, 1H), 8.15 (dd, 1H), 8.45 (dd, 1H).

Anal. Calcd. for $C_{14}H_{14}ClN_3O_2$ (291.73): C, 57.63; H, 4.48; N, 14.40. Found: C, 57.46; H, 4.93; N, 14.50.

3-(2'-Chlorobenzoyl)amino-2-(2'-hydroxyethyl)aminopyridine *N*-Oxide (**48**).

Compound **35** (2.83 g, 10.0 mmoles), ethanolamine (10 ml) and copper(I) chloride (0.2 g) were reacted as described for **46**. Crude product (2.1 g, 68%) was obtained on extraction from the aqueous suspension with ethyl acetate, and **48** was crystallized from methanol-ethyl acetate,

mp 214-217°; ir: 3370, 3200, 1652, 1370, 1240, 1110, 1080, 740, 690 cm^{-1}.

Anal. Calcd. for $C_{14}H_{14}ClN_3O_3$ (307.74): C, 54.63; H, 4.59; N, 13.66. Found: C, 54.38; H, 4.40; N, 13.79.

3-[(2''-Hydroxyethyl)-2'-aminobenzoyl]amino-2-chloropyridine (**49**).

3-(2'-Bromobenzoyl)amino-2-chloropyridine (1.55 g, 5 mmoles), ethanolamine (0.8 ml) and potassium carbonate (0.7 g) were heated in xylene (20 ml) at 140° during 6 hours. The solvent was evaporated and the major product was isolated by column chromatography (methylene chloride-ethyl acetate 1:1; $R_f \sim 0.5$, 0.7 g, 48%), mp 125-126° (from acetone); ir: 3450, 3340, 1665, 1590, 1573, 1515, 1460, 1385, 1305, 1255, 1220, 1085, 800, 730 cm^{-1}; nmr (deuteriochloroform): 3.43 (m, 2H), 3.83 (m, 2H), 4.10 (t, 1H, on addition of deuterium oxide it disappars), 6.7-7.0 (m, 1H), 7.3-7.8 (m, 4H), 8.21 (dd, 1H), 8.76 (dd, 1H), 8.75 (s, 1H, which disappears on addition of deuterium oxide).

Anal. Calcd. for $C_{14}H_{14}ClN_3O_2$ (291.73): C, 57.63; H, 4.83; N, 14.40. Found: C, 57.57; H, 4.83; N, 14.50.

1-[2'-(2''-Chloropyridylamido-3'')carboxy]phenyloxy-2-[2'-(2''-chloropyridylamido-3'')carboxy]phenylaminoethane (**50**).

This compound was isolated as the minor product in the previous preparation ($R_f \sim 0.25$, 0.20 g, 7%), mp 175-176° (from acetonitrile); ir: 3360, 3335, 3300, 1665, 1630, 1600, 1580, 1510, 1450, 1205, 810 cm^{-1}; nmr (deuteriochloroform): 3.90 (m, 2H), 4.60 (m, 2H), 6.85 (dd, 2H), 7.0-7.7 (m, 8H), 8.0-8.8 (m, 6H), 8.95 (dd, 1H).

Anal. Calcd. for $C_{26}H_{21}Cl_2N_5O_3$ (522.38): C, 59.78; H, 4.05; N, 13.40. Found: C, 59.78; H, 4.09; N, 13.50.

3-Amino-2-(2'-carboxyphenyl)aminopyridine *N*-Oxide (**51**).

Compound **37** (3.0 g, 13.2 mmoles) was dissolved in a mixture of toluene (80 ml) and 50% aqueous potassium hydroxide (50 ml), then 2.0 g (7.2 mmoles) of tetrabutylammonium chloride was added. After 4 hours heating under reflux the solvent mixture was separated by decantation and the residual mass dissolved in water (100 ml). The undissolved material was filtered off and the *p*H of the filtrate was adjusted to 3. Crude **51** precipitated, it was collected on a filter, washed with water and crystallized from DMF-water affording 2.1 g (65%) of the pure product, mp 228-230°; ir: 3465, 3310, 1628, 1665, 1518, 1255, 1220 cm^{-1}; nmr (DMSO-d_6): 5.4 (broad s, 2H), 6.1-8.1 (m, 8H).

Anal. Calcd. for $C_{12}H_{11}N_3O_3$ (245.23): C, 58.77; H, 4.52; N, 17.13. Found: C, 58.69; H, 4.69; N, 17.37.

3-Amino-2-(2'-carboxyphenyl-2-hydroxy)aminopyridine *N*-Oxide (**52**), and 1-Oxo-11-hydroxy-5,6-dihydro-11*H*-pyrido[2,3-*b*][1,4]benzodiazepin-6-one (**53**).

Compound **39** (2.0 g, 5.4 mmoles) was dissolved in a mixture of toluene (50 ml) and 50% aqueous potassium hydroxide (50 ml), and 0.5 g of tetrabutylammonium chloride was added. After 2 hours heating under reflux the reaction mixture was cooled and the *p*H adjusted to 3 with 2*N* hydrochloric acid. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 × 50 ml). The combined organic extracts were washed with water, dried and evaporated leaving 1.74 g of the crystalline product. This was recrystallized from ethyl acetate affording 1.2 g (91%) of the pure **53**, mp 274-275°; ir: 3370 (broad), 1668, 1606, 1245, 1280 cm^{-1}; nmr (DMSO-d_6): 6.7-8.0 (m, 7H), 8.88 (s, 1H, NH), 10.1 (s, 1H, OH).

Anal. Calcd. for $C_{12}H_9N_3O_3$ (243.22): C, 59.25; H, 3.72; N, 17.27. Found: C, 58.91; H, 3.36; N, 17.04.

From the mother liquor 0.28 g of the pure **52** was obtained after chromatography on a silica gel column (using ethyl acetate-light petroleum 8:2 as the eluent). On recrystallization from DMF-water **52** had mp 228-230°; ir: 3100-3600 (broad), 1695, 1610, 1590, 1515, 1390, 1290 cm^{-1}; nmr (DMSO-d_6): 4.8 (broad s, 1H), 6.5-7.5 (m, 5H), 8.1 and 8.55 (dd, 2H), 11.0 (broad s, 1H).

Anal. Calcd. for $C_{12}H_{11}N_3O_4$ (261.24): C, 55.16; H, 4.25; N, 16.09. Found: C, 55.04; H, 4.11; N, 15.78.

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