Novel Synthesis of 5,11-Dihydro-6*H*-pyrido[2,3-*b*]-[1,4]benzodiazepin-6-ones and Related Studies (1)

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5,11-Dihydro-6*H*-pyrido[2,3-*b*][1,4]benzodiazepin-6-one (**1**), a basic intermediate in the preparation of 11-α-aminoacetyl derivatives with important biological activities, has been obtained by a three-step synthesis starting from easily available isatoic anhydride and anhydro ornithine. Some model cyclisation reactions leading to 5-member ring derivatives **10** and **12** instead of 7-member ring analogues of **1**, are reported. Easy transformations of the tetrahydro congener of **1**, *i.e.*, compound **4** into **19**, which actually represents a tetrahedral intermediate in the transformation of **5** into **4**, is noticed. Further rearrangement of **19** into spiro compound **20**, and return of the latter into **5** is described.

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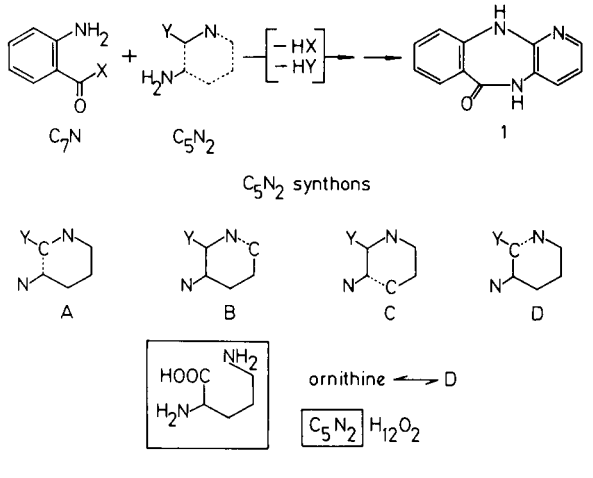
Introduction.

It has been reported in the patent literature (2,3) that tricyclic compound 5,11-dihydro-6*H*-pyrido[2,3-*b*][1,4]-benzodiazepin-6-one (**1**) could be prepared by cyclisation of 2-chloro-3-(2'-aminobenzoyl)aminopyridine under harsh conditions (boiling 1,2,4-trichlorobenzene). In our hands this approach afforded **1** in non-reproducible yields, while initiation of the reaction by strong acid was required. Besides, the overall yield on **1** starting from 2-nitrobenzoic acid and 2-chloro-3-aminopyridine did not exceed 20-25% (four steps), and required the not readily-available 2-chloro-3-aminopyridine. In another approach, sodium amide promoted condensation of the methyl ester of 2-aminobenzoic acid with 3-aminopyridine was claimed (4).

Searching for the more economic and shorter way to this crucial intermediate for preparation of its *N*-11-acyl-substituted derivatives with ulcerostatic, and possibly some other activities, simple retrosynthetic analysis suggested a convergent scheme that should make use of some anthranilic acid derivatives as a synthetic equivalent for C_7N synthon (5) and of a C_5N_2 unit which, in turn, should originate from the natural pool of small molecules (Scheme I). In the synthons **A** to **D** some logic connectivities in the C_5N_2 unit are exemplified. An additional bond formation, indicated by dotted line, is required to close the reduced pyridine ring.

SCHEME I.

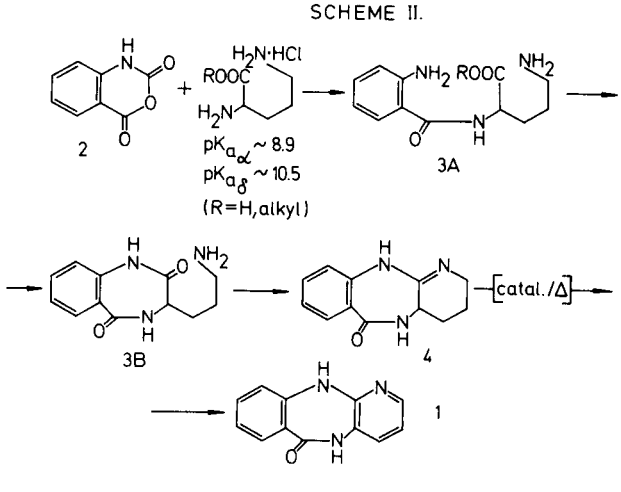


Such analysis indicated readily available diamino acid ornithine (6,7) as the synthetic equivalent of choice for synthon **D**, *i.e.*, for construction of 2,3-difunctionalized reduced pyridine moiety. This paper describes successful elaboration of this basic concept.

Results and Discussion.

In the first series of attempts isatoic anhydride was reacted with ornithine or its ethyl ester, both as the hydrochlorides. Varying reaction conditions *i.e.* solvent, temperature, *etc.* (see Experimental) only produced **4** in poor yields. Coppola reviewed (8) reactions between isatoic anhydride and α-amino acids; low to modest yields were cited regularly. Only recently Gates (9) found specific conditions for the conversion of isatoic anhydride with glycine into the parent 1,4-benzodiazepine-2,5-dione in 92% yield;

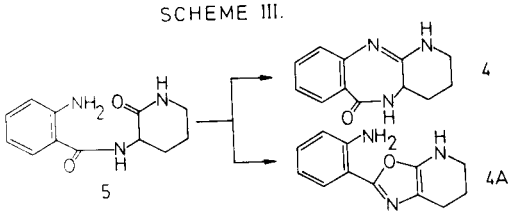
SCHEME II.



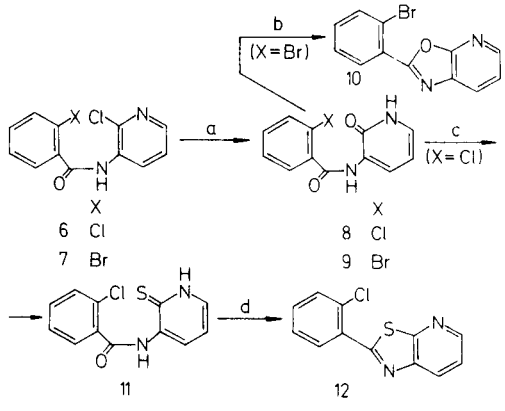
such a high yield seems to be reserved to the glycine case only. Designing the condensations with ornithine esters we anticipated that under proper reaction conditions partial deprotonation of the less basic α-amino group ($pK_a \sim 9$) should be assured, leaving completely protonated the δ-amino group ($pK_a \sim 10.5$). Consequently, we expected that the most satisfactory reaction sequence leading to **4** should be that represented in the Scheme II.

Formation of the 7-member ring in **3B** (Scheme II), being entropically less favourable, is regarded as indispensable before formation of the 6-member tetrahydropyridine ring in **5**, since this intermediate was expected to close to the 5-membered 4,5-disubstituted oxazole ring in **4A**, rather than to undergo 7-member ring closure in **4** (Scheme III). Such expectation was based on the results from the series of experiments performed simultaneously with the dehydro congeners of **5**, *i.e.*, compounds **6** and **7**, as shown in the Scheme IV.

SCHEME III.



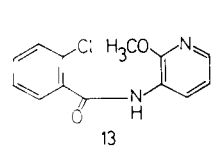
SCHEME IV.



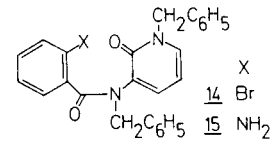
a. PPA/NH_4Cl/180°C, b. P_2O_5/200°C, c. P_2S_5/Py/60° d. Py/Δ.

Attempts to perform an ammonolysis reaction of the arylic halogen in **6** or **7** by heating in polyphosphoric acid in the presence of ammonium chloride gave pyridones **8** and **9** in high yields. When compound **6** was heated in the methyl ester of polyphosphoric acid/ammonium chloride, compound **13** was isolated.

The structure of the compound **9** was further confirmed by its double benzylation into **14** and subsequent transformation into **15**.



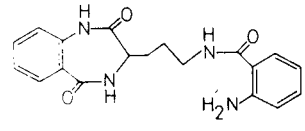
13



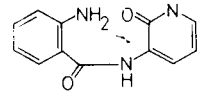
	X
14	Br
15	NH_2

Pyridone **8** and its thio analogue **11** cyclised easily into the oxazolopyridine **10** and the thiazolopyridine **12**, respectively. The intermediary thiolactam **11** was isolated quantitatively when thiation of **8** was performed at lower temperatures. Having these results in hand, it was interesting to see if the 2-amino congener of compounds **8** and **9**, *i.e.*, compound **16** will undergo cyclisation into a 7-member or a 5-member ring.

In order to prepare compound **16**, 3-aminopyrid-2-one (10) was required. Thus we investigated two approaches, *i.e.*, the modified procedure of Bintz (11) which starts from 2-hydroxypyridine and affords 3-aminopyrid-2-one on nitration and reduction, as well as site-selective ammonolysis of commercially available 2,3-dihydroxypyridine. The first two-step approach afforded compound **16** in 20% overall yield. The second approach, based on the general method for ammonolysis of phenols (12) actually led to the desired 3-amino isomer in rather low yield. Although the reaction with ammonia seemed to go to completion in the presence of an equimolar quantity of zinc(II) chloride, the elimination of the Zn(II) ions produced extensive coprecipitation and consequently lowered the yield of **16** (see Experimental).



17



16

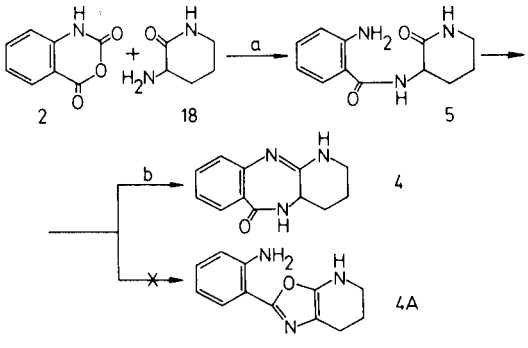
Compound **16**, however, neither cyclised into the tricyclic parent system **1**, nor into the imidazopyridine analogue of **10** and **12**, but yielded a complex mixture of presumably polymeric products. The elemental analysis of two of them indicated the absence of oxygen and a low percentage of oxygen, respectively. Their ir and nmr spectra were not readily interpretable in an unambiguous manner, therefore we hesitate to assign to these products possible structures.

Compound **15**, *i.e.*, a double *N*-protected derivative of **16** afforded complex mixture of degradation products on heating in phosphorus pentoxide.

From the above results it can be concluded that in the absence of complicating side reactions, compounds **8** and **11** cyclise into the bicyclic azolopyridines **10** and **12**

because of the driving force of aromaticity. Therefore we have carried out a number of trial reactions shown in Scheme II, *i.e.*, condensations of isatoic anhydride and ornithine or its esters as hydrochlorides. These trial reactions are summarized in Table I. Low yields with **4** were regularly obtained. The intermediate **3B** was not isolated. Instead, its γ-anthranylyl amide **17** has been isolated in some cases. Therefore we decided to try the use of "anhydro ornithine", which represents a convenient, intramolecularly protected derivative of ornithine, in spite of the fact that our earlier experience with **8** and **11** suggested formation of **4A** instead of **4** (Scheme V).

SCHEME V.



a. CH_3CN/Δ, b. AcOH/Δ or P_2O_5/Δ

When 3-aminopiperidin-2-one (**18**), "anhydro ornithine", prepared from ornithine by the modified procedure (13,14), was reacted with isatoic anhydride, compound **5** was formed in nearly quantitative yield. To our surprise its cyclisation into **4** was accomplished on brief heating in various solvents or in phosphorus pentoxide at 170°, while no formation of **4A** was observed. Obviously, during formation of **4** the strained, partially aromatic tetrahydrooxazolopyridine moiety in **4A** is disfavoured in favour to the less strained 7-member ring. Interestingly, there is only one example and that stems from the carbocyclic chemistry, where a systematic study revealed that cyclodehydration of 2-(4'-oxo)pentanylcyclohexane preferably led to a 5-member and not a 7-member bicyclic enones (16). There is a report (17) on the use of phosphorus pentoxide for arylation of dialkylamines with pyrid-2-one, that is an intermolecular reaction analogous to the ring closure into **4**.

The carbon-nitrogen double bond in **4** is formally represented as being within the 7-member ring. It is obvious, however, that there exists prototropic equilibrium within the amidine system **4**. The position of such equilibrium was determined for 2-anilinopyridines (15).

In the last step of our new approach to **1**, compound **4** was easily dehydrogenated using palladium on charcoal in some inert solvents (Scheme VI). Dehydrogenation in pyridine required prolonged heating, while in refluxing quinoline partial decomposition occurred. Some puzzling transformations of **4** offered an even more effective approach to **1**.

Thus, solution of hydrochloride **4** in water afforded, on prolonged standing at room temperature, compound **19**. It was already noted that the high basicity ($pK_a \sim 11$-12) of the amidinic system (18) makes it a very strong intramolecular nucleophile for amide bonds, whereby formation of a tetrahedral intermediate during acyl transfer from the *N*-acylamino to the *N*-acylamidino group was postulated (19). Compound **19** represents to our knowledge the first case where such a tetrahedral intermediate was isolated. It has been isolated as the hydrate-hydrochloride and exhibited rather high solubility in water and pyridine. Moreover, it underwent much faster aromatization by heating over palladium on charcoal in pyridine than the starting compound **4**.

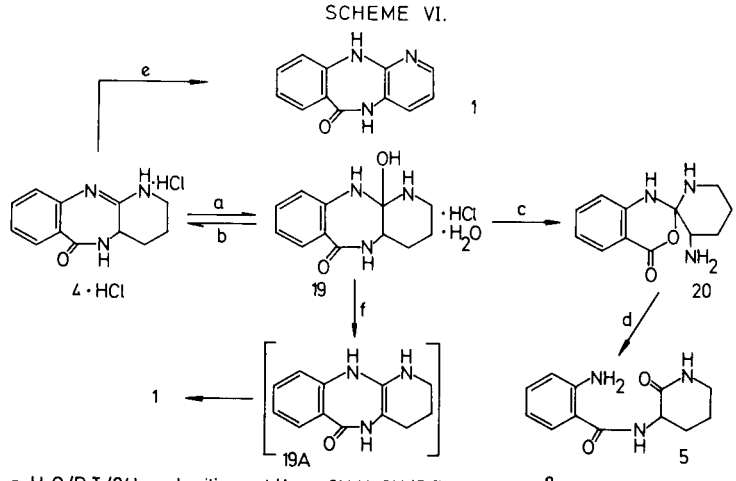
We tentatively explain such diverse rates of dehydrogenation of **4** and **19** by the formation of the isomeric **19A** in the first step of reaction of **19**, which should be more prone to aromatization than its double bond-regioisomer **4**. Furthermore, compound **19** on brief heating on silica gel plates could reversibly be dehydrated into **4**, while on solution in 2*N* sodium hydroxide it rearranged into the spiro compound **20**. The structure of this compound was confirmed by microanalytical data and by the characteristic ir bands at 3460, 3390 and 3350 cm^{-1} (NH, NH_2) as well as the broad band at 2900 cm^{-1} (hydrate) together with the band at 1645 cm^{-1} (carbonyl group of the cyclic vinylogous carbamate subunit). The nmr spectrum revealed the presence of aliphatic protons within the piperidine subunit and four aromatic protons. A similar lactam-lactone rearrangement, initiated by nucleophilic attack of an aminal oxygen anion, has been documented recently (20). Compound **20** rearranged on melting into the starting piperidinone derivative **5** in accordance with its unstable aminal-like structure. Some related carbon-nitrogen bond cleavage reactions in amidines have been intensively studied by Hesse *et al* (21).

In conclusion, it can be stated that a novel and economic approach to the important tricyclic compound **1** has been accomplished starting from "anhydro-ornithine" and isatoic anhydride. The easy availability of the starting materials and high (~80%) overall yield makes this three-step synthesis of **1** highly attractive for its large scale production.

EXPERIMENTAL

Melting points were determined on a Mettler FP 5 melting point apparatus and are uncorrected. Infrared spectra were obtained on a Perkin Elmer M 297 spectrometer using potassium bromide discs if not stated otherwise. The nmr spectra were determined on a Perkin Elmer R 12 instrument and the chemical shifts are given in ppm relative to TMS as the internal standard. Thin layer chromatography (tlc) was performed on aluminium plates precoated with Merck's silica gel 60 F_{254}. Column chromatographic purifications were carried out with Merck silica gel

SCHEME VI.



a. H_2O/R.T./24hrs, b. silica gel/Δ, c. 2N NaOH/R.T., d. Δ/ 200°C, e. Pd/C/solv./Δ, f. Pd/C/Py/1-2 hrs.

Table I

Results of Attempted Acylations of Ornithine and its Ester with Isatoic Anhydride

Run	Mol. ratio	Solvent	Temp. (°C)	Time (hours)	Yield (a) on **4**
1-6	1:1.0-2.0	DMF	130-180	1-4	5-8%
7-12	1:1.0-2.0	Pyridine	80-116	1-24	10-12%
13,14	1:1-2	Acetic acid	rt-110	1-24	3-4%
15-17	1:1-2	Water/acetic acid	rt-100	1-10	3-4%
18-21	1;1.1	Methanol	rt-64	12	traces

(a) Formation of a number of side-products indicated by tlc. One of them, compound **17**, was isolated in the preparation 7-12, as described in the Experimental.

(0.05-0.2 mm). Organic extracts were regularly dried over sodium sulfate and evaporated *in vacuo*.

3-Aminopiperidin-2-one (**18**).

Ornithine hydrochloride (33.7 g, 0.20 moles) was dissolved in methanol (200 ml) and to the ice-cooled solution thionyl chloride (29.8 g, 0.25 moles) was added dropwise. After stirring for 5-6 hours at room temperature, the precipitate initially formed and then dissolved completely. After stirring 14 hours, the solvent was evaporated, the residual glassy oil was dissolved in water (200 ml) and passed through a short column packed with Dowex-2 (250 g, OH-form). Fractions with *p*H 8.5-9 contained ornithine methyl ester as confirmed by tlc ($R_f \sim 0.2$, methanol-concentrated ammonia 7:3 as eluent). These fractions were collected, briefly heated on bath at 50°-60° and then evaporated. The oily residue (17.8 g, 90%) consisted of pure **18** which partially crystallized on standing. The oily crystals melted slowly above 30-35°, lit (22), mp 38-41°; ir (nujol): 3340, 3200 (broad), 1650, 1375, 1345, 1300, 995, 930, 640, 595 cm^{-1}; nmr (deuteriochloroform): 1.5-2.3 (m, 4H), 3.1-3.5 (m, 2H), 7.4 (broad s, 2H, NH_2).

Anal. Calcd. for $C_5H_{10}N_2O$ (114.15): C, 52.60; H, 8.76; N, 24.45. Found: C, 52.29; H, 8.87; N, 24.45.

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

Method A.

Isatoic anhydride (8.15 g, 0.05 moles) and ornithine ethyl ester dihydrochloride (11.7 g, 0.055 moles) were heated in pyridine (40 ml) under reflux for 8 hours. After about 1-2 hours the solid material dissolved completely. Upon tlc (ethyl acetate-methanol, 1:1 as eluent) numerous spots were observed. On chilling with ice overnight, 1.38 g (11%) of the pure hydrochloride of **4** separated as prismatic crystals. On recrystallization from ethanol, **4** melted above 300°; ir: 3180, 2830, 1685, 1642, 1478, 1230, 1195, 832, 820, 765, 758, 610 cm^{-1}; nmr (deuterium oxide): 2.1 (broad s, 4H), 3.55 (broad m, 2H), 4.4 (broad m, 1H), 7.1-8.1 (m, 4H).

Anal. Calcd. for $C_{12}H_{13}N_3O_2$·HCl (251.71): C, 57.26; H, 5.61; N, 16.69. Found: C, 56.80; H, 5.58; N, 16.63.

3-3'-(2''-Aminobenzoyl)aminopropyl-1,4-benzodiazepine-2,5-dione (**17**).

The mother liquors of the above reaction were evaporated to dryness. The residue was placed on a silica gel column (300 g) and eluted with ethyl acetate-ethanol (6:4). The main fractions contained unreacted isatoic anhydride, while in the fractions 210-215 (about 10 ml per fraction), 0.9 g (5%) of pure **17** was isolated, mp 204-205°; ir: 2900-3500 (broad), 1680, 1665, 1610, 1585, 1525, 1485, 1448, 1405, 1263, 1160, 755 cm^{-1}; nmr (DMSO-d_6): 1.5-1.9 (6H), 6.64 (t, 1H), 7.0-8.5 (m, 8H), 10.3 (broad s, 3H).

Anal. Calcd. for $C_{19}H_{20}N_4O_3$ (352.38): C, 64.76; H, 5.72; N, 15.90. Found: C, 64.77; H, 5.75; N, 15.21.

In Table I some variations of the conditions to the above procedure and the corresponding yields are presented.

Method B.

3-(2'-Aminobenzoyl)aminopiperidin-2-one **5** (5.3 g, 12.9 mmoles) was mixed to phosphorus pentoxide (6.0 g) and homogenous mixture melted. After 40 minutes heating at 220°, the reaction mixture was cooled and poured into ice-water (100 ml). Concentrated hydrochloric acid (2 ml) was added, undissolved material was filtered off and the *p*H of the filtrate was adjusted to *p*H 9 with 50% aqueous sodium hydroxide. After chilling

with ice, the crude product was collected on a filter, washed with water and dried affording 1.89 g (88%) of pure **4** as the free base, which on crystallization from dimethylformamide melted at 293-295°; ir: 3260, 3160, 1650, 1630, 1480, 1465, 1425, 1390, 1365, 1330, 1180, 810 cm^{-1}; nmr (DMSO-d_6): 2.1 (broad s, 4H), 3.55 (broad s, 2H), 4.3 (broad s, 1H), 7.2-8.1 (m, 4H), 8.9 (s, 1H, NH).

Anal. Calcd. for $C_{12}H_{13}N_3O$ (215.25): C, 66.96; H, 6.09; N, 19.52. Found: C, 66.78; H, 6.33; N, 19.74.

3-(2'-Aminobenzoyl)aminopiperidin-2-one (**5**).

3-Amino piperidin-2-one (**18**) (11.4 g, 0.1 mole) was dissolved in acetonitrile (110 ml) on heating at 55-60°. At this temperature isatoic anhydride (16.3 g, 0.1 mole) was added in portions. After 10-15 minutes stirring at reflux solution was complete, during which an intensive evolution of gas was observed. After about 30 minutes, product **5** began to crystallize. Reflux was continued for 3 hours. After chilling with ice the product was collected on a filter and dried (18-20 g). Evaporation of the mother liquors and crystallization of the residue from a small quantity of 2-propanol yielded an additional 2-3 g of **5** (total yield 22 g, 96%). On recrystallization from 2-propanol, **5** had mp 169-170°; ir: 3440, 3330, 1665, 1610, 1585, 1538, 1325, 1305, 1260, 1158, 755 cm^{-1}; nmr (DMSO-d_6): 1.88 (broad m, 4H), 3.16 (broad m, 2H), 4.35 (d, J = 8 Hz), 6.4-7.7 (m, 7H, NH, NH_2), 8.25 (d, 1H, NH).

Anal. Calcd. for $C_{12}H_{15}N_3O_2$ (233.27): C, 61.80; H, 6.25; N, 18.02. Found: C, 61.96; H, 6.55; N, 18.36.

3-(2'-Chlorobenzoyl)amino-2-chloropyridine (**6**).

To 2-chlorobenzoyl chloride (7.4 g, 41 mmoles) dissolved in toluene (30 ml), first pyridine (4 ml, 40 mmoles) and thereafter 2-chloro-3-aminopyridine (5.27 g, 41 mmoles) was added. The acylation was performed at reflux during 1 hour. After evaporation to dryness, the residue was slurried in water (200 ml), then extracted with chloroform (3 × 100 ml). The combined organic extracts were washed with dilute hydrochloric acid, dried and evaporated. The crude product (10.7 g, 98%) was crystallized from 2-propanol, mp 114-115°; ir: 3280, 1665, 1520, 1390, 1305, 1070, 810, 685, 650 cm^{-1}; nmr (deuteriochloroform): 7.2-7.7 (m, 4H), 8.5-8.9 (broad s, 1H).

Anal. Calcd. for $C_{12}H_8ClN_2O$ (267.12): C, 53.94; H, 3.02; N, 10.48. Found: C, 53.77; H, 2.92; N, 10.11.

3'-Bromobenzoylaminop-2-chloropyridine (**7**).

This compound has been prepared using the same procedure as described for **6** starting from 2-bromobenzoyl chloride (16.7 g, 10 ml, 76 mmoles). On recrystallization from 2-propanol, 21 g (89%) of pure **7** was obtained, mp 120-121°; ir: 3275, 1665, 1515, 1395, 1305, 1070, 805, 745, 675 cm^{-1}; nmr (deuteriochloroform): 7.2-7.9 (m, 5H), 8.22, 8.30 (dd, 1H), 8.5 (broad s, 1H), 8.9, 9.3 (dd, 1H).

Anal. Calcd. for $C_{12}H_8BrN_2O$ (311.66): C, 46.10; H, 2.90; N, 8.96. Found: C, 46.09; H, 2.62; N, 9.10.

3-(2'-Chlorobenzoyl)aminopyrid-2-one (**8**).

Compound **6** (3.0 g, 11.2 mmoles) and ammonium chloride (20.0 g, 0.26 moles) were slurried in polyphosphoric acid (PPA, 55 g). The reaction mixture was heated at 180° for 12 hours, then cooled and poured into water (300 ml). The crude product which precipitated was collected on a filter. On recrystallization from 96% ethanol, 2.50 g (89%) of pure **8** was obtained, mp 194-195°; ir: 3350, 1650, 1530, 1475, 1440, 1370, 1285, 1245, 1130, 1045, 752, 745, 655 cm^{-1}; nmr (deuteriochloroform): 6.45 (t, 1H), 7.1-8.0 (m, 5H), 8.70, 8.85 (dd, 1H), 9.2 (broad s, 1H, NH), 13.2 (broad s, 1H, NH).

Anal. Calcd. for $C_{12}H_9ClN_2O_2$ (248.66): C, 57.96; H, 3.65; N, 11.26. Found: C, 57.64; H, 3.57; N, 11.00.

3-(2'-Bromobenzoyl)aminopyrid-2-one (**9**).

This compound was prepared in 77% yield starting from **7** as described above in preparation of **8**. On recrystallization from methanol it melted at 201-202°; ir: 3230, 1630, 1510, 1465, 1360, 1245, 1135, 1040, 945, 890, 760 cm^{-1}; nmr (DMSO-d_6): 6.40 (t, 1H), 7.1-8.1 (m, 6H), 8.40, 8.52 (dd, 1H), 9.4 (broad s, 1H, NH).

Anal. Calcd. for $C_{12}H_9BrN_2O_2$ (293.12): C, 49.16; H, 3.09; N, 9.56. Found: C, 49.17; H, 3.07; N, 9.37.

2-(2'-Bromophenyl)oxazolo[5,4-*b*]pyridine (**10**).

Compound **9** (0.72 g, 2.5 mmoles) and phosphorus pentoxide (0.30 g) were well mixed and then the reaction vessel was immersed into oil-bath preheated to 200°. The resulting melt was stirred magnetically for 45 minutes then it was allowed to cool and water (20 ml) was added. The crystalline material which separated was collected on a filter, washed with water and dried affording 0.66 g (98%) of crude **10**, which on recrystallization from 2-propanol melted at 98-99°; ir: 1613, 1540, 1465, 1225, 1015, 805, 765, 725 cm^{-1}; nmr (deuteriochloroform): 7.2-8.7 (m, 7H).

Anal. Calcd. for $C_{12}H_7BrN_2O$ (275.11): C, 52.39; H, 2.56; N, 10.18. Found: C, 52.17; H, 2.58; N, 10.39.

3-(2'-Chlorobenzoyl)aminothiopyrid-2-one (**11**).

Compound **8** (1.0 g, 4.02 mmoles) and phosphorus pentasulfide (1.0 g, 4.5 mmoles) were slurried in pyridine (10 ml) at room temperature then the temperature was gradually raised to 60° during 0.5 hour and the reaction proceeded at that same temperature for another 3.5 hours. The cooled reaction mixture was poured into ice-water (100 ml) with vigorous stirring. After 1 hour, the precipitated crude product was filtered, dried, then treated with ethyl acetate and the undissolved material was filtered and dried affording 1.9 g (quantitative) of **11**. On recrystalization from ethyl acetate it had mp 159-160°; ir: 3350, 1690, 1650, 1609, 1530, 1482, 1430, 1395, 1355, 1298, 1235, 1135, 1045, 970, 890, 710 cm^{-1}; nmr (pyridine-d_5): 6.8-9.0 (m, 7H), 9.92 (s, 1H).

Anal. Calcd. for $C_{12}H_{19}ClOS$ (264.73): C, 54.44; H, 3.42; N, 10.58. Found: C, 54.70; H, 3.23; N, 10.27.

2-(2'-Chlorophenyl)thiazolo[5,4-*b*]pyridine (**12**).

This compound has been prepared from the same starting material as **11**, but the reaction time at reflux was 4 hours. On pouring the reaction mixture on ice and stirring, the crude product precipitated (1.9 g, 95%) which on crystallization from ethanol had mp 111-112°; ir: 1590, 1582, 1550, 1480, 1430, 1390, 1288, 1275, 1069, 800, 750 cm^{-1}; nmr (deuteriochloroform): 7.2-8.9 (m, 7H).

Anal. Calcd. for $C_{12}H_7ClN_2S$ (246.65): C, 58.43; H, 2.86; N, 11.36. Found: C, 58.50; H, 2.93; N, 11.36.

3-(2'-Chlorobenzoyl)amino-2-methoxypyridine (**13**).

3-(2'-Chlorobenzoyl)amino-2-chloropyridine (**6**, 2.0 g, 7.5 mmoles) and ammonium chloride (4.0 g, 75 mmoles) were added to polyphosphoric acid methyl ester (70 g) and then stirred and heated at 140° for 3 hours. On cooling to room temperature water (300 ml) was added to the reaction mixture and the resulting slurry was extracted with ethyl acetate (2 × 150 ml). Organic extracts were dried, evaporated and the residual oil crystallized from ether affording 1.8 g (94%) of pure **13**, mp 138-130°; ir: 3300, 1675, 1640, 1600, 1587, 1515, 1450, 1430, 1365, 1215, 1100, 1052, 1032, 905, 753 cm^{-1}; nmr (deuteriochloroform): 3.65 (s, 3H), 6.35 (t, 1H), 7.0-7.3 (m, 1H), 7.4-8.0 (m, 4H), 8.58, 8.70 (dd, 1H), 9.4 (broad s, 1H).

Anal. Calcd. for $C_{13}H_{11}ClN_2O_2$ (262.69): C, 59.43; H, 4.22; N, 10.66. Found: C, 59.75; H, 4.31; N, 10.76.

3-[*N*-(*o*-Bromobenzoyl)-*N*-benzyl]amino-1-benzylpyrid-2-one (**14**).

Compound **9** (8.0 g, 27.3 mmoles) was added to an ice-cooled mixture of toluene (150 ml) and 50% aqueous potassium hydroxide (125 ml). After short period of stirring benzyl chloride (8.6 g, 68.2 mmoles) and tributylbenzylammonium chloride (8.6 g, 68.2 mmoles) and tributylbenzylammonium chloride (3.8 g, 13.6 mmoles) were added. The reaction proceeded with vigorous stirring 2 hours in an ice-water bath, then 16 hours at ambient temperature. The reaction mixture was adjusted to *p*H 1-2 with concentrated hydrochloric acid and the crude product which separated was collected on a filter (8.5 g). A second crop (3.5 g) was obtained on evaporation of the separated and dried organic phase. Crude **14** (12.0 g, 98%) was recrystallized from ethanol, mp 157-158°; ir: 1655, 1605, 1400, 1380, 1310, 1212 cm^{-1}; nmr (deuteriochloroform): 4.15-6.10 (m, 4H),

6.8-7.7 (m, 17H).

Anal. Calcd. for $C_{26}H_{21}BrN_2O_2$ (473.36): C, 65.96; H, 4.47; N, 5.91. Found: C, 65.64; H, 4.51; N, 5.92.

3-[*N*-(*o*-Aminobenzoyl)-*N*-benzyl)amino-1-benzylpyrid-2-one (**15**).

Compound 14 (0.50 g, 1.06 mmoles) and copper(I) chloride (0.15 g) were added to concentrated aqueous ammonia (10 ml) in a Parr all purpose bomb. The reaction mixture was stirred magnetically and heated at 180° for 1 hour. Then the reaction mixture was allowed to cool fist to ambient temperature, then cooled to ice-bath temperature and crude product (0.31 g, 72%) was filtered. On recrystallization from 2-propanol it had mp 170-171°; ir: 3470, 3320, 1650, 1630, 1615, 1590, 1400, 1220, 1175, 725 693 cm^{-1}; nmr (deuteriochloroform): 4.6 (broad s, 2H, NH_2), 5.12 (s, 4H, $2CH_2$), 5.77 (t, 1H), 6.3-7.5 (m, 6H), 7.28 (s, 10H).

Anal. Calcd. for $C_{26}H_{23}N_3O_2$ (409.47): C, 76.26; H, 5.66; N, 10.26. Found: C, 76.27; H, 5.75; N, 10.13.

3-Aminopyrid-2-one.

To the concentrated aqueous ammonia (12 ml) placed in a Parr all-purpose bomb (45 ml), zinc(II) chloride (2.8 g, 20.0 mmoles) was added portionwise. To the resulting solution, 2,3-dihydroxypyridine (2.0 g, 18.0 mmoles) was added and the reaction mixture stirred on a magnetic stirrer and heated at 195-200° for 11 hours. The mixture was then allowed to cool to about 50°, and with 40% aqueous sodium hydroxide the *p*H was adjusted to 11. Thereafter a stream of hydrogen sulfide was passed into the solution and after 2 hours the final *p*H was about 8. The zinc sulfide precipitate was separated by centrifugation, the precipitate was washed in the curvette with alkaline water (*p*H 8, 2 × 50 ml) and the combined supernatants were evaporated to dryness. Crude 3-aminopyrid-2-one (1.7 g) was triturated with hot methanol (20 ml), the supernatant was separated, evaporated and the pure product obtained by sublimation at 220°/0.02 mm Hg (0.28 g, 14%); mp 132-133°, lit (11), mp 134-137°; ir: 3425, 3305, 3130, 3050, 2800 (broad), 1650, 1595, 1468, 1290, 1284, 1190, 965, 935, 922, 760 cm^{-1}; nmr (DMSO-d_6): 6.10 (m, 1H), 6.58 (dd, J_m = 2.0 Hz, 1H, J_o = 6.0 Hz), 6.72 (dd, J_o = 6.0 Hz), 11.5 (broad s, 1H).

3-(2'-Aminobenzoyl)aminopyrid-2-one (**16**).

Isatoic anhydride (2.38 g, 14.5 mmoles) and 3-aminopyrid-2-one (1.6 g, 14.5 mmoles) in toluene (20 ml) were heated under reflux for 12 hours. On cooling, crude **13** precipitated (3.2 g, 96%), which was purified first by dissolution in 5% hydrochloric acid, filtration with charcoal and precipitation with concentrated ammonia, then by recrystallization from ethyl acetate, mp 228-229°; ir: 3455, 3375, 3350, 3125, 1640, 1520, 1437, 1275, 1165 cm^{-1}; nmr (DMSO-d_6): 3.5 (broad s, 1H), 6.2-8.6 (m, 7H), 9.35 (s, 1H), 12.3 (broad s, 1H).

Anal. Calcd. for $C_{12}H_{11}N_3O_2$ (229.24): C, 62.87; H, 4.84; N, 18.32. Found: C, 62.70; H, 4.69; N, 18.61.

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

Hydrochloride of the compound **4** (5.02 g, 20.0 mmoles) was dissolved in pyridine (120 ml), palladium/charcoal (0.2 g) was added and the reaction mixture was heated under reflux for 24 hours. Thereafter the catalyst was filtered off, the solvent evaporated to dryness and the crude product was crystallized from DMF-water affording 4.8 g (quantitative) of pure **1**, mp 283-285°, lit (2); mp 286-288°; ir: 3260, 3180, 1670, 1603, 1470, 755, 740, 615 cm^{-1}; nmr (DMSO-d_6): 6.9-8.1 (m, 7H), 10.0 (broad s, 2H).

Anal. Calcd. for $C_{12}H_9N_3O$ (211.21): C, 68.23; H, 4.29; N, 19.90. Found: C, 68.41; H, 4.25; N, 20.15.

Compound **1** could be obtained using the above procedure but heating a solution of the compound **19** in pyridine for only 2 hours. The same isolation as described above afforded **1** in quantitative yield.

1,2,3,4,4a,5,11-Hexahydro-11a-hydroxy-6*H*-pyrido[2,3-*b*][1,4]benzodiazepin-6-one Hydrochloride Hydrate (**19**).

The hydrochloride of compound **4** (2.51 g, 10.0 mmoles) was dissolved in water (80 ml) and stirred at ambient temperature for 36 hours. The reaction was followed by tlc (methanol-concentrated ammonia 7:3) monitoring formation of the spot at $R_f \sim 0.5$. Thereafter the aqueous suspension was diluted with 2-propanol (20 ml) and the precipitate was collected on a filter (2.52 g, 88%), mp. During heating transformation into **4** occurred; ir: 3460, 3160, 1692, 1610, 1505, 1480, 1435, 1410, 1235, 800, 760 cm^{-1}; nmr (DMSO-d_6 + few drops of trifluoroacetic acid-d_1): 1.75 (broad s, 4H), 2.75 (broad s, 2H), 3.65 (broad s, 1H), 6.9-8.0 (m, 4H), 8.5 (broad s, 1H).

Anal. Calcd. for $C_{12}H_{18}ClN_3O_3$ (287.73): C, 50.09; H, 6.30; N, 14.60. Found: C, 49.73; H, 6.40; N, 14.83.

5-Amino-2-piperidino-6-spiro-2'-benzo-1',2',3',8'-tetrahydro-1',3'-oxazin-8'-one (**20**).

Compound **19** (350 mg, 1.5 mmoles) was dissolved in water (15 ml) and 1 ml of 25% aqueous sodium hydroxide was added dropwise under stirring at room temperature. The reaction proceeded for 2 hours and was followed by monitoring the disappearance of the tlc spot at $R_f \sim 0.65$ (methanol-concentrated ammonia 7:3 as eluent). Thereafter the *p*H of the reaction solution was adjusted to 7 with diluted hydrochloric acid and the water was evaporated *in vacuo*. The residue was dissolved in methanol and purified on a silica gel column (35 g) using methanol as the eluent. There was obtained 300 mg (79%) of pure **20**, mp 212-214° on crystallization from ethanol; ir: 3460, 3390, 3350, 2900, 1640, 1590, 1528, 1395, 1290, 1260, 960, 755 cm^{-1}; mr (deuterium oxide): 1.9 (broad s, 4H), 3.07 (t, 2H), 4.4 (broad s, 2H), 4.7 (s, HDO), 6.9 (d, 2H), 7.2-7.6 (m, 2H).

Anal. Calcd. for $C_{12}H_{17}N_3O_3$ (251.29): C, 57.35; H, 6.82; N, 16.72. Found: C, 57.35; H, 6.90; N, 16.51.

On cooling the melt of **20** and its dissolution in water, tlc revealed the presence of only one spot at $R_f \sim 0.3$ (ethyl acetate-methanol 9:1 as eluent), while the ir spectrum confirmed that **20** was quantitatively transformed on melting into compound **5**.

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