# Tetrahydrocyclopenta[*e*]pyrido[3,2-*b*][1,4]diazepine and -cyclopenta[*e*]pyrido[2,3-*b*][1,4]diazepine Derivatives



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In pursuing the study on compounds obtained by condensation of *N*-monoalkylated aromatic and heteroaromatic diamines with α- and β-ketoesters, 7,8,9,10-tetrahydrocyclopenta[*e*]pyrido[3,2-*b*][1,4]diazepin-6(5*H*)-ones **4a**, **4b** and 5,7,8,10-tetrahydrocyclopenta[*e*]pyrido[2,3-*b*][1,4]diazepin-9(6*H*)-ones **5a**, **5b** were prepared starting from 2,3-diaminopyridine or 2,3-diamino-5-chloropyridine and ethyl 2-oxo-cyclopentanecarboxylate. Compounds **4a,b** and **5a,b** suffer thermally induced ring contraction to the imidazolone derivatives **8a,b** and **7a,b** respectively and are unsuitable for preparing diazepinone derivatives. Thus the methylated diazepinones **15**, **17** and **18**, stable on heating, were prepared. Compound **17** was transformed into the clozapine analogue **22**, through the diazepinthione **20** and its *S*-methyl derivative **21**.

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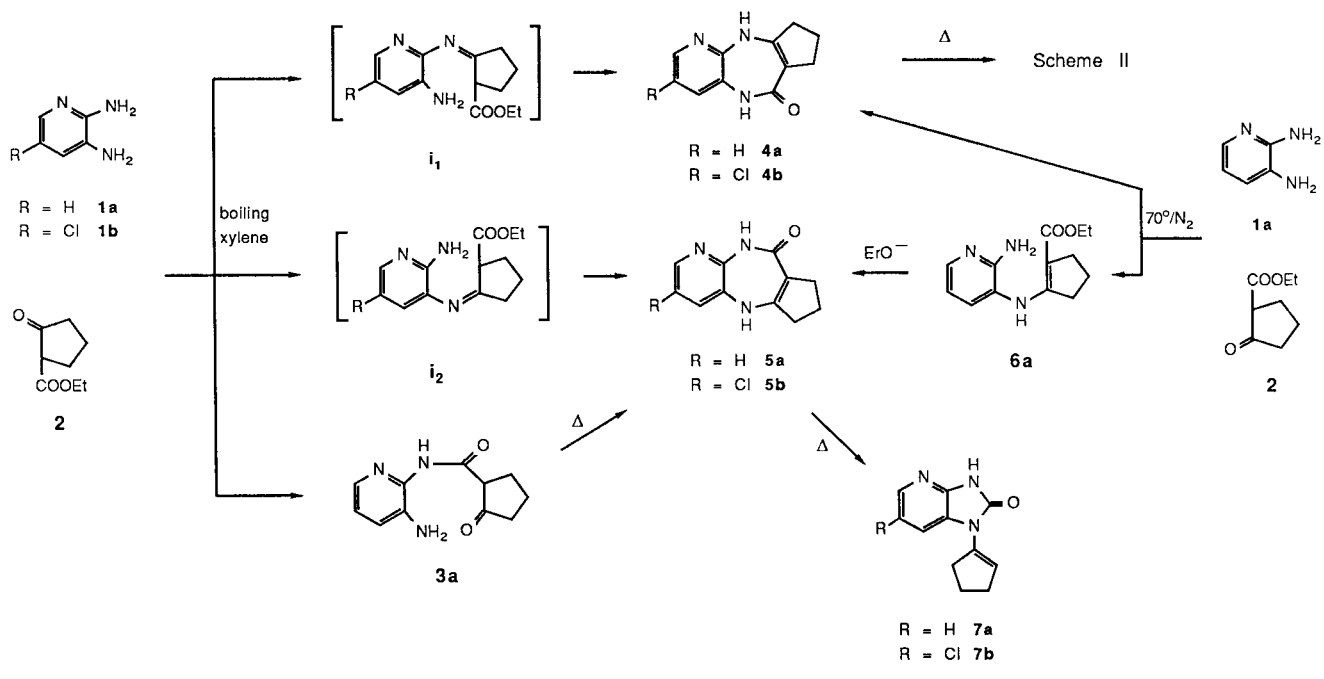
Developing our researches about psychotropic agents [1] obtained through the condensation of α- and β-ketoesters with unsymmetrical aromatic and heteroaromatic monoalkylated diamines, we prepared recently a series of pyrido[2,3-*b*][1,4]diazepinones [2] currently under biological evaluation.

By utilizing an analogous reaction, we have prepared now a few derivatives of new tricyclic ring systems which could be of interest in order to obtain clozapine and pirenzepine analogues.

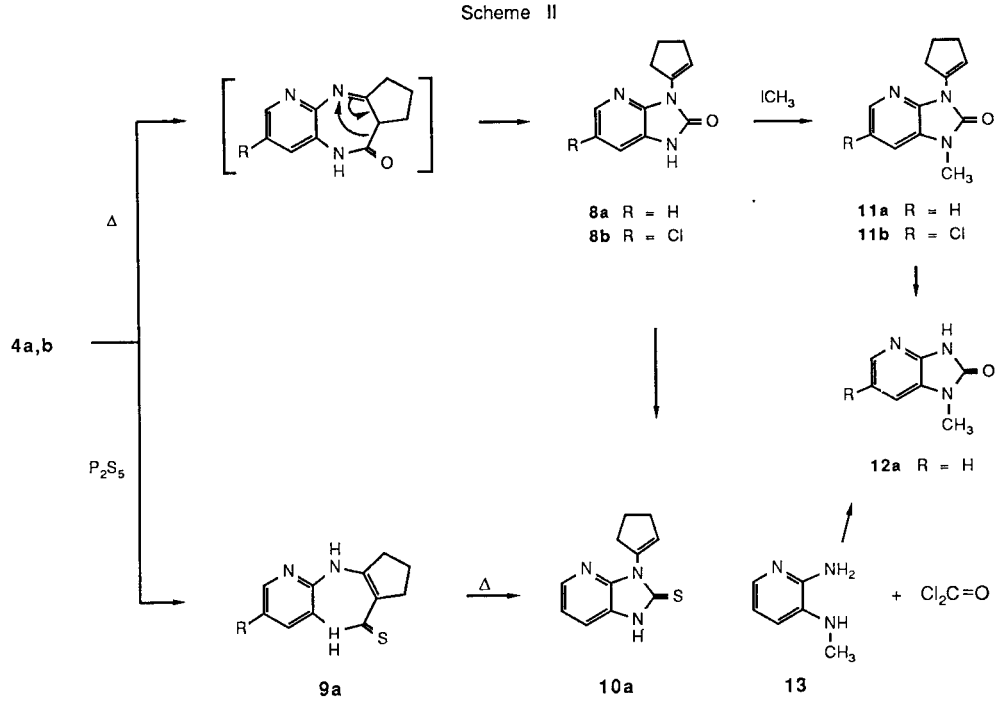
The condensation of 2,3-diaminopyridine (**1a**) with ethyl 2-oxocyclopentanecarboxylate (**2**) in boiling xylene without azeotropic removal of water, gave, besides a little amount of the amide **3a** and an unresolved mixture of imidazolones, the two possible isomeric diazepinones **4a** and **5a** in a ratio 4:1, in 50% total yield (Scheme 1). Compound **3a**, heated in ethanol, was transformed into **5a**.

The assignment of structure **4a** and **5a** to the diazepinones obtained was difficult owing to their similar spectral properties and initially has been done on the basis of a reaction mechanism proposed by other authors [3] for the analogous condensation of diaminopyridine with methyl tetrahydro-4-oxo-3-thiophenecarboxylate, and which justified the preferential formation of the isomer **4a**. The structural assignment was subsequently confirmed through the reaction sequence discussed later in this paper.

Scheme I



Scheme II




By condensation of the carbonyl group of **2** with the amino groups of **1a**, the reaction runs through the two intermediates $\mathbf{i}_1$ and $\mathbf{i}_2$, of which $\mathbf{i}_2$ was formed preferentially on account of the higher reactivity of 3-amino group. Yet the free amino group of $\mathbf{i}_1$ is more reactive than that of $\mathbf{i}_2$, thus $\mathbf{i}_1$ was subtracted from the hydrolytic equilibrium with ring closure to **4a** and progressive conversion of $\mathbf{i}_2$ to $\mathbf{i}_1$.

The reaction between **1a** and **2** carried out under milder conditions gave preferentially **6a**, the tautomeric form of $\mathbf{i}_2$, besides a small amount of **4a**. Compound **6a** when treated in boiling moist xylene was rather stable giving rise only to traces of an unresolved mixture of pyridodiazepinones, while when heated with sodium ethoxide in absolute ethanol it gave **5a** in good yield. In a similar manner the reaction of 2,3-diamino-5-chloropyridine (**1b**) with **2** afforded the two possible isomeric diazepinones **4b** and **5b** in a ratio of about 2:1, together with a small amount of a mixture of imidazolone derivatives. The formation of these imidazolones is supposed to require [4a,b] the transitory existence of tautomeric diazepinones with an azomethinic double bond (Scheme 2) whose formation seems not to be favored under the condensation conditions.

It is interesting to note that Israel and Jones [4c] reacting 2,3-diaminopyridine and 2-oxocyclohexanecarboxylate in boiling xylene, but with azeotropic removal of water, obtained 3-cyclohexenyl-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one in 74% yield, instead of the pyridodiazepinone.

The reaction of **4a** with phosphorus pentasulfide in refluxing pyridine (Scheme 2) afforded together with traces of **10a** only minor amount (18%) of the expected diazepinthione **9a**, while the imidazolone derivative **8a** was obtained as the main product (55% yield). Formation of **9a** is erratic and **8a** is often the only product of this reaction.

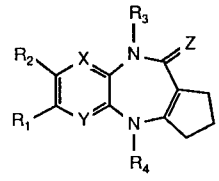
Actually **8a-b** and **7a-b** could be obtained from **4a-b** and **5a-b** by thermal rearrangement in refluxing pyridine, in about 60-80% yield. Variable amounts of **10a** were obtained by direct sulfuration of **8a** and, with 50% yield, by thermal ring contraction of **9a**. This means that the diazepinone ring contraction and the sulfuration could run independently.

The pyridoimidazolone system is characterized by its ultraviolet absorption (λ max ~294 nm), by a carbonyl peak at 1710 $cm^{-1}$ in the ir spectrum and signals at δ 11.5 ppm (NH) and δ 6.0 ppm (=CH) in the nmr spectrum, while the pyridodiazepinone system is characterized by amide group absorption at ~1650 $cm^{-1}$ and by two NH signals at δ 8.5 and 8.7 ppm.

The observed thermal conversion of diazepinones into imidazolones has been used for unequivocal assignment of the structure of **4a**. The ring contraction product **8a** was methylated by means of methyl iodide in presence of sodium ethoxide and from the resulting compound **11a**, by acid hydrolysis to remove the labile cyclopentenyl moiety, the compound **12a** was obtained. Comparison of this material with an authentic sample of 1,3-dihydro-1-methyl-2*H*-imidazo[4,5-*b*]pyridin-2-one prepared by cyclization of diamine **13** with phosgene, in warm toluene, showed identity by all criteria evaluated.

Table I

3,10-Substituted-7,8,9,10-tetrahydrocyclopenta[*e*]pyrido[3,2-*b*][1,4]diazepin-6(5*H*)-(thi)ones and
3,10-Substituted-5,7,8,10-tetrahydrocyclopenta[*e*]pyrido[2,3-*b*][1,4]diazepine-9(6*H*)-(thi)ones




| Formula Number | $R_1$ | $R_2$ | $R_3$ | $R_4$ | X | Y | Z | Yield % | MP °C | Molecular Formula | Analyses % Calcd./Found C | H | N |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **4a** | H | H | H | H | CH | N | O | 40 | 229-231 [a] | $C_{11}H_{11}N_3O$ | 65.67<br>65.64 | 5.51<br>5.50 | 20.88<br>20.74 |
| **4b** | H | Cl | H | H | CH | N | O | 31 | 239-242 [b] | $C_{11}H_{10}ClN_3O$ | 56.05<br>55.87 | 4.27<br>4.23 | 17.83<br>17.75 |
| **5a** | H | H | H | H | N | CH | O | 11 | 206-207 [a] | $C_{11}H_{11}N_3O$ | 65.67<br>65.38 | 5.51<br>5.50 | 20.88<br>20.64 |
| **5b** | Cl | H | H | H | N | CH | O | 18 | 220-222 [b] | $C_{11}H_{10}ClN_3O$ | 56.05<br>55.93 | 4.27<br>4.35 | 17.83<br>17.51 |
| **9a** | H | H | H | H | CH | N | S | 18 | 209-210 [c] | $C_{11}H_{11}N_3S$ | 60.80<br>61.05 | 5.10<br>5.03 | 19.34<br>19.39 |
| **15** | H | H | $CH_3$ | H | CH | N | O | 20 | 171-173 [b] | $C_{12}H_{13}N_3O$ | 66.95<br>66.89 | 6.09<br>6.14 | 19.52<br>19.40 |
| **17** | H | H | H | $CH_3$ | CH | N | O | 14 | 191-192 [b] | $C_{12}H_{13}N_3O$ | 66.95<br>67.06 | 6.09<br>6.10 | 19.52<br>19.63 |
| **19** | H | H | $CH_3$ | H | CH | N | S | 65 | 169-171 [b] | $C_{12}H_{13}N_3S$ | 62.30<br>61.99 | 5.66<br>5.60 | 17.93<br>17.93 |
| **20** | H | H | H | $CH_3$ | CH | N | S | 60 | 215-217 [b] | $C_{12}H_{13}N_3S$ | 62.30<br>62.17 | 5.66<br>5.61 | 17.93<br>17.83 |

[a] From ethyl acetate. [b] From ethanol. [c] From dichloromethane.

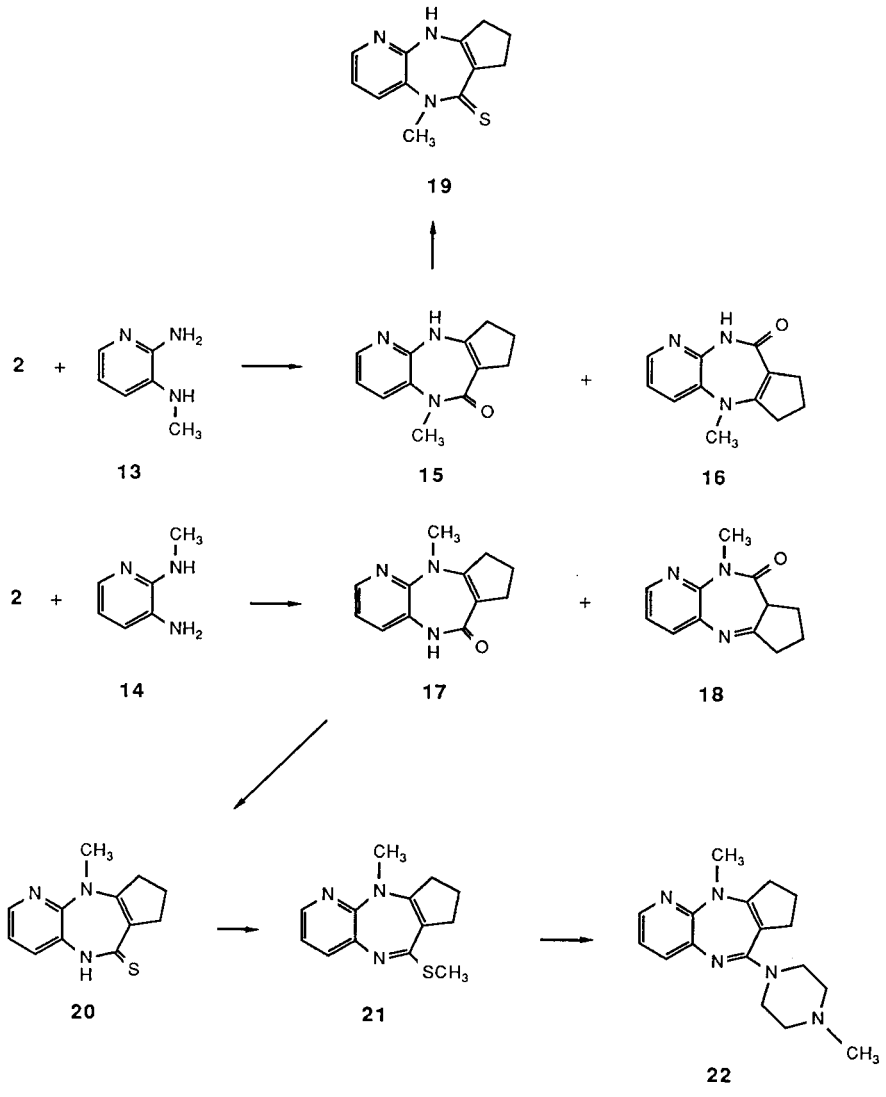
Owing to the diazepinone ring contraction, all attempts to obtain from **4a** pirenzepine and clozapine analogues failed. Thus in order to accomplish the original objective, the methylated derivatives of **4a** and **5a**, which appear to be stable on heating, were prepared as following.

The condensation of **2** and 2-amino-3-methylaminopyridine (**13**) in hot xylene for 4 hours (Scheme 3) afforded **15** (20%), and sometimes in addition to a small amount of the isomeric product **16**, with the recovery of about 20% of unreacted **13**. The condensation of **2** and 3-amino-2-methylaminopyridine (**14**) by heating in xylene for 20 hours afforded a mixture of two isomeric products, the diazepinones **17** and **18** (14% and 8% yield respectively). While the nmr spectrum of **18** did not reveal the presence of a NH group, those of **15** and **17** exhibited peaks at $\delta$ 7.7 and 8.3 ppm, respectively attributed to a NH of the amino and lactam group; in fact these peaks disappear after exchange with deuterium oxide.

Compounds **4a**, **15** and **17** showed in their nmr spectra doublets centered at $\delta$ 7.72, 7.94 and 7.96 ppm (J = 3.6 Hz) respectively, attributable to the $\alpha$-pyridyl hydrogen. Whereas **4a** and **17** exhibited a multiplet at $\delta$ 6.65-7.25 and 6.80-7.40 ppm, respectively, attributable to the $\beta$- and $\gamma$-pyridyl hydrogens, **15** exhibited for the same protons two distinct signals at $\delta$ 6.9-7.2 (m, $\beta$-pyridyl H) and 7.5 ppm (d, $\gamma$-pyridyl H). This observation seems to be consistent with the deshielding effect of the methyl on the amide nitrogen [5].

By the action of phosphorus pentasulfide, **15** and **17** were converted without suffering ring contraction into the corresponding diazepinthiones **19** and **20**, the last of which only could be *S*-alkylated to the methyl thioether **21**, supporting the assigned structure. Compound **21** was subsequently converted into the methyl derivative of a clozapine analogue **22**, by refluxing with *N*-methylpiperazine in xylene.

Scheme III




## EXPERIMENTAL

Melting points were determined by the capillary method on a Buchi 510 apparatus and are uncorrected. The uv spectra were measured in 95% ethanol with a Perkin-Elmer Model 550 S spectrophotometer. The ir spectra were taken in KBr on a Perkin-Elmer Model 297 spectrophotometer and the nmr spectra were recorded on a Hitachi Perkin-Elmer Model R-600 spectrometer with TMS as internal standard. The elemental analysis were performed at the Microanalytical Laboratory of Istituto di Scienze Farmaceutiche, Università di Genova.

Reaction Between 2,3-Diaminopyridine (**1a**) and Ethyl 2-Oxocyclopentanecarboxylate (**2**).

a) Formation of **4a**, **5a** and **3a**.

A solution of **1a** (3.9 g, 36 mmoles) in xylene (120 ml) was refluxed with stirring while a solution of **2** (5.6 g, 36 mmoles) in xylene (30 ml) was added over a period of 90 minutes. Reflux was continued for an additional 2.5 hours and after standing overnight the mixture was filtered to give a brown solid which was then suspended in boiling ethanol and filtered hot to afford 2.9 g (40%) of 7,8,9,10-tetrahydrocyclopenta[*e*]pyrido[3,2-*b*]-[1,4]diazepin-6(5*H*)-one (**4a**) (Tables I, II). Concentration of the ethanolic mother liquor gave a small amount of **5a**.

The xylene solution after filtration was extracted with 2*N* hydrochloric acid, thereby 5,7,8,10-tetrahydrocyclopenta[*e*]pyrido[2,3-*b*][1,4]diazepin-9(6*H*)-one hydrochloride (**5a**) (0.8 g) was collected and crystallized from ethanol, mp 254-256°.

*Anal.* Calcd. for $C_{11}H_{11}N_3O.HCl.1/4H_2O$: C, 54.55; H, 5.20; N, 17.35. Found: C, 54.51; H, 5.20; N, 17.15.

The aqueous acid solution was made alkaline with sodium hydroxide and extracted with methylene chloride. The organic layer was washed with water, dried (sodium sulfate) and evaporated to dryness to give a residue which by trituration with ethanol afforded 0.25 g (3%) of 3-amino-2-(oxocyclopentanecarboxamide)pyridine (**3a**).

The crude **3a** melted at 214-216°; uv: λ max 295 nm; ir: 1690, 1650 $cm^{-1}$; nmr (DMSO-$d_6$): δ 1.85 (mc, 2H, $CH_2$), 2.50 (mc, 5H, $2CH_2$ + CH),

Table II

UV, IR and NMR Spectral Data of Compounds in Table I

| Compound | UV, λ max nm (log ε) | IR, $cm^{-1}$ | | NMR, |
|---|---|---|---|---|
| **4a** | 210 (4.40), 232 (4.29), 253 sh (4.11), 320 (3.66) | 3240, 3200, 1645 | [a] | 1.74 (mc, 2H, $CH_2$), 2.42 (mc, 4H, $2CH_2$), 6.86 (mc, 2H), 7.72 (d, J = 3.6 Hz, 1H), 8.52 (broad s, 1H, NH, disappears with deuterium oxide), 8.76 (broad s, 1H, NH, disappears with deuterium oxide) |
| **4b** | 218 (4.38), 232 (4.32) 254 sh (4.11), 338 (3.67) | 3250, 3195, 1650 | [a] | 1.74 (mc, 2H, $CH_2$), 2.42 (mc, 4H, $2CH_2$), 7.15 (d, J = 2.4 Hz, 1H), 7.73 (d, J = 2.4 Hz, 1H), 8.65 (broad s, 1H, NH, disappears with deuterium oxide), 8.98 (broad s, 1H, NH; disappears with deuterium oxide) |
| **5a** | 211 (4.32), 233 (4.33), 251 sh (4.03), 327 (3.66) | 3295, 3270, 1645 | [a] | 1.72 (mc, 2H, $CH_2$), 2.42 (mc, 4H, $2CH_2$), 6.60-7.20 (m, 2H), 7.75 (d, J = 3.6 Hz, 1H), 8.22 (broad s, 1H, NH, disappears with deuterium oxide), 8.44 (broad s, 1H, NH, disappears with deuterium oxide) |
| **5b** | 215 (4.37), 239 (4.32) 258 sh (4.06), 336 (3.65) | 3250, 3170, 1650 | [a] | 1.72 (mc, 2H, $CH_2$), 2.42 (mc, 4H, $2CH_2$), 7.12 (d, J = 3.6 Hz, 1H), 7.74 (d, J = 3.6 Hz, 1H), 8.62 (broad s, 1H, NH, disappears with deuterium oxide), 8.96 (broad s, 1H, NH, disappears with deuterium oxide) |
| **9a** | 232 (4.33), 330 (4.30) | 3220, 3190, 1640 | [a] | 1.70 (mc, 2H, $CH_2$), 2.50 (mc, 4H, $2CH_2$), 6.60-7.30 (m, 2H), 7.70 (d, J = 3.6 Hz, 1H), 8.86 (broad s, 1H, NH, disappears with deuterium oxide), 9.78 (broad s, 1H, NH, disappears with deuterium oxide) |
| **15** | 211 (4.27), 234 (4.27), 314 (3.68) | 3220, 1630 | [a] | 1.78 (mc, 2H, $CH_2$), 2.58 (mc, 4H, $2CH_2$), 3.12 (s, 3H, $CH_3$), 6.90-7.22 (m, 1H), 7.50 (d, J = 8.4 Hz, 1H), 7.94 (d, J = 3.6 Hz, 1H), 9.5 (broad s, 1H, NH, disappears with deuterium oxide) |
| **17** | 239 (4.17), 317 (3.61) | 3180, 1640 | [a] | 1.78 (mc, 2H, $CH_2$), 2.55 (mc, 4H, $2CH_2$), 3.25 (s, 3H, $CH_3$), 6.85-7.40 (m, 2H), 7.96 (d, J = 3.6 Hz, 1H), 8.86 (broad s, 1H, NH, disappears with deuterium oxide) |
| **19** | 237 (4.15), 317 (4.33) | 3240, 3200, 1620 | [b] | 1.80 (mc, 2H, $CH_2$), 2.56 (mc, 2H, $CH_2$), 2.96 (mc, 2H, $CH_2$), 3.68 (s, 3H, $CH_3$), 6.60-7.50 (m, 2H), 7.94 (d, J = 4.8 Hz, 1H), 8.45 (broad s, 1H, NH, disappears with deuterium oxide) |
| **20** | 236 (4.18), 325 (4.33) | 3240, 3190, 1620 | [b] | 1.82 (mc, 2H, $CH_2$), 2.50-3.10 (m, 4H, $2CH_2$), 3.26 (s, 3H, $CH_3$), 6.70-7.35 (m, 3H, 2H + NH), 8.02 (d, J = 3.6 Hz, 1H) |

[a] DMSO-$d_6$. [b] Deuteriochloroform.

7.20 (mc, 2H), 7.80 (d, J = 5.4 Hz, 1H), 8.20 (broad s, 2H, $NH_2$), 8.45 (broad s, 1H, NH).

This product by boiling in ethanol was converted to **5a**.

The xylene solution residual from acid extraction was concentrated to a small volume to give a mixture (0.2 g) of imidazolone derivatives (identified by ir: 1710 $cm^{-1}$).

b) Formation of **4a** and **6a**.

A mixture of **1a** (1.1 g, 10 mmoles) and **2** (1.56 g, 10 mmoles) was stirred at 70° for 24 hours under nitrogen. After cooling, the solid formed gave by trituration with ethanol a mixture which was then suspended in boiling ethanol and filtered hot to yield variable amounts of **4a** (traces/20%). From the mother liquor 2-amino-3-(ethoxycarbonylcyclopenten-1-yl)aminopyridine **6a** was obtained (30-50%), mp 161-162° (ethanol); uv: λ max nm (log ε) 231 (4.01), 297 (4.10), 316 (4.15); ir: 3370, 3140, 1655 $cm^{-1}$; nmr (deuteriochloroform): δ 1.30 (t, J = 7.2 Hz, 3H, $CH_3$), 1.85 (mc, 2H, $CH_2$), 2.45 (mc, 4H, $2CH_2$), 4.20 (q, J = 7.2 Hz, 2H, $CH_2$), 4.75 (broad s, 2H, $NH_2$), 6.65 (mc, 1H), 7.24 (d, J = 7.2 Hz, 1H), 7.92 (d, J = 4.8 Hz, 1H), 8.70 (broad s, 1H, NH).

Transformation of **6a** to **5a**.

Compound **6a** (1.25 g, 5 mmoles) was added to 10 ml of absolute ethanol in which 115 mg (5 mmoles) of sodium was previously dissolved and the resulting solution was refluxed for 3 hours. After cooling, the reaction mixture was neutralized with 1*N* hydrochloric acid and concentrated under reduced pressure to half volume to give **5a** which was collected by filtration; yield, 0.6 g (60%).

Reaction of 2,3-Diamino-5-chloropyridine (**1b**) [6] with **2**. Formation of **4b** and **5b**.

To a mixture of **1b** (4.3 g, 30 mmoles) in xylene (100 ml) were added 4.7 g (30 mmoles) of **2**, following the same procedure described for **1a**. After standing overnight the mixture was filtered to give 2.2 g (31%) of 3-chloro-7,8,9,10-tetrahydrocyclopenta[*e*]pyrido[3,2-*b*][1,4]diazepin-6(5*H*)-one (**4b**, Tables I, II). The xylene filtrate was then extracted with dilute hydrochloric acid. The acid extract, from which a solid began to separate, was made alkaline with sodium hydroxide, stirred for 15 minutes and filtered to give 1.1 g (15%) of 3-chloro-5,7,8,10-tetrahydrocyclopenta[*e*]pyrido[2,3-*b*][1,4]diazepin-9(6*H*)-one (**5b**, Tables I, II).

The alkaline solution was extracted thoroughly with methylene chloride and the combined extracts were washed, dried (sodium sulfate) and evaporated to give an oily residue which was chromatographed on basic alumina. By elution with methylene chloride a small amount of **5b** was collected (overall yield 18%) and further elution with methylene chloride-methanol (97:3) gave unreacted **1b** (about 15%).

The residual xylene solution was evaporated to dryness to give a complex mixture (0.3 g) from which by trituration with ethanol-ether a very small amount of a mixture of imidazolone derivatives was obtained (ir: 1710 $cm^{-1}$).

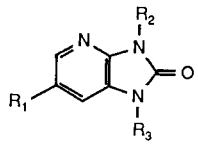
Reaction of **4a,b** and **8a** with Phosphorus Pentasulfide.

Formation of **8a**, **9a** and **10a** from **4a**.

To **4a** (2.01 g, 10 mmoles) suspended in pyridine was added phosphorus pentasulfide (0.88 g, 4 mmoles) and the mixture was refluxed with

Table III

1,3,6-Substituted-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-ones



| Formula Number | $R_1$ | $R_2$ | $R_3$ | Yield % | MP °C | Molecular Formula | Analyses % Calcd./Found C | H | N |
|---|---|---|---|---|---|---|---|---|---|
| **7a** | H | H | Cpl | 80 | 157-159 [a] | $C_{11}H_{11}N_3O$ | 65.67<br>65.23 | 5.51<br>5.52 | 20.88<br>20.68 |
| **7b** | Cl | H | Cpl | 80 | 159-161 [a] | $C_{11}H_{10}ClN_3O$ | 56.05<br>55.85 | 4.27<br>4.42 | 17.83<br>17.78 |
| **8a** | H | Cpl | H | [c] | 152-154 [a] | $C_{11}H_{11}N_3O$ | 65.67<br>65.64 | 5.51<br>5.63 | 20.88<br>20.69 |
| **8b** | Cl | Cpl | H | [c] | 231-232 [b] | $C_{11}H_{10}ClN_3O$ | 56.05<br>55.94 | 4.27<br>4.19 | 17.83<br>17.81 |
| **11a** | H | Cpl | $CH_3$ | 68 | 80-82 [a] | $C_{12}H_{13}N_3O$ | 66.95<br>66.89 | 6.09<br>6.36 | 19.52<br>19.11 |
| **11b** | Cl | Cpl | $CH_3$ | 72 | 168-170 [a] | $C_{12}H_{12}ClN_3O$ | 57.71<br>57.28 | 4.84<br>4.68 | 16.82<br>16.82 |

cpl = Cyclopentenyl. [a] From ethanol. [b] From dichloromethane. [c] See Experimental.

Table IV

UV, IR and NMR Spectral Data of Compounds in Table III

| Compound | UV, λ max nm (log ε) | IR, $cm^{-1}$ | | NMR, |
|---|---|---|---|---|
| **7a** | 230 sh (4.12), 294 (4.24) | 1710 | [a] | 2.12 (mc, 2H, $CH_2$), 2.50 (mc, 2H, $CH_2$), 2.94 (mc, 2H, $CH_2$), 6.34 (mc, 1H, CH), 6.80-7.50 (m, 2H), 8.08 (d, J = 4.8 Hz, 1H), 10.88 (broad s, 1H, NH, disappears with deuterium oxide) |
| **7b** | 235 sh (3.97), 305 (4.08) | 1720 | [b] | 2.09 (mc, 2H, $CH_2$), 2.50 (mc, 2H, $CH_2$), 2.95 (mc, 2H, $CH_2$), 6.05 (mc, 1H, CH), 7.64 (d, J = 2.4 Hz, 1H), 8.02 (d, J = 2.4 Hz, 1H), 11.98 (broad s, 1H, NH, disappears with deuterium oxide) |
| **8a** | 232 sh (3.98), 294 (4.06) | 1720 | [a] | 2.14 (mc, 2H, $CH_2$), 2.58 (mc, 2H, $CH_2$), 3.18 (mc, 2H, $CH_2$), 6.36 (t, J = 1.8 Hz, 1H, CH), 6.80-7.50 (m, 2H), 8.12 (d, J = 5.4 Hz, 1H), 10.05 (broad s, 1H, NH, disappears with deuterium oxide) |
| **8b** | 242 sh (3.95), 306 (4.05) | 1720 | [b] | 2.00 (mc, 2H, $CH_2$), 2.50 (mc, 2H, $CH_2$), 2.85 (mc, 2H, $CH_2$), 6.26 (t, J = 1.8 Hz, 1H, CH), 7.44 (d, J = 2.4 Hz, 1H), 8.02 (d, J = 2.4 Hz, 1H), 11.55 (broad s, 1H, NH, disappears with deuterium oxide) |
| **11a** | 235 sh (3.98), 295 (4.12) | 1700 | [a] | 2.14 (mc, 2H, $CH_2$), 2.55 (mc, 2H, $CH_2$), 3.05 (mc, 2H, $CH_2$), 3.42 (s, 3H, $CH_3$), 6.35 (mc, 1H, CH), 7.12 (mc, 2H), 8.08 (d, J = 5.4 Hz, 1H) |
| **11b** | 241 sh (3.91), 306 (4.04) | 1705 | [a] | 2.08 (mc, 2H, $CH_2$), 2.55 (mc, 2H, $CH_2$), 2.98 (mc, 2H, $CH_2$), 3.42 (s, 3H, $CH_3$), 6.30 (mc, 1H, CH), 7.18 (d, J = 2.4 Hz, 1H, CH), 8.00 (d, J = 2.4 Hz, 1H) |

[a] $CDCl_3$. [b] DMSO-$d_6$.

stirring for 4 hours and then the solvent was evaporated under reduced pressure. To the resulting oily residue, a solution of 5% sodium carbonate (25 ml) and methanol (1 ml) were added and the mixture was stirred for about 4 hours. A brown solid was filtered off, which was dried, suspended in methylene chloride (40 ml), stirred for 15 minutes and filtered. The insoluble solid (1 g) was fractionated by crystallization from ethanol. The solution, upon cooling, deposited a very small amount of 3-cyclopenten-1-yl-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridine-2-thione (**10a**) and, by concentration of the mother liquor, 1.1 g (55%) of 3-cyclopenten-1-yl-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one (**8a**, Tables III, IV).

The methylene chloride solution after filtration was concentrated to give red crystals (0.4 g, 18%) of 7,8,9,10-tetrahydrocyclopenta[*e*]pyrido-[3,2-*b*]diazepine-6(5*H*)-thione (**9a**, Tables I, II).

The course and the yields of the above reaction were not always reproducible; frequently **9a** and **10a** were not isolated and **8a** seemed to be the only product of the reaction.

Heating of **8a** with phosphorus pentasulfide in the above described conditions gave **10a** in variable yields.

Compound **10a**.

This compound had mp 148-152°; nmr (DMSO-$d_6$): δ 2.02 (mc, 2H, $CH_2$), 2.50 (mc, 2H, $CH_2$), 2.85 (mc, 2H, $CH_2$), 6.32 (mc, 1H, CH), 6.75-7.50 (m, 2H), 7.88 (d, J = 5.4 Hz, 1H), 11.35 (broad s, 1H, NH).

*Anal.* Calcd. for $C_{11}H_{11}N_3S$: C, 60.80; H, 5.10; N, 19.34. Found: C, 61.11; H, 5.10; N, 19.57.

Formation of **8b** from **4b**.

Starting from **4b** and following the identical procedure described above, very small amounts of sulfur derivatives were obtained, besides the 3-cyclopenten-1-yl-6-chloro-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one (**8b**, Tables III, IV). coming from the thermal rearrangement.

Conversion of Diazepinones to Imidazolone Derivatives.

Diazepinones **4a,b**, **5a,b** and diazepinthione **9a** by refluxing in pyridine for 4 hours were transformed respectively into **8a,b** (80%), **7a,b** (80%) and **10a** (50%).

Preparation of **11a**.

Compound **8a** (5 mmoles) suspended in absolute ethanol (15 ml) was treated with an equivalent amount of sodium ethoxide (0.1 *M* solution) and mehtyl iodide (0.5 ml). The mixture was stirred overnight at room temperature. The reaction mixture was concentrated to half volume and diluted with methylene chloride. The solution was washed with water, dried (sodium sulfate) and filtered through Florisil. Concentration of the eluate under reduced pressure gave 3-cyclopenten-1-yl-1,3-dihydro-1-methyl-2*H*-imidazo[4,5-*b*]pyridin-2-one (**11a**, 68%, Tables III, IV).

Preparation of **11b**.

Compound **8b** was treated as described for **8a**. From the reaction mixture gray bright plates (72%) of 6-chloro-3-cyclopenten-1-yl-1,3-dihydro-1-methyl-2*H*-imidazo[4,5-*b*]pyridin-2-one (**11b**, Tables III, IV) were filtered.

1,3-Dihydro-1-methyl-2*H*-imidazo[4,5-*b*]pyridin-2-one (**12a**).

a) Compound **11a** (0.4 g, 1.85 mmoles) was dissolved in 20 ml of a sulfuric acid-water-ethanol system (1:1:2 by volume) and the solution was warmed for 1 hour at 80°. The reaction mixture was diluted with water and extracted with methylene chloride to remove cyclopentanone and, after neutralization with sodium hydroxide to *p*H 7-8, again extracted with methylene chloride. The organic solution, dried (sodium sulfate) and evaporated, gives 0.19 g (yield 68%) of **12a**, mp 202-204° (ethanol); uv: λ max nm (log ε) 232 sh (3.50), 291 (4.01); ir: 1715 $cm^{-1}$; nmr (deuteriochloroform): δ 3.45 (s, 3H, $CH_3$), 7.16 (mc, 3H, 2H Ar + NH), 8.10 (m, 1H Ar).

*Anal.* Calcd. for $C_7H_7N_3O$: C, 56.37; H, 4.73; N, 28.18. Found: C, 56.57; H, 4.74; N, 28.47.

b) 2-Amino-3-methylaminopyridine (4.9 mmoles) (prepared as described in [7]) in 15 ml of toluene was added to 50 ml of 2*M* solution of phosgene in toluene. The mixture was stirred for 1 hour and then refluxed for 3 hours. The reaction mixture was concentrated to half volume and extracted several times with 10% sodium hydroxide solution (20 ml total). The combined extracts were neutralized with dilute hydrochloric acid to *p*H 7-8 and extracted with dichloromethane. The organic solution dried (sodium sulfate) and evaporated, gives 0.44 g of **12a** in 60% yield, mp 202-204° (lit [5] 201-202°).

The uv, ir and nmr spectra of this material were identical with those of **12a** prepared by procedure (a). A mixture melting point determination showed no depression.

Reaction of 2-Amino-3-methylaminopyridine (**13**) [7] with **2** Affording **15** and **16**.

To 2.5 g of **13** (20 mmoles), in 80 ml of xylene, were added, as described for the condensation of **1a** with **2**, over a period of 90 minutes, 3.4 g (22 mmoles) of **2** and refluxed for 2.5 hours. After cooling, a very small amount of a product was occasionally separated. It is presumably 5,7,8,10-tetrahydro-5-methylcyclopenta[*e*]pyrido[2,3-*b*][1,4]diazepin-9(6*H*)-one (**16**), green plates (insufficiently soluble in deuteriochloroform and DMSO-$d_6$ for nmr spectrum); mp 230-232° (ethanol); uv: λ max nm (log ε) 212 (4.35), 240 (4.44), 318 (3.81); ir: 3190, 1650 $cm^{-1}$.

*Anal.* Calcd. for $C_{12}H_{13}N_3O$: C, 66.95; H, 6.09; N, 19.52. Found: C, 66.82; H, 5.97; N, 19.53.

The xylene solution was extracted with 2*N* hydrochloric acid and the acid solution was made alkaline with sodium hydroxide and extracted with methylene chloride. The oily residue was chromatographed on basic alumina and eluted with methylene chloride to give 7,8,9,10-tetrahydro-5-methylcyclopenta[*e*]pyrido[3,2-*b*][1,4]diazepin-6(5*H*)-one (**15**) (yield 20%, Tables I, II) and subsequently unreacted **13** (15%).

Reaction of 3-Amino-2-methylaminopyridine (**14**) [8] with **2** to Afford **17** and **18**.

A solution of **14** (3.8 g, 30 mmoles) and **2** (5.15 g, 33 mmoles) in xylene (100 ml) was refluxed for 20 hours. After cooling, the xylene solution was extracted with 2*N* hydrochloric acid and the acid solution was made alkaline with sodium hydroxide and extracted with methylene chloride. The oily residue obtained after evaporation of the combined extracts was chromatographed on basic alumina to give a violet oil which by filtration through Florisil gave 0.5 g (8%) of 6,7,8,8a-tetrahydro-10-methylcyclopenta[*e*]pyrido[2,3-*b*][1,4]diazepin-9(10*H*)-one (**18**) mp 66-68° (ethanol); uv: λ max nm (log ε) 294 (3.81); ir: 1670, 1650 $cm^{-1}$; nmr (deuteriochloroform): δ 2.05 (mc, 3H, $CH_2$ + CH), 2.78 (mc, 4H, $2CH_2$), 3.55 (s, 3H, $CH_3$), 7.25 (mc, 1H), 7.72 (d, J = 7.2 Hz, 1H), 8.42 (d, J = 4.2 Hz, 1H).

*Anal.* Calcd. for $C_{12}H_{13}N_3O$: C, 66.95; H, 6.09; N, 19.52. Found: C, 67.09; H, 6.02; N, 19.52.

Subsequently 7,8,9,10-tetrahydro-10-methylcyclopenta[*e*]pyrido-[3,2-*b*][1,4]diazepin-6(5*H*)-one (**17**) (0.9 g, 14% yield, Tables I, II) and 20% of unreacted **14** were collected.

Reaction of **15** and **17** with Phosphorus Pentasulfide.

Compounds **15** and **17** were treated with phosphorus pentasulfide as described above for **4a,b**, giving rise respectively to the thioderivatives **19** and **20** (Tables I, II) (yield on crude about 65%). Compound **20** exhibits two orange crystalline forms (mp 169-171° and 192-193°) which showed different ir absorption in the solid state (potassium bromide) but the same ir spectrum in chloroform solution.

7,8,9,10-Tetrahydro-10-methyl-6(4-methylpiperazin-1-yl)cyclopenta[*e*]-pyrido[3,2-*b*][1,4]diazepine (**22**).

a) Compound **20** (2.3 g, 10 mmoles) was *S*-alkylated with methyl iodide/sodium ethoxide as described above (**8a,b** → **11a,b**) to give oily 7,8,9,10-tetrahydro-10-methyl-6-methylthiocyclopenta[*e*]pyrido[3,2-*b*][1,4]diazepine (**21**) (1.4 g, yield 57%); nmr (deuteriochloroform): δ 1.35 (mc, 2H, $CH_2$), 2.40 (mc, 7H, $2CH_2$ + $CH_3$), 3.00 (s, 3H, $CH_3$), 7.10 (mc, 2H), 7.85 (d, J = 4.2 Hz, 1H).

b) Crude **21** (0.9 g, 3.5 mmoles), 1-methylpiperazine (0.35 g, 3.5 mmoles) and acetic acid (3 drops) in xylene (30 ml) were refluxed for 24 hours. The reaction mixture was extracted with dilute hydrochloric acid and the acid extract was washed with diethyl ether. The acid solution was made alkaline with ammonia and extracted several times with dichloromethane. The combined extracts were dried (sodium sulfate) evaporated and the residue was chromatographed on alumina to give 0.8 g (yield 77%) of **22** as an oil bp 190°/0.2 mm; uv: λ max nm (log ε) 255 (4.19), 274 (4.20), 312 sh (3.71); nmr (deuteriochloroform): δ 1.88 (mc, 2H, $CH_2$), 2.40 (m, 11H, $2CH_2$ + $(CH_2)_2NCH_3$), 3.05 (s, 3H, $CH_3$), 3.45 (mc, 4H, $N(CH_2)_2$),

6.85 (mc, 1H), 7.22 (d, J = 4.2 Hz, 1H).

*Anal.* Calcd. for $C_{17}H_{23}N_5$: C, 68.65; H, 7.80; N, 23.56. Found: C, 68.26; H, 7.74; N, 22.98.

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