Synthesis of New Arylbenzofurodiazepin-6-ones

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Two new tetracyclic structures, containing the diazepine ring, were synthesized: 5,6-dihydro-12*H*-benzofuro[3,2-*b*][1,5]benzodiazepin-6-one and 5,6-dihydro-12*H*-benzofuro[3,2-*b*]pyrido[3,2-*f*][1,5]diazepin-6-one. Thus *N*-(2-haloaryl)-2-[(2-cyanophenyl)oxy]acetamides were cyclized to the corresponding *N*-(2-haloaryl)-3-amino-2-benzofurancarboxamides and then, through the formation of the central diazepine ring, to the title compounds. Formation of the diazepine ring took place only when an electron-withdrawing group was present in the molecule to facilitate the nucleophilic attack of an amine in the benzofuran intermediate.

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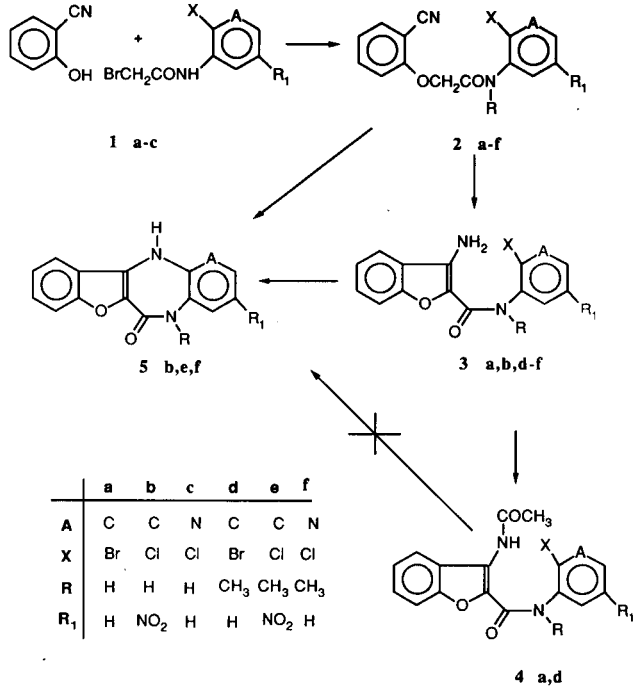
Great pharmacological interest has been devoted, for a long time, to tricyclic structures, such as dibenzo[b,e][1,4]-diazepine especially for their activity on CNS or on gastrointestinal tract [1].

In order to evaluate the influence of the substitution of one of the rings with another, bulkier, aromatic group, we have substituted a benzene ring with a benzofuran group obtaining new compounds with a tetracyclic structure: 5,6-dihydro-12*H*-benzofuro[3,2-*b*][1,5]benzodiazepin-6-ones **5b,e**. The further substitution of the second benzene ring with pyridine provided 5,6-dihydro-12*H*-benzofuro-[3,2-*b*]pyrido[3,2-*f*][1.5]diazepin-6-one (**5f**). These compounds were synthesized according Scheme 1. Thus *N*-(2-haloaryl)-2-[(2-cyanophenyl)oxy]acetamides **2a-f** were cyclized, in alkaline medium, to corresponding *N*-(2-haloaryl)-3-amino-2-benzofurancarboxamides **3a,b,d-f**. Further cyclization, through the formation of the central diazepine ring, to 5,6-dihydro-12*H*-benzofuro[3,2-*b*][1,5]-benzodiazepin-6-one, did not take place when R_1 = H **3a,d** either by heating in high boiling solvents, like DMF or dimethylacetamide, or in the presence of Cu, according to the Ullmann reaction [2], or to the Golberg modification (on the corresponding 3-acetylamino derivatives **4a** and **d**) [3], or according to the Cramer procedure with the Ni salt and dimethylaniline [4]. Introduction of an electron-withdrawing group, such as nitro, **3b** and **3e**, enhanced the electrophilic character of the carbon bearing the halogen atom, thus promoting a nucleophilic attack of the amine and the formation of the diazepine ring: in this case cyclization to compounds **5b** and **5e** could be obtained by simple heating in DMF in the presence of carbonate. The aza group of pyridine in compound **3f** gave, on the carbon atom bearing the halogen, a similar effect, leading to a ready cyclization to compound **5f**. In this case, compound **5f** could be also obtained without isolating the benzofuran intermediate **3f**, with an even better total yield, refluxing directly *N*-methyl-*N*-(2-chloro-3-pyridyl)-2-[(2-cyanophenyl)-oxy]acetamide (**2f**) in DMF with carbonate: the reaction, likely, proceeded *via* an intermediate **3f**, but under these conditions the rate of formation of the diazepine ring to compound **5f** seemed to be much higher than that of benzofuran **3f** to allow isolation of the latter.

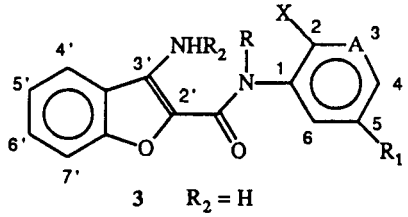
The proposed structures for the title compounds were confirmed by nmr (Tables 1,2,3), ms (Table 3), ir (Table 5) and elemental analysis (Table 5). Assignment of nmr resonances were accomplished with APT, COSY and HETCOR experiments [5], in addition to normal ^1H and ^{13}C spectra. In order to clearly identify hydrogen and carbon nucleous belonging to the benzofuran moiety in **3a,b,d-f** and **4a,d** compounds, propyl 3-amino-2-benzofurancarboxylate **B** and its 3-acetylamino derivative **C** were synthesized [6] and used as reference compounds (Table 1); likewise compounds **3a,b,d-f** constituted the reference compounds for our final products **5b**, **5e** and **5f**.

Scheme 1



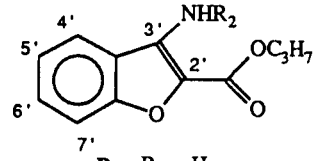
	a	b	c	d	e	f
A	C	C	N	C	C	N
X	Br	Cl	Cl	Br	Cl	Cl
R	H	H	H	CH_3	CH_3	CH_3
R_1	H	NO_2	H	H	NO_2	H

Table 1 : ^1H NMR Spectral Data of Benzofuran Derivatives (**3a,b,d-f** and **4a,d**)



3 $R_2 = H$

4 $R_2 = COCH_3$



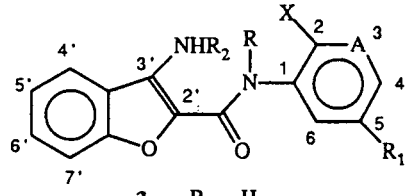
B $R_2 = H$

C $R_2 = COCH_3$

	(δ)										
	H-3	H-4	H-5	H-6	H-4'	H-5'	H-6'	H-7'	NR	NHR_2	$J_{Hi,Hj}$ (Hz)
B					7.98 d	7.23 m	7.4-7.5 m (H-6'+H-7')		[a]	6.35 NH_2	$J_{4',6'}$=2.0, $J_{4',5'}$=7.9, $J_{5',6'}$=6.1
3 a	7.66 dd	7.07 m	7.38 m	8.12 dd	8.00 d	7.28 m	7.48-7.55 m (H-6'+H-7')		9.00 s NH	6.44 s NH_2	$J_{3,4}$=8.0, $J_{4,5}$=7.4, $J_{5,6}$=8.1, $J_{4',5'}$=7.7 $J_{3,5}$=1.5, $J_{4,6}$=1.5
3 b	7.83 d	8.00 dd		9.02 d	7.96 d	7.29 m	7.50-7.53 m (H-6'+H-7')		9.21 s NH	6.56 s NH_2	$J_{3,4}$=8.9,$J_{4',5'}$=7.9, $J_{4,6}$=3.6
3 d	7.72 dd	7.35 m	7.4-7.5 m (H-5+H-6)		7.85 dd	7.14 m	7.27 m	6.75 v br s	3.27 s CH_3	6.38 s NH_2	$J_{3,4}$=7.5, $J_{4',5'}$=7.2, $J_{5',6'}$=6.9
3 e	7.84 d	8.26 dd		8.43 d	7.87 d	7.13 m	7.26 m	6.84 br d	3.24 s CH_3	6.08 s NH_2	$J_{3,4}$=8.8, $J_{6',7'}$=7.9, $J_{4,6}$=2.8
3 f		8.44 dd	7.51 dd	8.00 dd	7.85 d	7.16 m	7.30 m	6.81 br s	3.29 s CH_3	6.44 s NH_2	$J_{4,5}$=5.0, $J_{5,6}$=8.0, $J_{4,6}$=1.6, $J_{4',5'}$=7.6, $J_{6',7'}$=8.0
C					7.79 d	7.32 m	7.51 m	7.66 d	[a]	9.95-2.18 s NH-s CH_3	$J_{4',5'}$=7.7, $J_{5',6'}$=7.3, $J_{6',7'}$=8.2, $J_{4',6'}$=1.3, $J_{5',7'}$=0.9
4 a	7.76 dd	7.22 m	7.44 m	7.77 dd	7.93 d	7.35 m	7.54 m	7.67 br d	10.09 - 2.17 s (2H, 2NH)	s CH_3	$J_{3,4}$=7.2, $J_{4,5}$=7.8, $J_{5,6}$=8.0, $J_{4',5'}$=7.8, $J_{5',6'}$=7.3, $J_{6',7'}$=8.2, $J_{3,5}$=1.4, $J_{4,6}$=1.6, $J_{4',6'}$=1.3, $J_{5',7'}$=1.1
4 d	7.05 - 7.75 m (8H, aromatic CH)								3.27 s CH_3	10.0-2.13 s NH-s CH_3	

[a] OC_3H_7: 4.2 (t, 2H), 1.7 (m, 2H), 0.9 (t, 3H)

Table 2 : ^{13}C NMR Spectral Data of Benzofuran Derivatives (**3a,b,d-f** and **4a,d**)



3 $R_2 = H$

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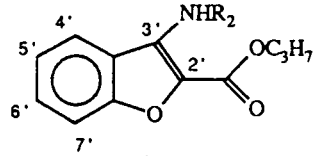


B $R_2 = H$

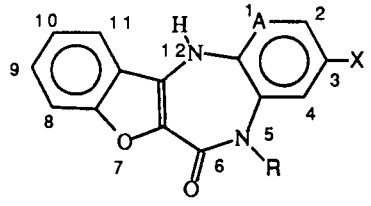
C $R_2 = COCH_3$

(δ) [a]

	C-3d	C-4d	C-5d	C-6d	C-4'd	C-5'd	C-6'd	C-7'd	COs	R (CH_3q)	R_2 (CO_s-CH_3q)	other C s
B					121.8	122.2	129.1	112.1	161.2	[b]		122.0, 123.6, 140.0 153.9
3 a	132.7	126.0	128.5	124.2	121.7	122.5	128.9	112.1	159.5			116.1, 122.7, 125.7 136.3, 138.6, 153.1
3 b	136.2	125.1		123.6	127.3	128.1	134.8	117.6	164.8			127.8, 130.4, 137.1, 141.6, 144.1, 152.3 , 158.7
3 d	133.0	129.5	130.6	128.9	121.2	121.9	128.2	111.4	161.5	36.6		121.8, 123.1, 126.4, 139.4, 143.6, 152.6
3 e	131.0	123.8		125.4	121.4	122.1	128.5	111.5	161.2	36.4		121.6, 125.9, 140.0, 140.1, 143,1, 147.2, 152.7
3 f		148.5	124.1	139.4	121.4	122.2	128.6	11.4	161.3	36.3		121.8, 126.2, 132.3, 139.9, 149.5, 152.6
C					124.1	123.5	129.6	112.3	159.6	[b]	168.6 23.0	123.8, 127.4, 134.6, 153.6
4 a	133.0	127.7	128.4	127.0	124.8	123.5	128.5	112.2	158.2		168.9 23.4	118.8, 123.7, 126.2, 135.7, 135.9, 152.9
4d[c]	133.3	128.9	129.9	127.4	123.5	123.0	130.2	111.4	160.5	36.7	168.3 23.2	122.3, 122.8, 124.2, 136.4, 142.4, 152.4

[a] Superscripts indicate the partial proton decoupling pattern
[b] OC_3H_7 : 10.1 (CH_3 q), 21.5 and 66.4 (2 CH_2 t)
[c] assignement based on similarity with **4a**

Table 3: NMR and Mass Spectral Data of Benzofuro[3,2-b][1,5]diazepine Derivatives (5b, e, f)



^{1}H NMR (δ)

	H-1	H-2	H-3	H-4	H-8	H-9	H-10	H-11	H-12	R	J Hi,Hj (Hz)
5 b	7.92 d	8.23 dd		8.45 d	7.55 m (H-8 + H-9)		7.32 m	8.02 d	6.77 s (2H, H-12+ R)		$J_{1,2}$=8.9, $J_{10,11}$=7.8, $J_{2,4}$=2.0
5 e	7.31 d	8.02 dd		8.01 d	7.60 d	7.53 m	7.36 m	8.08 d	9.58 s	3.30 s (CH_3)	$J_{1,2}$=9.4, $J_{10,11}$=7.8, $J_{2,4}$=3.1
5 f		8.02 d	7.19 dd	7.66 d	7.51 dd	7.53 m	7.31 m	8.23 dd	9.67 s	3.23 s (CH_3)	$J_{2,3}$=4.8, $J_{3,4}$=8.0, $J_{8,9}$=7.6, $J_{9,10}$=7.4, $J_{10,11}$=7.6, $J_{2,4}$=1.6, $J_{8,10}$=1.6, $J_{9,11}$=1.4

^{13}C NMR (δ) [a]

	C-1^d	C-2^d	C-3^d	C-4^d	C-8^d	C-9^d	C-10^d	C-11^d	CO-6^s	R (CH_3^{q})	other C ^{s}
5 b	111.1	120.1		113.7	112.2	129.3	122.9	121.8	160.1		122.0, 128.6, 138.9, 143.1, 145.5, 153.4, 154.8
5 e	120.1	121.7		120.2	112.5	129.2	123.5	121.4	162.4	36.8	120.9, 131.7, 134.2, 137.1 143.6, 150.3, 154.3
5 f		144.7	121.1	134.1	113.4	130.1	124.3	123.1	163.7	37.2	122.2, 129.8, 133.5, 137.5, 155.1, 155.7

[a] Superscripts indicate the partial proton decoupling pattern

MS (m/z)

	principal fragments [a]					other fragments
5 b	295(100) M+	249(63) M+-NO_2	221(10) 249-CO	91(19)		
5 e	309(68) M+	308(100) M+-1	280(85) 308-CO	234(57) 280-NO_2	206(20)	164(25), 149(18),
5 f	265(100) M+	237(76) M+-CO	236(51) 237-H	221(29) 236-CH_3	208(24) 237-NCH_3	179(11), 149(11), 119(11)

[a] relative abundance in parenthesis

Table 4: NMR Spectral Data of 2-Halogen-3-acylamino-arenes (**1a-c** and **2a-f**)

	^{1}H NMR (δ)
1 a	4.20 (s, 2H), 7.01 (m, 1H), 7.31 (m, 1H), 7.52 (dd, 1H, J=8.4, 1.5), 8.32 (dd, 1H, J= 8.2, 1.5), 8.9 (br s, 1H)
1 b	4,45 (s, 2H), 7.81 (d, 1H, J=8.7), 8.02 (dd, 1H, J=8.7, 3.0), 8.73 (d, 1H, J=30), 10.18 (s, 1H)
1c[a]	4.20 (s, 2H), 7.25, (dd, 1H, J=8.0, 4.5), 8.11 (dd, 1H,J=4.5, 1.7), 8.66 (dd, 1H, J=8.0, 1.7), 8.85 (br s, 1H)
2 a	5.01 (s, 2H), 7.1-7.45 (m, 4H), 7.6-7.9 (m, 4H), 9.62 (s, 1H)
2 b	5.1O (s, 2H), 7.1-7.4 (m, 2H), 7.6-8.1 (m, 4H), 8.89 (d, 1H, J=2.7), 9.95 (s, 1H)
2 c	5.06 (s, 2H), 7.1-7.9 (m, 5H), 8.2-8.4 (m, 2H), 9.85 (s, 1H)
2 d	3.10 (s, 3H), 4.37+4.67 (dd, 2H, J=15.8), 6.9-7.1 (m, 2H), 7.3-7.8 (m, 6H)
2 e	3.15 (s, 3H), 4.52+4.80 (dd, 2H, J=15.8), 7.O-7.2 (m, 2H), 7.5-7.7 (m, 3H) 7.95 (m, 1H), 8.2-8.4 (m, 2H)
2 f	3.12 (s, 3H), 4.54+4.75 (dd, 2H, J=15.7), 7.0-7.1 (m, 2H), 7.5-7.7 (m, 3H) 8.21 (dd, 1H, J=7.8, 1.7), 8.49 (dd, 1H, J=4.7, 1.7)

[a] in deuteriochloroform

EXPERIMENTAL

All melting points are uncorrected. The ir spectra were recorded with a Perkin-Elmer Model 1710 spectrophotometer and mass spectra with a Hewlett-Packard 5988 spectrometer. Elemental analyses for C, H and N were performed by the Analytical Department of Menarini S.r.l., Florence, Italy. All nmr spectra were recorded on Varian Gemini-200 spectrometer using, unless otherwise stated, deuteriodimethyl sulfoxide as the solvent. The APT, COSY and HETCOR experiments [5], in addition to ^{1}H and ^{13}C nmr spectra, were performed utilizing standard Varian software (version 6.2).

N-Bromoacetyl-2-bromoaniline (**1a**) [7].

A stirred solution of 2-bromoaniline (0.1 mole) and pyridine (10 ml) in dioxane (150 ml) was slowly treated with bromoacetyl chloride (0.11 mole) keeping the temperature below 40° with the aid of an water bath. When the addition was over, the mixture was kept at room temperature for three hours and poured in approximately 500 g crushed ice: the solid material was collected by filtration and recrystallized.

N-Bromoacetyl-2-chloro-5-nitroaniline (**1b**) and 2-chloro-3-bromoacetylamino pyridine (**1c**) were obtained by an analogous reaction.

N-(2-Bromophenyl)-2-[(2-cyanophenyl)oxy]acetamide (**2a**).

Compound **1a** (0.07 mole) was added to a suspension of 2-cyanophenol sodium salt (0.07 mole) in 300 ml of ethanol and refluxed for 5 hours. Sodium bromide was filtered off and the filtrate concentrated to dryness to give an oil which crystallized in petroleum ether.

Similarly *N*-(2-chloro-5-nitrophenyl)-2-[(2-cyanophenyl)oxy]acetamide (**2b**) and *N*-[3-(2-chloropyridinyl)]-2-[(2-cyanophenyl)oxy]-acetamide (**2c**) were prepared.

N-(2-Bromophenyl)-N-methyl-2-[(2-cyanophenyl)oxy]acetamide (**2d**).

A solution of compound **2a** (0.05 mole) in 200 ml of DMF was treated with sodium hydride 80% (0.05 mole). When the evolution of gas was over, methyl iodide (0.1 mole) was added and the suspension was stirred at room temperature for 8 hours. The reaction mixture was poured into water and extracted with ethyl acetate. The solvent was evaporated to give an oil which crystallized on standing.

Similarly *N*-(2-chloro-5-nitrophenyl)-*N*-methyl-2-[(2-cyanophenyl)oxy]acetamide (**2e**) and *N*-[3-(2-chloropyridinyl)]-N-methyl-2-[(2-cyanophenyl)oxy]acetamide (**2f**) were prepared.

N-(2-Bromophenyl)-*N*-methyl-3-amino-2-benzofurancarboxamide (**3d**).

Compound **2d** (0.02 mole) was refluxed in 200 ml of propanol with sodium carbonate (0.02 mole) for 9 hours. The mixture was poured into water and the solid collected by filtation. If reagent **2d** was still present, the collected material was dissolved in the minimum volume of dioxane and hydrogen chloride was bubbled in, until all the hydrochloride precipitated; free amine was regenerated as a white crystalline solid by simply pouring its hydrochloride in a 5% sodium bicarbonate solution.

Similarly *N*-(2-chloro-5-nitrophenyl)-3-amino-2-benzofurancarboxamide (**3b**) and *N*-(2-chloro-5-nitrophenyl)-*N*-methyl-3-amino-2-benzofurancarboxamide (**3e**) were prepared. In some cases higher boiling solvents had to be used: *N*-[3-(2-chloropyridinyl)]-*N*-methyl-3-amino-2-benzofurancarboxamide (**3f**) was ob-

Table 5

	IR cm-1			Mp[a]	Reaction Yield	Time	Analytical data found %			calcd. %			Formula
	CO	CN	NH	°C	%	hours	C	H	N	C	H	N	
1a	1670		3250	75-6 ethanol	70	3	32.44	2.25	4.82	32.8	2.41	4.78	$C_8H_7Br_2NO$
1b	1680		3269	125-8 2-propanol	87	3	32.96	2.15	9.25	32.74	2.06	9.54	$C_8H_6BrClN_2O_3$
1c	1670		3330	100-1 ethanol	93	3	33.62	2.2	10.93	33.7	2.42	11.23	$C_7H_6BrClN_2O$
2a	1700	2230	3353	143-4 ethanol	71	5	54.25	3.51	8.52	54.4	3.35	8.46	$C_{15}H_{11}BrN_2O_2$
2b	1713	2231	3374	232-5 ethanol	91	5	54.55	3.12	12.8	54.31	3.04	12.67	$C_{15}H_{10}ClN_3O_4$
2c	1700	2227	3336	194-6 acetone	80	8	58.42	3.68	14.46	58.45	3.50	14.61	$C_{14}H_{10}ClN_3O_2$
2d	1680	2226		140-1 ethanol	65	24	55.99	3.98	8.32	55.67	3.8	8.12	$C_{16}H_{13}BrN_2O_2$
2e	1689	2232		150-2 ethanol	80	30	55.67	3.57	12.31	55.58	3.5	12.15	$C_{16}H_{12}ClN_3O_4$
2f	1685	2230		134-6 ethanol	57	16	59.78	4.13	3.78	59.71	4.01	13.93	$C_{15}H_{12}ClN_3O_2$
3a	1658		3430 3382 3345	176-8 ethanol	85	9	54.66	3.44	8.65	54.4	3.35	8.46	$C_{15}H_{11}BrN_2O_2$
3b	1673		3453 3379 3352	225(dec) propanol	82	16	54.20	3.33	12.49	54.31	3.04	12.67	$C_{15}H_{10}ClN_3O_4$
3d	1626		3413 3302	119-121 ethanol	87	9	55.28	4.03	8.42	55.67	3.80	8.11	$C_{16}H_{13}BrN_2O_2$
3e	1636		3442 3338	155-6 2-propanol	74	18	55.32	3.2	12.31	55.58	3.5	12.15	$C_{16}H_{12}ClN_3O_4$
3f	1628		3457 3329	132-4 propanol	70	16	59.98	4.32	4.05	59.71	4.01	13.93	$C_{15}H_{12}ClN_3O_2$
4a	1672 1622		3386 3267	230-1 ethanol	98	8	54.88	3.82	7.54	54.71	3.51	7.51	$C_{17}H_{13}BrN_2O_3$
4d	1682 1636		3240[b]	118-9 2-propanol	97	8	54.63	4.27	7.61	54.42	4.03	7.47	$C_{17}H_{15}BrN_2O_3$
5b	1626		3452 3327	275-7 DMSO	16	5	61.13	3.09	14.15	61.02	3.07	14.23	$C_{15}H_9N_3O_4$
5e	1636		3313	310(dec) DMSO	45	6	62.01	3.77	13.35	62.14	3.58	13.59	$C_{16}H_{11}N_3O_4$
5f	1635		3349	215(dec) ethanol	72 [c] 70 [d]	5 4	66.54	4.51	16.51	66.4	4.38	16.59	$C_{14}H_{11}N_3O_2$

[a] recrystallization solvent indicated below
[b] very broad
[c] based on the direct cyclization of **2f**
[d] based on **3f**

tained in *n*-butanol and *N*-(2-bromophenyl)-3-amino-2-benzofurancarboxamide (**3a**) in DMF or dimethylacetamide.

Acetylation in acetic anhydride, according well known procedure, afforded the 3-acetylamine derivatives **4a** and **4d**.

5,6-Dihydro-5-methyl-3-nitro-12(*H*)-benzofuro[3,2-*b*][1,5]benzodiazepin-6-one (**5e**).

A mixture of compound **3e** (0.01 mole) and sodium carbonate (0.01 mole) in 100 ml of DMF was refluxed for 5 hours, cooled down and poured in 500 ml of water. The brown solid material was collected and recrystallized.

Similarly 5,6-dihydro-3-nitro-12(*H*)-benzofuro[3,2-*b*][1,5]benzodiazepin-6-one (**5b**) and 5,6-dihydro-5-methyl-12(*H*)-benzofuro-[3,2-*b*]pyrido[3,2-*f*][1,5]diazepin-6-one (**5f**) were prepared.

Compound **5f** could be also obtained directly from compound **2f**. Thus, a mixture of compound **2f** (0.006 mole) and sodium carbonate (0.006 mole) was refluxed in DMF for 5 hours, cooled down and poured into water. The solid material was collected and recrystallized.

On the contrary, compounds **2b** and **2e**, when heated, as above, in DMF for several hours, gave dark brown material in extremely low yield from which compounds **5b** and **5e**, if present, could not be isolated in pure form.

Several attempts were done to obtain compounds **5a** and **5d** refluxing the corresponding 3-aminobenzofuran derivatives **3a,d** in DMF/sodium carbonate, DMF/sodium bicarbonate, dimethylacetamide/sodium carbonate, DMF/sodium carbonate/Cu [2], dimethyl aniline/Ni [4] and the corresponding 3-acetylaminobenzofuran derivatives **4a,d** in DMF/sodium carbonate/Cu [3], but in all cases black tars were obtained from which no well defined product could be isolated.

Propyl 3-Amino-3-benzofurancarboxylate (**B**).

This product was obtained according to the known method [6] with minor modifications starting from 2-cyanophenol sodium salt and ethyl 2-bromoacetate in propanol in the presence of sodium carbonate; propanol, used as solvent, gave a transesterification reaction producing the propyl ester instead of the expected ethyl ester.

Acetylation with acetic anhydride gave the corresponding propyl 3-acetylamino-2-benzofurancarboxylate (**C**).

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