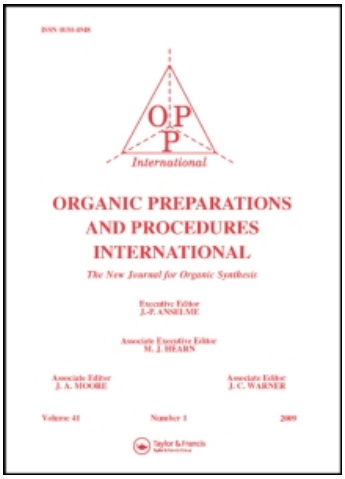


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

β-TRIFLUOROACETYLATION OF LACTAMS AND BENZOLACTAMS

J. P. Bouillon[a]; C. Atès[a]; C. Maliverney[ab]; Z. Janousek[a]; H. G. Viehe[a]
[a] Laboratoire de Chimie Organique, Univesité Catholique de Louvain, Louvain-la-Neuve, BELGIUM [b] Rhone-Poulenc, Centre de Recherche des Carrières, Saint-Fons Cedex, FRANCE

To cite this Article Bouillon, J. P. , Atès, C. , Maliverney, C. , Janousek, Z. and Viehe, H. G.(1994) 'β-TRIFLUOROACETYLATION OF LACTAMS AND BENZOLACTAMS', Organic Preparations and Procedures International, 26: 2, 249 — 255
To link to this Article: DOI: 10.1080/00304949409458029
URL: http://dx.doi.org/10.1080/00304949409458029

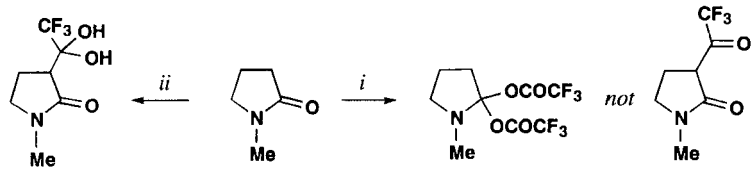
ORGANIC PREPARATIONS AND PROCEDURES INT., 26 (2), 249-255 (1994)

β-TRIFLUOROACETYLATION OF LACTAMS AND BENZOLACTAMS

J.-P. Bouillon, C. Atès, C. Maliverney†, Z. Janousek and H. G. Viehe*

Univesité Catholique de Louvain
Laboratoire de Chimie Organique
Place L. Pasteur 1, B-1348 Louvain-la-Neuve, BELGIUM

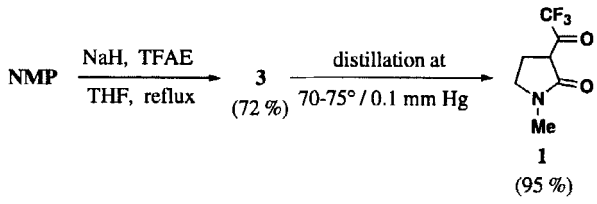
During our ongoing search for new methods of preparation of trifluoromethylated heterocycles, we have developed a practical synthesis of N-alkylated β-trifluoroacetyllactams and -benzolactams.[1] We previously postulated the intermediacy of 1-methyl-3-trifluoroacetyl-2-pyrrolidinone **1** when 1-methyl-2-pyrrolidinone (NMP) was used as the solvent.[2] Although β-trifluoroacetylation of cyclic ketones,[3] lactones[4] and tertiary aliphatic amides[5] is a well-known process, only one paper describes the preparation of **1** during a Claisen condensation between NMP and ethyl trifluoroacetate (TFAE) in the presence of sodium methoxide.[6] While attempting to duplicate this synthesis, we obtained a colorless oil corresponding to amide acetal **2** (Eq. 1). This result is supported by recent work dealing with the condensation of cyclohexanone with trifluoroacetic anhydride (TFAA).[7] Subsequent experiments showed that NMP reacts rapidly with TFAA at room temperature to give **2** which upon treatment with NaH gives a low yield (18%) of **3** as the hydrated form of **1** (Eq. 1).



3 (18%) (NMP) **2** **1**

i) NaOMe, TFAE, PhH, D *ii*) a) TFAA, 25° b) NaH, THF (1)

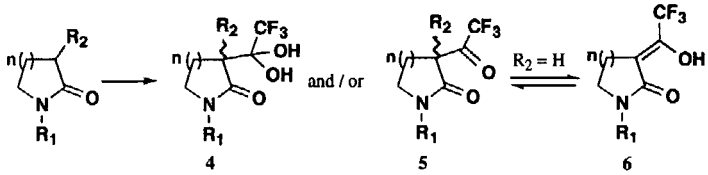
This preliminary result enabled us to develop an expedient synthesis of **1** which avoids the isolation of **2**. In fact, when NMP is treated first with 1.5 eq. of NaH in boiling THF followed by ethyl trifluoroacetate (1.5 eq.), **3** is obtained in 72% yield, dehydration of **3** takes place upon vacuum distillation (Eq. 2).



1
(95 %)

(2)

This procedure was extended to other 5,6,7-membered lactams (Eq. 3 and Table 1). The former sequence (**Method 1**) worked perfectly in most cases but **Method 2** using lithium diisopropylamide (LDA) at -78° followed by the addition of TFAE at -20° was used when the **Method 1** did not work satisfactorily.



4 5 6

(3)

a) n = 1, R_1 = R_2 = Me b) n = 1, R_1 = cyclohexyl, R_2 = H c) n = 1, R_1 = Ph, R_2 = H

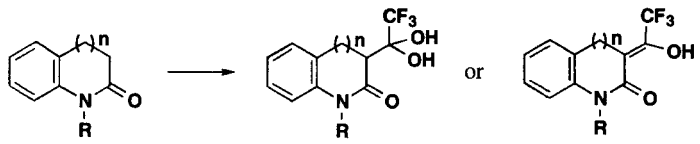
d) n = 1, R_1 = $PhCH_2$, R_2 = H e) n = 2, R_1 = Me, R_2 = H f) n = 3, R_1 = Me, R_2 = H

TABLE 1. Yields of Trifluoroacetyllactams

Cmpd	Method	Yield (%)
3	1	72[a]
4a	1	-
4a	2	69[a]
4b:6b (75 : 25)	1	68[a]
4c	1	83[a]
6d	1	49[b]
6e	1	77[c]
6e	2	40[c]
5f	1	-
4f:5f (40 : 60)	2	70[a]

a) After chromatography on silica gel. b) Chromatography and Kugelrohr distillation. c) Kugelrohr distillation.

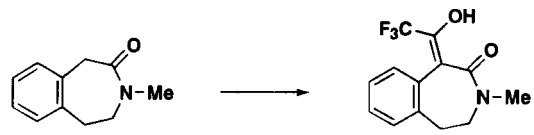
In view of the interesting pharmacological properties of benzoannulated lactams,[8] we performed the above trifluoroacetylation also on these compounds. As models we chose lactams **7** and benzazepinone **10**. The results are collected in Eqs. 4 and 5, Table 2.



(4)

7 8 9

a) n = 0, R = Me b) n = 1, R = Me c) n = 2, R = Me d) n = 2, R = $PhCH_2$



(5)

10 11

TABLE 2. Yields of Trifluoroacetyl Benzolactams

Benzolactam	Method	Product	Yield (%)
7a[9]	1	**9a**	88[a]
7b[10]	1	**8b**	51[a]
7c[10]	1	–	–
7c[10]	2	**8c**	70[b]
7d[10]	1	–	–
7d[10]	2	**8d**	25[b]
10[11]	1	**11**	62[c]

a) After chromatography on silica gel. b) Chromatography and recrystallization from pet. ether-ether. c) Chromatography and Kugelrohr distillation.

In conclusion, we have prepared a series of new trifluoroacetylated lactams via straightforward procedures. These lactams as other 1,3-dicarbonyl compounds, are useful building blocks in heterocyclic synthesis.[12]

EXPERIMENTAL SECTION

Mps were taken using a Leitz Wetzlar microscope and are uncorrected. Bps were estimated using a Kugelrohr apparatus. IR and mass spectra were measured on a Perkin-Elmer 1710 and a Finnigan Mat TSQ70 apparatus, respectively. ^1H, ^{19}F and ^{13}C NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 solutions on a Varian WXR or a Varian Gemini 200 spectrometer using TMS as an internal reference for ^1H and ^{13}C spectra and $CFCl_3$ for ^{19}F spectra. Chemical shifts are in ppm on the δ scale and coupling constants J are given in Hz. The following abbreviations are used : s singlet, br s broad singlet, d doublet, t triplet, q quartet, q_t quintet and m multiplet.

General Procedures for Trifluoroacetylation of Lactams. Method 1. - The lactam (20 mmoles) was added to a suspension of NaH (30 mmoles) in 30 mL of THF under argon. Under reflux, ethyl trifluoroacetate (30 mmoles) in 10 mL THF was then slowly added during 1 hour. After further

refluxing (3 hrs), the mixture was cooled, diluted with ether and neutralized with a 1N HCl solution. The organic phase was washed with brine, dried over $MgSO_4$ and evaporated. The crude product was chromatographed on silica gel to give **3**, **4b**, **4c**, **9a** and **8b**. Functionalized lactams **6d**, **6e** and **11** were distilled *in vacuo*.

Method 2.- *n*-Butyllithium (13 mmoles) was added to a solution of diisopropylamine (14 mmoles) at -78° and the temperature was allowed to reach -30°. The lactam (10 mmoles) in THF (10 mL) was added dropwise at -78°. Ethyl trifluoroacetate (12 mmoles) in THF (10 mL) was then added at -20°. The reaction mixture was stirred for 12 hrs at room temperature, diluted with ether and neutralized by 1N HCl. After extraction with ether (2x100 mL), the organic phase was washed with brine, dried over $MgSO_4$ and concentrated. Lactams **4a** and **5f** were obtained after chromatography on silica gel; compounds **8c** and **8d** were also recrystallized from pet. ether/ether mixture. Lactam **6e** was distilled under reduced pressure.

3-(1,1-Dihydroxy-2,2,2-trifluoroethyl)-1-methyl-2-pyrrolidinone (3), mp. 80-84°. MS (m/z): 214 (M^+), 195, 126, 99, 98, 83, 69. IR (KBr): 3300 (OH), 3000, 2940, 2900, 1650 (C=O), 1495, 1263, 1165, 1010, 902 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.2 (br s, OH), 3.9 (br s, OH), 3.4-3.3 (m ,2H), 2.92 (s, 3H), 2.86 (m, 1H), 2.3-2.2 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 174.2 (s), 122.4 (qd, $^1J_{C,F}$ = 286.9; $^3J_{C,H}$ = 8.5), 93.1 (q, $^2J_{C,F}$ = 32.0), 47.5 (t, $^1J_{C,H}$ = 142.9), 43.1 (d, $^1J_{C,H}$ = 135.1), 29.4 (q, $^1J_{C,H}$ = 139.0), 20.1 (t, $^1J_{C,H}$ = 136.4). ^{19}F NMR ($CDCl_3$): δ -79.8 (s).

Anal. Calcd. for $C_7H_{10}F_3NO_3$: C, 39.44; H, 4.73; N, 6.57. Found : C, 39.40; H, 5.25; N, 6.63

3-(1,1-Dihydroxy-2,2,2-trifluoroethyl)-1,3-dimethyl-2-pyrrolidinone (4a) , mp. 79-80°. MS (m/z): 227 (M^+), 209, 113, 112, 98, 83, 69, 55, 43. IR ($CHCl_3$): 3581 (OH), 3262 (OH), 3018, 2982, 2941, 2883, 1672 (C=O), 1467, 1409, 1270 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.62 (s, OH), 4.7 (br s, OH), 3.4-3.3 (m, 2H), 2.88 (s, 3H), 2.64 (dd, 1H, J = 13.5; 4.6), 1.9-1.8 (m, 1H), 1.31 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 178.1 (s), 122.9 (qd, $^1J_{C,F}$ = 289.1; $^3J_{C,H}$ = 9.1), 95.5 (q, $^2J_{C,F}$ = 31.1), 47.7 (s), 46.4 (t, $^1J_{C,H}$ = 143.2), 29.5 (q, $^1J_{C,H}$ = 139.3), 27.9 (t, $^1J_{C,H}$ = 136.0), 18.0 (q, $^1J_{C,H}$ = 130.0). ^{19}F NMR ($CDCl_3$): δ -80.7 (s).

Anal. Calcd. for $C_8H_{12}F_3NO_3$: C, 42.26; H, 5.32; N, 6.17. Found : C, 41.40; H, 5.27; N, 6.15

1-Cyclohexyl-3-(1,1-dihydroxy-2,2,2-trifluoroethyl)-2-pyrrolidinone (4b), mp. 123-125°. MS (m/z): 282, 281 (M^+), 263, 220, 212, 200, 182, 83, 69. IR (KBr): 3349 (OH), 3264 (OH), 2941, 2930, 2863, 1639 (C=O), 1495, 1468, 1456, 1444, 1292, 1260, 1172. ^1H NMR ($CDCl_3$): δ 8.1 (br s, OH), 7.2 (br s, OH), 3.9-3.7 (m, 1H), 3.4-3.2 (m, 2H), 2.83 (dd, 1H, J = 9.3;9.3), 2.1-2.0 (m, 2H), 1.8-1.3 (m, 10H). ^{13}C NMR ($CDCl_3$): δ 173.7 (s), 123.2 (qd, $^1J_{C,F}$ = 288.7; $^3J_{C,H}$ = 8.2), 93.2 (q, $^2J_{C,F}$ = 31.3), 51.1 (d, $^1J_{C,H}$ = 135.7), 44.1 (d, $^1J_{C,H}$ = 130.4), 41.3 (t, $^1J_{C,H}$ = 143.4), 29.9 (t, $^1J_{C,H}$ = 128.4), 29.6 (t, $^1J_{C,H}$ = 127.7), 25.25 (t, $^1J_{C,H}$ = 126.2), 25.22 (t, $^1J_{C,H}$ = 126.2), 25.1 (t, overlapped), 20.6 (t, $^1J_{C,H}$ = 134.0). ^{19}F NMR ($CDCl_3$): δ -83.3 (s).

1-Cyclohexyl-3-(1-hydroxy-2,2,2-trifluoroethylidene)-2-pyrrolidinone (6b), selected chemical shifts of ^{13}C NMR: 107.9 (s, C(8)=C(10)), 145.7 (q, =C(10)—CF_3, $^2J_{C,F}$ = 36.3), 119.9 (q, —CF_3, $^1J_{C,F}$ = 276.5), 171.5 (s, C=O). ^{19}F NMR ($CDCl_3$): δ -70.2 (s).

3-(1,1-Dihydroxy-2,2,2-trifluoroethyl)-1-phenyl-2-pyrrolidinone (4c), mp. 98-100°. MS (m/z): 275 (M^+), 257, 189, 188, 160, 106, 77, 69. IR ($CHCl_3$): 3581 (OH), 3247 (OH), 3023, 3015, 2897, 1673 (C=O), 1600, 1502, 1488, 1463, 1208 cm^{-1}. ^1H NMR ($CDCl_3$): δ 12.4-12.2 (br s, OH), 8.13 (s, OH), 7.61 (d, 2H, J = 8.6), 7.41 (dd, 2H, J = 7.8; 7.7), 7.23 (t, 1H, J = 6.6), 4.0-3.9 (m, 1H), 3.9-3.8 (m, 1H), 3.08 (dd, 1H, J = 9.7; 9.7), 3.1-2.9 (m, 1H), 2.5-2.3 (m, 1H). ^{13}C NMR (DMSO-d_6): δ 173.8 (s), 138.5 (stdd, $^3J_{C,H}$ = 9.1; 1.7; 1.6), 128.8 (dd, $^1J_{C,H}$= 161.5; $^3J_{C,H}$ = 7.9), 125.1 (dt, $^1J_{C,H}$ = 162.1; $^3J_{C,H}$ = 7.9), 123.0 (q, $^1J_{C,F}$ = 288.5), 120.3 (ddd, $^1J_{C,H}$ = 162.9; $^3J_{C,H}$ = 7.5; $J_{C,H}$ = 5.2), 93.3 (q, $^2J_{C,F}$ = 31.3), 46.5 (t, $^1J_{C,H}$ = 144.7), 45.2 (d, $^1J_{C,H}$ = 132.5), 20.2 (t, $^1J_{C,H}$ = 134.8). ^{19}F NMR ($CDCl_3$): δ -85.5 (s).

Anal. Calcd. for $C_{12}H_{12}F_3NO_3$: C, 52.37; H, 4.39; N, 5 .09. Found : C, 52.31; H, 4.07; N, 4.99

1-Benzyl-3-(1-hydroxy-2,2,2-trifluoroethylidene)-2-pyrrolidinone (6d), yellowish oil, bp. 64-67° (0.04 mm Hg). MS (m/z): 271 (M^+), 251, 202, 174, 91, 77, 69. IR (CCl_4): 3591 (OH), 3090, 2930, 1694 (C=O), 1606 (C=C), 1497, 1463, 1456, 1386, 1278, 1148 cm^{-1}. ^1H NMR ($CDCl_3$): δ 12.2 (br s, OH), 7.4-7.2 (m, 5H), 4.50 (s, 2H), 3.35 (t, 2H, J = 7.1), 2.85 (tq, 2H, $J_{H,H}$ = 7.0; $J_{H,F}$ = 3.0). ^{13}C NMR ($CDCl_3$): δ 171.8 (sq_t, $^3J_{C,H}$ = 2.9), 147.8 (qt, $^2J_{C,F}$ = 37.1; $^3J_{C,H}$ = 3.1), 135.1 (st, $^3J_{C,H}$ = 4.9), 128.7 (ddd, $^1J_{C,H}$ = 160.3; $^3J_{C,H}$ = 6.8; $^2J_{C,H}$ = 2.0), 128.0 (dddd, $^1J_{C,H}$ = 160.3; $^3J_{C,H}$ = 7.2; $J_{C,H}$ = 4.7; 4.7), 127.8 (dt, $^1J_{C,H}$ = 160.4; $^3J_{C,H}$ = 7.1), 119.6 (qt, $^1J_{C,F}$ = 274.7; $^4J_{C,H}$ = 1.4), 105.6 (s), 46.5 (tt, $^1J_{C,H}$ = 138.9; $J_{C,H}$ = 4.4), 44.8 (t, $^1J_{C,H}$ = 143.3), 19.8 (ttt, $^1J_{C,H}$ = 137.2; $^2J_{C,H}$ = 2.4; $^4J_{C,H}$ = 2.3). ^{19}F NMR ($CDCl_3$): δ -71.3 (s).

1-Methyl-3-(1-hydroxy-2,2,2-trifluoroethylidene)-2-piperidone (6e), yellowish oil, bp. 49-52° (0.01 mm Hg). MS (m/z): 209 (M^+), 189, 140, 113, 69. IR (film): 3352 (OH), 2942, 2872, 1641 (C=O), 1388, 710 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.37 (t, 2H, J = 5.7), 3.04 (s, 3H), 2.58 (m, 2H), 1.88 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 169.3 (sdq, $J_{C,H}$ = 6.2; $^3J_{C,H}$ = 3.1), 154.3 (qt, $^2J_{C,F}$ = 33.9; $^3J_{C,H}$ = 3.6), 119.6 (q, $^1J_{C,F}$ = 277.2), 100.0 (s), 48.9 (ttq, $^1J_{C,H}$ = 140.2; $^2J_{C,H}$ = 6.2; $^3J_{C,H}$ = 3.1), 34.4 (qt, $^1J_{C,H}$ = 139.2; $^3J_{C,H}$ = 1.7), 21.6 (ttq, $^1J_{C,H}$ = 131.8; $^2J_{C,H}$ = 5.8; $^4J_{C,F}$ = 2.5), 21.3 (tq_t, $^1J_{C,H}$ = 130.2; $^2J_{C,H}$ = 4.1). ^{19}F NMR ($CDCl_3$): δ -68.0 (s).

Anal. Calcd. for $C_8H_{10}F_3NO_2$: C, 45.94; H, 4.82; N, 6.70. Found : C, 45.90; H, 4.79; N, 6.54

1-Methyl-3-trifluoroacetyl-2-caprolactam (5f), mp. 57-60°. MS (m/z): 223 (M^+), 154, 125, 98, 69, 44. IR (KBr): 2947, 2941, 1773 (CF_3-C=O), 1639 (C=O lactam), 1496, 1437, 1404, 1198 cm^{-1}. ^1H NMR ($CDCl_3$): δ 4.06 (d, 1H, J = 10.5), 3.8-3.5 (m, 1H), 3.4-3.2 (m, 1H), 3.00 (s, 3H), 2.3-1.4 (m, 6H). ^{13}C NMR ($CDCl_3$): δ 188.5 (q, $^2J_{C,F}$ = 34.7), 171.0 (s), 115.2 (q, $^1J_{C,F}$ = 292.4), 52.5 (d, $^1J_{C,H}$ = 136.7), 50.7 (t, $^1J_{C,H}$ = 143.1), 34.8 (qdd, $^1J_{C,H}$ = 139.4; $^3J_{C,H}$ = 4.3; 4.3), 27.5 (t, $^1J_{C,H}$ =132.2), 26.3 (t, $^1J_{C,H}$ = 129.8), 23.6 (t, $^1J_{C,H}$ = 138.5). ^{19}F NMR ($CDCl_3$): δ -78.0 (s).

3-(1,1-Dihydroxy-2,2,2-trifluoroethyl)-1-methyl-2-caprolactam (4f), ^{13}C NMR ($CDCl_3$): δ 175.9, 123.0 (q, $^1J_{C,F}$= 289.1), 94.5 (q, $^2J_{C,F}$ = 30.5), 49.7, 43.6, 34.8, 26.8, 25.0, 22.7. ^{19}F NMR ($CDCl_3$): δ -83.5 (s).

3-(1-Hydroxy-2,2,2-trifluoroethylidene)-1-methyloxindole (9a), mp. 105-107°. MS (m/z): 244, 243 (M^+), 224, 175, 174, 117. IR (KBr): 3300 (OH), 3025, 3015, 2950, 1666 (C=O), 1609, 1468, 1356,

1212, 1162 cm^{-1}. ^1H NMR ($CDCl_3$): δ 13.5 (br s, OH), 7.62 (d, 1H, J = 7.7), 7.33 (ddd, 1H, J = 7.7; 7.7; 1.3), 7.16 (ddd, 1H, J = 7.7; 7.7; 1.2), 7.01 (d, 1H, J = 8.0), 3.40 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 171.2 (sq, $^3J_{C,H}$ = 3.0), 157.3 (q, $^2J_{C,F}$ = 39.4), 139.2 (s), 127.5 (ddd, $^1J_{C,H}$ = 163.1; $^3J_{C,H}$ = 7.5; $^2J_{C,H}$ = 2.2), 123.3 (ddd, $^1J_{C,H}$ = 161.7; $^3J_{C,H}$ = 7.2; $^2J_{C,H}$ = 1.9), 122.1 (d, $^1J_{C,H}$ = 163.2), 119.4 (q, $^1J_{C,F}$ = 277.3), 118.5 (s), 108.9 (ddd, $^1J_{C,H}$ = 162.4; $^3J_{C,H}$ = 8.7; $^2J_{C,H}$ = 1.3), 102.4 (s), 26.1 (q, $^1J_{C,H}$ = 140.4). ^{19}F NMR ($CDCl_3$): δ -71.4 (s).

Anal. Calcd. for $C_{11}H_8F_3NO_2$: C, 54.33; H, 3.32; N, 5.76. Found : C, 54.30; H, 3.36; N, 5.71

3-(1,1-Dihydroxy-2,2,2-trifluoroethyl)-1-methyl-3,4-dihydroquinolone (8b), mp. 93-94°. MS (m/z): 275 (M^+), 258, 257, 256, 186, 160, 77. IR (KBr): 3327 (OH), 2930, 2910, 1621 (C=O), 1604, 1596, 1485, 1458, 1277, 955 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.5 (br s, OH), 7.4-7.0 (m, 4H), 4.2-3.9 (m, 1H), 3.89 (s, OH), 3.42 (s, 3H), 3.2-3.0 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 171.5 (s), 138.3 (s), 128.0 (d, $^1J_{C,H}$ = 161.3), 127.8 (ddd, $^1J_{C,H}$ = 162.6; $^3J_{C,H}$ = 7.7; $^2J_{C,H}$ = 1.3), 124.8 (s), 124.1 (dd, $^1J_{C,H}$ = 162.5; $^3J_{C,H}$ = 7.3), 122.6 (q, $^1J_{C,F}$ = 286.1), 114.9 (dd, $^1J_{C,H}$ = 160.0; $^3J_{C,H}$ = 7.8), 94.3 (q, $^2J_{C,F}$ = 31.6), 42.5 (d, $^1J_{C,H}$= 126.6), 30.1 (q, $^1J_{C,H}$ = 140.4), 26.4 (t, $^1J_{C,H}$ = 131.9). ^{19}F NMR ($CDCl_3$): δ -83.0 (s).

Anal. Calcd. for $C_{12}H_{12}F_3NO_3$: C, 52.31; H, 4.30; N, 5.10. Found : C, 52.28; H, 4.32; N, 4.97

3-(1,1-Dihydroxy-2,2,2-trifluoroethyl)-1-methylbenzo[f]tetrahydroazepin-2-one (8c), mp. 100-103°. MS (m/z): 290, 289 (M^+), 271, 220, 146, 120, 118, 91, 77. IR (KBr): 3373 (OH), 3036, 1635 (C=O), 1604, 1492, 1459, 1400, 1267, 1175, 769 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.4-7.2 (m, 4H), 6.88 (s, OH), 4.18 (s, OH), 3.40 (s, 3H), 2.81 (t, 1H, J = 7.6), 2.7-2.6 (m, 2H), 2.4-2.3 (m, 1H), 2.3-2.1 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 174.4 (s), 141.6 (s), 134.9 (s), 129.2 (d, $^1J_{C,H}$ = 160.3), 128.1 (ddd, $^1J_{C,H}$ = 162.2; $^3J_{C,H}$ = 7.7; $^2J_{C,H}$ = 2.2), 127.4 (dd, $^1J_{C,H}$ = 161.9; $^3J_{C,H}$ = 7.5), 123.3 (dd, $^1J_{C,H}$ = 159.7; $^3J_{C,H}$ = 6.5), 122.5 (qd, $^1J_{C,F}$ = 287.5; $^3J_{C,H}$ = 2.1), 94.9 (q, $^2J_{C,F}$ = 31.9), 42.4 (d, $^1J_{C,H}$ = 129.9), 35.3 (q, $^1J_{C,H}$ = 140.4), 30.4 (t, $^1J_{C,H}$ = 132.4), 29.0 (t, $^1J_{C,H}$ = 129.1). ^{19}F NMR ($CDCl_3$): δ -84.1 (s).

Anal. Calcd. for $C_{13}H_{14}F_3NO_3$: C, 53.98; H, 4.88; N, 4.84. Found : C, 53.90; H, 4.75; N, 4.80

1-Benzyl-3-(1,1-dihydroxy-2,2,2-trifluoroethyl)benzo[f]tetrahydroazepin-2-one (8d), ^1H NMR (DMSO-d_6, 35°): δ 9.18 (s, OH), 8.04 (s, OH), 7.7-7.0 (m, 9H), 3.5-3.3 (m, 1H), 2.4-1.7 (m, 6H). ^{13}C NMR (DMSO-d_6, 35°): δ 176.1 (s), 144.0 (s), 135.6 (s), 135.5 (s), 129.5 (d, $^1J_{C,H}$ = 159.6), 128.9 (d, $^1J_{C,H}$ = 159.6), 128.45 (d, $^1J_{C,H}$ = 160.8), 128.41 (d, $^1J_{C,H}$ = 162.2), 128.1 (ddd, $^1J_{C,H}$ = 160.0; $^3J_{C,H}$ = 6.8; $^2J_{C,H}$ = 1.6), 127.6 (d, $^1J_{C,H}$ = 162.5), 124.0 (dd, $^1J_{C,H}$ = 160.0; $^3J_{C,H}$ = 6.7), 116.2 (q, $^1J_{C,F}$ = 293.5), 94.0 (q, $^2J_{C,F}$ = 29.5), 73.5 (dt, $^1J_{C,H}$ = 135.7; J = 3.5), 33.4 (t, $^1J_{C,H}$ = 133.8), 28.2 (t, $^1J_{C,H}$ = 129.4), 27.7 (t, $^1J_{C,H}$ = 134.1). ^{19}F NMR (DMSO-d_6, 25°): δ -80.0 (s).

3-(1-Hydroxy-2,2,2-trifluoroethylidene)-1-methylbenzo[d]tetrahydroazepin-2-one (11), mp. 82-85°. MS (m/z): 272, 271 (M^+), 202, 77, 58, 44, 43, 42. IR (KBr): 3400 (OH), 3025, 2974, 2939, 2862, 1677 (C=O), 1600, 1581, 1498, 1325, 1193, 977, 761 cm^{-1}. ^1H NMR ($CDCl_3$): δ 14.4 (br s, OH), 7.4-7.1 (m, 4H), 3.6-3.4 (m, 2H), 3.5-3.4 (m, 1H), 2.95 (s, 3H), 2.8-2.7 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 169.9 (s), 153.7 (q, $^2J_{C,F}$ = 33.6), 138.3 (s), 132.2 (s), 130.1 (ddq, $^1J_{C,H}$ = 160.8; $^3J_{C,H}$ = 7.1; $^5J_{C,F}$ = 2.7), 128.8 (ddd, $^1J_{C,H}$ = 161.1; $^3J_{C,H}$ = 6.7; $^2J_{C,H}$ = 1.7), 126.52 (d, $^1J_{C,H}$ = 161.6), 126.45 (d, $^1J_{C,H}$ =

161.5), 119.7 (q, $^{1}J_{C,F}$ = 277.3), 108.3 (s), 54.5 (t, $^{1}J_{C,H}$ = 141.5), 36.7 (qd, $^{1}J_{C,H}$ = 139.1; $^{3}J_{C,H}$ = 2.8), 31.4 (t, $^{1}J_{C,H}$ = 129.8). ^{19}F NMR ($CDCl_3$): δ -65.7 (s).

Acknowledgements.- H. G. Viehe and Z. Janousek are grateful to the *Services de la Programmation de la Politique Scientifique* (Belgium) for a grant. J.-P. Bouillon thanks Rhône-Poulenc-Rorer (Paris) for financial support; the authors also thank Dr. A.-M. Frisque-Hesbain and Dr. C. Wynants for valuable discussions.

REFERENCES

† Present address: Rhône-Poulenc, Centre de Recherche des Carrières 62, F-69120 Saint-Fons Cedex, FRANCE

1. J.-P. Bouillon, Thèse de Doctorat, Université Catholique de Louvain (1994).

2. J.-P. Bouillon, C. Maliverney, R. Merényi and H. G. Viehe, *J. Chem. Soc., Perkin Trans I*, 2147 (**1991**).

3. E. P. Kramarova, Yu. I. Baukov and I. F. Lutsenko, *Zh. Obshch. Khim.*, **45**, 478 (1975); *C. A.*, **82**, 112129y (1975); K. A. K. Ebraheem, S. T. Hamdi and M. N. Khalaf, *Can. J. Spectrosc.*, **26**, 225 (1981); K. Hagiwara, T. Iihama, H. Ishikawa and T. Yoshioka, *Jpn. Kokai Tokyo Koho* JP 86-127325 (**1987**); *C. A.*, **108**, 200234q (1987); H. Rempfler and D. Duerr, *Eur. Pat. Appl.* EP 89-810252 (**1989**); *C.A.*, **112**, 139043r (1989).

4. S. Archer and C. Perianayagam, *J. Med. Chem.*, **22**, 306 (1979); K. N. Allen and R. H. Abeles, *Biochemistry*, **28**, 8466 (1989).

5. M. M. Joullié, S. Navsfay and L. Rypstat, *J. Chem. Soc.*, **21**, 1358 (1956); A. N. Fomin, V. I. Saloutin, M. N. Rudaya and K. I. Pashkewich, *Zh. Org. Khim.*, **22**, 1603 (1986).

6. I. L. Knunyants, *Izv. Akad. Nauk. SSSR, Ser. Khim.*, **7**, 1688 (1986).

7. M. Tojo and S. Fukuoka, *Jpn Kokai Tokyo Koho* JP 63-54332 (**1964**).

8. K. Orito, H. Kaga and H. Suginome, *Org. Prep. Proced. Int.*, **21**, 321 (1989).

9. R. Stollé, *Ber.*, **47**, 2120 (1914).

10. L. H. Briggs and G. C. De Ath, *J. Chem. Soc.*, **99**, 456 (1937).

11. K. Orito and T. Matsuzaki, *Tetrahedron*, **36**, 1017 (1980).

12. J.-P. Bouillon, C. Atès, Z. Janousek and H. G. Viehe, *Tetrahedron Lett.*, **34**, 5075 (1993).

(Received August 9, 1993; in revised form January 3, 1994)