New Experimental Strategies in Amide Synthesis using *N,N*-Bis[2-oxo-3-oxazolidinyl]phosphorodiamidic Chloride

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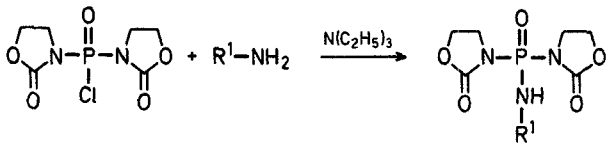
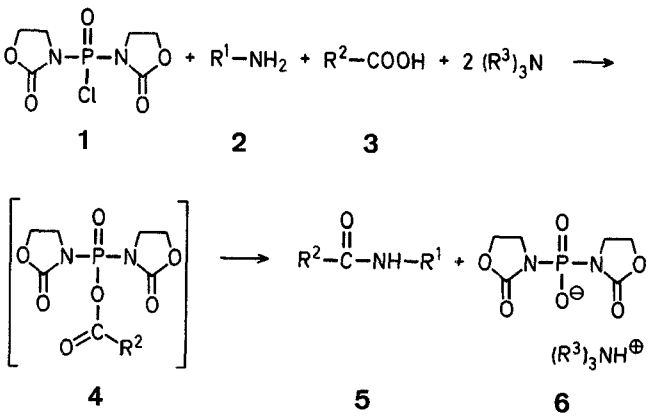
Carboxylic group activation by means of *N,N*-bis[2-oxo-3-oxazolidinyl]phosphorodiamidic chloride (**1**) was described in a previous paper[1]. In the preparation of the corresponding amides and esters, a complete selectivity was observed using different nucleophilic species, aromatic amines and alcohols. This selectivity made possible the one-step synthesis shown in Scheme **A**.



1 **2** **7**

Scheme **A**

Studying the influence of the amine basicity, we found that amines having higher basicity than the aromatic ones, for the preparation of amides of type **5**, gave, in addition, the phosphorotriamides **7** as a by-product. These compounds were prepared by reacting **1** with amines **2** in the presence of a tertiary base (Scheme **B**, Table 1). It was also demonstrated that such phosphorotriamides do not react with carboxylic acid salts to form the corresponding amides. This result invalidates Method C[1] as a procedure for preparation of amides, since, in the work described[1], compounds **7** are formed partially and consequently the yield of amide corresponds to the presence of **1** and **2**.



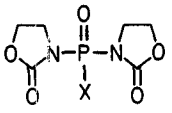
1 **2** **3**

4 **5** **6**

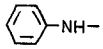
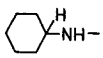
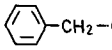
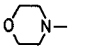
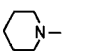
Scheme **B**

The main object of the work described here was to preserve the selectivity of the reaction while maintaining a one-step synthesis (Scheme **A**). The Methods A, B, and C shown in Scheme **C** are based on the following experimental results (in all cases conversion of the acid **3** into the amide **5** occurs).

Table 1. Phosphorotriamides **7a–g** prepared



7a-g

Product No.	X	Reaction Conditions[a] solvent/time	Isolation[b]	Yield [%]	m.p. [°C] (solvent)	Molecular formula[c]	I.R. (KBr) ν [cm^{-1}] NH	C=O	P=O
7a		CH_3CN/120 min	II	70[d]	204.5–205° (i-C_3H_7OH)	$C_{12}H_{14}N_3O_5P$ (311.2)	3175	1770	1176, 1195
7b	n-C_4H_9–NH–	CH_2Cl_2/45 min	I	100	125–126° (i-C_3H_7OH)	$C_{10}H_{18}N_3O_5P$ (291.2)	3210	1765	1228
7c		CH_2Cl_2/30 min	II	84	147.5–148.5° (H_2O)	$C_{12}H_{20}N_3O_5P$ (317.3)	3382	1761	1221, 1201
7d		CH_2Cl_2/15 min	II	91	133–134° (H_2O)	$C_{14}H_{18}N_3O_5P$ (339.3)	3348	1752	1231, 1185
7e		CH_2Cl_2/36 min	I	60	151.5–152° (C_2H_5OAc)	$C_{10}H_{16}N_3O_6P$ (305.2)	–	1760	1227, 1195
7f		CH_3CN/30 min	II	83	97–99° (H_2O)	$C_{11}H_{18}N_3O_5P$ (303.3)	–	1760, 1748	1208
7g	t-C_4H_9–NH–	CH_2Cl_2/210 min	III	99[e]	152–154° (C_2H_5OAc)	$C_{10}H_{18}N_3O_5P$ (291.2)	3205	1758	1200

[a] Reaction at 20–25 °C in the presence of triethylamine.

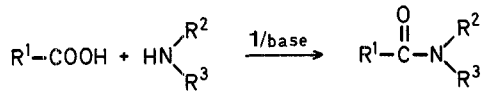
[b] Isolation methods:
I – Addition of aqueous hydrochloric acid to pH = 1, drying of organic layer with sodium sulfate, evaporation to dryness, suspension of residue in ether, filtration, and drying.
II – Solution evaporated to dryness, aqueous hydrochloric acid added to pH = 1, filtration of precipitate which is washed with water.
III – Base hydrochloride is filtered, solution evaporated to dryness, residue suspended in ether, filtered, and dried.

[c] Satisfactory microanalyses obtained: C ±0.25, H ±0.21, N ±0.33, P ±0.25.

[d] Ratio of amine: **1** = 2:1.

[e] t-Butylamine in place of triethylamine.

Table 2. Amides **5** prepared



3 **5**

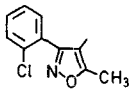
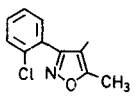
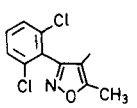
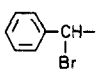
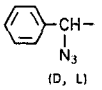
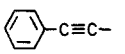
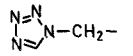
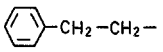
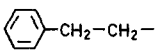
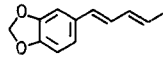
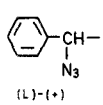
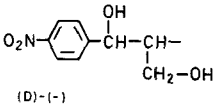
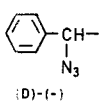
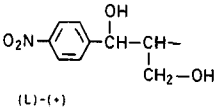
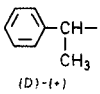
Product No.	R^1	R^2	R^3	Solvent/base System[a]	Method/Reaction Time	Isolation Method[b]	Yield [%]	m.p. [°C] (solvent)	Molecular Formula[c] or Lit. m.p. [°C]	I.R. (KBr) ν [cm^{-1}] NH	C—O
5a		H	n-C_4H_9	*a*	C/60 min	I	94	65–67° (n-C_6H_{14})	$C_{15}H_{17}ClN_2O_2$ (292.8)	3322, 3294	1650
				b	C/60 min	I	99				
5b		H		*a*	C/70 min	I	84	158–159.5° (i-C_3H_7OH)	$C_{17}H_{19}ClN_2O_2$ (318.8)	3247	1645
				c	C/75 min	II	94				
5c		H		*c*	C/60 min	II	98	133.5–134° (i-C_3H_7OH)	$C_{17}H_{18}Cl_2N_2O_2$ (353.3)	3330	1660
5d		H		*b*	C/60 min	I	82	136–137° (i-C_3H_7OH)	$C_{14}H_{18}BrNO$ (296.2)	3298	1654
5e	 (D, L)	H		*b*	C/120 min	I	95	112–113° (i-C_3H_7OH/H_2O)	$C_{14}H_{18}N_4O$ (258.3)	3336	1660

Table 2. (Continued)

Product No.	R^1	R^2	R^3	Solvent/ base System[a]	Method/ Reaction Time	Isolation Method[b]	Yield [%]	m.p. [°C] (solvent)	Molecular Formula[c] or Lit. m.p. [°C]	I.R. (KBr) ν [cm^{-1}] NH	C=O
5f	t-C_4H_9	H		*b*	A/120 min	III	84[d]	130–131°	128–131°[13]	3315	1650
5g		H		*a*	A/60 min	I	98	125.5–126.5° (CH_3CN/H_2O)	128°[18]	3232	1627
5h		H		*d*	B/60 min	I	94	182–182.5° (C_2H_5OH)	$C_{11}H_{13}N_5O$ (231.3)	3350	1663
5i		H		*d*	B/120 min	V	85	b.p. 155–160°/ 0.8 torr	b.p. 150–154°/ 0.7 torr[5]	3320	1645
5j		$-(CH_2)_2-O-(CH_2)_2-$		*d*	B/120 min	V	94	47–49.5° (n-C_6H_{14})	b.p. 112–115°/ 0.15 torr[5]	–	1652, 1632
5k		$-(CH_2)_5-$		*d*	B/120 min	V	92	b.p. 215–217°/ 1.8 torr	b.p. 215–217°/ 1.8 torr[5]	–	1647, 1620
5l	$H_3C-CH=CH-$	$-(CH_2)_5-$		*b*	B/60 min	V	100	−3 to +5°	$C_9H_{15}NO$ (153.2)	–	1665, 1621
5m		$-(CH_2)_5-$		*b*	B/90 min	I	91	69–72° (n-C_6H_{14})	$C_{12}H_{14}ClNO$ (223.7)	–	1636
5n		$-(CH_2)_5-$		*b*	B/60 min	IV	90	129–130° (C_2H_5OH)	129°[16]	–	1641, 1624
5o		H	 (D)-(+)	*e*	C/75 min	II	45[e]	108–109° (n-C_6H_{14})	$C_{13}H_{17}NO$ (203.3)	3352	1654, 1628
5p		H	 (L)-(−)	*c* *f* *c*	C/75 min C/75 min C/75 min	II II II	77 74 76[f]	108–109° (n-C_6H_{14})	$C_{13}H_{17}NO$ (203.3)	3350	1654, 1628
5q	 (L)-(+)	H	 (D)-(−)	*c*[g]	C/90 min	II	90[h]	142–143.5° ($ClCH_2CH_2Cl$)	$C_{17}H_{17}N_5O_5$ (371.4)	3365	1645
5r	 (D)-(−)	H	 (L)-(+)	*e*[g]	C/90 min	II	91[i]	142.5–143.5° ($ClCH_2CH_2Cl$)	$C_{17}H_{17}N_5O_5$ (371.4)	3365	1645
5s	t-C_4H_9	H	 (D)-(+)	*b*	D/75 min	I	91	119–119.5° (n-C_6H_{14})	$C_{13}H_{19}NO$ (205.3)	3340	1638

[a] *a*: dichloromethane/*N*-ethylpiperidine; *b*: dichloromethane/triethylamine; *c*: dimethylacetamide/triethylamine; *d*: dichloromethane/*N*-ethylmorpholine; *e*: dimethylacetamide/*N*-ethylmorpholine; *f*: dimethylacetamide/diazabicycloundec-7-ene (DBU).

[b] I: Addition of water (10 ml) and hydrochloric acid to pH = 1, extraction, treatment of the organic layer with water (10 ml) and solid sodium hydrogen carbonate, and decantation. The resulting solution is dried with sodium sulfate and evaporated to dryness.

II: Reaction mixture is poured into water (50 ml/0.005 mol of amide), the precipitate is filtered and washed with water.

III: Reaction mixture is evaporated to dryness and the residue is treated with ether to give the amide.

IV: Reaction mixture is evaporated to dryness, the residue is suspended in water, acidified to pH = 1 with hydrochloric acid, the solid is filtered, and washed with water.

V: As method I, then the solid obtained is treated with ether and filtered. The solution is then evaporated to dryness on a rotatory evaporator.

[c] Satisfactory microanalyses obtained: C ±0.22, H ±0.26, N ±0.33.

[d] The dioxaphosphoramidic anhydride (8.5%) and the aniline triamide (5%) are also obtained.

[e] $[\alpha]_D$: +95.15° (1% in dimethylformamide).

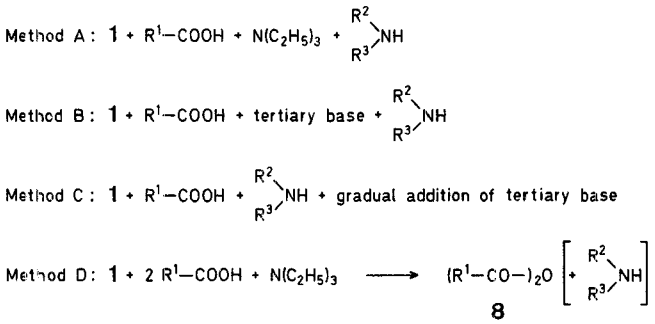
[f] $[\alpha]_D$: −95.15° (1% in dimethylformamide).

[g] The ammonium salt is used[17].

[h] Yield of isolated product: 83%; conversion: 90%.

[i] Yield of isolated product: 84%; conversion: 91%.

(1) In the carboxylic acid ammonium salt, the carboxylate group's nucleophilic character is retained. However, the amino group's nucleophilic character decreases significantly.
(2) The reaction is performed according to Method B (Scheme **C**) when the pK_b of the tertiary base is at least 0.4 units bigger than the pK_b of the amine.
(3) A one-step synthesis can be controlled by gradual addition of a tertiary base stronger than the amine (Method C).



Scheme **C**

All these results make possible the use of carboxylic acids and primary, secondary and cyclic amines while avoiding undesirable side-reactions. The present work shows for the first time that the amidic bond is formed from ammonium salts at room temperature, avoiding, among other problems, racemization reactions[2].

Formation of anhydride **8** as an operative intermediate in the amide synthesis (Method D) was demonstrated in a previous work[3]. However, the isolation of compound **4**, as well as the appreciably different yields obtained when a one-step synthesis or a two-step synthesis was operating[1], showed that **4** is the principal intermediate. In the present work, some additional results on this subject will be discussed.

The fact that phenylpropynoic, tetrazolylacetic and α-azidophenylacetic acids give excellent yields of their corresponding amides (products **5e, h, g, q** and **r**; Table 2) demonstrates that the reaction takes place without participation of the respective anhydrides **8**, since their formation reaction from the acid and reagent **1** was reported in a previous work[3] with less satisfactory results. With hindered and softly basic amines, the reaction can take place through **8**, since the reaction of **2** with **4** (Scheme **A**) proceeds slowly.

Reaction of **1** with **6** (Scheme **A**) is generally not relevant due to the low nucleophilicity of **6** compared with other more active agents present in the medium. Nevertheless, the mentioned reaction is important as a competitive one when either strong carboxylic acids (trifluoro- and trichloroacetic) or highly hindered acids (pivalic) are employed. Method D constitutes a limited alternative to the two-step synthetic pathway, particularly for the acidic amides derived from *p*-nitroaniline and diphenylamine. The latter amine did not react with **1** to yield **7** after having been refluxed in acetonitrile for 40 h.

The problem of selectivity in the formation of amides in a one-step or a two-step synthesis is a well known phenomenom that depends on the nature of the carboxylic acid used and on possible intermediates in the synthesis. Thus, product **5i** (Table 2) was obtained using dicyclohexylcarbodiimide after 12 h reaction in a 15% yield; the β-phenylethylamide of 3,3-dimethylacrylic acid was obtained in 27% yield and, in general, yields are very poor[5]. Phenylpropynoic acid yields 1-phenyl-2,3-naphthalenedicarboxylic anhydride in 90% yield[6].

Concerning two-step synthetic pathways, use of ethyl carbonochloridate caused racemization of enantiomers and gave rise to the ethyl ester instead of the expected mixed anhydride[7] (acids **3e**, **3q** and **3r**). The yield in the corresponding anilide was also very low[8] (acid **3a**). Similarly, methyl and isobutyl carbonochloridates gave amides in a low yield because of a lack of selectivity[5].

The use of diphenylphosphinic chloride for activation of carboxylic acids needs long reaction times (12 h) and presents limitations with secondary amines (morpholine, piperidine)[5]; yields are also moderate[9]. Mono-, di-, and triesters of phosphorous acid as condensing agents refluxed in pyridinium-*N*-phosphonate salts[10] gave excellent yields. The same happened with 1-methyl-2-halopyridinium iodide in only one step and refluxing for 1 h in dichloromethane[11]. However, these two methods are not feasible with structurally thermolabile acids (**3e, h, q**, and **r**), acids that carry an active halogen (**3d**) or those that undergo fast cyclodimerization (**3g**).

Cyanuric chloride forms the acid chloride in 3 h with excess of the acid salt (100%)[12]; 2,4,6-trinitrofluorobenzene, in two steps, requires long reaction periods with highly hindered acids (**3f**)[13]. Direct conversion of carboxylic acids into amides by means of *o*-nitrophenyl thiocyanate and tri-*n*-butylphosphine needs of an excess of reagents and of amine; furthermore, the reaction produces toxic hydrogen cyanide[14]. The use of tetrabutylammonium salts requires long reaction time; however, high reaction yields have been published[15]. Finally, product **5n** was obtained from the acid chloride after 24 h reaction with a large excess of amine in poor yield (64%)[16].

Melting points were determined with a Reichert Thermovar microscope and are not corrected. I.R. spectra were obtained using a Beckmann Acculab 4 instrument. Specific optical rotation were determined with a Hartnack-HA model 4001 polarimeter.

Amides 5; General Procedure:

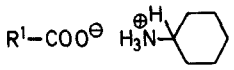
Method A: Reagent **1** (1.28 g, 5 mmol) is added to a solution at 18°C of carboxylic acid **3** (5 mmol), triethylamine (1.40 ml, 10 mmol) and amine **2** (5 mmol) in dichloromethane (10 ml). The solution process takes 10 min at 20–25°C and the work-up is as described in Table 2.

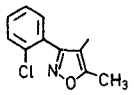
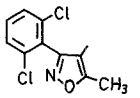
Method B: Tertiary base (10 mmol) and reagent **1** (1.28 g, 5 mmol) are added to a solution or suspension or the amine salt (5 mmol) in the solvent (10 ml). The solution process takes from 10 to 20 min at 20–25°C and the working-up is as described in Table 2. [The amine salt may be prepared *in situ* by mixing carboxylic acid **3** (5 mmol), amine **2** (5 mmol), and solvent (10 ml) or it may be added as a solid (Table 3) to the same amount of solvent].

Method C: Reagent **1** is added to a solution (or suspension) of the amine salt (see above) in the solvent (7 ml). Then, a solution of tertiary base (10 mmol) in solvent (3 ml) is added dropwise for 30 min at 20–25°C. Work-up is as described in Table 2.

Method D: (One pot procedure): Reagent **1** is added to a solution of carboxylic acid **3** (10 mmol) and triethylamine (1.40 ml, 10 mmol) in dichloromethane (10 ml). The mixture is stirred for 3 h at 20–25°C and then triethylamine (0.70 ml, 5 mmol) and amine **2** (5 mmol) are added, stirring is continued for a period of 75 min at the same temperature. Work-up is as described in Table 2.

Table 3. Cyclohexylammonium Carboxylates prepared



R^1	Solvent	Yield [%]	m.p. [°C]	Molecular Formula[a]	I.R. (KBr) ν [cm^{-1}]
	CH_3CN	92	158–170.5°	$C_9H_{17}N_5O_2$ (227.3)	1636, 1580, 1550
	CH_2Cl_2	94	152–152.5°	$C_{14}H_{20}N_4O_2$ (276.3)	2120, 1643, 1590
	CH_3CN	100	143–144°	$C_{14}H_{20}BrNO_2$ (314.2)	1640, 1580
	CH_3OH	85	182.5–186.5°	$C_{17}H_{21}ClN_2O_3$ (336.8)	1638, 1616, 1566, 1547
	CH_2Cl_2	99	168–169°	$C_{17}H_{20}Cl_2N_2O_3$ (371.3)	1638, 1616, 1565
$H_3C-CH=CH-$	$(H_3C)_2CO$	92	139–140°	$C_{10}H_{19}NO_2$ (185.3)	1664, 1639, 1567, 1528

[a] Satisfactory microanalyses obtained: C ± 0.32, H ± 0.21, N ± 0.39, Br ± 0.35, Cl ± 0.38.

***N,N*-Bis(2-oxo-3-oxozolidinyl)-*N*-β-phenylethylphosphorotriamide (7d); Typical Procedure:**

Reagent **1** (1.28 g, 5.0 mmol) is added to a solution (at 15 °C) of 2-phenylethylamine (0.68 ml, 98%, 5.0 mmol) and triethylamine (0.70 ml, 5.0 mmol) in dichloromethane (10 ml). Solution of **1** takes place immediately and there is an exothermic process. Reaction is completed in 15 min at 20–25 °C and the final mixture is evaporated to dryness. The resulting solid is mixed with water (10 ml) and hydrochloric acid (0.1 ml, 37%), stirred for 10 min at room temperature, filtered, washed with water (5 ml), and dried to give the desired product; yield: 1.54 g (91%); m.p. 133–134 °C (from water).

$C_{14}H_{18}N_3O_5P$	calc.	C 49.56	H 5.35	N 12.39	P 9.13
(339.3)	found	49.5	5.3	12.2	9.0

I.R. (KBr): ν = 3348 (NH); 1752 (C=O); 1231, 1189 cm^{-1} (P=O).

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(Revised form: November 21, 1983)

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[2] E. Gross, J. Meinhofer, *The Peptides*, Academic Press, New York, Vol. I (1979) p. 317, Vol. II (1980) p. 486.
[3] J. Cabré Castellví, A Palomo Coll, A. L. Palomo Coll, *Synthesis* **1982**, 616.
[4] J. Cabré Castellví, A. L. Palomo Coll, *Tetrahedron Lett.* **21**, 4179 (1980).
[5] S. Bernasconi, A. Comini, A. Corbella, P. Gariboldi, M. Sisti, *Synthesis* **1980**, 385.
[6] P. A. Cadby, M. T. W. Heran, A. D. Ward, *Aust. J. Chem.* **26**, 557 (1973).
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[9] A. G. Jackson, G. W. Kenner, G. A. Moore, R. Ramage, W. D. Thorpe, *Tetrahedron Lett.* **1976**, 3627.
[10] N. Yamazaki, F. Higashi, S. A. Kazaryan, *Synthesis* **1974**, 436.
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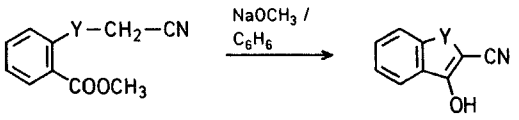
[14] P. A. Grieco, D. S. Clark, G. P. Withers, *J. Org. Chem.* **44**, 2945 (1979).
[15] Y. Watanabe, T. Mukaiyama, *Chem. Lett.* **1981**, 285.
[16] H. Normant, C. Fengeas, *C. R. Acad. Sci. Ser. C.* **258**, 2486 (1964).
[17] A. L. Palomo Coll, *Afinidad* **28**, 141 (1971).
[18] J. von Braun, H. Ostermayer, Ber. Dtsch. Chem. Ges. **70**, 1002 (1937).

Errata and Addenda 1984

M.H. Elnagdi, M.R.H. Elmoghayar, G.E.H. Elgemeie, *Synthesis* **1984** (1), 1–26:

The second paragraph on page 2 should read:
Cyclic 3-oxoalkanenitriles **11** are obtained via cyclisation of methyl *N*-acetyl-*N*-cyanomethylanthranilate (**10a**)[61a], methyl 2-(cyanomethoxy)-benzoate (**10b**)[61b], or methyl 2-(cyanomethylthio)-benzoate (**10c**)[61] under basic conditions.

The formula scheme **10** → **11** (p. 3) should be:



10a Y = N–CO–CH$_3$
b Y = O
c Y = S

11a-c

The experimental procedure for **11a** (p. 3) should read:

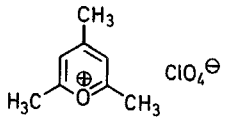
2-Cyano-3-hydroxyindole (11a; Y = NH)[61]:
A mixture of freshly prepared sodium methoxide (10 mmol) and methyl *N*-acetyl-*N*-cyanomethylanthranilate (**10a**; 10 mmol) in benzene (25 ml) is stirred for 2 h at room temperature then left for 12 h at room temperature. The mixture is poured into water. Carbon dioxide is bubbled into the resulting solution till no more solid separates. The product is collected and recrystallised; yield: 64%; m.p. 165–167°C (dec.).

The following references should be added (p. 23):

[61] (a) D. Vorländer, *Ber. Dtsch. Chem. Ges.* **35**, 1683, 1696 (1902).
(b) R. Bryant, D.L. Haslam, *J. Chem. Soc.* **1965**, 2361.

P. Molina, A. Tárraga, E. Romero, M.L. Peña, *Synthesis* **1984** (1), 71–73:

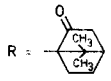
The structure of compound **6** (p. 71) should be:



6

Abstract 6803, *Synthesis* **1984** (1), 82:

The substituent R should be:

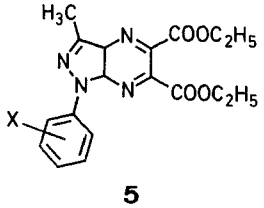


F. Pochat, *Synthesis* **1984** (2), 146–148:

Compounds **3c**, **5c**, and **5g** (p. 147 and 148) should be named as *N'*-acyl-*N'*-(methylthiomethyl)-hydrazones.

P.G. Baraldi, D. Simoni, V. Periotto, S. Manfredini, M. Guarneri, *Synthesis* **1984** (2), 148–149:

The structure of compound **5** (p. 149) should be:



5

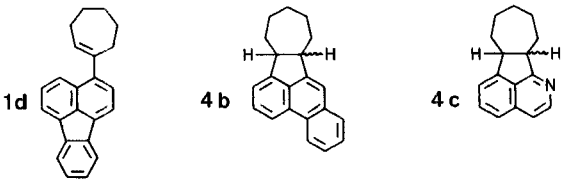
S.C.W. Coltman, S.C. Eyley, R.A. Raphael, *Synthesis* **1984** (2), 150–152:

The first line of the experimental procedure for esters **4** should read:
To a solution of **2** (0.1 mol) in absolute ethanol (30 ml) is added a 1

R. Lapouyade, A. Nourmamode, *Synthesis* **1984** (2), 161–164:

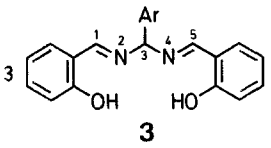
The title should read:
A New Synthesis of 6b,8,9,10,11,11a-Hexahydro-7*H*-cyclohepta[*a*]acenaphthylenes by Base-Catalyzed Photocyclization of 1-Arylcycloheptenes

The structures of products **1d**, **4b**, and **4c** in Tables 2 and 3 (p. 163) should be:



T. Takajo, S. Kambe, W. Ando, *Synthesis* **1984** (3), 256–259:

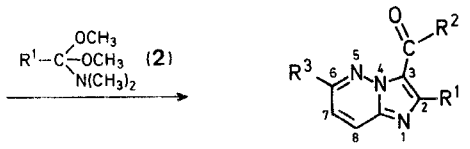
The structure of product **3** (p. 257, left) should be:



3

S. Podergajs, B. Stanovnik, M. Tišler, *Synthesis* **1984** (3), 263–265:

The structures of reagent **2** and products **5a–d** (p. 264) should be:



5a-d

U. Schöllkopf, U. Busse, R. Kilger, P. Lehr, *Synthesis* **1984** (3), 271–274:

The heading for the first experimental procedure (p. 274) should be:
(3*S*,6*S*)-3,6-Diisobutyl-2,5-dioxohexahydropyrazine (**9**):

J. Cabré, A.L. Palomo, *Synthesis* **1984** (5), 413–417:

The authors' address should read:
Gema S.A., Beethoven-15, Barcelona-21; Centro Marga para la Investigación, Muntaner 212, Barcelona-36, Spain
The formulae of Schemes **A** and **B** (p. 413) should be interchanged.
The following experimental procedure should be added:

Cyclohexylammonium Carboxylates (Tables 3); General Procedure:
To a solution of cyclohexylamine (1.15 ml, 10.0 mmol) in the solvent (20 ml, Table 3), the carboxylic acid is added at room temperature. The mixture is stirred for 15 min at room temperature and then cooled to 0–5°C. The precipitate is filtered and washed with cold (0 to −5°C) solvent (10 ml).

D.P. Stack, R.M. Coates, *Synthesis* **1984** (5), 434–436:

The structure of product **2e** (Table, p. 435) should be: