Synthesis of 1-Amino-[1,2,3]oxadiazolo[4,3-*a*]phthalazin-4-ium Chloride and Substituted Dihydro Derivatives. New Annelated Sydnonimines

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The sydnonimine **5** has been prepared by an original one-pot nitrosation and cyclisation procedure of the carbonyl chloride Reissert adduct **14** of phthalazine. This synthetic method could be extended to the preparation of dihydro derivatives **7a** to **7f** and represents a new access to annelated sydnonimines. The para anisoyl and ethoxycarbonyl derivatives of these sydnonimines were also prepared with analogy to molsidomine **1** or pirsidomine **2**.

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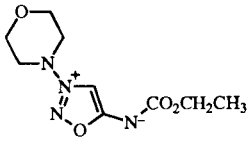
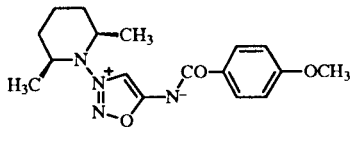
Sydnonimines are well-known mesoionic derivatives and some like molsidomine **1** (Figure 1) or pirsidomine **2** (Figure 1) show interesting properties in the cardiovascular field (vasodilation) [1a-b]. The active metabolites are SIN-1 **3a** (Figure 1) for molsidomine and C87-3754 **3b** (Figure 1) for pirsidomine and the cardiovascular activity can be explained by the ability of these metabolites to release chemically NO [1-3].

With the increasing importance of the NO production in the organism [4,5], we were interested in the preparation of new sydnonimines. To our knowledge, bridged analogues **4** of molsidomine (or pirsidomine) (Figure 1) have never been described and we started a chemical program with the target of 1-amino[1,2,3]oxadiazolo[4,3-*a*]phthalazin-4-ium chloride **5** (Figure 2), some of its derivatives **6a-b** (Figure 2) and its dihydro substituted derivatives **7a-f** and **8aa-fa** (Figure 2).

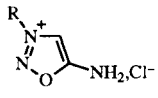
The usually used synthetic pathway to sydnonimines is

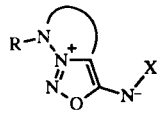


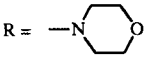
1
Molsidomine



2
Pirsidomine





3a R =  SIN-1

4
Bridged analogues

X = H,HCl
X = CO_2Et
X = CO-*p*-$PhOCH_3$

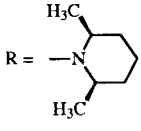
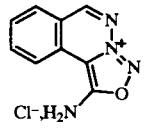
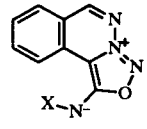
3b R =  C87-3754

Figure 1



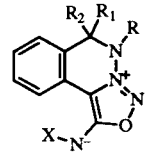
5



6a-b

6a X = CO-*p*-$PhOCH_3$
6b X = $COOCH_2CH_3$

7a-f



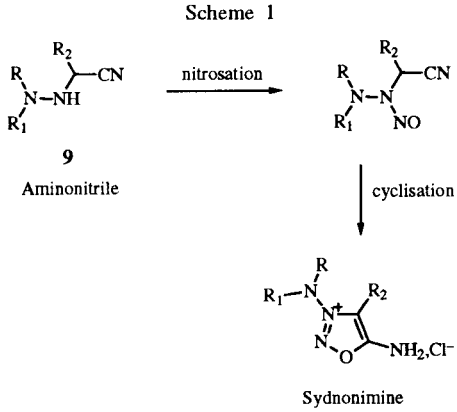
8aa-fa

7	R	R_1	R_2
a	CH_3	H	H
b	CH_3	CH_3	H
c	CH_3	CH_3	CH_3
d	Bu	H	H
e	Bu	CH_3	H
f	Bu	CH_3	CH_3

8	R	R_1	R_2	X
aa	CH_3	H	H	CO-*p*-$PhOCH_3$
ab	CH_3	H	H	$COOCH_2CH_3$
ba	CH_3	CH_3	H	CO-*p*-$PhOCH_3$
bb	CH_3	CH_3	H	$COOCH_2CH_3$
ca	CH_3	CH_3	CH_3	CO-*p*-$PhOCH_3$
cb	CH_3	CH_3	CH_3	$COOCH_2CH_3$
da	Bu	H	H	CO-*p*-$PhOCH_3$
db	Bu	H	H	$COOCH_2CH_3$
ea	Bu	CH_3	H	CO-*p*-$PhOCH_3$
fa	Bu	CH_3	CH_3	CO-*p*-$PhOCH_3$

Figure 2

Scheme 1



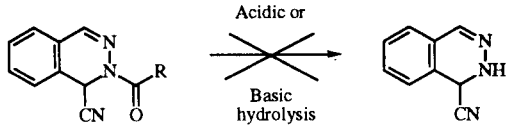
9
Aminonitrile

Sydnonimine

given in Scheme 1 [6-8] and starts from the aminonitrile intermediate **9** which is nitrosated and then cyclised to the sydnonimine.

In our case, convenient precursors of the corresponding aminonitrile **10** could be the Reissert adducts **11** (Scheme 2) but it is well known that acidic or basic cleavage of the amide bond of **11** never affords the aminonitrile **10** (aromatic derivatives only isolated) [9-11].

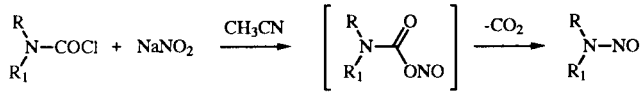
Scheme 2



11 **10**

In the literature nevertheless is described a neutral nitrosating method [12] of carbamoyl chlorides (Scheme 3) which avoids isolation of the free base before nitrosation. The mechanism of the reaction is not elucidated yet, but an hypothesis is the way through intermediate **12** (Scheme 3).

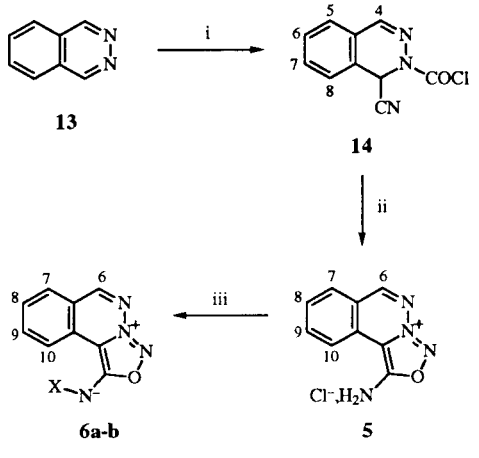
Scheme 3



12

We adapted this method to the synthesis of **5** (Scheme 4). The carbonyl chloride **14** was obtained from phthalazine **13** by a modification of the Reissert reaction using phosgene in toluene, trimethylsilyl cyanide and catalytic amounts of boron trifluoride diethyl etherate in 52% yield. The same reaction could be performed with diphosgene (58% yield) or triphosgene (62% yield), the easier to handle phosgene substitutes. The stable carbonyl chloride **14** was then nitrosated with sodium nitrite in acetonitrile and immediately cyclised to **5** in a methanolic gaseous hydrogen chloride solution with 12% overall yield. The bad yield can be explained by the instability of the nitrosated intermediate before cyclisation. Derivatisation of **5** was accomplished without problems to **6a** and **6b** (61% and 58% yield respectively).

Scheme 4



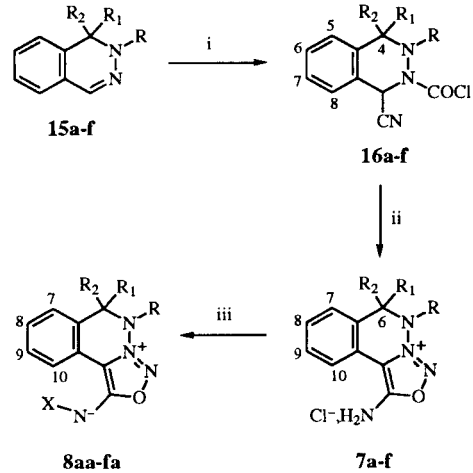
13 **14** **5** **6a-b**

6a X = CO-*p*-PhOCH$_3$
6b X = CO$_2$CH$_2$CH$_3$

i: $COCl_2$ in toluene/CH_2Cl_2/TMSCN/BF_3OEt_2 (52%) or diphosgene/CH_2Cl_2/TMSCN/BF_3OEt_2 (58%) or triphosgene/CH_2Cl_2/TMSCN/BF_3OEt_2 (62%)
ii: 1) $NaNO_2/CH_3CN/H_2O$ 2) HCl gas/MeOH (12%)
iii: ClCO-*p*-PhOCH$_3$/CH_3CN/Pyridine (61% for **6a**) $ClCOOCH_2CH_3/CH_3CN$/Pyridine (58% for **6b**)

With the success of this synthetic approach, we used the same strategy for the preparation of the dihydro com-

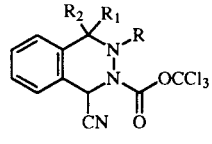
Scheme 5



15a-f **16a-f** **8aa-fa** **7a-f**

8	R	R$_1$	R$_2$	X	7, 15, 16, 17	R	R$_1$	R$_2$
aa	CH_3	H	H	CO-*p*-PhOCH$_3$	**a**	CH_3	H	H
ab	CH_3	H	H	$COOCH_2CH_3$	**b**	CH_3	CH_3	H
ba	CH_3	CH_3	H	CO-*p*-PhOCH$_3$	**c**	CH_3	CH_3	CH_3
bb	CH_3	CH_3	H	$COOCH_2CH_3$	**d**	Bu	H	H
ca	CH_3	CH_3	CH_3	CO-*p*-PhOCH$_3$	**e**	Bu	CH_3	H
cb	CH_3	CH_3	CH_3	$COOCH_2CH_3$	**f**	Bu	CH_3	CH_3
da	Bu	H	H	CO-*p*-PhOCH$_3$				
db	Bu	H	H	$COOCH_2CH_3$				
ea	Bu	CH_3	H	CO-*p*-PhOCH$_3$				
fa	Bu	CH_3	CH_3	CO-*p*-PhOCH$_3$				

i: $COCl_2$ in toluene/CH_2Cl_2/TMSCN/BF_3OEt_2 (65% for **16a**, 74% for **16b**, 69% for **16c**, 33% for **16d**, 64% for **16e**, 90% for **16f**)
ii: 1) $NaNO_2/CH_3CN/H_2O$ 2) MeOH/HCl gas (27% for **7a**, 42% for **7b**, 39% for **7c**, 41% for **7d**, **7e** not isolated, 31% for **7f**)
iii: X = CO-*p*-PhOCH$_3$: ClCO-*p*-PhOCH$_3$/Pyridine (59% for **8aa**, 58% for **8ba**, 66% for **8ca**, 78% for **8da**, 39% for **8ea**, 65% for **8fa**)
X = $COOCH_2CH_3$: $ClCO_2CH_2CH_3$/Pyridine (30% for **8ab**, 67% for **8bb**, 79% for **8cb**, 44% for **8db**)



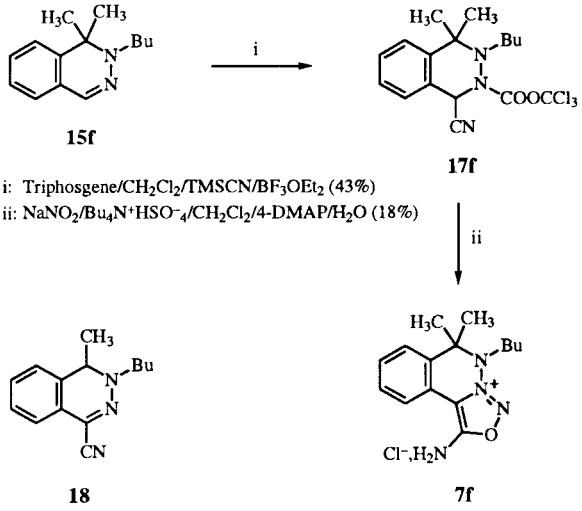
17a-f

pounds **7a-f** and **8aa-fa** (Scheme 5). With phosgene, the carbonyl chlorides **16a-f** were obtained with yields ranging from 33% to 90%. In the case of **16b** and **16e** only one diastereoisomer was isolated.

It is noteworthy that with these derivatives when triphosgene was used preferably to phosgene, a mixture of the wanted carbonyl chloride **16a-f** with the intermediate trichloromethyl ester **17a-f** (Scheme 5) was generally obtained (same work-up, dedoubling of some of the signals in the ^{13}C nmr spectra and also dedoubling of the CO band in the ir spectra).

In the case of the reaction of **15f** with triphosgene (Scheme 6), we could only isolate the trichloromethyl ester **17f** with 43% yield. Compound **17f** is an intermediate in the preparation of the carbonyl chloride **16f** with triphosgene [13]. An explanation can be the better stability of the trichloromethyl esters in the dihydro family in comparison with phthalazine.

Scheme 6

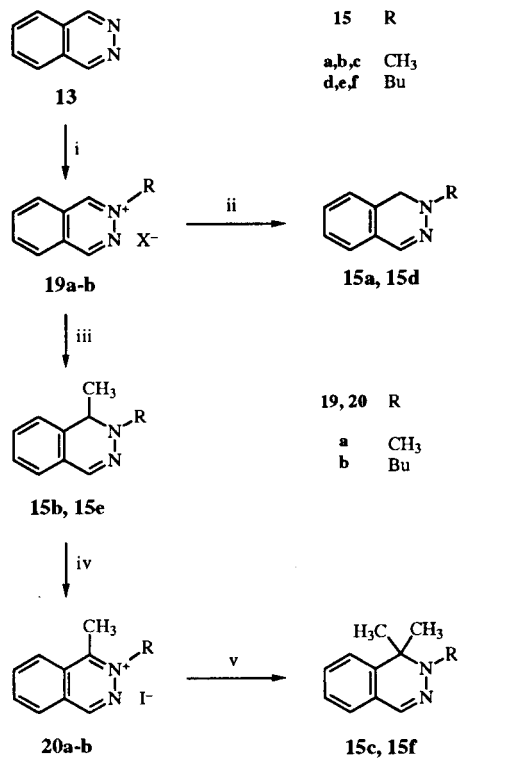


The cyclisation to the sydnonimines **7a-f** was accomplished starting from the pure carbonyl chloride **16a-f** (obtained with phosgene) with yields ranging from 27% to 42%. In the case of the triphosgene method, the mixture of the carbonyl chloride and the trichloromethyl ester was submitted to cyclisation without separation but with lower cyclisation yields. In the case of **17f** (Scheme 6), the cyclisation conditions had to be changed (phase transfer conditions) but the yield in cyclised compound **7f** was only 18%.

Compound **7e** could not be isolated because of its instability (loss of NO with formation of **18** (Scheme 6)) and was used immediately for the condensation with anisoyl chloride to **8ea**.

The condensation of compounds **7a-f** with anisoyl chloride to mimic pirsidomine **2** were achieved with yields ranging from 39% to 78%. The substitution with ethyl

Scheme 7



chloroformate was performed on compounds **7a** to **7d** with yields of 30% to 79%.

The starting dihydrophthalazines **15a-f** were prepared according to scheme 7.

Compounds **19a** and **15a** are described in the literature [14,15] and had the characteristics already given. Compound **19b** is very hygroscopic and no satisfactory elemental analysis could be obtained for this product used immediately after preparation (97% yield). Compound **15d** prepared by sodium borohydride reduction of **19b** was very instable (impossible to get a satisfactory elemental analysis) and on standing gave compound **21** (Scheme 7) by air oxidation (very similar to **15a** as described [15]). Classical Grignard reaction with methylmagnesium iodide on **19a** and **19b** gave the methylated dihydro derivatives **15b** and **15e** (87% and 58% yield respectively) which also had to be used rapidly after isolation because of their instability.

Rearomatisation of **15b** and **15e** was performed with iodine in 65% and 83% yield respectively to **20a** and **20b**. The reaction of methylmagnesium iodide on these

iminium salts gave compounds **15c** (50%) and **15f** (76%).

Compounds **15a-f** are instable oils (elemental analysis had to be performed immediately after isolation) and were used rapidly after isolation for the next steps.

Conclusion.

We describe a new method for the synthesis of annelated sydnonimines. All the prepared sydnonimines were checked for vasodilating properties and showed interesting activities on isolated rat aortas and also *in-vivo* (pig or dog) and a detailed structure activity relationship discussion will be described elsewhere.

EXPERIMENTAL

Commercially available reagents were used without further purification and were purchased from the usual suppliers like Aldrich, Janssen, Merck and Prolabo. Yields are not optimized. Melting points were determined on a Kofler bank and are uncorrected. The nmr spectra were recorded on a Brucker AC 200 MHz or on a Brucker AC 100 MHz spectrometer. Chemical shifts are given in ppm relative to tetramethylsilane. Infrared spectra (ir) were obtained on a Fourier Nicolet 5 DXB FT-IR spectrophotometer and only the prominent peaks are indicated. Chromatographic separations were accomplished with a Büchi System 680 medium pressure apparatus using silica gel 60 (15-40 µm particule size) from Merck as solid phase. Thin layer chromatography (tlc) were performed on silica gel 60 F_{254} precoated glass plates from Merck and the spots were located by the uv light or by iodide vapors. Elemental analysis were accomplished with a Carlo Erba model 1106 or Fisons EA 1108 apparatus.

2-Methylphthalazinium Iodide (**19a**).

The procedure described in the literature was used [14] and the solid recrystallized from methanol gave an analytical sample of **19a** (81%); mp 250° dec (lit [14] 243-244° dec); tlc Rf 0.2 (methanol-dichloromethane 10-90 v/v); ir (potassium bromide): 3415, 3024, 2983, 2946, 2919, 1609, 1590, 1578, 1543, 1523, 1509, 1495, 1482, 1456, 1432, 1401, 1384, 1354, 1326, 1277, 1251, 1233, 1161, 1125, 1084, 987, 941, 907, 877, 771, 766, 729 cm^{-1}; ^1H nmr (DMSO-d_6): δ 4.59 (s, 3H, NCH_3), 8.38-8.65 (m, 4H, aromatics), 10.1 (s, 1H, N=CH), 10.7 (s, 1H, N^+=CH); ^{13}C nmr (DMSO-d_6): δ 51.0 (CH_3), 127.3-127.7 (2 Cq), 128.4-130.1-136.3-138.9 (4 aromatic CH), 151.6 (CH=N), 154.5 (CH=N^+).

Anal. Calcd. for $C_9H_9IN_2$: C, 39.73; H, 3.33; N, 10.30. Found: C, 39.9; H, 3.4; N, 10.5.

1,2-Dihydro-2-methylphthalazine (**15a**).

The compound was prepared by the method described in the literature [15] and purified by chromatography on silica gel (dichloromethane) yielding **15a** (90%), oil; tlc Rf 0.8 (methanol-dichloromethane 10-90 v/v); ^1H nmr (deuteriochloroform): δ 2.98 (s, 3H, CH_3), 3.91 (s, 2H, CH_2N), 7.00-7.12 (m, 2H, aromatics), 7.23-7.29 (m, 2H, aromatics), 7.41 (s, 1H, CH=N); ^{13}C nmr (deuteriochloroform): δ 40.5 (CH_3), 46.3 (CH_2N), 116.9-119.9-122.6-124.7 (4 aromatic CH), 120.5-125.7 (2 Cq), 133.1 (CH=N).

The unstable oil was used immediately for the next steps without further analysis because of air oxidation [15].

1,2-Dihydro-1,2-dimethylphthalazine (**15b**).

To a well stirred ethereal solution of methylmagnesium iodide prepared from magnesium (2.7 g, 0.11 mole) and iodomethane (7 ml, 15.9 g, 0.11 mole) in 150 ml of diethyl ether is added in small portions at room temperature 2-methylphthalazinium iodide **19a** (27.2 g, 0.10 mole). After the end of addition (half an hour), the mixture is stirred at room temperature during 1 hour, cooled to 0° in an ice bath and then poured on crashed ice. The aqueous phase is decanted and extracted twice with diethyl ether. The organic phases are combined, dried over sodium sulfate and evaporated to dryness under reduced pressure. The oily residue is chromatographed on silica gel (elution with dichloromethane-heptane 50:50 v/v) and the interesting fractions collected and evaporated to dryness giving product **15b** (13.9 g, 87%) used immediately for the next steps. An analytical sample was obtained by renewed chromatography on silica gel (elution with dichloromethane); oil; tlc Rf 0.7 (methanol-dichloromethane 5-95 v/v); ir (potassium bromide): 3448, 3065, 3028, 2970, 2925, 2890, 2868, 2804, 1545, 1488, 1453, 1415, 1366, 1332, 1291, 1270, 1235, 1221, 1206, 1167, 1121, 1108, 1073, 1055, 1029, 1026, 1005, 951, 876, 842, 807, 753, 731, 705 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.15 (d, 3H, J = 6.5 Hz, CH_3), 3.07 (s, 3H, N-CH_3), 4.23 (q, 1H, J = 6.5 Hz, CH), 6.95-7.07 (m, 2H, aromatics), 7.16-7.30 (m, 2H, aromatics), 7.37 (s, 1H, CH=N); ^{13}C nmr (deuteriochloroform): δ 13.4 (CH_3), 41.9 (NCH_3), 54.9 (CH), 123.5-124.2-127.2-129.6 (4 aromatic CH), 124.3-134.8 (2 Cq), 136.2 (CH=N).

Anal. Calcd. for $C_{10}H_{12}N_2$: C, 74.97; H, 7.55; N, 17.48. Found: C, 74.6; H, 7.3; N, 17.2.

1,2-Dimethylphthalazinium Iodide (**20a**).

To a solution of 1,2-dihydro-1,2-dimethylphthalazine **15b** (3.2 g, 20 mmoles) in 20 ml of dichloromethane is added a solution of iodine (5.08 g, 20 mmoles) in 50 ml of dichloromethane. A small exothermy is noted and the mixture is stirred at room temperature until the starting compound has disappeared (usually 1 hour) on tlc (methanol-dichloromethane 10-90 v/v). The mixture is evaporated to dryness under reduced pressure and the remaining black solid is recrystallized from 2-propanol giving **20a** (5.4 g, 65%) sufficiently pure for the next steps. An analytical sample was obtained by chromatography on silica gel (methanol-dichloromethane gradient from 5-95 to 10-90 v/v), mp 211°; tlc Rf 0.2 (methanol-dichloromethane 10-90 v/v); ir (potassium bromide): 3441, 3077, 3055, 3044, 3008, 2983, 2939, 2896, 2858, 1611, 1592, 1572, 1509, 1471, 1459, 1445, 1419, 1403, 1387, 1373, 1347, 1327, 1287, 1250, 1161, 1105, 1020, 1013, 943, 893, 778, 748 cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.30 (s, 3H, CH_3), 4.55 (s, 3H, NCH_3), 8.35-8.57 (m, 3H, aromatics), 8.90 (d, J = 8.0 Hz, 1H, aromatic), 9.91 (s, 1H, N=CH); ^{13}C nmr (DMSO-d_6): δ 17.4 (CH_3), 49.5 (NCH_3), 126.7-128.3 (2 Cq), 128.1-128.7-135.9-137.8 (4 aromatic CH), 152.4 (N=CH), 162.2 (N^+=C-CH_3).

Anal. Calcd. for $C_{10}H_{11}IN_2$: C, 41.98; H, 3.88; N, 9.79. Found: C, 41.7; H, 3.9; N, 9.7.

1,2-Dihydro-1,1,2-trimethylphthalazine (**15c**).

To a well stirred ethereal solution of methylmagnesium iodide prepared from magnesium (1 g, 41 mmoles) and iodomethane (2.5 ml, 5.7 g, 40 mmoles) in 70 ml of diethyl ether is added in small portions at room temperature 1,2-dimethylphthalazinium iodide **20a** (10.3 g, 36 mmoles). After the addition, the mixture is refluxed during 1 hour and then cooled in an ice bath. After addi-

tion of 2 ml of methanol (exothermy), the mixture is poured on crushed ice, decanted and the aqueous phase extracted with dichloromethane. The organic extracts are regrouped, dried over sodium sulfate and evaporated under reduced pressure. The residue is chromatographed on silica gel (dichloromethane). The first eluting spot (tlc methanol-dichloromethane 5-95 v/v) is collected giving **15c** (3.1 g, 50%), light yellow oil; tlc Rf 0.4 (methanol-dichloromethane 5-95 v/v); ir (potassium bromide): 3443, 3064, 3029, 2982, 2968, 2927, 2877, 2860, 2804, 2789, 1556, 1489, 1455, 1450, 1381, 1364, 1357, 1351, 1290, 1225, 1189, 1178, 1161, 1136, 1115, 1113, 1102, 1035, 973, 933, 912, 874, 857, 841, 787, 755, 677 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.42 (s, 6H, $2CH_3$), 3.12 (s, 3H, NCH_3), 7.05-7.32 (m, 4H, aromatics), 7.44 (s, 1H, N=CH); ^{13}C nmr (deuteriochloroform): δ 21.5 ($2CH_3$), 39.0 (NCH_3), 56.2 ($C(CH_3)_2$), 121.7-123.8-126.8-129.9 (4 aromatic CH), 124.7-137.9 (2 Cq), 136.4 (N=CH).

Anal. Calcd. for $C_{11}H_{14}N_2$: C, 75.82; H, 8.10; N, 16.08. Found: C, 76.0; H, 8.2; N, 16.4.

2-Butylphthalazinium Bromide (**19b**).

To a solution of phthalazine **13** (60 g, 0.46 mole) in 300 ml of acetonitrile is added at room temperature *n*-butyl bromide (108 ml, 137 g, 1 mole) and the resulting mixture is stirred at room temperature during 3 days. The solution is evaporated to dryness under reduced pressure and the oily residue is crystallized in carbon tetrachloride, the filtered and hygroscopic crystals are dried at 50° under reduced pressure, giving **19b** (120 g, 97%), hygroscopic crystals (no melting point); tlc Rf 0.7 (methanol-dichloromethane 20-80 v/v); ir (potassium bromide): 3450, 2965, 2938, 2877, 1650, 1484, 1403, 1376, 1331, 1285, 1239, 1218, 1171, 1121, 1094, 986, 890, 770 cm^{-1}; ^1H nmr (DMSO-d_6): δ 0.93 (t, 3H, J = 7.3 Hz, CH_3), 1.29-1.45 (m, 2H, CH_2), 1.98-2.13 (m, 2H, CH_2), 4.83 (t, 2H, J = 7.3 Hz, NCH_2), 8.42-8.67 (m, 4H, aromatics), 10.2 (s, 1H, CH=N), 10.9 (s, 1H, $CH=N^+$); ^{13}C nmr (DMSO-d_6): δ 13.5 (CH_3), 19.0 (CH_2), 31.2 (CH_2), 63.3 (NCH_2), 127.7-127.9 (2 Cq), 128.5-130.4-136.3-139.1 (4 aromatic CH), 151.4 (C=N), 155.0 ($C=N^+$).

No satisfactory elemental analysis could be obtained (compound too hygroscopic) and the product was used immediately for the next steps.

2-Butyl-1,2-dihydrophthalazine (**15d**) and 2-Butyl-1(2*H*)-phthalazinone (**21**).

To a solution of 2-butylphthalazinium bromide **19b** (26.7 g, 0.1 mole) in 300 ml of water was added in small portions sodium borohydride (11.3 g, 0.3 mole) maintaining the temperature under +15° with an ice bath. At the end of the addition, the mixture is stirred at room temperature during 1/2 hour and then extracted twice with 250 ml of dichloromethane. The combined organic phases are dried over sodium sulfate and concentrated under reduced pressure. The remaining oil is **15d** (17 g, 90%) and was used immediately for the next step; tlc Rf 0.9 (methanol-dichloromethane 10-90 v/v); ^1H nmr (DMSO-d_6): δ 0.89 (t, 3H, J = 7.2 Hz, CH_3), 1.25-1.41 (m, 2H, CH_2), 1.54-1.68 (m, 2H, CH_2), 3.07 (t, 2H, J = 7.2 Hz, NCH_2), 3.92 (s, 2H, CH_2Ph), 7.09-7.18 (m, 2H, aromatics), 7.25-7.31 (m, 2H, aromatics), 7.41 (s, 1H, CH=N); ^{13}C nmr (DMSO-d_6): δ 14.0 (CH_3), 19.9 (CH_2), 28.7 (CH_2), 49.4-57.2 ($2NCH_2$), 123.7-125.4-127.8-129.7 (4 aromatic CH), 126.3-130.8 (2 Cq), 136.6 (CH=N).

No satisfactory elemental analysis could be obtained, the product on standing giving compound **21**, oil; Rf 0.5 (dichloromethane); ir (potassium bromide): 3425, 2957, 2932, 2872, 1655, 1650, 1590, 1483, 1466, 1453, 1431, 1345, 1305, 1277, 1236, 1174, 1114, 1102, 1077, 957, 925, 897, 761 cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.94 (t, 3H, J = 7.2 Hz, CH_3), 1.29-1.48 (m, 2H, CH_2), 1.73-1.88 (m, 2H, CH_2), 4.22 (t, 2H, J = 7.3 Hz, NCH_2), 7.63-7.78 (m, 3H, aromatics), 8.14 (s, 1H, CH=N), 8.38-8.43 (m, 1H, aromatic); ^{13}C nmr (DMSO-d_6): δ 13.6 (CH_3), 19.4 (CH_2), 30.2 (CH_2), 49.8 (NCH_2), 125.8-126.8-131.9-133.4 (4 aromatic CH), 127.1-129.3 (2 Cq), 137.8 (CH=N), 158.3 (CO).

Anal. Calcd. for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; N, 13.85. Found: C, 70.9; H, 6.7; N, 13.6.

2-Butyl-1,2-dihydro-1-methylphthalazine (**15e**).

To a well stirred ethereal solution of methylmagnesium iodide prepared from magnesium (2.7 g, 0.11 mole) and iodomethane (7 ml, 15.9 g, 0.11 mole) in 100 ml of diethyl ether is added within half an hour in small portions 2-butylphthalazinium bromide **19b** (26.7 g, 0.1 mole). The addition is exothermic and after the end of addition, the mixture is refluxed during 1 hour. After cooling at 5°, 10 ml of methanol are added slowly and the solution is poured on 300 ml of a saturated solution of sodium chloride. The organic phase is decanted and the aqueous phase extracted twice with diethyl ether. The ethereal solutions are regrouped, dried over sodium sulfate and evaporated to dryness under reduced pressure. The residual oil is chromatographed on silica gel (elution with dichloromethane-heptane 50-50 v/v) and the interesting fractions regrouped, evaporated to dryness under reduced pressure giving **15e** (11.8 g, 58%) used immediately for the next steps. An analytical sample was obtained by renewed chromatography on silica gel (elution with dichloromethane-heptane 50-50 v/v), instable oil; tlc Rf 0.6 (dichloromethane); ir (potassium bromide): 3064, 3027, 2958, 2928, 2864, 1544, 1488, 1449, 1364, 1331, 1319, 1306, 1268, 1239, 1221, 1207, 1155, 1109, 1081, 1069, 1029, 959, 941, 901, 875, 839, 805, 752, 704 cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.96 (t, 3H, J = 7.2 Hz, CH_3), 1.15 (d, 3H, J = 6.5 Hz, $CHCH_3$), 1.31-1.50 (m, 2H, CH_2), 1.63-1.79 (m, 2H, CH_2), 3.12-3.26 (m, 1H, part A of ABX_2, NCH_2), 3.35-3.49 (m, 1H, part B of ABX_2, NCH_2), 4.37 (q, 1H, J = 6.5 Hz, $CHCH_3$), 6.99-7.12 (m, 2H, aromatics), 7.20-7.33 (m, 2H, aromatics), 7.40 (s, 1H, CH=N); ^{13}C nmr (deuteriochloroform): δ 13.9-14.4 ($2CH_3$), 20.1 (CH_2), 30.3 (CH_2), 53.8 (CH_2), 54.3 (CH), 123.5-124.5-127.3-129.5 (4 aromatic CH), 125.1-134.9 (2 Cq), 135.0 (CH=N).

Anal. Calcd. for $C_{13}H_{18}N_2$: C, 77.18; H, 8.97; N, 13.85. Found: C, 77.0; H, 9.0; N, 14.0.

2-Butyl-1-methylphthalazinium Iodide (**20b**).

To a solution of 2-butyl-1,2-dihydro-1-methylphthalazine **15e** (68.8 g, 0.34 mole) in 500 ml of dichloromethane is added iodine (43.2 g, 0.17 mole) and the mixture is stirred at room temperature during 24 hours. The solution is evaporated to dryness under reduced pressure and the residual solid taken up in 200 ml of hot tetrahydrofurane is filtered. The filtrate is cooled and the yellow crystals are filtered, washed with diethyl ether and dried under reduced pressure giving a first crop of **20b** (35 g, 31%). The mother liquors are concentrated under reduced pressure and the black residue is taken with 500 ml dichloromethane. Sodium acetate (28 g, 0.34 mole) is added and then iodine (43.2 g, 0.17 mole). The solution is stirred during 3 hours and evaporated to dryness, taken with dichloromethane and decolorized with charcoal and the filtrate evaporated to dryness. The black solid is

extracted twice with 200 ml of hot tetrahydrofurane and the regrouped tetrahydrofurane solutions are concentrated to 100 ml and cooled. The yellow solid is filtered, washed with diethyl ether giving a second crop of **20b** (58 g, 52%). The two crops are used for the next step (93 g, 83%), mp 140°; tlc Rf 0.2 (methanol-dichloromethane 10-90 v/v); ir (potassium bromide): 3451, 2967, 2927, 2877, 1503, 1460, 1420, 1401, 1372, 1283, 1251, 1166, 1144, 1125, 990, 970, 784, 764, 737 cm^{-1}; ^1H nmr (DMSO-d_6): δ 0.95 (t, 3H, J = 7.2 Hz, CH_3), 1.40-1.55 (m, 2H, CH_2), 1.92-2.07 (m, 2H, CH_2), 3.39 (s, 3H, CH_3), 4.84 (t, 2H, J = 7.5 Hz, NCH_2), 8.34-8.58 (m, 3H, aromatics), 8.90 (d, 1H, J = 8.0 Hz, aromatic), 9.90 (s, 1H, CH=N); ^{13}C nmr (DMSO-d_6): δ 13.5 (CH_3), 17.5 (CH_3), 19.1 (CH_2), 30.3 (CH_2), 60.8 (N^+CH_2), 126.4-128.6-161.7 (3 Cq), 128.5 (2 aromatic CH), 135.8-137.8 (2 aromatic CH), 152.5 (N=CH).

Anal. Calcd. for $C_{13}H_{17}IN_2$: C, 47.58; H, 5.22; N, 8.54. Found: C, 47.5; H, 5.2; N, 8.6.

2-Butyl-1,2-dihydro-1,1-dimethylphthalazine (**15f**).

To a well stirred ethereal solution of methylmagnesium iodide prepared from magnesium (8.25 g, 0.34 mole) and iodomethane (22 ml, 50.2 g, 0.35 mole) in 2 l of diethyl ether is added 2-butyl-1-methylphthalazinium iodide **20b** (92 g, 0.28 mole) in small portions. The mixture reaches reflux and after the addition (1/2 hour), the reflux is maintained during 1 hour. The reaction mixture is then cooled at +5° and 10 ml of acetic acid are added slowly and the whole poured on crushed ice (200 g) with hydrochloric acid (100 ml, 0.5 mole). The solution is decanted and the aqueous phase extracted twice with ether. The organic phases are combined, washed with sodium bicarbonate, dried over sodium sulfate with charcoal decolorization and then evaporated to dryness giving **15f** (46 g, 76%), oil; tlc Rf 0.5 (dichloromethane); ir (potassium bromide): 3068, 3031, 2961, 2932, 2895, 1561, 1480, 1466, 1450, 1384, 1350, 1287, 1183, 1158, 1104, 1032, 934, 905, 860, 850, 841, 787, 755 cm^{-1}; ^1H nmr (DMSO-d_6): δ 0.88 (t, 3H, J = 7.2 Hz, CH_3), 1.21-1.40 (m, 2H, CH_2), 1.36 (s, 6H, $2CH_3$), 1.51-1.65 (m, 2H, CH_2), 3.23 (t, 2H, J = 7.1 Hz, N-CH_2), 7.10-7.14 (m, 2H, aromatics), 7.21-7.34 (m, 2H, aromatics), 7.39 (s, 1H, CH=N); ^{13}C nmr (DMSO-d_6): δ 13.9 (CH_3), 19.5 (CH_2), 22.9 ($2CH_3$), 31.7 (CH_2), 49.3 (N-CH_2), 56.1 (Cq), 122.3-123.3-126.9-129.7 (4 aromatic CH), 124.6-137.9 (2 Cq), 134.3 (CH=N).

Anal. Calcd. for $C_{14}H_{20}N_2$: C, 77.73; H, 9.32; N, 12.95. Found: C, 77.6; H, 9.3; N, 13.1.

1-Cyano-1,2-dihydro-2-phthalazinecarbonyl Chloride (**14**).

Method with Phosgene.

To a solution of phthalazine **13** (26 g, 0.2 mole) in 2000 ml of dichloromethane cooled at -20°, are added under inert atmosphere trimethylsilyl cyanide (37.7 ml, 29.8 g, 0.3 mole) and the solution is kept at -20° during half an hour. Then is added at the same temperature boron trifluoride diethyl etherate (1 ml, 1.13 g, 8 mmoles) and again after half an hour is added slowly (during 1 hour) a 1.93 *M* solution of phosgene in toluene (135 ml, 0.26 mole). The reaction mixture is stirred 6 hours to reach room temperature. The solution is evaporated to dryness under reduced pressure and the residue is chromatographed on silica gel (dichloromethane). The first eluting spot (tlc dichloromethane) is collected and the white solid is recrystallized from diisopropyl ether yielding white crystals of **14** (22.8 g, 52%), mp 160°; tlc Rf 0.7 (dichloromethane); ir (potassium bromide): 3401, 3067, 2963, 2921, 2853, 2245, 1711, 1495, 1453, 1359, 1285, 1232, 1222, 1142, 1111, 953, 938, 916, 890, 812, 769, 738 cm^{-1}; ^1H nmr (deuteriochloroform): δ 6.49 (s, 1H, CH-CN), 7.26-7.65 (m, 4H, H_5-H_6-H_7-H_8), 7.90 (s, 1H, CH=N); ^{13}C nmr (deuteriochloroform): δ 44.2 (CH-CN), 114.2 (CN), 122.6-124.6 (C_{4a}-C_{8a}), 126.6-127.6-131.2-133.5 (C_5-C_6-C_7-C_8), 144.8 (C_4), 151.7 (CO).

Anal. Calcd. for $C_{10}H_6ClN_3O$: C, 54.69; H, 2.75; Cl, 16.14; N, 19.13. Found: C, 54.7; H, 2.7; Cl, 16.3; N, 19.3.

Method with Diphosgene.

To a solution of phthalazine **13** (10 g, 77 mmoles) in 450 ml of dichloromethane cooled at -15° under an inert atmosphere are added boron trifluoride diethyl etherate (1 ml, 1.13 g, 8 mmoles) and trimethylsilyl cyanide (14.5 ml, 11.5 g, 115 mmoles) and the solution is stirred at -15° during half an hour. Within 1 1/2 hour is added slowly (temperature maintained under -13°) a solution of diphosgene (7 ml, 11.5 g, 58 mmoles) in 100 ml of dichloromethane. After the end of the slightly exothermic addition, the solution is stirred to reach room temperature within 3 hours. The reaction mixture is evaporated to dryness under reduced pressure and the residue is chromatographed on silica gel (dichloromethane). The first eluting spot (tlc dichloromethane) is collected giving white crystals of **14** (9.8 g, 58%). An analytical sample having the characteristics already described was obtained by recrystallization from diisopropyl ether.

Method with Trisphosgene.

To a solution of phthalazine **13** (10 g, 77 mmoles) in 450 ml of dichloromethane cooled at -15° are successively added under an inert atmosphere boron trifluoride diethyl etherate (1 ml, 1.13 g, 8 mmoles) and trimethylsilyl cyanide (14.5 ml, 11.5 g, 115 mmoles). The solution is stirred at -15° during half an hour and then a solution of triphosgene (11.5 g, 38.8 mmoles) in 100 ml of dichloromethane is added slowly (quarter of an hour) maintaining the temperature under -13°. The mixture is stirred during 1/2 hour at -10° and then allowed to reach room temperature in 4 hours. The reaction mixture is evaporated to dryness under reduced pressure and the residue is chromatographed on silica gel (dichloromethane). The first eluting spot (tlc dichloromethane) is collected yielding **14** (10.5 g, 62%) as a white solid. An analytical sample having the characteristics already described was obtained by recrystallization from diisopropyl ether.

1-Amino[1,2,3]oxadiazolo[4,3-*a*]phthalazin-4-ium Chloride (**5**).

To a solution of **14** (20 g, 91 mmoles) in 300 ml of acetonitrile under an inert atmosphere and maintained at -20° is added sodium nitrite (7.45 g, 107 mmoles, 1.2 equivalents). Then 3 ml of water are added to start the reaction (precipitation) and the reaction mixture is stirred one night during which time the temperature is raised to room temperature. The precipitate is filtered, dissolved in dichloromethane and the organic phase washed with water, dried over magnesium sulfate and evaporated to dryness. The residual precipitate is taken up in 200 ml of methanol, cooled to 0° and then a methanolic solution (7 *M*) of gaseous hydrogen chloride added (39 ml). After half an hour, the mixture is evaporated to dryness and the residue triturated with acetone. The precipitate is filtered giving **5** (2.5 g, 12%). An analytical sample was obtained by recrystallization from methanol-diethyl ether giving crystals, mp 200° dec; tlc Rf 0.7 (methanol-dichloromethane 10-90 v/v); ir (potassium bromide): 3420, 3021, 2875, 2770, 1673, 1621, 1581, 1556, 1479, 1454, 1365, 1342, 1316, 1257, 1229, 1085, 961, 798, 784, 761, 741, 683 cm^{-1}; ^1H nmr (DMSO-d_6): δ

7.97 (t, 1H, $J_{8,9}$ = 7.5 Hz, $J_{8,7}$ = 7.7 Hz, H_8), 8.16-8.24 (m, 1H, $J_{9,10}$ = 8.0 Hz, $J_{9,8}$ = 7.5 Hz, H_9), 8.43 (d, 1H, $J_{7,8}$ = 7.7 Hz, H_7), 9.02 (d, 1H, $J_{10,9}$ = 8.0 Hz, H_{10}), 9.88 (s, 1H, H_6), 11.25 (br s, 2H, NH_2); ^{13}C nmr (DMSO-d_6): δ 107.0 (C_{10b}), 120.4-124.6 (C_{6a}-C_{10a}), 122.4-130.6-130.9-137.0 (C_7-C_8-C_9-C_{10}), 159.4 (C_6), 164.0 (C_1).

Anal. Calcd. for $C_9H_7ClN_4O$: C, 48.55; H, 3.17; Cl, 15.92; N, 25.17. Found: C, 48.3; H, 3.1; Cl, 15.5; N, 25.0.

1-[(4-Methoxybenzoyl)amino][1,2,3]oxadiazolo[4,3-*a*]phthalazin-4-ium Inner Salt (**6a**).

To a mixture of **5** (3 g, 13.5 mmoles) in 30 ml of pyridine and 30 ml of acetonitrile cooled at 0° is added dropwise anisoyl chloride (4.6 g, 27 mmoles, 2 equivalents). A precipitate forms immediately and the mixture is maintained at 0° during 1 hour. The precipitate is filtrated giving **6a** (2.65 g, 61%). An analytical sample was obtained by recrystallization from methanol, mp 242° dec; tlc Rf 0.7 (methanol-dichloromethane 10-90 v/v); ir (potassium bromide): 3450, 3050, 3025, 2996, 2969, 2936, 2844, 1638, 1616, 1598, 1570, 1560, 1495, 1466, 1447, 1372, 1345, 1316, 1281, 1220, 1170, 1160, 1110, 1061, 1040, 982, 936, 830, 785 cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.85 (s, 3H, OCH_3), 7.06 (d, 2H, J = 8.7 Hz, anisoyl), 7.90 (t, 1H, $J_{8,9}$ = 7.6 Hz, $J_{8,7}$ = 7.9 Hz, H_8), 8.17-8.28 (m, 1H, $J_{9,8}$ = 7.6 Hz, $J_{9,10}$ = 7.8 Hz, H_9), 8.24 (d, 2H, J = 8.7 Hz, anisoyl), 8.30 (d, 1H, $J_{7,8}$ = 7.9 Hz, H_7), 8.74 (d, 1H, $J_{10,9}$ = 7.8 Hz, H_{10}), 9.65 (s, 1H, H_6); ^{13}C nmr (DMSO-d_6): δ 55.3 (OCH_3), 108.0 (C_{10b}), 121.2-126.4 (C_{6a}-C_{10a}), 120.7-129.5-130.0-136.6 (C_7-C_8-C_9-C_{10}), 113.5-131.3 (4 anisoyl CH), 129.5-161.5 (2 Cq anisoyl), 158.0 (C_6), 162.2 (C_1), 170.9 (CO).

Anal. Calcd. for $C_{17}H_{12}N_4O_3$: C, 63.75; H, 3.78; N, 17.49. Found: C, 63.5; H, 3.7; N, 17.5.

1-[(Ethoxycarbonyl)amino][1,2,3]oxadiazolo[4,3-*a*]phthalazin-4-ium Inner Salt (**6b**).

To a suspension of **5** (3.5 g, 15.7 mmoles) in 20 ml of acetonitrile and 25 ml of pyridine cooled to +5° is added dropwise ethyl chloroformate (4.6 ml, 5.2 g, 48.3 mmoles, 3 equivalents). A precipitate appears with a large exotherm and with gas evolution. The solution is maintained at room temperature during 1 hour and then filtered. The solid is **6b** (2.4 g, 58%). An analytical sample was obtained by recrystallization from methanol, mp 215°; tlc Rf 0.7 (methanol-dichloromethane 10-90 v/v); ir (potassium bromide): 3450, 3007, 2986, 2944, 2925, 1671, 1616, 1580, 1490, 1470, 1391, 1372, 1320, 1280, 1175, 1105, 1050, 1000, 955, 930, 910, 778 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.26 (t, 3H, J = 7.1 Hz, CH_3), 4.12 (q, 2H, J = 7.1 Hz, CH_2), 7.78-7.87 (m, 1H, $J_{8,9}$ = 7.6 Hz, $J_{8,7}$ = 7.9 Hz, H_8), 8.08-8.16 (m, 1H, $J_{9,8}$ = 7.6 Hz, $J_{9,10}$ = 7.8 Hz, H_9), 8.25 (d, 1H, $J_{7,8}$ = 7.9 Hz, H_7), 8.47 (d, 1H, $J_{10,9}$ = 7.8 Hz, H_{10}), 9.63 (s, 1H, H_6); ^{13}C nmr (DMSO-d_6): δ 14.5 (CH_3), 60.7 (CH_2), 107.0 (C_{10b}), 120.4-126.3 (C_{6a}-C_{10a}), 120.8-129.3-129.9-136.5 (C_7-C_8-C_9-C_{10}), 158.0 (C_6), 158.3 (CO), 161.5 (C_1).

Anal. Calcd. for $C_{12}H_{10}N_4O_3$: C, 55.81; H, 3.90; N, 21.70. Found: C, 55.9; H, 3.8; N, 21.9.

1-Cyano-1,2,3,4-tetrahydro-3-methyl-2-phthalazinecarbonyl Chloride (**16a**).

To a solution of **15a** (14 g, 96 mmoles) in 300 ml of dichloromethane maintained at 0° under an inert atmosphere is added trimethylsilyl cyanide (19 ml, 14.1 g, 142 mmoles, 1.48 equivalents). The mixture is stirred at 0° during half an hour and then boron trifluoride diethyl etherate (1 ml, 8 mmoles) is added. After a quarter af an hour is added a toluene solution (1.93 *M*) of phosgene (67 ml, 129 mmoles, 1.35 equivalents). A small exotherme is noted (+8°) and the mixture is stirred at room temperature during the night. The reaction mixture is evaporated to dryness under reduced pressure, and the residue chromatographed on silica gel (dichloromethane). The first eluting spot (tlc dichloromethane) is collected and crystallized from diisopropyl ether then filtered and dried under vacuum, giving product **16a** (14.9 g, 65%), mp 198°; tlc Rf 0.8 (methanol-dichloromethane 10-90 v/v); ir (potassium bromide): 3409, 3004, 2973, 2936, 2853, 2243, 1714, 1503, 1454, 1370, 1305, 1240, 1204, 1150, 1123, 1072, 983, 951, 938, 919, 799, 750, 711 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.84 (s, 3H, NCH_3), 3.85 (d, 1H, part A of AB, J_{AB} = 16.5 Hz, Ph CH_2N), 4.39 (d, 1H, part B of AB, 1H, J_{AB} = 16.5 Hz, Ph CH_2N), 5.98 (s, 1H, CHCN), 7.19-7.27 (m, 1H, aromatic), 7.38-7.51 (m, 3H, aromatics); ^{13}C nmr (deuteriochloroform): δ 41.4 (CH-CN), 42.2 (N-CH_3), 55.0 (CH_2Ph), 116.7 (CN), 124.1-128.8 (2 Cq), 126.7-127.9-128.4-129.7 (4 aromatic CH), 151.7 (CO).

Anal. Calcd. for $C_{11}H_{10}ClN_3O$: C, 56.06; H, 4.28; Cl, 15.05; N, 17.83. Found: C, 55.9; H, 4.3; Cl, 15.1; N, 17.9.

1-Amino-5,6-dihydro-5-methyl[1,2,3]oxadiazolo[4,3-*a*]phthalazin-4-ium Chloride (**7a**).

To a mixture of **16a** (8.7 g, 37 mmoles) in 100 ml of acetonitrile under an inert atmosphere is added at room temperature a solution of sodium nitrite (4.14 g, 60 mmoles) in 5 ml of water. The mixture is heated and the temperature reaches 45°. The reaction mixture is stirred at room temperature during 3 hours and a precipitate forms slowly. The mixture is filtered and the filtrate is concentrated under reduced pressure leaving a partially crystallized residue. The residue is dissolved in 50 ml methanol and a solution of gaseous hydrogen chloride (4 *M*) in methanol (30 ml, 120 mmoles) is slowly added and the solution is then stirred at room temperature during 1/4 hour. The solvent is removed under vacuum and the solid recrystallized from ethanol giving **7a** (2.4 g, 27%), mp 240° dec; tlc Rf 0.8 (methanol-dichloromethane 10-90 v/v); ir (potassium bromide): 3033, 2919, 2895, 1673, 1505, 1455, 1393, 1357, 1330, 1272, 1220, 1190, 1133, 1009, 971, 878, 778 cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.37 (s, 3H, NCH_3), 4.80 (s, 2H, CH_2), 7.44-7.55 (m, 3H, aromatics), 8.01-8.05 (m, 1H, aromatic), 10.0 (broad s, 2H, NH_2); ^{13}C nmr (DMSO-d_6): δ 40.0 (NCH_3), 55.3 (CH_2), 104.1 (C_{10b}), 118.8-127.0 (C_{6a}-C_{10a}), 122.6-126.1-128.6-129.6 (C_7-C_8-C_9-C_{10}), 162.6 (C_1).

Anal. Calcd. for $C_{10}H_{11}ClN_4O$: C, 50.32; H, 4.65; N, 23.47; Cl, 14.85. Found: C, 49.9; H, 4.6; N, 23.3; Cl, 14.4.

5,6-Dihydro-1-[(4-methoxybenzoyl)amino]-5-methyl[1,2,3]oxadiazolo[4,3-*a*]phthalazin-4-ium Inner Salt (**8aa**).

To a mixture of **7a** (3.7 g, 15.5 mmoles) in 30 ml of pyridine at room temperature is added anisoyl chloride (5.29 g, 31 mmoles, 2 equivalents) and the solution is heated at 60° during 1 hour and then maintained at room temperature during 3 days. The precipitate is filtered, and recrystallized from ethanol giving **8aa** (3.1 g, 59%), mp 174°; tlc Rf 0.7 (methanol-dichloromethane 10-90 v/v); ir (potassium bromide): 3450, 3060, 3006, 2970, 2932, 2838, 1648, 1603, 1574, 1505, 1445, 1310, 1300, 1250, 1185, 1164, 1010, 986, 945, 830, 759 cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.33 (s, 3H, NCH_3), 3.83 (s, 3H, OCH_3), 4.73 (s, 2H, Ph CH_2N), 7.01 (d, 2H, J = 8.8 Hz, anisoyl), 7.40-7.55 (m, 3H, H_7-H_8-H_9), 8.11-

8.16 (m, 1H, H_{10}), 8.15 (d, 2H, J = 8.8 Hz, anisoyl); ^{13}C nmr (DMSO-d_6): δ 40.0 (NCH_3), 55.3 (OCH_3), 55.7 (C_6), 105.8 (C_{10b}), 113.3 (2 CH anisoyl), 121.2-130.1 (C_{6a}-C_{10a}), 121.8-125.9-128.7-128.8 (C_7-C_8-C_9-C_{10}), 127.1-161.8 (Cq anisoyl), 130.9 (2 CH anisoyl), 162.0 (C_1), 170.3 (CO).

Anal. Calcd. for $C_{18}H_{16}N_4O_3$: C, 64.28; H, 4.79; N, 16.66. Found: C, 64.2; H, 4.7; N, 16.7.

1-[(Ethoxycarbonyl)amino]-5,6-dihydro-5-methyl[1,2,3]oxadiazolo[4,3-*a*]phthalazin-4-ium Inner Salt (**8ab**).

To a mixture of **7a** (4.63 g, 19.4 mmoles) in 35 ml of pyridine, 50 ml of acetonitrile and 100 ml of nitromethane cooled at -5°, is dropwise added ethyl chloroformate (5.82 ml, 6.63 g, 61.1 mmoles, 3.1 equivalents). After the addition, the mixture is stirred at room temperature during the night. The solution is evaporated to dryness under reduced pressure and the residue dissolved in 100 ml of dichloromethane, washed with water, dried over sodium sulfate with charcoal decolorization and evaporated to dryness. The solid is recrystallized from ethanol-water (50-50 v/v) giving **8ab** (1.6 g, 30%), mp 146°; tlc Rf 0.9 (methanol-dichloromethane 15-85 v/v); ir (potassium bromide): 3450, 2981, 2932, 2900, 2870, 1663, 1627, 1522, 1455, 1370, 1337, 1280, 1258, 1175, 1077, 1016, 786 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.21 (t, 3H, J = 7.1 Hz, CH_3), 3.30 (s, 3H, NCH_3), 4.04 (q, 2H, J = 7.1 Hz, OCH_2), 4.69 (s, 2H, H_6), 7.36-7.43 (m, 3H, H_7-H_8-H_9), 7.88-7.93 (m, 1H, H_{10}); ^{13}C nmr (DMSO-d_6): δ 14.5 (CH_3), 39.9 (NCH_3), 55.7 (C_6), 60.2 (OCH_2), 104.6 (C_{10b}), 121.0-126.6 (C_{6a}-C_{10a}), 121.4-125.8-128.5-128.7 (C_7-C_8-C_9-C_{10}), 158.7 (CO), 162.0 (C_1).

Anal. Calcd. for $C_{13}H_{14}N_4O_3$: C, 56.93; H, 5.14; N, 20.43. Found: C, 56.9; H, 5.1; N, 20.5.

1-Cyano-1,2,3,4-tetrahydro-3,4-dimethyl-2-phthalazinecarbonyl Chloride (**16b**).

At room temperature, to a solution of **15b** (3.5 g, 21.8 mmoles) in 100 ml of dichloromethane is added under an inert atmosphere boron trifluoride diethyl etherate (0.5 ml, 4 mmoles) and then trimethylsilyl cyanide (4.15 ml, 3.27 g, 33 mmoles). After stirring at room temperature during 1/4 hour, the mixture is cooled to 0° and then a toluene solution (1.93 *M*) of phosgene (17 ml, 33 mmoles) is added within 1 hour by maintaining the temperature under +2°. The mixture is stirred at 0° during 1 hour and evaporated to dryness under reduced pressure. The oily residue is chromatographed on silica gel (dichloromethane) and the first eluting spot (tlc dichloromethane) is collected and evaporated to dryness giving white crystals of **16b** (4.0 g, 74%). An analytical sample was obtained by recrystallization from diisopropyl ether, mp 110°; tlc Rf 0.8 (dichloromethane); ir (potassium bromide): 3425, 3012, 2976, 2920, 2895, 2874, 2242, 1731, 1641, 1493, 1447, 1371, 1305, 1234, 1194, 1165, 1125, 1104, 1073, 1049, 1032, 1008, 963, 933, 775, 744, 712 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.35 (d, 3H, J = 6.9 Hz, $CHCH_3$), 2.82 (s, 3H, NCH_3), 3.98 (q, 1H, J = 6.9 Hz, CH), 5.93 (s, 1H, CHCN), 7.17-7.26 (m, 1H, aromatic), 7.36-7.50 (m, 3H, aromatics); ^{13}C nmr (deuteriochloroform): δ 22.0 ($CHCH_3$), 41.3 (N-CH_3), 42.9 (CH-CH_3), 60.1 (CHCN), 116.6 (CN), 123.0-134.3 (C_{4a}-C_{8a}), 126.9-128.0-128.1-129.6 (4 aromatic CH), 152.7 (COCl).

Anal. Calcd. for $C_{12}H_{12}ClN_3O$: C, 57.72; H, 4.84; N, 16.83. Found: C, 57.8; H, 4.8; N, 16.7.

1-Amino-5,6-dihydro-5,6-dimethyl[1,2,3]oxadiazolo[4,3-*a*]-phthalazin-4-ium Chloride (**7b**).

To a solution of **16b** (25.1 g, 0.10 mole) in 300 ml of acetonitrile under an inert atmosphere and at room temperature, is added sodium nitrite (10.3 g, 0.15 mole) and then 5 ml of water. A small exotherm is noticed and the reaction mixture is stirred one night at room temperature. The solution is then filtered and the filtrate evaporated to dryness under reduced pressure. The residue is dissolved in 100 ml of methanol, cooled to 0° and 100 ml of a methanolic solution of gaseous hydrogen chloride (3 *M*) are added. The mixture is stirred at 0° during 2 hours and then evaporated to dryness. The solid is recrystallized from 2-propanol giving **7b** (10.6 g, 42%), mp 190° dec; tlc Rf 0.4 (methanol-dichloromethane-acetic acid 15-84-1 v/v/v); ir (potassium bromide): 3436, 3376, 3027, 2979, 2895, 1686, 1490, 1430, 1420, 1391, 1380, 1353, 1320, 1310, 1289, 1208, 1113, 1081, 1070, 990, 961, 774, 708 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.31 (d, 3H, J = 6.7 Hz, CH_3), 3.36 (s, 3H, NCH_3), 5.19 (q, 1H, J = 6.7 Hz, H_6), 7.41-7.53 (m, 3H, H_7-H_8-H_9), 8.03-8.07 (m, 1H, H_{10}), 10.1 (broad s, 2H, NH_2); ^{13}C nmr (DMSO-d_6): δ 15.2 (CH_3), 37.4 (CH), 60.8 (NCH_3), 103.6 (C_{10b}), 117.4-131.9 (C_{6a}-C_{10a}), 122.7-125.8-128.5-130.0 (C_7-C_8-C_9-C_{10}), 162.9 (C_1).

Anal. Calcd. for $C_{11}H_{13}ClN_4O$: C, 52.28; H, 5.19; N, 22.17; Cl, 14.03. Found: C, 51.9; H, 5.1; N, 22.4; Cl, 13.6.

5,6-Dihydro-1-[(4-methoxybenzoyl)amino]-5,6-dimethyl-[1,2,3]oxadiazolo[4,3-*a*]phthalazin-4-ium Inner Salt (**8ba**).

To a mixture of **7b** (2.53 g, 10 mmoles) in 40 ml of acetonitrile and 4 ml of pyridine is added at +5° anisoyl chloride (8.5 g, 50 mmoles). The solution is stirred at room temperature during the night and evaporated to dryness under reduced pressure. The residue is dissolved in dichloromethane, and the organic phase washed with water, dried over magnesium sulfate and evaporated to dryness. The residue is chromatographed on silica gel (dichloromethane) and the interesting fractions are collected, evaporated to dryness and recrystallized from ethyl acetate-diethyl ether giving **8ba** (2.05 g, 58%), mp 155° dec; tlc Rf 0.7 (methanol-dichloromethane 10-90 v/v); ir (potassium bromide): 3450, 3025, 2973, 2927, 1638, 1603, 1515, 1445, 1285, 1250, 1162, 1131, 1027, 978, 866, 845, 771 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.28 (d, 3H, J = 6.7 Hz, CH_3), 3.32 (s, 3H, NCH_3), 3.82 (s, 3H, OCH_3), 5.04 (q, 1H, J = 6.7 Hz, H_6), 7.01 (d, 2H, J = 8.8 Hz, anisoyl), 7.40-7.63 (m, 3H, H_7-H_8-H_9), 8.14-8.19 (m, 1H, H_{10}), 8.16 (d, 2H, J = 8.8 Hz, anisoyl); ^{13}C nmr (DMSO-d_6): δ 15.3 (CH_3), 37.2 (C_6), 55.4 (OCH_3), 60.8 (NCH_3), 105.3 (C_{10b}), 113.4 (2CH anisoyl), 131.1 (2CH anisoyl), 119.6-130.3 (C_{6a}-C_{10a}), 122.1-125.6-128.6-129.3 (C_7-C_8-C_9-C_{10}), 132.0-162.0 (2 Cq anisoyl), 162.1 (C_1), 170.6 (CO).

Anal. Calcd. for $C_{19}H_{18}N_4O_3$: C, 65.13; H, 5.18; N, 15.99. Found: C, 65.1; H, 5.1; N, 15.7.

1-[(Ethoxycarbonyl)amino]-5,6-dihydro-5,6-dimethyl[1,2,3]oxadiazolo[4,3-*a*]phthalazin-4-ium Inner Salt (**8bb**).

To a mixture of **7b** (2.5 g, 10 mmoles) in 20 ml of acetonitrile cooled to -5° under an inert atmosphere is added 4 ml pyridine and then ethyl chloroformate (1.15 ml, 1.3 g, 12 mmoles). The solution is maintained at 0° during half an hour and then stirred at room temperature during one night. The mixture is evaporated to dryness under reduced pressure and the residue taken with 100 ml of dichloromethane and 100 ml of water. The organic phase is decanted and dried over magnesium sulfate, evaporated to dryness and the solid residue recrystallized from ethyl acetate and diethyl ether giving **8bb** (1.95 g, 67%), mp 97°; tlc Rf 0.9 (methanol-dichloromethane 10-90 v/v); ir (potassium bromide): 3450, 2975,

2934, 2909, 1671, 1630, 1515, 1445, 1360, 1328, 1287, 1243, 1205, 1177, 1160, 1060, 1000, 799, 774 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.21 (t, 3H, J = 7.1 Hz, CH_3), 1.26 (d, 3H, J = 6.6 Hz, CH_3), 3.28 (s, 3H, NCH_3), 4.04 (q, 2H, J = 7.1 Hz, CH_2), 5.04 (q, 1H, J = 6.6 Hz, H_6), 7.38-7.47 (m, 3H, H_7-H_8-H_9), 7.90-7.93 (m, 1H, H_{10}); ^{13}C nmr (DMSO-d_6): δ 14.4 (CH_3), 15.0 (CH_3), 37.3 (C_6), 60.0 (CH_2), 60.5 (NCH_3), 103.8 (C_{10b}), 119.2-131.4 (C_{6a}-C_{10a}), 121.4-125.3-128.2-128.9 (C_7-C_8-C_9-C_{10}), 158.2 (CO), 161.8 (C_1).

Anal. Calcd. for $C_{14}H_{16}N_4O_3$: C, 58.32; H, 5.59; N, 19.44. Found: C, 58.4; H, 5.5; N, 19.4.

1-Cyano-1,2,3,4-tetrahydro-3,4,4-trimethyl-2-phthalazinecarbonyl Chloride (**16c**).

To a solution of **15c** (2.8 g, 16 mmoles) in 100 ml of dichloromethane is added under an inert atmosphere boron trifluoride diethyl etherate (0.5 ml, 4 mmoles) and then trimethylsilyl cyanide (3 ml, 2.37 g, 24 mmoles). After stirring at room temperature during 1/4 hour, a toluene solution (1.93 *M*) of phosgene (12.5 ml, 24 mmoles) is added within 1/4 hour. The mixture is stirred during 1 hour at room temperature and then evaporated to dryness under reduced pressure. The residue is then chromatographed on silica gel (dichloromethane). The first eluting spot (tlc dichloromethane) is collected giving **16c** (2.9 g, 69%). An analytical sample was obtained by recrystallization from diisopropyl ether, mp 141°; tlc Rf 0.8 (dichloromethane); ir (potassium bromide): 3432, 2985, 2975, 2918, 2892, 2230, 1734, 1706, 1489, 1460, 1445, 1387, 1371, 1307, 1261, 1238, 1225, 1209, 1192, 1175, 1162, 1143, 1127, 966, 941, 926, 757, 744 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.30 (s, 3H, CH_3), 1.59 (s, 3H, CH_3), 2.65 (s, 3H, NCH_3), 5.86 (s, 1H, CHCN), 7.29-7.45 (m, 4H, aromatics); ^{13}C nmr (deuteriochloroform): δ 24.7 (CH_3), 30.3 (CH_3), 38.4 (NCH_3), 42.3 (CHCN), 60.0 (C_4), 116.6 (CN), 123.0-137.9 (C_{4a}-C_{8a}), 125.8-126.6-127.8-129.8 (C_5-C_6-C_7-C_8), 152.3 (COCl).

Anal. Calcd. for $C_{13}H_{14}ClN_3O$: C, 59.21; H, 5.35; N, 15.93. Found: C, 59.2; H, 5.4; N, 15.9.

1-Amino-5,6-dihydro-5,6,6-trimethyl[1,2,3]oxadiazolo[4,3-*a*]-phthalazin-4-ium Chloride (**7c**).

To a solution of **16c** (37 g, 0.14 mole) in 800 ml of acetonitrile under an inert atmosphere is added sodium nitrite (29 g, 0.42 mole) and 10 ml of water and tetrabutylammonium hydrogen sulfate (1 g, 2.9 mmoles). The reaction is started by heating at 30° and the reaction mixture is then stirred during 16 hours at room temperature. The solution is filtered and the filtrate evaporated to dryness under reduced pressure. The oily residue is dissolved in 200 ml of methanol cooled to -20° and then 200 ml of a methanolic solution of gaseous hydrogen chloride (1.2 *M*) is added. The mixture is stirred at room temperature during 1 hour and evaporated to dryness under reduced pressure. The residue is treated with acetone and the crystals filtered, giving after drying under reduced pressure **7c** (14.6 g, 39%). An analytical sample was obtained by recrystallization from a mixture of ethanol-water (90-10 v/v); mp 205° dec; tlc Rf 0.8 (methanol-dichloromethane 15-85 v/v), ir (potassium bromide): 3450, 3031, 2892, 1673, 1516, 1450, 1368, 1340, 1285, 1193, 1173, 1160, 1090, 1050, 1006, 969, 924, 870, 841, 786, 763, 728 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.60 (s, 6H, CH_3), 3.30 (s, 3H, NCH_3), 7.50-7.70 (m, 3H, H_7-H_8-H_9), 7.98-8.03 (m, 1H, H_{10}), 10.0 (broad s, 2H, NH_2); ^{13}C nmr (DMSO-d_6): δ 22.4 ($2CH_3$), 33.6 (NCH_3), 64.9 (C_6), 103.9 (C_{10b}), 117.3-134.8 (C_{6a}-C_{10a}), 122.6-124.2-128.4-130.2 (C_7-C_8-C_9-C_{10}), 163.1 (C_1).

Anal. Calcd. for $C_{12}H_{15}ClN_4O$: C, 54.04; H, 5.67; N, 21.00; Cl, 13.29. Found: C, 54.3; H, 5.5; N, 21.4; Cl, 13.3.

5,6-Dihydro-1-[(4-methoxybenzoyl)amino]-5,6,6-trimethyl-[1,2,3]oxadiazolo[4,3-*a*]phthalazin-4-ium Inner Salt (**8ca**).

To a suspension of **7c** (3.0 g, 11.2 mmoles) in 10 ml of acetonitrile are added at room temperature anisoyl chloride (3.8 g, 22.3 mmoles) and pyridine (2.75 ml, 34 mmoles). The solution is stirred at room temperature during 16 hours and then 250 ml of diethyl ether are added. The crystals are filtered, dissolved in 50 ml of dichloromethane and the organic phase washed with water, dried over magnesium sulfate with charcoal decolorization and evaporated to dryness under reduced pressure. The solid is recrystallized from methanol giving **8ca** (2.73 g, 66%), mp 163°; tlc Rf 0.7 (methanol-dichloromethane 5-95 v/v); ir (potassium bromide): 3450, 3077, 3035, 2963, 2925, 2895, 1638, 1603, 1572, 1511, 1436, 1328, 1285, 1249, 1156, 1005, 986, 866, 847, 772 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.57 (s, 6H, $2CH_3$), 3.24 (s, 3H, NCH_3), 3.83 (s, 3H, OCH_3), 7.02 (d, 2H, J = 8.8 Hz, anisoyl), 7.45-7.62 (m, 3H, H_7-H_8-H_9), 8.16 (d, 2H, J = 8.8 Hz, anisoyl), 8.20-8.24 (m, 1H, H_{10}); ^{13}C nmr (DMSO-d_6): δ 22.5 ($2CH_3$), 34.1 (NCH_3), 55.3 (OCH_3), 64.0 (C_6), 105.6 (C_{10b}), 113.3 (2CH anisoyl), 119.4-130.1 (C_{6a}-C_{10a}), 122.1-124.0-128.4-129.5 (C_7-C_8-C_9-C_{10}), 131.0 (2CH anisoyl), 134.8-161.9 (2 Cq anisoyl), 162.0 (C_1), 170.5 (CO).

Anal. Calcd. for $C_{20}H_{20}N_4O_3$: C, 65.92; H, 5.53; N, 15.37. Found: C, 66.3; H, 5.6; H, 15.7.

1-[(Ethoxycarbonyl)amino)]-5,6-dihydro-5,6,6-trimethyl-[1,2,3]oxadiazolo[4,3-*a*]phthalazin-4-ium Inner Salt (**8cb**).

To a suspension of **7c** (3 g, 11.2 mmoles) in 10 ml acetonitrile cooled at -10° and under an inert atmosphere are successively added ethyl chloroformate (3.2 ml, 3.6 g, 33.6 mmoles) and then pyridine (4.5 ml, 4.41 g, 55.8 mmoles). The solution is stirred at room temperature during 16 hours and then evaporated to dryness under reduced pressure. The residue is dissolved in 50 ml of dichloromethane and the organic phase washed with water, dried over sodium sulfate and evaporated to dryness. The solid residue is recrystallized from methanol-diethyl ether giving **8cb** (2.71 g, 79%), mp 152° dec; tlc Rf 0.7 (methanol-dichloromethane 5-95 v/v); ir (potassium bromide): 3450, 3079, 3039, 2983, 2950, 1665, 1627, 1522, 1492, 1445, 1355, 1331, 1289, 1245, 1183, 1125, 1100, 1071, 1004, 955, 921, 875, 830, 795, 765 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.22 (t, 3H, J = 7.1 Hz, CH_3), 1.54 (s, 6H, $2CH_3$), 3.20 (s, 3H, NCH_3), 4.05 (q, 2H, J = 7.1 Hz, CH_2), 7.40-7.60 (m, 3H, H_7-H_8-H_9), 7.96-8.01 (m, 1H, H_{10}); ^{13}C nmr (DMSO-d_6): δ 14.5 (CH_3), 22.4 ($2CH_3$), 34.0 (NCH_3), 60.2 (CH_2), 64.0 (C_6), 104.4 (C_{10b}), 119.2-134.4 (C_{6a}-C_{10a}), 121.7-123.9-128.2-129.3 (C_7-C_8-C_9-C_{10}), 158.4 (CO), 162.0 (C_1).

Anal. Calcd. for $C_{15}H_{18}N_4O_3$: C, 59.59; H, 6.00; N, 18.53. Found: C, 59.5; H, 6.0; N, 18.6.

3-Butyl-1-cyano-1,2,3,4-tetrahydro-2-phthalazinecarbonyl Chloride (**16d**).

To a stirred solution of **15d** (6.5 g, 34.5 mmoles) in 250 ml of dichloromethane is added under an inert atmosphere boron trifluoride diethyl etherate (1 ml, 8 mmoles) and then trimethylsilyl cyanide (6.5 ml, 5.14 g, 51.7 mmoles). The mixture is stirred during 10 minutes and then a toluene solution (1.93 *M*) of phosgene (22 ml, 42 mmoles) is added within half an hour. After an initial exotherm, the solution is stirred at room temperature during 4 hours. The reaction mixture is evaporated to dryness under

reduced pressure and the residue is chromatographed on silica gel (dichloromethane). The first eluting spot (tlc dichloromethane) is collected and recrystallized from diisopropyl ether giving **16d** (3.2 g, 33%). An analytical sample was obtained by a second recrystallization from diisopropyl ether, mp 102°; tlc Rf 0.8 (dichloromethane); ir (potassium bromide): 3450, 2960, 2934, 2916, 2860, 2205, 1730, 1491, 1466, 1458, 1434, 1380, 1365, 1343, 1320, 1309, 1287, 1236, 1224, 1203, 1144, 1087, 963, 948, 945, 937, 795, 750 cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.93 (t, 3H, J = 7.2 Hz, CH_3), 1.31-1.55 (m, 2H, CH_2), 1.55-1.68 (m, 2H, CH_2), 2.72-2.85 (m, 1H, CH_2N), 3.02-3.15 (m, 1H, CH_2N), 3.95 (d, 1H, part A of AB, J_{AB} = 16.5 Hz, $PhCH_2N$), 4.35 (d, 1H, part B of AB, J_{AB} = 16.5 Hz, $PhCH_2N$), 6.01 (s, 1H, CHCN), 7.18-7.25 (m, 1H, aromatic), 7.38-7.50 (m, 3H, aromatics); ^{13}C nmr (deuteriochloroform): δ 13.7 (CH_3), 20.0 (CH_2), 29.0 (CH_2), 41.6 (C_1), 53.5-53.9 ($2CH_2N$), 116.4 (CN), 124.5-129.2 (C_{4a}-C_{8a}), 126.7-127.8-128.3-129.6 (C_5-C_6-C_7-C_8), 153.0 (CO).

Anal. Calcd. for $C_{14}H_{16}ClN_3O$: C, 60.54; H, 5.81; N, 15.13. Found: C, 60.8; H, 5.9; N, 15.1.

1-Amino-5-butyl-5,6-dihydro[1,2,3]oxadiazolo[4,3-*a*]phthalazin-4-ium Chloride (**7d**).

To a solution of **16d** (42 g, 0.15 mmoles) in 600 ml of acetonitrile is added at room temperature and under an inert atmosphere a solution of sodium nitrite (31 g, 0.45 mole) in 10 ml of water. The solution is brought to 30° with vigorous stirring and the temperature slowly reaches 45°. After 5.5 hours stirring at room temperature, the solution is filtered and the filtrate is cooled at 0°. A methanolic solution of gaseous hydrogen chloride (150 ml, 3 *M*, 0.45 mole) is then added and stirring is continued during 1/4 hour. The mixture is evaporated to dryness under reduced pressure, and the residue taken with 300 ml ethanol. The crystallization is started by addition of diethyl ether. After one night at 0°, the solid is filtered giving compound **7d** (17.3 g, 41%). An analytical sample was obtained by recrystallization from ethanol, mp 184° dec; tlc Rf 0.3 (methanol-dichloromethane 10-90 v/v); ir (potassium bromide): 3058, 2959, 2875, 1679, 1600, 1519, 1440, 1409, 1385, 1351, 1310, 1280, 1262, 1170, 1130, 1100, 1005, 967, 924, 840, 773 cm^{-1}; ^1H nmr (DMSO-d_6): δ 0.92 (t, 3H, J = 7.3 Hz, CH_3), 1.25-1.50 (m, 2H, CH_2), 1.60-1.85 (m, 2H, CH_2), 3.67 (t, 2H, J = 7.3 Hz, NCH_2), 4.80 (s, 2H, H_6), 7.45-7.55 (m, 3H, H_7-H_8-H_9), 7.95-8.00 (m, 1H, H_{10}), 10.0 (broad s, 2H, NH_2); ^{13}C nmr (DMSO-d_6): δ 13.6 (CH_3), 19.5 (CH_2), 26.2 (CH_2), 52.6 (NCH_2), 53.0 (C_6), 104.8 (C_{10b}), 119.1-126.4-128.7-129.8 (C_7-C_8-C_9-C_{10}), 122.6-127.2 (C_{6a}-C_{10a}), 162.7 (C_1).

Anal. Calcd. for $C_{13}H_{17}ClN_4O$: C, 55.62; H, 6.10; N, 19.96; Cl, 12.63. Found: C, 55.2; H, 6.1; N, 19.8; Cl, 12.9.

5-Butyl-5,6-dihydro-1-[(4-methoxybenzoyl)amino][1,2,3]oxadiazolo[4,3-*a*]phthalazin-4-ium Inner Salt (**8da**).

To a solution of **7d** (4 g, 14.2 mmoles) in 30 ml of pyridine is added at room temperature anisoyl chloride (4.9 g, 28.7 mmoles). After stirring 5 hours at room temperature, the solution is added diethyl ether and the crystals are filtered. The solid is recrystallized twice from ethanol giving **8da** (4.2 g, 78%), mp 174°; tlc Rf 0.8 (methanol-dichloromethane 10-90 v/v); ir (potassium bromide): 3450, 2961, 2934, 2868, 1637, 1593, 1561, 1508, 1449, 1283, 1254, 1187, 1164, 1100, 1036, 990, 911, 847, 772 cm^{-1}; ^1H nmr (DMSO-d_6): δ 0.93 (t, 3H, J = 7.2 Hz, CH_3), 1.30-1.50 (m, 2H, CH_2), 1.65-1.81 (m, 2H, CH_2), 3.60 (t, 2H, J = 7.2 Hz, NCH_2), 3.82 (s, 3H, OCH_3), 4.75 (s, 2H, H_6), 7.02 (d, 2H, J = 8.8 Hz, anisoyl), 7.40-7.60 (m, 3H, H_7-H_8-H_9), 8.13 (d, 1H, J = 7.5 Hz, H_{10}), 8.15 (d, 2H, J = 8.8 Hz, anisoyl); ^{13}C nmr (DMSO-d_6): δ 13.6 (CH_3), 19.5 (CH_2), 26.8 (CH_2), 52.7 (NCH_2), 53.2 (C_6), 55.3 (OCH_3), 106.4 (C_{10b}), 113.4 (2CH anisoyl), 121.2-127.1 (C_{6a}-C_{10a}), 121.9-126.1-128.7-129.0 (C_7-C_8-C_9-C_{10}), 130.1-161.9 (2 Cq anisoyl), 131.0 (2CH anisoyl), 162.0 (C_1), 170.4 (CO).

Anal. Calcd. for $C_{21}H_{22}N_4O_3$: C, 66.65; H, 5.86; N, 14.80. Found: C, 66.6; H, 5.9; N, 14.6.

5-Butyl-1-[(ethoxycarbonyl)amino]-5,6-dihydro[1,2,3]oxadiazolo[4,3-*a*]phthalazin-4-ium Inner Salt (**8db**).

To a suspension of **7d** (3.4 g, 12.1 mmoles) in 50 ml of acetonitrile cooled at 0°, are added successively 23 ml of pyridine and ethyl chloroformate (3.5 ml, 3.99 g, 36.7 mmoles). After 5 hours stirring at room temperature, the solution is evaporated to dryness under reduced pressure. The residue is dissolved in dichloromethane and the organic solution washed with water, dried over magnesium sulfate and evaporated to dryness. The solid residue is recrystallized from ethanol giving **8db** (1.7 g, 44%), mp 88°; tlc Rf 0.7 (methanol-dichloromethane 10-90 v/v); ir (potassium bromide): 3450, 2967, 2907, 2878, 1663, 1632, 1528, 1486, 1455, 1372, 1258, 1177, 1083, 1007, 946, 787, 759 cm^{-1}; ^1H nmr (DMSO-d_6): δ 0.92 (t, 3H, J = 7.2 Hz, CH_3), 1.21 (t, 3H, J = 7.1 Hz, CH_3), 1.26-1.50 (m, 2H, CH_2), 1.60-1.85 (m, 2H, CH_2), 3.57 (t, 2H, J = 7.2 Hz, NCH_2), 4.04 (q, 2H, J = 7.1 Hz, OCH_2), 4.71 (s, 2H, H_6), 7.35-7.55 (m, 3H, H_7-H_8-H_9), 7.91 (d, 1H, J = 7.2 Hz, H_{10}); ^{13}C nmr (DMSO-d_6): δ 13.6 (CH_3), 14.5 (CH_3), 19.5 (CH_2), 26.8 (CH_2), 52.6 (NCH_2), 53.1 (C_6), 60.2 (OCH_2), 105.2 (C_{10b}), 121.0-126.7 (C_{6a}-C_{10a}), 121.4-126.0-128.5-128.8 (C_7-C_8-C_9-C_{10}), 158.4 (CO), 162.0 (C_1).

Anal. Calcd. for $C_{16}H_{20}N_4O_3$: C, 60.75; H, 6.37; N, 17.71. Found: C, 60.9; H, 6.4; N, 17.7.

3-Butyl-1-cyano-1,2,3,4-tetrahydro-4-methyl-2-phthalazinecarbonyl Chloride (**16e**).

To a solution cooled at 0° of **15e** (8.7 g, 43 mmoles) in 250 ml of dichloromethane is added under an inert atmosphere boron trifluoride diethyl etherate (1 ml, 8 mmoles) and then trimethylsilyl cyanide (6.9 ml, 5.2 g, 52 mmoles). After stirring during half an hour at 0°, a toluene solution (1.93 *M*) of phosgene (27 ml, 52 mmoles) is added within 1 hour maintaining the temperature under +2°. The mixture is stirred at 0° during 2 hours and then evaporated to dryness under reduced pressure. The residue is chromatographed on silica gel (dichloromethane) and the first eluting spot (tlc dichloromethane) is collected and evaporated to dryness. The product is recrystallized from petroleum ether giving **16e** (8.1 g, 64%), mp 52°; tlc Rf 0.8 (dichloromethane); ir (potassium bromide): 3407, 2984, 2961, 2928, 2869, 2245, 1715, 1494, 1474, 1447, 1369, 1306, 1285, 1261, 1229, 1205, 1157, 1129, 1106, 1085, 1038, 974, 969, 946, 932, 917, 807, 779, 758, 734, 715 cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.92 (t, 3H, J = 7.2 Hz, CH_3), 1.37 (d, 3H, J = 6.9 Hz, $CHCH_3$), 1.30-1.55 (m, 2H, CH_2), 1.58-1.70 (m, 2H, CH_2), 2.69-2.83 (m, 1H, part A of ABX_2, NCH_2), 2.94-3.08 (m, 1H, part B of ABX_2, NCH_2), 4.06 (q, 1H, J = 6.9 Hz, H_4), 5.97 (s, 1H, H_1), 7.13-7.20 (m, 1H, aromatic), 7.35-7.49 (m, 3H, aromatics); ^{13}C nmr (deuteriochloroform): δ 13.7 (CH_3), 20.1 (CH_2), 22.0 (CH_3), 28.9 (CH_2), 41.5 ($CHCH_3$), 55.1 (CH_2N), 58.7 (CHCN), 116.3 (CN), 123.3-134.7 (C_{4a}-C_{8a}), 126.8-127.8-

128.1-129.5 (C_5-C_6-C_7-C_8), 153.5 (CO).

Anal. Calcd. for $C_{15}H_{18}ClN_3O$: C, 61.75; H, 6.22; N, 14.40. Found: C, 61.6; H, 6.2; N, 14.4.

1-Amino-5-butyl-5,6-dihydro-6-methyl[1,2,3]oxadiazolo[4,3-*a*]-phthalazin-4-ium Chloride (**7e**) and 2-Butyl-4-cyano-1,2-dihydro-1-methylphthalazine (**18**).

To a solution of **16e** (30 g, 103 mmoles) in 300 ml of acetonitrile is added at room temperature a solution of sodium nitrite (21.3 g, 309 mmoles) in 15 ml of water. The mixture is stirred at room temperature during 18 hours and then evaporated to dryness under reduced pressure. The residue is treated with 50 ml of water and 50 ml of dichloromethane, the organic phase is separated and the aqueous phase extracted twice with dichloromethane. The organic phases are combined, dried over sodium sulfate and evaporated to dryness under reduced pressure. The residual oil is dissolved in 100 ml of methanol and cooled to -30°. To this cold solution is added a methanolic solution (3.6 *M*) of hydrogen chloride (50 ml, 180 mmoles) and then the solution is maintained at 0° during 2 hours. The mixture is evaporated to dryness under reduced pressure. The residue is treated with water and extracted with dichloromethane. After decolorization of the organic layer with charcoal and evaporation under reduced pressure, one obtains an instable oil (12 g, 39%) which was used without further purification and characterisation for the next step. A purification trial of this oil by chromatography on silica gel (dichloromethane) only gave a sample of **18**, as an oil; tlc Rf 0.8 (dichloromethane); ir (potassium bromide): 3060, 3028, 2961, 2930, 2871, 2213, 1729, 1585, 1509, 1493, 1447, 1393, 1370, 1313, 1289, 1245, 1197, 1121, 1076, 1062, 1028, 969, 945, 817, 764 cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.93 (t, 3H, J = 7.2 Hz, CH_3), 1.23 (d, 3H, J = 6.6 Hz, $CHCH_3$), 1.28-1.45 (m, 2H, CH_2), 1.62-1.77 (m, 2H, CH_2), 3.33-3.68 (m, 2H, NCH_2), 4.66 (q, 1H, J = 6.6 Hz, H_4), 6.98-7.04 (m, 1H, aromatic), 7.29-7.42 (m, 3H, aromatics); ^{13}C nmr (deuteriochloroform): δ 13.7 (CH_3), 18.5 (CH_3), 19.7 (CH_2), 30.3 (CH_2), 55.3 (C_4), 55.4 (NCH_2), 114.7-116.2 (C_1 + CN), 121.5-124.8-128.2-130.4 (C_5-C_6-C_7-C_8), 122.7-130.0 (C_{4a}-C_{8a}).

Anal. Calcd. for $C_{14}H_{17}N_3$: C, 73.98; H, 7.54; N, 18.49. Found: C, 73.6; H, 7.2; N, 18.1.

5-Butyl-5,6-dihydro-1-[(4-methoxybenzoyl)amino]-6-methyl-[1,2,3]oxadiazolo[4,3-*a*]phthalazin-4-ium Inner Salt (**8ea**).

A solution of crude **7e** (4.4 g, 15 mmoles) in 10 ml of acetonitrile is cooled to 0° under an inert atmosphere. One adds anisoyl chloride (7.6 g, 45 mmoles) and pyridine (3.6 ml, 3.52 g, 45 mmoles) and the reaction mixture is stirred at room temperature during 18 hours and then evaporated to dryness under reduced pressure. The oily residue is dissolved in dichloromethane and the organic phase is washed with water, 1*N* hydrochloric acid and dried over magnesium sulfate. After evaporation to dryness under reduced pressure, the residue is chromatographed on silica gel (dichloromethane and then acetone). The interesting fractions are collected evaporated to dryness and recrystallized from methanol-diethyl ether giving **8ea** (2.3 g, 39%), mp 163° dec; tlc Rf 0.6 (methanol-dichloromethane 5-95 v/v); ir (potassium bromide): 3450, 2963, 2932, 2875, 1638, 1603, 1511, 1443, 1384, 1333, 1287, 1256, 1160, 1029, 980, 868, 845, 780 cm^{-1}; ^1H nmr (DMSO-d_6): δ 0.91 (t, 3H, J = 7.2 Hz, CH_3), 1.27 (d, 3H, J = 6.7 Hz, CH_3), 1.28-1.44 (m, 2H, CH_2), 1.61-1.73 (m, 2H, CH_2), 3.57-3.68 (m, 2H, NCH_2), 3.83 (s, 3H, OCH_3), 5.10 (q, 1H, J = 6.7 Hz, H_6), 7.02 (d, 2H, J = 8.7 Hz, anisoyl), 7.45-7.60 (m, 3H, H_7-H_8-H_9), 8.16 (d, 2H, J = 8.7 Hz, anisoyl), 8.15-8.18 (m, 1H, H_{10}); ^{13}C nmr (DMSO-d_6): δ 13.5 (CH_3), 16.8 (CH_3), 19.4 (CH_2), 27.9 (CH_2), 51.9 (NCH_2), 55.3 (OCH_3), 59.0 (C_6), 106.0 (C_{10b}), 113.3 (2CH anisoyl), 119.3-130.0 (C_{6a}-C_{10a}), 122.1-125.9-128.5-129.4 (C_7-C_8-C_9-C_{10}), 131.0 (2CH anisoyl), 131.9 (Cq anisoyl), 161.9-162.0 (C_1 and Cq anisoyl), 171.0 (CO).

Anal. Calcd. for $C_{22}H_{24}N_4O_3$: C, 67.33; H, 6.16; N, 14.28. Found: C, 67.5; H, 6.1; N, 14.4.

3-Butyl-1-cyano-1,2,3,4-tetrahydro-4,4-dimethyl-2-phthalazinecarbonyl Chloride (**16f**).

To a solution of **15f** (10.8 g, 50 mmoles) in 300 ml of dichloromethane cooled to 0° is added under an inert atmosphere boron trifluoride diethyl etherate (1 ml, 8 mmoles) and then trimethylsilyl cyanide (8.13 ml, 6.0 g, 61 mmoles). After stirring during half an hour at 0°, a toluene solution (1.93 *M*) of phosgene (31 ml, 60 mmoles) is added within one hour. The mixture is stirred at 0° during 1 hour and then evaporated to dryness under reduced pressure. The residue is chromatographed on silica gel (dichloromethane) and the first eluting spot (tlc dichloromethane) is collected and evaporated to dryness giving white crystals of **16f** (13.7 g, 90%), mp 104°; tlc Rf 0.6 (*n*-hexane-dichloromethane 15-85 v/v); ir (potassium bromide): 3450, 2965, 2938, 2915, 2878, 2838, 2242, 1732, 1470, 1445, 1389, 1368, 1316, 1231, 1191, 1150, 1077, 944, 807, 766, 748, 736, 713 cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.92 (t, 3H, J = 7.7 Hz, CH_3), 1.28-1.45 (m, 2H, CH_2), 1.36 (s, 3H, $C(CH_3)$), 1.67 (s, 3H, $C(CH_3)$), 1.56-1.72 (m, 2H, CH_2), 2.53-2.67 (m, 1H, part A of ABX_2, CH_2N), 2.79-2.93 (m, 1H, part B of ABX_2, CH_2N), 5.93 (s, 1H, CHCN), 7.26-7.42 (m, 4H, aromatics); ^{13}C nmr (deuteriochloroform): δ 13.8 (CH_3), 20.4 (CH_2), 25.3 (C-CH_3), 28.6 (CH_2), 30.8 (C-CH_3), 42.6 (CHCN), 48.8 (CH_2N), 60.6 (C_4), 116.1 (CN), 123.6-138.8 (C_{4a}-C_{8a}), 125.4-126.6-127.8-129.7 (C_5-C_6-C_7-C_8), 153.7 (CO).

Anal. Calcd. for $C_{16}H_{20}ClN_3O$: C, 62.84; H, 6.59; Cl, 11.60; N, 13.74. Found: C, 63.2; H, 6.7; Cl, 11.6; N, 13.8.

3-Butyl-1-cyano-1,2,3,4-tetrahydro-4,4-dimethyl-2-phthalazinecarboxylic Acid Trichloromethyl Ester (**17f**).

To a solution of **15f** (30 g, 140 mmoles) in 500 ml of dichloromethane cooled at 0° are added under an inert atmosphere boron trifluoride diethyl etherate (1.5 ml, 12 mmoles) and then trimethylsilyl cyanide (22.4 ml, 16.7 g, 167 mmoles). The solution is stirred at 0° during 1/2 hour and then a solution of triphosgene (16.4 g, 55 mmoles) in 50 ml of dichloromethane is added maintaining the temperature under +2° (1 hour). The mixture is allowed to stand at room temperature during the night and then evaporated to dryness under reduced pressure. The residue is chromatographed on silica gel (dichloromethane) and the first eluting compound collected, evaporated to dryness. The product crystallizes from methanol giving **17f** (24.4 g, 43%), mp 110°; tlc Rf 0.8 (dichloromethane-hexane 90-10 v/v); ir (potassium bromide): 3450, 2980, 2961, 2932, 2873, 1742, 1451, 1396, 1360, 1256, 1189, 1067, 1013, 940, 915, 890, 797, 770, 740, 724 cm^{-1}; ^1H nmr (DMSO-d_6): δ 0.88 (t, 3H, J = 6.8 Hz, CH_3), 1.27-1.59 (m, 4H, $2CH_2$), 1.27 (s, 3H, CH_3), 1.59 (s, 3H, CH_3), 2.35-2.50 (m, 1H, part A of ABX_2, NCH_2), 2.75-2.90 (m, 1H, part B of ABX_2, NCH_2), 6.51 (s, 1H, CHCN), 7.40-7.49 (m, 4H, aromatics); ^{13}C nmr (DMSO-d_6): δ 13.8 (CH_3), 19.9 (CH_2), 25.0 (CCH_3), 28.5 (CH_2), 30.4 (CCH_3), 41.0 (CHCN), 47.5 (NCH_2), 59.7 (C_4), 107.6 (CCl_3), 117.6 (CN), 124.1-137.9 (C_{4a}-C_{8a}), 125.6-126.6-127.6-129.3 (C_5-C_6-C_7-C_8), 149.1 (CO).

Anal. Calcd. for $C_{17}H_{20}Cl_3N_3O_2$: C, 50.45; H, 4.98; N, 10.38; Cl, 26.28. Found: C, 50.4; H, 5.0; N, 10.4; Cl, 26.0.

1-Amino-5-butyl-5,6-dihydro-6,6-dimethyl[1,2,3]oxadiazolo[4,3-*a*]phthalazin-4-ium Chloride (**7f**).

From **16f**.

To a solution of **16f** (14.7 g, 48 mmoles) in 200 ml of acetonitrile under an inert atmosphere and at room temperature, is added sodium nitrite (9.95 g, 144 mmoles) and then 2 ml of water. The solution is stirred during 18 hours at room temperature and then evaporated to dryness under reduced pressure. The residue is extracted twice with 100 ml of dichloromethane and the combined organic phases are washed twice with 50 ml of water, dried over magnesium sulfate and evaporated to dryness under reduced pressure. The residue is dissolved in 50 ml of a methanolic solution of gaseous hydrogen chloride (3 *M*) and then evaporated to dryness under reduced pressure. The residue is crystallized from acetone and ether. The filtered crystals are dissolved in dichloromethane for charcoal decolorization and after evaporation to dryness again crystallized from acetone and diethyl ether giving **7f** (4.6 g, 31%), mp 163° explosive; tlc Rf 0.4 (methanol-dichloromethane 10-90 v/v); ir (potassium bromide): 3450, 2965, 2932, 2865, 1673, 1522, 1493, 1460, 1375, 1358, 1320, 1285, 1205, 1167, 1015, 990, 948, 786, 755 cm^{-1}; ^1H nmr (DMSO-d_6): δ 0.88 (t, 3H, J = 7.2 Hz, CH_3), 1.23-1.42 (m, 2H, CH_2), 1.50-1.62 (m, 2H, CH_2), 1.62 (s, 6H, $2CH_3$), 3.60 (t, 2H, J = 7.0 Hz, NCH_2), 7.45-7.65 (m, 3H, H_7-H_8-H_9), 8.01-8.05 (m, 1H, H_{10}), 10.1 (broad s, 2H, NH_2); ^{13}C nmr (DMSO-d_6): δ 13.6 (CH_3), 19.5 (CH_2), 24.0 ($2CH_3$), 28.9 (CH_2), 48.4 (CH_2N), 65.1 (C_6), 104.5 (C_{10b}), 117.4-135.0 (C_{6a}-C_{10a}), 122.9-124.7-128.5-130.5 (C_7-C_8-C_9-C_{10}), 163.5 (C_1).

Anal. Calcd. for $C_{15}H_{21}ClN_4O$: C, 58.34; H, 6.85; N, 18.14; Cl, 11.48. Found: C, 58.1; H, 7.0; N, 18.2; Cl, 11.5.

From **17f**.

To a mixture of **17f** (19.4 g, 48 mmoles) in 200 ml of dichloromethane are added under an inert atmosphere and at room temperature, 4-dimethylaminopyridine (4 g, 33 mmoles), sodium nitrite (20 g, 0.28 mole) and tetrabutylammonium hydrogen sulfate (4 g, 12 mmoles) and 20 ml of water. The reaction mixture is stirred during 24 hours at room temperature and then evaporated to dryness under reduced pressure. The residue is dissolved in 50 ml of ethyl acetate, cooled to -20° and 50 ml of a methanolic solution of gaseous hydrogen chloride (3 *M*) is added. The mixture is stirred at -20° during one night and then evaporated to dryness under reduced pressure. The residue is crystallized from acetone and filtered. The solid is recrystallized in a mixture of acetone, ethyl acetate and diethyl ether giving **7f** (2.7 g, 18%) having the characteristics described before.

5-Butyl-5,6-dihydro-1-[(4-methoxybenzoyl)amino]-6,6-dimethyl[1,2,3]oxadiazolo[4,3-*a*]phthalazin-4-ium Inner Salt (**8fa**).

To a mixture of **7f** (5.25 g, 17 mmoles) in 20 ml of acetonitrile and 6.8 ml of pyridine cooled to 0°, is added anisoyl chloride (9.0 g, 53 mmoles). The solution is stirred at room temperature during 18 hours and evaporated to dryness under reduced pressure. The residue is dissolved in dichloromethane, and the organic phase washed with water, dried over magnesium sulfate and evaporated to dryness. The residue is chromatographed on silica gel (dichloromethane) and the interesting fractions are collected and evaporated to dryness under reduced pressure. The residue is crystallized from methanol and diethyl ether giving **8fa** (4.5 g, 65%), mp 163°; tlc Rf 0.7 (methanol-dichloromethane 5-95 v/v); ir (potassium bromide): 3450, 2961, 2932, 2875, 1632, 1598, 1570, 1511, 1436, 1293, 1252, 1187, 1160, 1110, 1031, 990, 949, 868, 847, 773, 759 cm^{-1}; ^1H nmr (DMSO-d_6): δ 0.88 (t, 3H, J = 7.2 Hz, CH_3), 1.24-1.42 (m, 2H, CH_2), 1.47-1.55 (m, 2H, CH_2), 1.56 (s, 6H, $2CH_3$), 3.44 (t, 2H, J = 7.2 Hz, NCH_2), 3.83 (s, 3H, OCH_3), 7.03 (d, 2H, J = 11 Hz, anisoyl), 7.46-7.64 (m, 3H, H_7-H_8-H_9), 8.14-8.26 (m, 3H, H_{10} + 2 anisoyl); ^{13}C nmr (DMSO-d_6): δ 13.6 (CH_3), 19.3 (CH_2), 24.2 ($2CH_3$), 29.4 (CH_2), 48.8 (NCH_2), 55.3 (OCH_3), 63.9 (C_6), 106.3 (C_{10b}), 113.4 (2CH anisoyl), 119.3-134.9 (C_{6a}-C_{10a}), 122.3-124.4-128.4-129.7 (C_7-C_8-C_9-C_{10}), 130.0-162.1 (2 Cq anisoyl), 131.0 (2CH anisoyl), 161.9 (C_1), 171.0 (CO).

Anal. Calcd. for $C_{23}H_{26}N_4O_3$: C, 67.96; H, 6.45; N, 13.78. Found: C, 67.9; H, 6.6; N, 13.8.

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