Hydroxylation of 5*H*-3-Oxo-2,3,6,7,8,9-hexahydro-imidazo[1,2-*a*]azepine Derivatives by Molecular Oxygen

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O-Methylcaprolactim **3** reacts in hot dimethylsulfoxide with α-amino acids **4** to give 5*H*-3-oxo-2,3,6,7,8,9-hexahydroimidazo[1,2-*a*]azepines **6** and, unexpectedly, hydroxylated derivatives **7a,c** and **8c**. The structures of the hydroxylated compounds have been elucidated by spectroscopic means and, when necessary, further confirmed by an independent unequivocal synthesis. The formation of **7** as well as the isomerization of **7c** to **8c** are discussed in detail.

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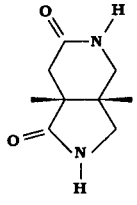
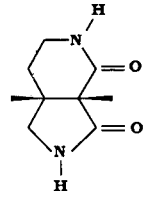
Our continuous investigations on the synthesis of potential biologically active nitrogen heterocycles [1-9] led us recently to the discovery of very interesting cognition activating properties in bicyclic isomeric lactam derivatives **1** and **2** [10].



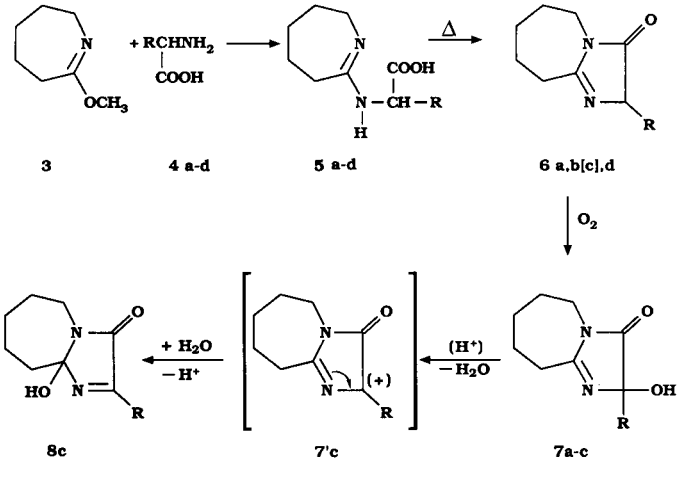
1



2

In order to explore the structure-activity relationship in this relatively new class of nootropic agents [11] and to have a simpler access to bicyclic systems containing a lactam functionality, we planned to prepare imidazo[1,2-*a*]-azepinones **6**; some of them were already known [12,13] being obtained by reacting *O*-methylcaprolactim **3** and α-amino acids **4** through a two step pathway according to the upper part of the following Scheme.

Scheme I



3 **4 a-d** **5 a-d** **6 a,b[c],d**

8c **7'c** **7a-c**

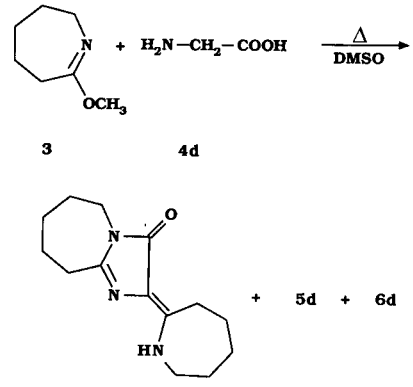
a : R = $(CH_3)_2CH$; **b** : R = $C_6H_5CH_2$; **c** : R = C_6H_5 ; **d** : R = H.

We tried to avoid the time consuming isolation and purification steps of intermediate amidines **5**, by reacting *O*-methylcaprolactim **3** and α-aminoacids **4** in dimethyl sulfoxide at high temperature (~ 110°).

In this paper we wish to describe the interesting results obtained during the study of this reaction.

By reacting **3** with glycine **4d**, in an equimolar ratio, three products were isolated: the expected amidino acid **5d** and imidazoazepinone **6d**, and an additional compound for which analytical and spectral data unequivocally indicated structure **9** (Scheme II).

Scheme II



3 **4d**

9

Compound **9** could arise from the nucleophilic displacement of the methoxy group of a further caprolactim ether molecule by C-2 of imidazoazepinone **6d**, as it was previously observed in similar reactions with methylene CH-acid compounds [14]. In fact, by increasing the molar ratio caprolactim:glycine up to 2, compound **9** was the major product formed, while the yield of **6d** became very low.

The reaction of **3** with **4a,b** afforded a mixture of amidino acids **5a,b**, imidazo[1,2-*a*]azepinones **6a,b**, together with the unexpected hydroxylated derivatives **7a,b** as the major products; no compound similar to **9** was detected [15]. The hydroxylation reaction seems therefore to take place only when a substituent is present at C-2. These results are consistent with the formation of a radical inter-

mediate at C-2 which is more stable (tertiary) when a substituent is present in position 2. Such a radical can easily react with oxygen from the air to give the hydroxylated compound **7**.

The correctness of this interpretation was proved by the results obtained from the same reaction carried out under nitrogen stream: under these conditions no hydroxylated derivative **7** was formed.

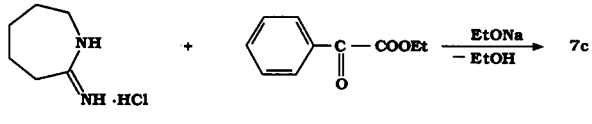
Moreover, the reaction of **3** with **4c**, under an air atmosphere, yielded two isomeric oxygenated compounds **7c** and **8c**. The intermediate imidazo[1,2-*a*]azepinone **6c** could not be isolated even when the reaction was carried out under nitrogen.

The isolation of **6c** probably failed because it could very easily give rise to a highly stable benzylic radical which even with oxygen traces could produce the hydroxylated derivative **7c**. This high sensitivity of the 5-imidazolinone moiety carrying a phenyl substituent at C-4 to the oxidation by air has been occasionally reported in the literature [16].

However the formation of **6c** was revealed by the analysis of the ^{1}H nmr spectra of amidino acid **5c** in DMSO-d_6 recorded at constant time intervals while the temperature was increased from 25° to 110°. The progressive disappearance of the singlet signal due to the C(2)-H proton resonance of **5c** at 4.21 ppm, and the appearance and continuous increase of a new singlet signal at 4.82 ppm, was taken as a clear evidence of the transformation of **5c** into **6c**.

The structure of **7c** was first supposed by comparison of spectrometric data, and was fully confirmed by its unequivocal synthesis from 2-imino-1,3,4,5,6,7-hexahydroazepine hydrochloride **10** and ethyl benzoylformate **11** (Scheme III).

Scheme III



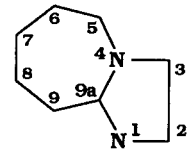
10 11

Most significantly, the ^{1}H nmr spectral data of **7c** are very similar to those of compounds **7a,b** thus further supporting the structural assignment to all the hydroxylated compounds **7**.

In Table I the ^{13}C chemical shifts of selected carbon atoms are reported for structural comparison between compounds **6** and **7**. They are in good agreement with published data on similar structures [17]. As can be seen from Table I the C-2 chemical shifts of **7** are significantly shifted downfield with respect to the corresponding signals in **6**, because of the strong electron withdrawing effect of the hydroxyl group.

Table I

Selected ^{13}C nmr Chemical Shifts ($CDCl_3$, δ, ppm) of compounds **6**, **7** and **8c** [a]



Compound	C-3	C-9a	C-2
6a	181.89	167.17	72.94
6b	181.46	167.08	68.12
7a	179.91	168.71	94.28
7b	178.73	168.35	92.71
7c	178.69	169.25	91.26
8c	163.10	104.76	162.31

[a] Complete assignments of ^{13}C nmr spectral data are reported in the Experimental

An interesting feature was also observed in the ^{1}H nmr spectra of compound **6b** and **7b** carrying a benzylic substituent in position 2. Two protons were strongly shielded giving rise to two complex multiplets centered at about 0.74 and 1.02 ppm for **6b** and 0.54 and 0.80 ppm for **7b**.

This shielding effect could be ascribed to a preferred conformation in solution in which some aliphatic protons of the azepine nucleus are located under the shielding cone of the aromatic benzylic ring. Decoupling experiments allowed us to assign the observed upfield signals to H-6 and H-8 protons (see Experimental).

The already discussed structure assignment to **7c** left for the isomeric by-product **8c** two possible structures: either the azacyclol structure with the hydroxyl group shifted to the 9a position with respect to **7c**, or the ten-membered monocyclic structure **8d** derivable by the opening of the bicyclic system (Figure 1).

Figure 1

Accurate analysis of all the spectral data allowed us to decide for the azacyclol structure **8c**. Firstly, the ^{13}C nmr spectrum showed only two trigonal carbon atoms linked to electron withdrawing atoms, instead of three as required

Table II

Physical, Analytical and Spectral Data of Compounds **6-8**

Compd.	Mp °C (Solvent)[a]	Analyses % Calcd./Found			Ir [b] νO-H, νC=O, cm^{-1}	UV (Ethanol) λ_{max}, nm (log ε)
		C	H	N		
6a	oil	68.01	9.34	14.42	1720	202 (3.24)
		67.74	9.30	14.18		234 (3.66)
6b	69-71dec	74.35	7.49	11.56	1730	206 (3.99)
	A	74.11	7.20	11.29		236 (2.56)
7a	136-138dec	62.85	8.57	13.33	3080[c], 1740	242 (3.49)
	A	63.15	8.78	13.43		
7b	162-165dec	69.76	6.97	10.85	3040[c], 1745	244 (3.41)
	B	70.07	7.18	11.04		
7c	150-152dec	68.85	6.55	11.47	3040[c], 1740	252 (4.00)
	B	68.60	6.53	11.39		
8c	138-140dec	68.85	6.55	11.47	3385, 1690	262 (4.54)
	B	68.50	6.50	11.25		

[a] Crystallization solvents: A, uncrystallized (purified by column chromatography, see Experimental); B, chloroform-hexane.
[b] The ir spectra were taken in potassium bromide disks except for **6a** (neat).
[c] broad signal.

by structure **8d**; the shift pattern of **8c** as assigned in Table I is consistent with that reported for other 2*H*-imidazoles [17].

Moreover, the ^1H nmr spectrum of the compound showed strong unequivalence of geminal H-couples, as it was observed in most bicyclic structures **6** and **7**, all including a chiral center; a pattern not explainable by the flexible structure **8d**, lacking asymmetric carbons.

The ir and uv spectral variations are consistent with structural differences between **7c** and **8c**: the ir carbonyl stretching band and uv maximum of **8c** (Table II) are respectively 50 cm^{-1} lower and 10 nm higher than those observed in **7c**, thus demonstrating a greater extent of conjugation.

Compound **8c** could arise from **7c** *via* the formation of an intermediate benzylic carbocation **7'c**, which could easily transpose and undergo nucleophilic attack by a water molecule as outlined in Scheme I.

Accordingly, slow isomerization of **7c** to **8c** could be observed also in chloroform solution at room temperature: after 48 hours a mixture of the two isomers was easily detected by thin layer chromatography. The same phenomenon could be monitored by the ^{13}C nmr APT spectrum too.

In conclusion, the present study has made available three different kinds of hexahydroimidazoazepinone structures **6**, **7** and **8**, for which a pharmacological screening has been planned.

Physical, analytical and spectral data of compounds **6-8** are presented in Table II.

EXPERIMENTAL

Melting points were determined by the capillary method on an Electrothermal (Mark II) apparatus and are uncorrected. Elemental analyses were made on a Carlo Erba 1106 C, H, N analyzer. The ir spectra were recorded using potassium bromide disks on a Perkin-Elmer 283 spectrophotometer, only the most significant and diagnostic absorption bands being reported. The nmr spectra were recorded on a Varian XL-200, chemical shifts were expressed in δ (ppm) and the coupling constants J in Hz. Exchange with deuterium oxide was used to identify -OH and -NH protons. Mass spectra were measured on a HP-5995C spectrometer and the uv spectra on a HP-8452A diode array spectrophotometer. Chromatographic separation were carried out on silica gel columns (230-400 mesh, Aldrich-Chemie) by using the "flash" technique.

Reaction of *O*-Methylcaprolactim **3** with L-Valine **4a**.

O-Methylcaprolactim **3** (4.5 ml, 31.5 mmoles) was added to a suspension of L-valine **4a** (1.85 g, 15.75 mmoles) in anhydrous dimethyl sulfoxide (10 ml). The mixture was heated at 110° with stirring for three hours and then allowed to cool to room temperature. After standing overnight the crystalline precipitate was removed by filtration to yield **5a**. The filtrate was diluted with water (70 ml) and extracted with chloroform (2 x 35 ml). The

organic phase was then washed with water (70 ml) and dried on anhydrous sodium sulfate. The mixture obtained after solvent evaporation under vacuum, was separated by flash column chromatography [ethyl acetate-chloroform-methanol (90:9:1) as an eluent] to give **6a** and **7a** (Rf = 0.35 and 0.14, respectively).

N-[3'H-4',5',6',7'-Tetrahydroazepin-2'-yl]-3-methyl-2-aminobutyrric Acid (**5a**).

This compound was recrystallized from ethanol-ether, mp 173-175°, 25% yield; ir: 3200-2600, 1670, 1595 cm^{-1}; ^1H nmr (methanol-d_4): δ 1.01 (d, 6H, J = 6.8, two CH_3), 1.50-1.95 (m, 6H, three CH_2), 2.26 (oct, 1H, J = 6.8, C*H*$(CH_3)_2$), 2.65-2.95 (m, 2H, N=C-CH_2), 3.40-3.65 (m, 2H, N-CH_2), 3.83 [d, 1H, J = 6.8, C*H*-$CH(CH_3)_2$]; ms: (m/e) 194 (M^+ -18).

Anal. Calcd. for $C_{11}H_{20}N_2O_2$: C, 62.26; H, 9.43; N, 13.20. Found: C, 61.88; H, 9.30; N, 13.39.

2-Isopropyl-5*H*-3-oxo-2,3,6,7,8,9-hexahydroimidazo[1,2-*a*]azepine (**6a**).

This compound was obtained as an oil in 20% yield; ^1H nmr (deuteriochloroform): δ 0.72 (d, 3H, J = 6.9, CH_3), 0.98 (d, 3H, J = 6.9, CH_3), 1.15-1.90 (m, 6H, three CH_2), 2.10-2.30 (m, 1H, C*H*$(CH_3)_2$), 2.40-2.75 (m, 2H, N=C-CH_2), 3.30-3.70 (m, 2H, N-CH_2), 3.75-3.85 (m, 1H, -C*H*-$CH(CH_3)_2$); ^{13}C nmr (deuteriochloroform): [18] δ 181.89 (C=O), 167.17 (N-C=N), 72.94 (N-*C*-C=O), 40.28 (N-CH_2), 31.45 (N=C-*C*H_2), 30.48 (*C*$(CH_3)_2$), 30.44, 29.39, 25.91 (three CH_2), 19.12 (CH_3), 16.59 (CH_3); ms: (m/e) 194 (M^+).

2-Isopropyl-2-hydroxy-5*H*-3-oxo-2,3,6,7,8,9-hexahydroimidazo-[1,2-*a*]azepine (**7a**).

This compound was obtained in 45% yield; ^1H nmr (deuteriochloroform): δ 0.82 (d, 3H, J = 6.8, CH_3), 0.94 (d, 3H, J = 6.8, CH_3), 1.40-1.95 (m, 6H, three CH_2), 2.07 (sept, 1H, J = 6.8, C*H*-$(CH_3)_2$], 2.50-2.80 (m, 2H, N=C-CH_2), 3.30-3.80 (m, 2H, N-CH_2), 6.01 (br, 1H, OH, exchangeable with deuterium oxide); ^{13}C nmr (deuteriochloroform): [18] δ 179.91 (C=O), 168.71 (N-C=N), 94.28 (N-*C*-C=O), 40.33 (N-CH_2), 35.04 [*C*(CH_3)], 34.09, 30.33, 29.10, 25.57 (four CH_2), 15.90 (CH_3), 15.56 (CH_3); ms: (m/e) 210 (M^+).

Reaction of *O*-Methylcaprolactim **3** with L-Phenylalanine (**4b**).

Under the same experimental conditions described above for L-valine, L-phenylalanine **4b** reacts with *O*-methylcaprolactim **3** giving amidino acid **5b** as a crystalline precipitate after the addition of chloroform to the reaction mixture and cooling. Compounds **6b** and **7b** were then obtained by flash column chromatography [ethyl acetate-methanol (9:1) as an eluent, Rf = 0.74 and 0.43, respectively], from the mother liquors of **5b**.

N-[3'*H*-4',5',6',7'-Tetrahydroazepin-2'-yl]-3-phenyl-2-aminopropionic Acid (**5b**).

This product was crystallized from dimethyl sulfoxide-chloroform, mp 139-141°, yield 5%; ir: 3700-2600, 1655, 1610 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 1.10-1.40 (m, 2H, CH_2), 1.50-1.85 (m, 4H, two CH_2), 2.50-2.70 (m, 2H, N=C-CH_2), 2.91 (dd, 1H, J = 14.1, 10.0, benzylic CH_2), 3.22-3.34 (m, 2H, N-CH_2), 3.42 (dd, 1H, J = 14.1, 4.0, benzylic CH_2), 4.29 (dd, 1H, J = 10.0, 4.0, C*H*-CH_2-Ar), 7.20-7.80 (m, 5H, ArH); ms: (m/e) 242 (M^+ -18).

Anal. Calcd. for $C_{15}H_{20}N_2O_2$: C, 69.20; H, 7.74; N, 10.76. Found: C, 69.44; H, 8.03; N, 10.61.

2-Benzyl-5*H*-3-oxo-2,3,6,7,8,9-hexahydroimidazo[1,2-*a*]azepine (**6b**).

This compound was obtained in 25% yield; ^1H nmr (deuteriochloroform): δ 0.40-0.88 (m, 1H, H-6), 0.90-1.15 (m, 1H, H-8), 1.20-1.90 (m, 4H, H-6, two H-7 and H-8), 2.35 (apparent tt, 1H, H-9, J = 14.5, 1.5), 2.58 (dd, 1H, H-9, J = 14.5, 7.0), 2.80-3.30 (m, 3H, H-5 and C*H*$_2$-Ar), 3.63 (dd, 1H, H-5, J = 14.0, 6.0), 4.20-4.30 (m, C*H*-CH_2-Ar), 7.00-7.30 (m, 5H, ArH); ^{13}C nmr (deuteriochloroform): [18] δ 181.46 (C=O), 167.08 (N-C=N), 135.49, 130.77, 127.86, 126.62 (six aromatic C), 68.12 (N-*C*-C=O), 40.28 (N-*C*H_2), 36.74 (*C*H_2-Ar), 31.18, 30.18, 28.55, 25.90 (four *C*H_2); ms: (m/e) 242 (M^+).

2-Benzyl-2-hydroxy-5*H*-3-oxo-2,3,6,7,8,9-hexahydroimidazo[1,2-*a*]-azepine (**7b**).

This product was obtained in 65% yield; ^1H nmr (deuteriochloroform): δ 0.40-0.68 (m, 1H, H-6), 0.70-0.95 (m, 1H, H-8), 1.15-1.80 (m, 4H, H-6, two H-7 and H-8), 2.30 (apparent td, 1H, H-9, J = 14.5, 1.5), 2.54 (dd, 1H, H-9, J = 14.5, 7.5), 2.96 (dd, 1H, H-5, J = 14.0, 10.0), 3.21 (s, 2H, C*H*$_2$-Ar), 3.64 (dd, 1H, H-5, J = 14.0, 6.0), 7.00-7.20 (m, 5H, ArH), 7.61 (br, 1H, OH, exchangeable with deuterium oxide); ^{13}C nmr: [18] δ 178.73 (C=O); 168.35 (N-C=N); 133.80, 130.71, 127.86, 126.92 (six aromatic C); 92.71 (N-*C*-C=O), 44.40 (benzylic C), 40.22 (N-*C*H_2), 30.67, 29.94, 27.94, 24.37 (four *C*H_2); ms: (m/e) 258 (M^+).

Reaction of *O*-Methylcaprolactim **3** with L-Phenylglycine **4c**.

Under the same experimental conditions described above for L-valine, L-phenylglycine reacts with *O*-methylcaprolactim **3** to give **8c** and **7c** by flash column chromatography [ethyl acetate-petroleum ether (85:15) as an eluent, Rf = 0.80 and 0.20, respectively] of the reaction mixture obtained after dilution with water and extraction with chloroform. Amidino acid **5c** was isolated only when the reaction was carried out under nitrogen stream.

N-[3'H-4',5',6',7'-Tetrahydroazepin-2'-yl]-2-aminophenylacetic Acid (**5c**).

This product was recrystallized from methanol-ether, mp 167-168° dec; ir: 3450 br, 1655, 1615 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 1.20-1.80 (m, 6H, three CH_2), 2.80-2.95 (m, 2H, N=C-CH_2), 3.10-3.50 (m, 2H, N-CH_2), 4.82 (s, 1H, CH), 7.10-7.40 (m, 5H, ArH), 8.50-10.0 (br, 2H, COOH and NH, exchangeable with deuterium oxide); ms: (m/e) 228 (M^+ -18).

Anal. Calcd. for $C_{14}H_{18}N_2O_2$: C, 68.27; H, 7.37; N, 11.37. Found: C, 67.94; H, 7.50; N, 11.21.

2-Phenyl-2-hydroxy-5*H*-3-oxo-2,3,6,7,8,9-hexahydroimidazo-[1,2-*a*]azepine (**7c**).

This product was obtained in 40% yield; ^1H nmr (deuteriochloroform): δ 1.30-1.90 (m, 6H, three CH_2), 2.40-2.70 (m, 2H, N=C-CH_2), 3.30-3.70 (m, 2H, N-CH_2), 7.15-7.30 (m, 3H, ArH), 7.40-7.60 (m, 2H, ArH), 5.65 (br, 1H, OH, exchangeable with deuterium oxide); ^{13}C nmr: [18] δ 178.9 (C=O), 169.25 (N-C=N), 138.58, 128.59, 128.29, 125.80 (six aromatic C), 91.26 (N-*C*C=O), 40.68 (N-CH_2), 31.20, 30.22, 28.86, 25.26 (four *C*H_2); ms: (m/e) 226 (M^+ -18).

2-Phenyl-9a-hydroxy-5*H*-3-oxo-3,6,7,8,9,9a-hexahydroimidazo[1,2-*a*]azepine (**8c**).

This product was obtained in 30% yield; ^1H nmr (deuteriochloroform): δ 0.80-1.10 (m, 1H, 0.5 CH_2), 1.30-1.85 (m, 5H, 2.5 CH_2), 2.10-2.50 (m, 2H, N-CH(OH)C*H*$_2$), 3.20-3.40 (m, 1H, 0.5 N-CH_2),

3.70-3.90 (m, 1H, 0.5 N-CH_2), 4.10 (br, 1H, OH, exchangeable with deuterium oxide), 7.35-7.65 (m, 3H, ArH), 8.35-8.50 (m, 2H, ArH); ^{13}C nmr (deuteriochloroform): [18] δ 163.18 (C=O), 162.31 (N=*C*-C=O), 104.76 (N-C-N), 132.40, 129.38, 129.00, 128.53 (six aromatic C), 40.87 (N-*C*H_2), 38.30, 29.19, 26.15, 22.00 (four *C*H_2); ms: (m/e) 244 (M^+).

When the reactions of *O*-methylcaprolactim with α-amino acids **4a-c** were carried out under nitrogen stream according to the procedure previously described compounds **5-8** were isolated in the following yields: **5a**, 5%; **5b**, 5%; **6a**, 65%; **6b**, 90%; **7a**, 2%; **7b**, 2%; **7c**, 12%; **8c**, 34%.

When the reactions were carried under nitrogen stream and worked up after half hour **5a-c** were isolated in 60%, 80% and 65% yield respectively.

Reaction of *O*-Methylcaprolactim **3** with Glycine **4d**.

O-Methylcaprolactim **3** (1.43 ml, 10 mmoles) was added to a suspension of glycine **4d** (0.75 g, 10 mmoles) in anhydrous dimethyl sulfoxide (5 ml). The mixture was heated at 110° for three hours and then allowed to cool to room temperature. After standing overnight the precipitate was collected and treated with boiling ether to extract compound **9**. The residue from boiling ether was then crystallized from methanol to give **5d**. The mother liquors of the reaction were diluted with water (35 ml) and extracted with chloroform (2 x 18 ml). The organic phase was then washed with water (35 ml) and dried on anhydrous sodium sulphate. The mixture obtained after solvent evaporation under vacuum, was separated by flash column chromatography [ethyl acetate-methanol 9:1 as an eluent] to give **9** and **6d** (Rf = 0.41 and 0.28, respectivly).

N-[3'H-4',5',6',7'-Tetrahydroazepin-2'-yl]aminoacetic Acid (**5d**).

This compound was obtained in 7% yield and proved to be identical with a specimen prepared according to reference [13], mp 176-177° [lit 173-174°]; ms: (m/e) 152 (M^+ -18).

Under the same experimental conditions described above amidino acid **5d** was obtained in 95% yield when the reaction was worked up after 0.5 hour.

5*H*-3-Oxo-2,3,6,7,8,9-hexahydroimidazo-[1,2-*a*]azepine (**6d**).

This compound was found identical to that already described in reference [13]. It was obtained in 30% yield; ir (liquid film): 1725, 1630 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.40-1.90 (m, 6H, three CH_2), 2.45-2.75 (m, 2H, N=C-C*H*$_2$), 3.30-3.70 (m, 2H, N-C*H*$_2$), 4.04 (m, 2H, COC*H*$_2$); ms: (m/e) 152 (M^+).

2-[3'*H*-4',5',6',7'-Tetrahydroazepin-2'-yl]-5*H*-3-oxo-2,3,6,7,8,9-hexahydroimidazo[1,2-*a*]azepine (**9**).

This compound was obtained in 25% yield, mp 170-172° (from ether); ir: 3260, 1650, 1615 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.50-1.85 (m, 12H, six CH_2), 2.62-2.74 (m, 2H, CH_2), 2.86-3.00 (m, 2H, CH_2), 3.35-3.48 (m, 2H, CH_2), 3.62-3.78 (m, 2H, CH_2), 9.49 (br, 1H, NH, exchangeable with deuterium oxide); uv (ethanol): 336 (4.32), 228 (4.02), 204 (3.71) nm (log ε); ms: (m/e) 247 (M^+).

Under the same experimental conditions previously described, compound **9** was formed in 90% yield after six hours when the molar ratio *O*-methylcaprolactim:glycine was increased to 2:1.

Preparation of 2-Phenyl-2-hydroxy-5*H*-3-oxo-2,3,6,7,8,9-hexahydroimidazo[1,2-*a*]azepine (**7c**) from Amidine Hydrochloride **10** and Ethyl Benzoylformate **11**.

Amidine hydrochloride **10** (20 mmoles) was added to a solution of sodium ethoxide prepared by dissolving sodium (20 mg-atoms) in ethanol (20 ml). After one hour stirring the precipitate of sodium chloride was filtered off and ethyl benzoylformate **11** (20 mmoles) was added to the free amidine solution. After stirring three more hours the precipitate was removed by filtration to give **7c** in 60% yield.

Amidine hydrochloride **10** was obtained by reacting *O*-methylcaprolactim with ammonium chloride in ethanol as previously reported [19], mp 165-167° (from ether).

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