Studies on Pyrrolidinones. Preparation of 1,5,6-10b-tetrahydro-2*H*-pyrrolo[1,2-*c*]quinazoline-3-ones from Pyroglutamic Acid.

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Tetrahydro-2*H*-pyrrolo[1,2-*c*]quinazoline-3-ones are easily obtained from the Friedel-Crafts cyclization of *N*-arylaminomethyl pyroglutamic acids. This reaction occurrs *via* an acyliminium salt formed by decarboxylation of the acid function.

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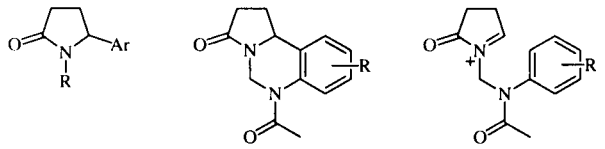
Many 5-aryl-2-pyrrolidinones **1** are important products because for their potential as psychotropes [1]. In a search for new lactams in these series, we were interested by the 5-aryl-2-pyrrolidinones **2** which possess a tetrahydroquinazoline system and are rigid analogs of **1** [2]. Numerous syntheses of pyrrolidinones **1** are known [2], and it would be possible to start from these compounds to obtain products **2**, but as a first approach we choose the cyclization of acyliminium salts **3** (Scheme 1).

Scheme 1

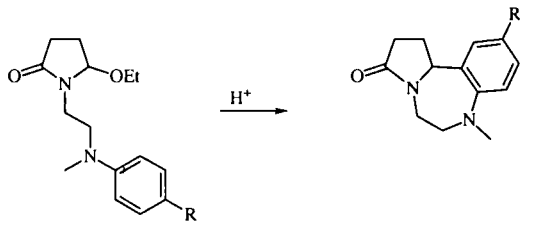


1 **2** **3**

An acid treatment of an *N*-acyl N,O-acetal is a common way to obtain an acyliminium salt [4] which then can cyclize on an aromatic group [5]. This approach has already been used for the synthesis of the benzodiazepines **4** [6] which are analogs of pyrrolidinones **2** (Scheme 2).

We tried these reactions starting from acids **5** which were obtained by a Mannich reaction of pyroglutamic methyl or trimethylsilyl ester [7]. An anodic oxidation [8] of acids **5** in methanol gives a quantitative yield of crude N,O-acetals **6** (Scheme 3). It is noteworthy that the oxidation of the electron rich aryl group [9] was not observed.

Scheme 2



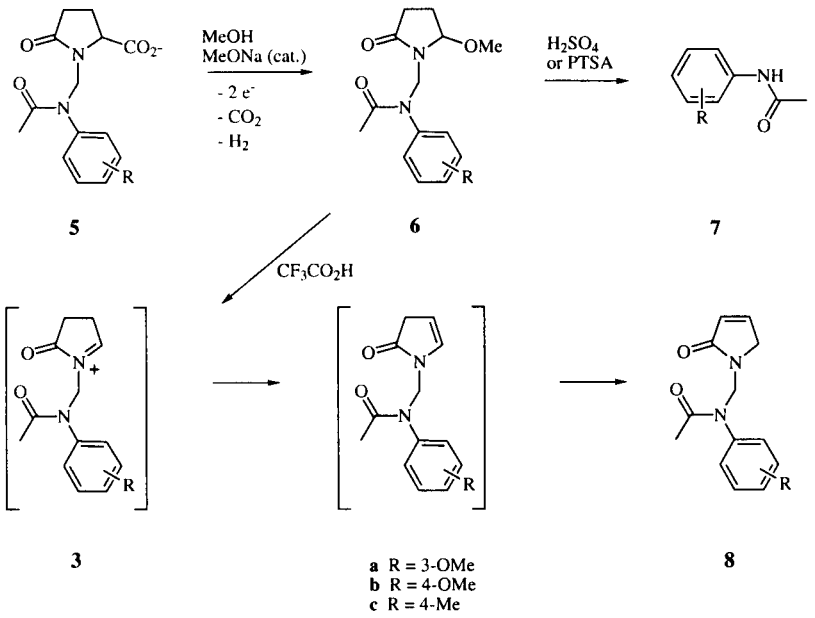
R = H, OMe, Cl

4

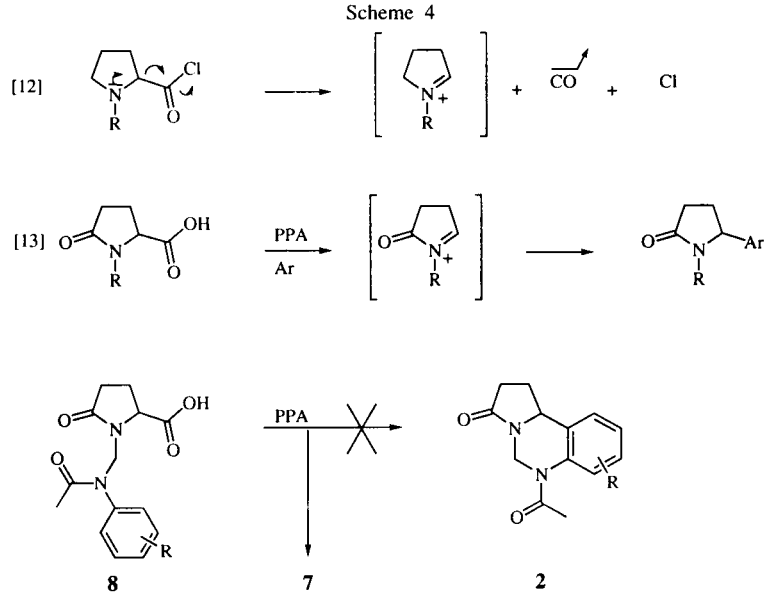
Unfortunately, the cyclization of *N*-acyl N,O-acetals **6** to lactams **2** does not succeed. Treatment of **6** with sulfuric or paratoluene sulfonic acid in dichloromethane yields only the amides **7** formed by a retro Mannich reaction. Reaction with trifluoroacetic acid at room temperature allowed us to obtain a low amount (about 12%) of the ethylenic compounds **8**. Such a formation of an unsaturated lactam from N,O-acetals was known [10]; in these reactions, a minute amount of heterocycles **2** have also been observed by nmr.

Another way to obtain an acyliminium salt from a pyroglutamic acid is reminiscent of the decarboxylation of amino acids (Scheme 4) [12]. Treatment of a pyroglutamic acid with polyphosphoric acid gives an acyliminium salt which can engage in a reaction with an aromatic to give an aryl lactam [13] (Scheme 4). When this reaction was tried with acids **5** formation of acetanilides **7** were the only products observed (Scheme 4).

Scheme 3



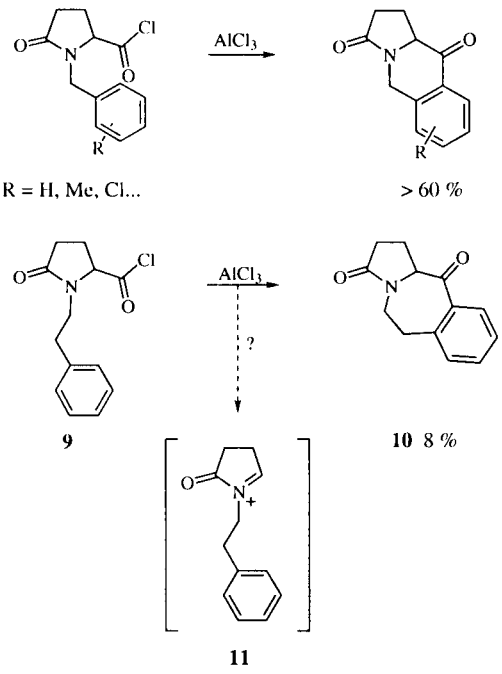
Scheme 4



It has been known for a long time that the Friedel-Crafts reaction of *N*-arylmethylpyroglutamoyl chloride gives good yields of cyclic six members ring ketones [14]. A result from Merour [15] is interesting in this context; the cyclization of acid chloride **9** gives only an 8% yield of ketone **10**. We thought that the formation of an iminium salt **11** from chloride **9** can explain this result (Scheme 5) and that, with a favorable ring size, the rate of the cyclization reaction would be higher than the rate of decarboxylation. Whereas, for the less favorable seven member ring size, decarboxylation leading to an iminium salt would be favored.

Thus, the formation of compounds **2** from the acid chlorides **12** and a Lewis acid was investigated, and indeed, products **2** were obtained in low to medium yields. The best catalyst was often aluminum chloride; in the proline series, aluminum bromide was used to avoid the formation of an iminium salt [12b]. However, in our case, it gives the same yield of lactam **2** as with aluminum chloride. With very sensitive compounds (**2e**), it is necessary to use tin tetrachloride. In all the cases tried, decomposition was only observed when using boron trifluoride and mixed anhydrides such as **14**. However, heating acids **5** with a

Scheme 5

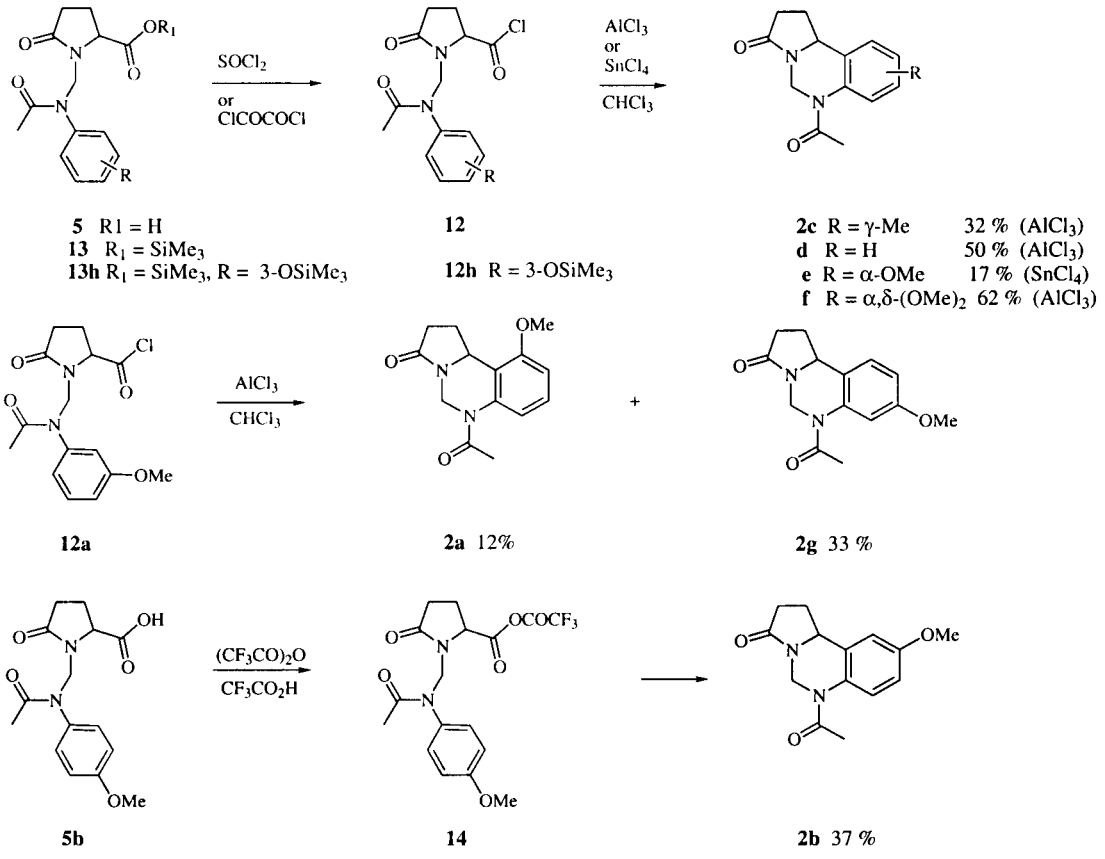


mixture of trifluoroacetic acid and trifluoroacetic anhydride sometimes gives the best yield of lactams **2**. When a methoxy substituent is placed in the meta position (**12a**), a mixture of two products (**2a** and **2g**) was obtained. As for the trimethylsilyloxy derivative **13h**, it quantitatively yields an acid chloride **12h** but this one was not cyclized (Scheme 6).

Some aspects of the reactivity of heterocycles **2** were studied (Scheme 7). A retro Mannich reaction occurred after two days reflux of lactam **2d** in glacial acetic acid or in 2*N* hydrochloric acid. By reflux in aqueous ammonia, or in a 50/50 mixture of 2*N* sodium hydroxide and methanol, the opening of the lactam ring was observed. Interestingly, in anhydrous conditions with sodium methylate in methanol, amines **15d,f** were obtained. We thought that, under these conditions, opening of the lactam ring is reversible (intramolecular reaction) while cleavage of the acetyl group, yielding amines **15** and methyl acetate, is an irreversible reaction.

The amino function of compound **15d** proved to be rather unreactive. There was no reaction with methyl acrylate either with or without potassium carbonate or sodium hydroxide, and a phase transfer agent. With the lithium salt of the amine, obtained from butyllithium, there was addition of several units of methyl acrylate to give **16**. The best yield of a pure alkylation product (**17**) (6%) was obtained when the reaction was performed with

Scheme 6



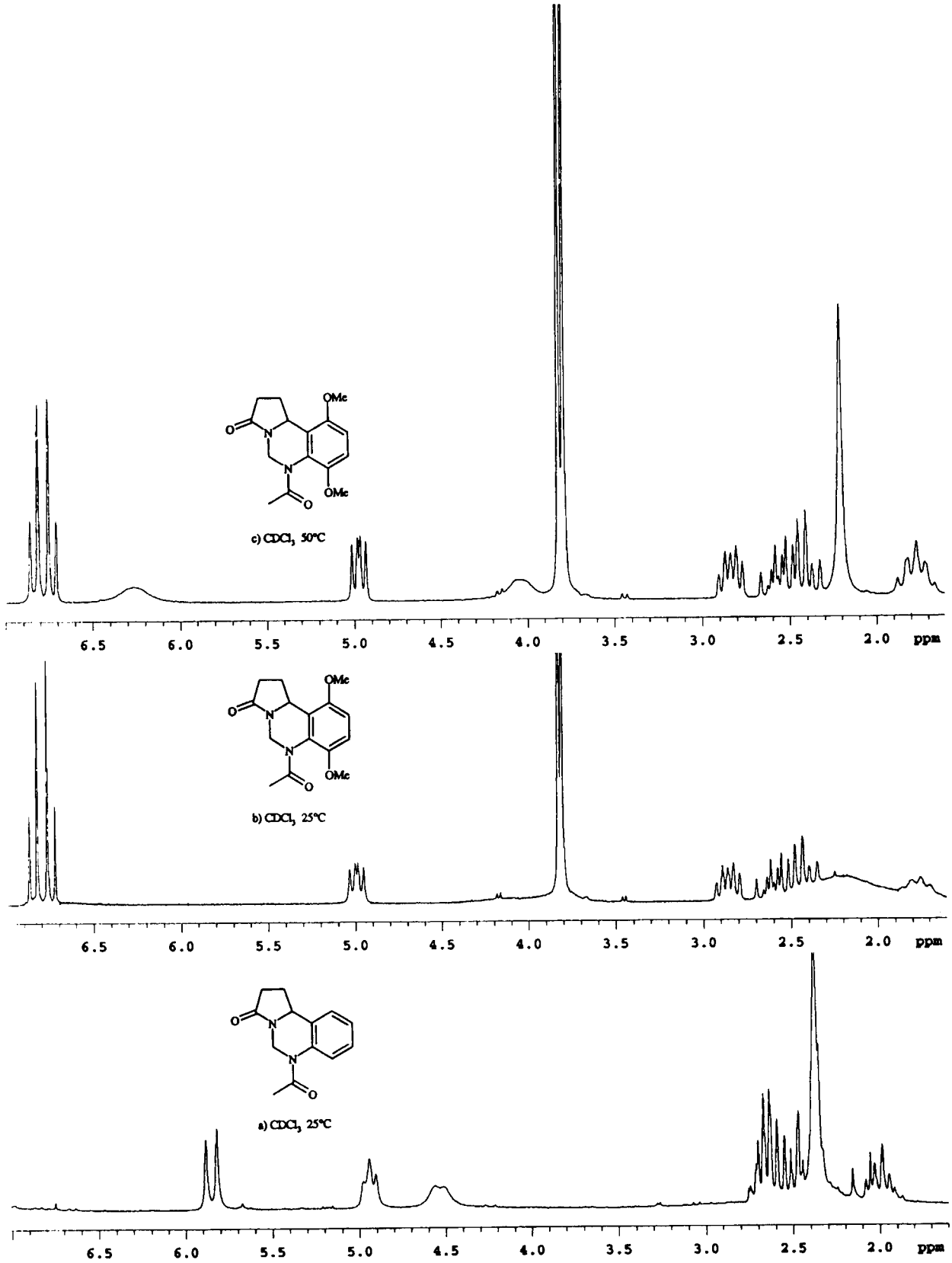
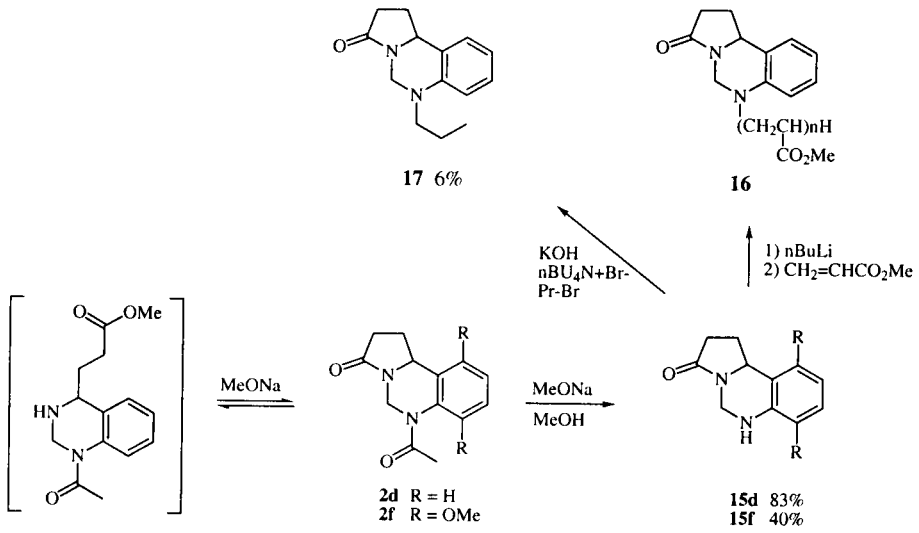


Figure 1. 200 MHz ^{1}H nmr spectra of ketones **2**: a) Compound **2d**, 25°; **b**) Compound **2f**, 25°; c) Compound **2f**, 50°.

Scheme 7



3-bromopropane in the presence of potassium hydroxide and a phase transfer agent [16] (Scheme 7).

In the ^1H nmr spectra of these compounds, as for other nitrogen heterocycles, the N-CH_2-X group yields two coupled signals. In lactams **2**, the equatorial proton N-CHe-N resonates at a very low field (about 6.5 ppm), while the axial proton N-CHa-N resonates near 4 ppm. We thought that this is probably due to the proximity of this equatorial proton with the two carbonyl groups. Hindered rotation can be observed for many of these compounds. For instance, the acetyl group of amide **2f** is observed as a very broad signal at room temperature and in many cases the two peaks N-CHe-N and N-CHa-N are also very broad. In addition, it is necessary to perform the nmr experiment at a higher temperature (50°) in order to find their position (Figure 1, ^1H nmr spectra of compound **2d** at room temperature and of **2d** and **2f** at 50°). Thus, hindered rotation explains why many peaks are very broad in the ^{13}C nmr spectra of these compounds as well.

EXPERIMENTAL

Melting points are uncorrected. The ir spectra were recorded on a 'Perkin-Elmer 700' spectrometer and the nmr spectra on a Varian 'Gemini 2000' at 200 MHz for ^1H and 50 MHz for ^{13}C, using tetramethylsilane as an internal reference. Elemental analyses were performed by the «Service Central de Microanalyses» (CNRS, Vernaison, France). Melting points, ir spectra and elemental analyses were not determined for moisture sensitive compounds. Pyroglutamic acid was a gift of UCIB, Ivry-la-Bataille, France, which can provide this chemical in bulk quantities.

6-Acetyl-9-methoxy-1,5,6,10b-tetrahydro-2*H*-pyrrolo[1,2-*c*]-quinazolin-3-one (**2b**).

A stirred solution of acid **5b** (6 g, 0.020 mole) in trifluoroacetic acid (5 ml) and trifluoroacetic anhydride (30 ml) was refluxed for one day. After evaporation, the residue was solubilized in dichloromethane (100 ml) and the solution was washed with carbonated water. After drying (sodium sulfate), volatiles were evaporated and the residue was purified by flash chromatography (ethyl acetate), giving a 37% yield of lactam **2b**, mp 123° (methanol); ir (potassium bromide): ν cm^{-1} 1690, 1660 (C=O), 1600, 1590, 1500 (C=C); ^1H nmr (deuteriochloroform): δ ppm 1.8-2.05 (m, 1H), 2.4-2.75 (m, 3H), 2.38 (s, 3H), 3.81 (s, 3H), 4.48 bs (1H), 4.8-5 (m, 1H), 5.85 (d, J = 12.7 Hz, 1H), 6.8-7.2 (m, 3H).

Anal. Calcd. for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76; O, 18.44. Found: C, 64.41; H, 6.55; N, 10.39; O, 18.82.

6-Acetyl-9-methyl-1,5,6,10b-tetrahydro-2*H*-pyrrolo[1,2-*c*]-quinazolin-3-one (**2c**).

This compound was obtained as for lactam **2d** (aluminum chloride: 3 equivalents, room temperature for 3 days); crude yield: 60%; crystallized yield: 32%; mp 134° (methanol); ir (potassium bromide): ν cm^{-1} 1700, 1660 (C=O), 1610, 1500, 1460 (C=C); ^1H nmr (deuteriochloroform): δ ppm 1.8-2.1 (m, 1H), 2.35 (s, 6H), 2.4-2.75 (m, 3H), 4.48 (bs, 1H), 4.8-5 (m, 1H), 5.84 (d, J = 12.9 Hz, 1H), 6.95 (s, 1H), 7.10 (d, J = 8.8 Hz, 1H), 7.2-7.3 (m, 1H), ^{13}C nmr (deuteriochloroform): δ ppm 21 (Ar-*C*H_3), 23 (CO-*C*H_3), 29.7 (CH-*C*H_2), 31.8 (CO-*C*H_2), 52.7 (N-*C*H_2 N), 56.1 (CH_2-*C*H), 125.6 (N-C-*C*H), 125.8 (N-C-CH-*C*H), 127.6 (CH-*Ar*), 128.3 (CH_3-C-*C*H-C), 130.6 (CH_3-*Ar*), 136.1 (N-*Ar*), 169.8 (*C*O-CH_3), 173.9 (*C*O-N).

Anal. Calcd. for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47; O, 13.10. Found: C, 68.43; H, 6.54; N, 11.53; O, 12.88.

6-Acetyl-1,5,6,10b-tetrahydro-2*H*-pyrrolo[1,2-*c*]quinazolin-3-one (**2d**).

Aluminum chloride (248 g, 1.86 mole) was slowly added to an ice cooled solution of acid chloride **12d** (0.62 mole) in dichloromethane (300 ml), while keeping the temperature below 5°. After 30 minutes, the cooling bath was removed and the mixture was stirred at room temperature for 3 days. After washes with water, carbonated water, then water, the organic phases were dried (sodium sulfate) then evaporated. The residue was distilled (Kugelrohr), giving a yellow oil (50%) which crystal-

lized in ethyl acetate containing a small amount of hydrated methanol. Lactam **2d** was obtained as an hydrate, in a 40% yield of pure compound, bp 140° (0.2 mbar, Kugelrohr), mp 65° (hydrate, ethyl acetate/ether 2/3); ir (potassium bromide): ν cm^{-1} 1680, 1650 (C=O), 1600, 1590, 1490, 1460 (C=C); ^1H nmr (deuteriochloroform): δ ppm 1.85-2.15 (m, 1H), 2.37 (s, 3H), 2.35-2.75 (m, 3H), 4.45 (bd, J = 12.5 Hz, 1H), 4.85-5.05 (m, 1H), 5.85 (d, J = 12.5 Hz, 1H), 7.1-7.8 (m, 4 H); ^{13}C nmr (deuteriochloroform): δ ppm 23 (CO-*CH_3*), 27.7 (CH-*CH_2*), 31.7 (CO-*CH_2*), 52.6 (N-*CH_2* N), 55.9 (CH_2-*CH*), 125.3 (2 ArH), 126 and 127.2 (2 ArH), 130.5 (*CH*-Ar), 136 (N-*Ar*), 169.6 (*CO*-CH_3), 173.7 (*CO*-N).

Anal. Calcd. for $C_{13}H_{14}N_2O_2$, H_2O: C, 67.81; H, 6.13; N, 12.17; O, 13.90. Found: C, 67.40; H, 6.21; N, 11.84; O, 14.21.

6-Acetyl-7-methoxy-1,5,6,10b-tetrahydro-2*H*-pyrrolo[1,2-*c*]-quinazolin-3-one (**2e**).

This compound was obtained as for **2d** (tin chloride: 4 equivalents, 4 hours reflux). A 41% crude yield of lactams **2e** was obtained whose flash chromatography purification (ethyl acetate) gives a 17% yield of pure **2e** (oil), bp 165° (0.2 mbar, kugelrohr); ir (potassium bromide): ν cm^{-1} 1690, 1660 (C=O), 1600, 1500, 1460 (C=C); ^1H nmr (deuteriochloroform): δ ppm 1.7-2 (m, 1H), 2.3 (s, 3H), 2.3-2.7 (m, 3H), 3.81 (s, 3H), 4.35 (bs, 1H), 4.8-5 (bs, 1H), 5.8 (bd, J = 12.3 Hz, 1H), 6.9-7.5 (m, 3H).

Anal. Calcd. for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76; O, 18.44. Found: C, 64.42; H, 6.18; N, 11.05; O, 18.66.

6-Acetyl-7,10-dimethoxy-1,5,6,10b-tetrahydro-2*H*-pyrrolo-[1,2-*c*]quinazolin-3-one (**2f**).

This compound was obtained as for **2d**, (aluminum chloride: 5 equivalents). After distillation, a 62% yield of **2f** was obtained in a 26% yield of crystallized product; bp 165° (0.4 mbar, kugelrohr), mp 173° (methanol); ir (potassium bromide): ν cm^{-1} 1685 (C=O), 1600, 1490, 1450 (C=C), 1255, 1250 (C-O); (55°, deuteriochloroform) 2 conformers: δ ppm 1.6-1.9 (m, 1H), 2.21 (s, 3H), 2.25-2.7 (m, 2H), 2.7-2.95 (m, 1H), 3.78-3.79 (2 s, 3H), 3.81, 3.82 (2 s, 3H), 4.05 (bs, 1H), 4.96 (d, J = 9.8 Hz, 0.5 H), 4.99 (d, J = 9.8 Hz, 0.5 H), 6.28 (bs, 1H), 6.73, 6.74 (2 d, J = 8.9 Hz, 1H), 6.84 (d, J = 8.9 Hz, 1H); ^{13}C nmr (deuteriochloroform): δ ppm 22.3 (CO-*CH_3*), 28.7 (CH-*CH_2*), 32.1 (CO-*CH_2*), 52.9 (N-*CH_2* N), 54.6 (CH_2-*CH*), 55.8 and 56.3 (O-*CH_3*), 108.2 (CH-C-$COCH_3$-*CH*), 111.1 (N-C-$COCH_3$-CH), 121.2 (CH-*C*), 128.1 (N-*C*), 147.7 (N-C-*C*-OCH_3), 150.8 (CH-C-*C*-OCH_3), 171.6 (*CO*-CH_3), 174.3 (*CO*-N).

Anal. Calcd. for $C_{15}H_{18}N_2O_4$: C, 62.06; H, 6.25; N, 9.65; O, 22.04. Found: C, 62.07; H, 6.29; N, 9.67; O, 22.22.

6-Acetyl-8-methoxy-1,5,6,10b-tetrahydro-2*H*-pyrrolo[1,2-*c*]-quinazolin-3-one (**2g**).

This compound was obtained as for **2d** (aluminum chloride: 5 equivalents; 3 hours reflux). A 54% crude yield of lactams **2a** and **2g** was obtained whose flash chromatography purification (ethyl acetate) gives a 33% yield of pure **2g**, mp 127° (ethyl acetate/heptane, 60/40, bp 160° (0.2 mbar, kugelrohr); ir (potassium bromide): ν cm^{-1} 1700, 1670 (C=O), 1610, 1580, 1510, 1470 (C=C), 1220 (C-O); ^1H nmr (deuteriochloroform): δ ppm 1.8-2.05 (m, 1H), 2.41 (s, 3H), 2.3-2.7 (m, 3H), 3.82 (s, 3H), 4.18 (bd, J = 12.8 Hz, 1H), 4.90 (t, J = 7.4 Hz, 1H), 5.86 (d, J = 12.8 Hz, 1H), 6.8 (dd, J = 8.3; 2.6 Hz, 1H), 7.05 (d, J = 8.3 Hz, 1H), 7.28 (bs, 1H); ^{13}C nmr (deuteriochloroform): δ ppm 23.3 (CO-*CH_3*), 28.3 (CH-*CH_2*), 31.8 (CO-*CH_2*), 52.9 (N-*CH_2* N), 55.6 and 55.9 (CH_2-*CH* and O*CH_3*), 110.6 (N-C-*CH*), 113 (C-CH-*CH*) 126.2 (CH_3O-C-CH-*CH*), 123.1 (CH-*Ar*), 137.1 (N-*Ar*), 158.6 (CH_3O-*C*), 169.8 (*CO*-CH_3), 173.9 (*CO*-N).

Anal. Calcd. for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76; O, 18.44. Found: C, 64.70; H, 6.41; N, 10.75; O, 18.55.

N-{[Acetyl-(3-methoxyphenyl)-amino]-methyl}-5-methoxy-2-pyrrolidinone (**6a**).

A mixture of acid **5a** (10 g, 0.031 mole) and sodium methylate (0.1 ml, 40% in methanol) in methanol (150 ml) was added into an undivided jacketed cell [11] equipped with four graphite-rods anodes and four graphite-rods cathodes, an exit tube for venting purposes, and a magnetic stirring bar. The carbon rods (6.1 mm in diameter, immersed 80 mm into the solution, resulting in a working electrodes surface of 60 cm^2 and a current density of 3.6 mA/cm^2) were spaced 10 mm apart. During the electrolysis, the temperature of the reaction mixture was maintained at 15°. After 2.18 F/mole of electricity (1.09 th.) (250 mA, 7 hours; initially the cell voltage was 15.6 V) has been passed, the current was stopped, the solvent was removed under reduced pressure, methylene dichloride was added and the solution was washed with a potassium carbonate aqueous solution and dried with sodium sulfate. After removing the solvent a crude yield of 85% of compound **6a** was obtained. This product was purified by distillation in a Kugelrohr apparatus, bp 135° (0.08 mb); ir (potassium bromide): ν cm^{-1} 1715, 1670, 1650 (C=O), 1605, 1510, 1450 (C=C), 1250 (C-O); ^1H nmr (deuteriochloroform): δ ppm 1.9 (s, 3H), 1.95-2.1 (m, 2H), 2.2-2.3 (m, 1H), 2.35-2.6 (m, 1H), 3.38 (s, 3H), 3.81 (s, 3H), 5.02-5.12 (m, 1H), 5.13 (d, J = 13.6 Hz, 1H), 5.31 (d, J = 13.6 Hz, 1H), 6.73-6.80 (m, 2H), 6.85-6.93 (m, 1H), 7.30 (t, J = 8.5 Hz, 1H); ^{13}C nmr (deuteriochloroform): δ ppm 22.7 (CO-*CH_3*), 24.6 (CO-*CH_2*), 28.2 (CH-*CH_2*), 52.9 (CH-O-*CH_3*), 54.8 (N-*CH_2*-N), 55.4 (Ar-O-*CH_3*), 90.5 (CH_2-*CH*), 113.8 (N-C-*CH*-C-O), 114.3 (O-C-*CH*-CH), 120.5 (N-C-*CH*-CH), 130.6 (CH-*CH*-CH), 143 (N-*Ar*), 161.7 (O-*Ar*), 172 (CH_3-*CO*), 175.8 (CH_2-*CO*).

Anal. Calcd. for $C_{15}H_{20}N_2O_4$: C, 61.63; H, 6.90; N, 9.58; O, 21.89. Found: C, 61.63; H, 6.99; N, 9.81; O, 21.52.

N-{[Acetyl-(4-methoxyphenyl)-amino]-methyl}-5-methoxy-2-pyrrolidinone (**6b**).

This compound was obtained in the same way as for lactam **6a**, crude yield 80%, bp 150° (0.1 mb); ir (potassium bromide): ν cm^{-1} 1720, 1665, 1650 (C=O), 1605, 1510, 1450 (C=C), 1250 (C-O); ^1H nmr (deuteriochloroform): δ ppm 1.85 (s, 3H), 1.94-2.14 (m, 2H), 2.15-2.30 (m, 1H), 2.32-2.60 (m, 1H), 3.40 (s, 3H), 3.82 (s, 3H), 5.02-5.07 (m, 1H), 5.10 (d, J = 13.2 Hz, 1H), 5.31 (d, J = 13.2 Hz, 1H), 6.89 (d, J = 8.9 Hz, 2H), 7.10 (d, J = 8.9 Hz, 2H); ^{13}C nmr (deuteriochloroform): δ ppm 22.7 (CO-*CH_3*), 24.7 (CO-*CH_2*), 28.2 (CH-*CH_2*), 53 (CH-O-*CH_3*), 54.8 (N-*CH_2*-N), 55.5 (Ar-O-*CH_3*), 90.5 (CH), 114.9 (O-C-*CH*), 129.3 (N-C-*CH*), 134.5 (N-*Ar*), 159.4 (O-*Ar*), 172.3 (CH_3-*CO*), 175.7 (CH_2-*CO*).

Anal. Calcd. for $C_{15}H_{20}N_2O_4$: C, 61.63; H, 6.90; N, 9.58; O, 21.89. Found: C, 61.69; H, 6.70; H, 9.48; O, 22.25.

N-[(Acetyl-*p*-tolylamino)-methyl]-5-methoxy-2-pyrrolidinone (**6c**).

This compound was obtained in the same way as for the lactam **6a**, crude yield 99%, bp 120° (0.08 mb); ir (potassium bro-

mide): ν cm^{-1} 1710, 1680, 1670 (C=O), 1610, 1510, 1450 (C=C), 1240 (C-O); ^1H nmr (deuteriochloroform) δ ppm 1.85 (s, 3H), 1.95-2.15 (m, 2H), 2.2-2.3 (m, 1H), 2.36 (s, 3H), 2.3-2.6 (m, 1H), 3.39 (s, 3H), 5-5.1 (m, 1H), 5.11 (d, J = 13.8 Hz, 1H), 5.33 (d, J = 13.8 Hz, 1H), 7.05 (d, J = 8 Hz, 2H), 7.19 (d, J = 8 Hz, 2H); ^{13}C nmr (deuteriochloroform): δ ppm 21.2 (Ar-*CH_3*), 22.7 (CO-*CH_3*), 24.6 (CO-*CH_2*), 28.2 (CH-*CH_2*), 52.8 (OCH_3), 54.8 (N-*CH_2*-N), 90.4 (CH), 127.9 (N-C-*CH*), 130 (CH_3-C-*CH*), 138.4 (*Ar*-CH_3), 139.1 (N-*Ar*), 172.3 (CH_3-*CO*), 175.7 (CH-*CO*).

Anal. Calcd. for $C_{15}H_{20}N_2O_3$: C, 65.20; H, 7.30; N, 10.14; O, 17.37. Found: C, 64.86; H, 7.60; N, 9.73; O, 17.72.

N-(3-Methoxyphenyl)-*N*-(2-oxo-2,5-dihydropyrrol-1-ylmethyl)-acetamide (**8a**).

A mixture of compound **6a** (1.4 g, 0.05 mole) and trifluoroacetic acid (0.55 g, 0.005 mole) in dichloromethane (10 ml) was stirred at room temperature for three days. The product obtained after distillation (Kugelrohr) was purified by flash chromatography (silica, 230-400 Mesh, ethyl acetate), yield 15%, bp 150° (0.3 mb); ir (potassium bromide): ν cm^{-1} 1720, 1680 (C=O), 1600, 1490, 1460 (C=C), 1230 (C-O); ^1H deuteriochloroform: δ ppm 1.92 (s, 3H), 3.80 (s, 3H), 4.22 (t, J = 1.8 Hz, 2H), 5.34 (s, 2H), 6.09 (dt, J = 5.9; 1.8 Hz, 1H), 6.6-7 (m, 3H), 7.14 (dt, J = 5.9; 1.8 Hz, 1H), 7.25-7.35 (m, 1H); ^{13}C nmr: δ ppm 22.6 (CO-*CH_3*), 53.1 (CH-*CH_2*), 54.1 (N-*CH_2*-N), 55.5 (O-*CH_3*), 113.9 and 114 (O-C-*CH*), 120.1 (CH_3O-*C*), 127.3 (CO-*CH*), 130.6 (O-C-*CH*-C), 142.7 (N-C), 144.3 (*CH*-CH_2), 160.7 (O-C), 171.7 (CH_3-*CO*), 174.4 (CH-*CO*).

Anal. Calcd. for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76; O, 18.44. Found: C, 64.22; H, 6.29; N, 10.41; O, 18.36.

N-(4-Methoxyphenyl)-*N*-(2-oxo-2,5-dihydropyrrol-1-ylmethyl)-acetamide (**8b**).

This compound was obtained in the same way as for the lactam (**8a**), yield 13%, bp 145° (0.07 mb, Kugelrohr); ir (potassium bromide): ν cm^{-1} 1710, 1660 (C=O), 1580, 1510, 1440 (C=C), 1245 (C-O); ^1H nmr (deuteriochloroform): δ ppm 1.87 (s, 3H), 3.80 (s, 3H), 4.19 (t, J = 1.8 Hz, 2H), 5.31 (s, 2H), 6.08 (dt, J = 6; 1.8 Hz, 1H), 6.89 (d, J = 9.1 Hz, 2H), 7 (d, J = 9.1 Hz, 2H), 7.14 (dt, J = 6; 1.8 Hz, 1H); ^1H nmr (deuteriochloroform): δ ppm 22.6 (CO-*CH_3*), 53 (CH-*CH_2*), 54.3 (N-*CH_2*-N), 55.5 (O-*CH_3*), 115.1 (O-C-*CH*), 127.3 (CO-*CH*), 128.7 (N-C-*CH*), 134.2 (N-*Ar*), 144.3 (*CH*-CH_2), 159.6 (O-*Ar*), 171.6 (CH_3-*CO*), 174.6 (CH-*CO*).

Anal. Calcd. for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76; O, 18.44. Found: C, 64.72; H, 6.11; N, 10.38; O, 18.63.

1-[(*N*-Acetyl-3-methoxyanilino)methyl]pyroglutamoyl chloride (**12a**).

This compound was obtained in a 100% nmr yield, as for chloride **12d**, starting from acid **5a** (5 hours reflux). ^1H nmr (deuteriochloroform): δ ppm 1.82 (s, 3H), 2.1-2.8 (m, 4H), 3.88 (s, 3H), 4.8-5.1 (m, 1H), 5.1-5.3 (m, 2H), 6.7-7.4 (m, 4H).

1-[(*N*-Acetyl-4-methoxyanilino)methyl]pyroglutamoyl chloride (**12b**).

This compound was obtained in a 100% nmr yield, as for chloride **12d**, starting from acid **5b**. ^1H nmr (deuteriochloroform): δ ppm 1.84 (s, 3H), 2-2.4 (m, 4H), 3.80 (s, 3H), 4.7-5 (m, 1H), 5.13 (bs, 2H), 6.87 (d, J = 9.4 Hz, 2H), 7.13 (d, J = 9.4 Hz, 2H).

1-[(*N*-Acetyl-4-methylanilino)methyl]pyroglutamoyl chloride (**12c**).

This compound was obtained in a 100% nmr yield, as for chloride **12d**, starting from acid **5c** (30 minutes reflux). ^1H nmr (deuteriochloroform): δ ppm 1.88 (s, 3H), 2-2.7 (m, 4H), 2.38 (s, 3H), 4.7-5 (m, 1H), 5.17 (bs, 2H), 7.06 (d, J = 8.5 Hz, 2H), 7.2 (d, J = 8.5 Hz, 2H).

1-[(*N*-Acetylanilino)methyl]pyroglutamoyl chloride (**12d**).

Thionyl chloride (103.2 g, 63.3 ml, 0.87 mole) was slowly (15 minutes) added to a stirred solution of silyl ester **13d** (216 g, 0.62 mole) in dichloromethane (500 ml). The mixture was refluxed for 30 minutes, then volatiles were evaporated, giving a 100% nmr yield of acid chloride **12d**; ^1H nmr (deuteriochloroform): δ ppm 1.84 (s, 3H), 2.1-2.6 (m, 4H), 4.6-4.9 (m, 1H), 5.16 (bs, 2H), 6.9-7.5 (m, 5H).

The same compound was also obtained quantitatively starting from acid **5d** instead of silyl ester **13d**.

1-[(*N*-Acetyl-2,5-dimethoxyanilino)methyl]pyroglutamoyl chloride (**12f**).

This compound was obtained in a 100% nmr yield, as for chloride **12d**, starting from acid **5f** (30 minutes reflux). ^1H nmr (deuteriochloroform): δ ppm 1.81 (s, 3H), 2-2.5 (m, 4H), 3.76 (s, 3H), 3.78 (s, 3H), 4.7-5 (m, 1H), 5.06 (d, J = 8 Hz, 1H), 5.23 (d, J = 8 Hz, 1H), 6.5-7 (m, 2H).

1-[(*N*-Acetyl-3-trimethylsilyloxyanilino)methyl]pyroglutamoyl chloride (**12h**).

Oxalyl chloride (2.2 g, 1.5 ml, 0.017 mole) was slowly (15 minutes) added to a stirred solution of silyl ester **13h** (7.9 g, 0.017 mole) in dichloromethane (75 ml). The mixture was stirred at room temperature for 2 hours then volatiles were evaporated, giving a 100% nmr yield of acid chloride **12h**, ^1H nmr (deuteriochloroform): δ ppm 0.27 (s, 9H), 1.87 (s, 3H), 2.2-2.6 (m, 4H), 4.75-4.9 (m, 1H), 5.15 (s, 2H), 6.6-6.9 (m, 4H).

1,5,6,10b-Tetrahydro-2*H*-pyrrolo[1,2-*c*]quinazolin-3-one (**15d**).

A solution of amide **2d** (84.4 g, 0.33 mole) and sodium methylate (57.4 g, 0.68 mole) in methanol (700 ml) was stirred at room temperature for 5 days. After evaporation, addition of dichloromethane and washings with water, the organic solution was dried (sodium sulfate). The residue obtained after evaporation was distilled, giving an 83% yield of amine **15d** as an oil, bp 185° (0.15 mbar); ir (potassium bromide): ν cm^{-1} 3300 (NH), 1700, 1680 (C=O), 1610, 1585, 1510, 1450 (C=C). ^1H nmr (deuteriochloroform): δ ppm 1.8-2.1 (m, 1H), 2.4-2.75 (m, 3H), 4.09 (bs, 1H, deuterium oxide exchangeable), 4.24 (d, J = 11 Hz, 1H), 4.88-4.98 (m, 1H), 5.18 (d, J = 11 Hz, 1H), 6.63 (d, J = 8.2 Hz, 1H), 6.82 (t, J = 7.3 Hz, 1H), 7 (d, J = 7.3 Hz, 1H), 7.07 (t, J = 8.2 Hz, 1H); ^{13}C nmr: δ ppm 27 (CH-*CH_2*), 31.9 (CO-*CH_2*), 50.8 (N-*CH_2*-N), 55.5 (N-CH), 116.9 (N-C-*CH*), 118.8 (CH-C-CH-*CH*), 124.6 (CH-*Ar*), 125.7 (N-C-CH-*CH*), 127.9 (CH-C-*CH*), 142.1 (N-*Ar*), 173.4 (CO).

Anal. Calcd. for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.88; O, 8.50. Found: C, 70.51; H, 6.73; N, 15.19; O, 8.14.

7,8-Dimethoxy-1,5,6,10b-tetrahydro-2*H*-pyrrolo[1,2-*c*]quinazolin-3-one (**15f**).

This amine was obtained as for **15f**, in a 40% yield (oil); ir (potassium bromide): ν cm^{-1} 3280 (NH), 1700 (C=O), 1600,

1590, 1500 (C=C), 1250 (C-O); ^{1}H nmr (deuteriochloroform): δ ppm 1.7-1.9 (m, 1H), 2.3-2.7 (m, 3H), 3.76 (s, 3H), 3.78 (s, 3H), 3.8 (bs, deuterium oxide exchangeable, 1H), 4.09 (d, J = 10.9 Hz, 1H), 4.90-5 (m, 1H), 5.23 (d, J = 10.9 Hz, 1H), 6.24 (d, J = 8.7 Hz, 1H), 6.62 (d, J = 8.7 Hz, 1H); ^{13}C nmr: δ ppm 27.5 (CH-*CH*$_2$), 32.2 (CO-*CH*$_2$), 50.1 (N-CH$_2$-N), 53.9 (N-CH), 55.4 and 56 (OCH_3), 99.3 (CH-C-C-*CH*), 108.5 (N-C-C-*CH*), 112.9 (CH-*Ar*), 133.8 (N-*Ar*), 141.8 (N-C-*C*-OCH_3), 151.4 (CH-C-*C*-OCH_3), 173.8 (CO).

Anal. Calcd. for $C_{13}H_{16}N_2O_3$: C, 62.89; H, 6.50; N, 11.28; O, 19.33. Found: C, 62.86, H, 6.15; N, 11.51; O, 19.65.

6-Propyl-1,5,6,10b-tetrahydro-2*H*-pyrrolo[1,2-*c*]quinazolin-3-one (**17**).

A mixture of amine **15d** (1 g, 4.3 mmoles), potassium hydroxide powder (0.68 g, 12 mmoles), tetrabutylammonium bromide (0.05 g) and bromopropane (3.25 g, 2.4 ml, 26 mmoles) was refluxed for 3 hours (magnetic stirrer). The product was purified by flash chromatography (ethyl acetate), yield 6% (oil); ir (potassium bromide): ν cm^{-1} 1700 (C=O), 1605, 1570, 1500, 1460 (C=C); ^{1}H nmr (deuteriochloroform): δ ppm 0.96 (t, J = 7.2 Hz, 3H), 1.4-1.8 (m, 2H), 1.8-2.1 (m, 1H), 2.4-2.7 (m, 3H), 3.18 (t, J = 7.6 Hz, 2H), 4.22 (d, J = 10.8 Hz, 1H), 4.92 (m, 1H), 5.03 (d, J = 10.8 Hz, 1H), 6.74 (d, J = 7.6 Hz, 1H), 6.79 (t, J = 7.6 Hz, 1H), 6.99 (d, J = 7.6 Hz, 1H), 7.15 (t, J = 7.6 Hz, 1H); ^{13}C nmr: δ ppm 11.6 (CH_3), 20.3 (CH_3-*CH*$_2$), 27.4 (CH-*CH*$_2$), 32 (CO-*CH*$_2$), 52.8 (N-*CH*$_2$-N), 55.7 and 56 (N-CH and N-CH$_2$), 114.3 (N-C-*CH*), 118.7 (CH-C-CH-*CH*), 120.5 (CH-*Ar*), 125.5 (CH-C-*CH*), 128.1 (N-C-CH-*CH*), 142.5 (N-*Ar*), 173.9 (CO).

Anal. Calcd. for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88; N, 12.16; O, 6.95. Found: C, 72.68; H, 7.86; N, 11.92; O, 7.30.

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