Organic Sonochemistry. Synthesis and Use of Reissert Compounds under PTC-Ultrasound

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Use of phase transfer catalysis and ultrasound stirring improved the synthesis, alkylation and hydrolysis of several Reissert derivatives.

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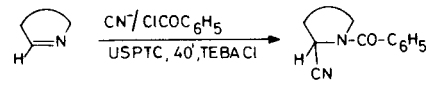
Carbanions derived from Reissert compounds are valuable intermediates in organic synthesis [1-5]. Their reactions with benzyl halides and aldehydes provide a convenient route to 1-substituted isoquinolines -the most classically studied heterocycle- and related systems, all key steps in the synthesis of alkaloids and other products of chemical and biological interest.

Phase transfer catalysis [5-7] has been successfully applied either to the synthesis of Reissert compounds or to alkylation processes. In the synthesis, although the trimethylsilyl cyanide route has been successfully expanded over the last years [4,6,8-11], the use of a phase transfer catalyst in the classical methylene chloride-water method is usually helpful in increasing the yield of Reissert compound, reducing at the same time psuedo-base formation [6,12]. In the alkylation, the mixture sodium hydride-dimethylformamide remains as the more popular method [5-7], but hydroxide ion in phase transfer catalysis processes has been successfully applied either with alkyl halides or carbonyl derivatives [13-19].

We have recently found that phase transfer catalysis alkylation can be improved in terms of reaction rate and yield by the use of ultrasound stirring [20]. Independently, two other groups described similar effects on the *N*-alkylation of amines [21], and on the oxidation of alkylnitroaromatic derivatives [22], so the technique (ultrasound stirred phase transfer catalysis) can open an unexplored area in

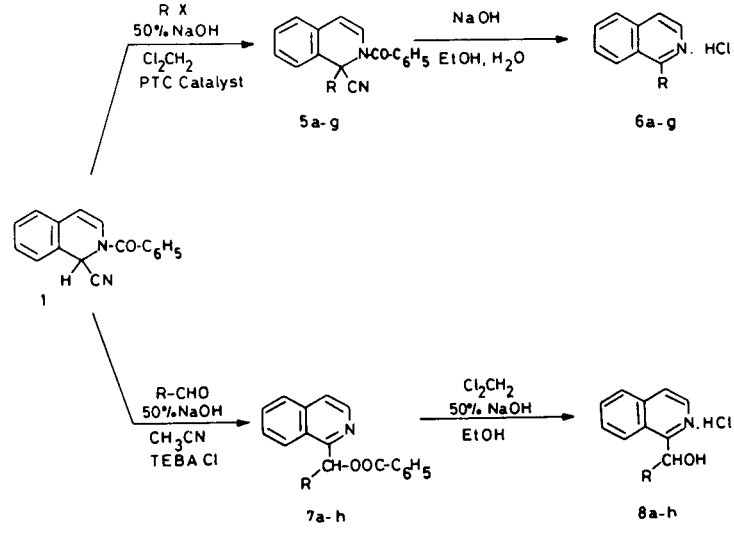
Table I

Reissert Compounds



Compound	Starting Heterocycle	% Yield [a] Found (Reported)
1	Isoquinoline	69 (69) [b]
2	3,4-dihydroisoquinoline	18 (40) [c]
3	6,7-diMeO-3,4-dihydroisoquinoline	42 (18) [d]
4	Phthalazine	13 (10) [e]

[a] Isolated pure product. [b] Described in [23,24]. [c] Described in [25]. [d] Described in [26]. [e] Described in [27]. Unfortunately, we could not reproduce the 55% yield described in [28].



Scheme 1

Table II

Reaction of **1** with Benzyl Halides

			Step by Step Procedure					One Step Procedure		
			1 Alkylation Process			5 Hydrolysis Process				
Compound	R	X	Reaction Time (minutes)	**5** Yield [a,b] (%)	**5** mp (°C)	Reaction Time (minutes)	**6** Yield [a] (%)	Reaction Time (minutes)	**6** Yield [a] (%)	**6** mg [g] (°C)
a	$C_6H_5CH_2$	Cl	20	60 [c] (50)	126 [d,e]	40	70	50	80	172-173 [f]
b	$2\text{-}ClC_6H_4CH_2$	Cl	25	88 [c] (80)	167 [e]	40	72	50	70	189-190
c	$4\text{-}ClC_6H_4CH_2$	Cl	25	50 [c] (26)	139-140 [e]	40	80	50	74	190-191
d	$4\text{-}NO_2C_6H_4CH_2$	Br	25	50 [h] (40)	194-195 [i]	— [j]	—	120	— [k]	——
d	$4\text{-}NO_2C_6H_4CH_2$	Cl	25	76 [h] (46)	194-195 [i]	— [j]	—	120	— [k]	——
e	$4\text{-}CH_3C_6H_4CH_2$	Cl	25	—— [l]	——	—	—	50	79	220-222
f	$4\text{-}CH_3OC_6H_4CH_2$	Cl	25	73 [c]	150-151 [e]	40	43	50	77	192-193
g	$3,4\text{-}CH_2O_2C_6H_3CH_2$	Cl	25	——[l]	——	—	—	50	90	222-223

[a] Of isolated pure products, all new compounds gave satisfactory spectral and microanalytical data (C, H, N) within ± 0.4%. [b] Yields without ultrasound in brackets, after 120 minutes. [c] Method A as described in the experimental, tetrabutylammonium chloride was used as catalyst. [d] 129° in [13]. [e] From methanol. [f] 172-173° in [30]. [g] From ethanol. [h] Method B as described in the experimental, cetyltrimethylammonium bromide as the catalyst. [i] From butanol. [j] The starting material was recovered unchanged after 2 hours in over 80% yield. [k] **5d** was isolated in 76% yield. [l] Hygroscopic mixture.

Table III

Reaction of **1** with Aldehydes

		Step by Step Procedure					One Step Procedure		
		1 Alkylation Process			8 Hydrolysis Process				
Compound	R	Reaction Time (minutes)	**7** Yield [a,b] (%)	**7** mp [d] (°C)	Reaction Time (minutes)	**8** Yield [a,c] (%)	Reaction Time (minutes)	**8** Yield (%)	**8** mp [e] (°C)
a	C_6H_5	3	88 (88)*	165-166	60	92 (93)	90	94	212-213
b	$3\text{-}ClC_6H_4$	5	100 (95)	156-157	60	99	90	100	227-228
c	$4\text{-}ClC_6H_4$	5	98 (84)*	161-162	60	97 (97)	90	82	193-194
d	$4\text{-}CH_3C_6H_4$	5	93	170-171	60	93	90	97	189-190
e	$4\text{-}CH_3OC_6H_4$	5	95 (80)	122-123	60	95	90	83	170-171
f	$3,4\text{-}CH_2C_6H_3$	5	93	158	60	81	90	86	209-210
g	2-Thienyl	5	94 (51)	275-276	60	85	90	97	160-161
h	2-Furyl	5	86 (79)*	146-148	60	82	90	98	181-182

[a] In isolated pure product, all new compounds gave satisfactory spectral and microanalytical data (C, H, N) within ± 0.4%. [b] Yields without ultrasound in brackets, after 30 minutes, when marked * taken from [17]. [c] Yield without ultrasound in brackets, after 9 hours of reflux, taken from [17]. [d] From ethanol. [e] From methanol.

the field of organic sonochemistry.

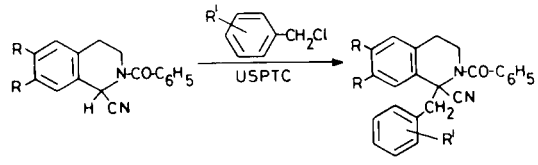
After the initial experiments [20] we decided to explore the usefulness of ultrasound stirred phase transfer catalysis on the sequence heterocycle-Reissert compound-substituted Reissert compound-substituted heterocycle. The first results, presented in Table I, were obtained by modification of the traditional method of synthesis of Reissert derivatives; as can be seen, yields were not significantly improved except for **3**, but reaction time was reduced from about 4 hours to 40 minutes.

Then, *N*-benzoyl-1,2-dihydroisoquinaldonitrile [23,24] was taken as a model (Scheme 1), and reacted with benzyl halides (Table II) and aldehydes (Table III). Two Methods were studied, one step by step, in which the intermediates **5** and **7** were isolated and then hydrolyzed, and a one step method, in which sonication was prolonged to produce **6** and **8** directly.

The reaction with halides (Table II, **1** to **5**) has been performed by sonication [22] of two already described phase transfer catalysis methods, one by Makosza [13] (Method

Table IV

Alkylation of **2**, **3** with Benzyl Halides



Compound	R	R'	Yield % [a] (Lit Yield)	mp °C (Lit mp)
2a	H	H	71 (95) [b]	128-129 (128-129) [b,c]
2b	H	2-Cl	71	104-106 [d]
2c	H	4-Cl	88	185-187 [d]
3a	CH_3O	H	90 (91) [b]	198-200 (198-200) [b,d]

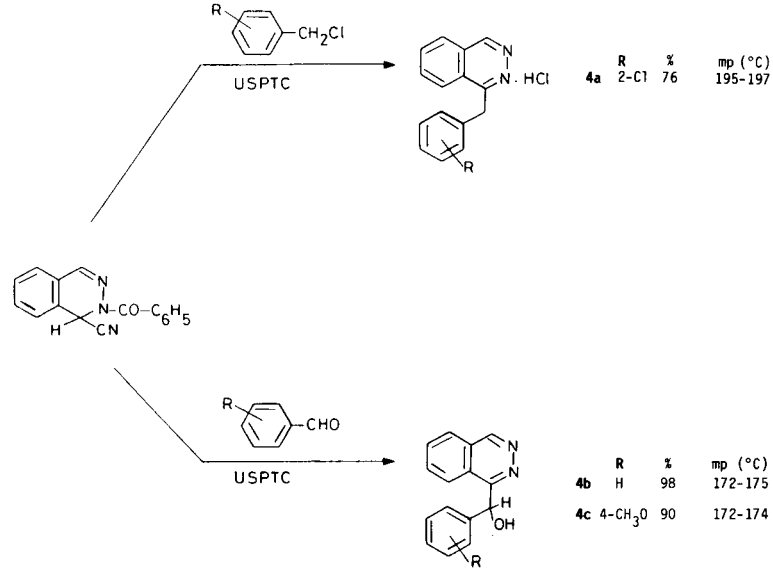
[a] Of isolated pure product, all new compounds gave satisfactory spectral and microanalytical data (C, H, N) within ± 0.4%. [b] As described in [6]. [c] From methanol. [d] From dichloromethane/*n*-hexane.

A) and the other one by Skiles and Cava [16] (Method B). Together with ultrasound stirred phase transfer catalysis experiments, classical phase transfer catalysis methods were performed to compare yields (in brackets). As can be seen, sonication reduced the reaction time for 2 hours to 25 minutes and yields were significantly improved. As it is usual in phase transfer catalysis methods using halides, yields depend greatly on the halide, the highest being obtained with chlorides (see **5d** Table II). Bromides produced lower or gave only traces of alkylation (as with 1-bromomethylnaphthalene and *o*-nitrobenzyl bromide) and methyl iodide did not react at all.

Hydrolysis of **5** was achieved after 40 minutes of sonication at room temperature in the presence of aqueous 50% sodium hydroxide and no comparative experiments were performed. Usually, the step in described as requiring 2 hours of reflux [23], so the present method is, at least, a mild alternative. The product **5d**, however, could not be hydrolyzed even after 2 hours of sonication, due to its insolubility. The one-step method, without isolation of **5**, seems superior in yield and simplicity, in all examples studied.

Reaction with aldehydes is represented in Table III. One previously described method [17] was modified to perform the step by step and direct methods. Yields obtained using classical phase transfer catalysis techniques are presented in brackets, taken either from literature (*) [7] or performed by us. Yields were superior in all examples, and time was reduced from 20 minutes to 5 for **1-7** and from 9 hours to one for **7-8**. The one-step conversion **1-8** was achieved in 90 minutes. All reactions were performed at 24-30°.

Conversions **1-5** and **1-7** were repeated as described with ultrasound but without catalyst, to check to what extent they occurred by a real phase transfer mechanism or were simply interfacial effects. Attempts of synthesis of **5a,b,c** without catalyst, produced recovery of **1** in more than 80%. So it should be concluded that interfacial effects are of minor importance, and the micellar medium induced by the ultrasound produces an overall improvement of the phase transfer catalysis process. Reaction with aldehydes, however, produced slightly different results, as experiments performed to prepare **7a,b,d** under non catalytic two-phase conditions yielded 67, 60 and 69% respectively, of **7**, after 5 minutes of sonication. In this case, although the catalyst seems to improve yields, reaction should mainly occur at the interface.



Scheme II

Table V

Elemental Analyses of Newly Described Compounds

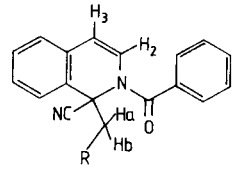
Compound	mp (lit) °C	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
5a	126 (129) [a]	$C_{24}H_{16}N_2O$	82.26	5.17	7.99	82.62	5.17	7.59
5b	167	$C_{24}H_{17}ClN_2O$	74.90	4.45	7.27	74.59	4.19	6.97
5c	139-140	$C_{24}H_{17}ClN_2O$	74.90	4.45	7.27	74.75	4.51	6.90
5d	194-195	$C_{24}H_{17}N_3O_3.1/4\ C_4H_{10}O$	72.53	4.74	10.06	72.43	4.57	9.89
5f	150-151	$C_{25}H_{20}N_2O_2$	78.92	5.29	7.36	78.71	5.48	7.74
6a	172-173 (172-173) [b]	$C_{16}H_{14}ClN$	———	———	———			
6b	189-190	$C_{16}H_{13}ClN$	66.22	4.51	4.82	66.10	4.44	4.68
6c	190-191	$C_{16}H_{13}ClN.1/2\ H_2O$	64.23	4.71	4.68	64.33	4.33	4.46
6e	220-222	$C_{17}H_{16}ClN$	75.68	5.97	5.19	75.58	5.82	5.19
6f	192-193	$C_{17}H_{16}ClNO$	71.45	5.64	4.90	71.29	5.54	5.06
6g	222-223	$C_{17}H_{14}ClNO_2$	68.11	4.70	4.67	68.45	4.75	5.06
7a	165-166 (164-166) [c]	$C_{23}H_{17}NO_2$	———	———	———	———	———	———
7b	156-157	$C_{23}H_{16}ClNO_2$	73.89	4.31	3.74	73.77	4.23	3.56
7c	161-163 (161-162) [c]	$C_{23}H_{16}ClNO_2$	———	———	———	———	———	———
7d	170-171	$C_{24}H_{19}NO_2$	81.56	5.41	3.96	81.29	5.38	3.80
7e	122-123 (140.5-141.5) [d]	$C_{24}H_{19}NO_3$	78.03	5.18	3.79	78.10	4.83	3.53
7f	158	$C_{24}H_{17}NO_4$	75.18	4.46	3.65	74.94	4.09	3.50
7g	175-176 (174-175) [e]	$C_{21}H_{15}NO_2S$	73.02	4.37	4.05	73.40	4.02	4.38
7h	145-146 (144-146) [c]	$C_{21}H_{15}NO_3$	———	———	———	———	———	———
8a	212-213	$C_{16}H_{14}ClNO$	70.71	5.19	5.15	71.02	5.16	5.31
8b	227-228	$C_{16}H_{13}Cl_2NO$	62.76	4.27	4.57	62.70	4.31	4.79
8c	193-194	$C_{16}H_{13}Cl_2NO$	62.76	4.27	4.57	62.73	4.01	4.71
8d	189-190	$C_{17}H_{16}ClNO$	71.45	4.64	4.90	71.15	4.89	4.84
8e	170-171	$C_{17}H_{16}ClNO.\ 1/2\ H_2O$	65.70	5.51	4.50	65.91	5.49	4.89
8f	209-210	$C_{17}H_{14}ClNO_3$	64.66	4.46	4.43	64.90	4.68	4.70
8g	160-161	$C_{14}H_{12}ClNOS$	60.89	4.35	5.04	60.83	4.30	5.37
8h	181-182	$C_{14}H_{12}ClNO_2$	64.25	4.62	5.35	64.10	4.65	5.59
2a	198-199 (198-199) [f]	$C_{24}H_{20}N_2O$	———	———	———	———	———	———
2b	185-187	$C_{24}H_{19}ClN_2O$	74.51	4.95	7.24	74.87	4.49	7.14
3a	198-199 (198-200) [f]	$C_{26}H_{26}N_2O_3$	———	———	———	———	———	———
4a	195-197	$C_{15}H_{12}Cl_2N_2$	61.87	4.15	9.62	61.92	4.58	9.31
4b	172-175 (172-175) [g]	$C_{15}H_{12}N_2O$	———	———	———	———	———	———
4c	172-174	$C_{16}H_{14}N_2O_2$	72.17	5.30	10.52	72.03	5.58	10.17

[a] in [13]. [b] In [23]. [c] In [17]. [d] In [32]. [e] In [33]. [f] In [16]. [g] In [28].

Other complementary experiments, using the one step method were performed on the substrates **2**, **3** and **4**. Results of alkylation of **2** and **3** with benzyl halides are presented in Table IV. Alkylation was performed in 20 minutes of irradiation, but hydrolysis of the adduct was not achieved even by sonication for 2 hours. With **3**, two experiments failed, with *o*- and *p*-Cl derivatives, as starting material was recovered unchanged in more than 80% yield. Alkylation of phthalazine derivative **4** is described in Scheme II. Reaction with benzyl halide produced **4a** in 50 minutes of irradiation, likewise reaction with aldehydes produced carbinols **4b** and **4c** in 90 minutes of irradiation at room temperature. A previously published method [28] described a roughly similar yield for **4b**.

Table VI

^{1}H NMR of Compounds **5** [a]

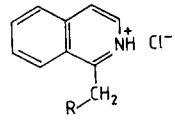


Compound	R	H_3 (coupl $J_{2,3}$)	H_3 (coupl)	Ha (coupl $J_{a,b}$)	Hb (coupl)	Others
5a	C_6H_5	6.35 (d, 6)	5.55 (d)	3.79 (d, 12)	3.49 (d)	6.8-7.7 (m, 14H)
5b	2-ClC_6H_4	6.36 (d, 9)	5.55 (d)	4.17 (d, 15)	3.50 (d)	6.9-7.7 (m, 13H)
5c	4-ClC_6H_4	6.35 (d, 8)	5.55 (d)	3.70 (d, 12)	3.40 (d)	6.6-7.7 (m, 13H)
5d	4-$NO_2C_6H_4$	6.45 (d, 8)	5.56 (d)	3.90 (d, 12)	3.60 (d)	7.0-8.1 (m, 13H)
5f	4-$CH_3OC_6H_4$	6.36 (d, 7)	5.54 (d)	3.71 (d, 12)	3.42 (d)	7.6 (bs, 5H), 7.2 (bs, 4H), 6.7 (s, 4H), 3.7 (s, 3H)

Footnotes [a] All spectra were recorded in a Perkin Elmer R-24B (60 MHz) spectrometer. Deuteriochloroform was used as the solvent and TMS as the internal standard. Chemical shifts in ppm and coupling constants in Hz.

Table VII

^{1}H NMR of Compounds **6** [a]



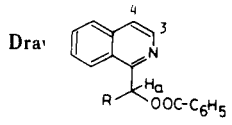
Compound		-CH_2- (coupl)	H Phenyl	H Isoquinoline	Others
6a [b]	C_6H_5	4.6 (s)	7.45 (bs, 5H)	8.0-8.45 (m, 5H) 8.6-8.7 (d, 1H, J = 6)	
6b	2-ClC_6H_4	5.2 (s)	7.0-7.6 (m, 4H)	7.8-8.7 (m, 6H)	
6c	4-ClC_6H_4	5.2 (s)	7.36 (d, 2H, J = 7) 7.65 (d, 2H)	7.9-8.82 (m, 6H)	
6e	4-$CH_3C_6H_4$	5.1 (s)	7.13 (d, 2H, J = 8) 7.40 (d, 2H)	7.8-8.8 (m, 6H)	2.25 (s, 3H)
6f	4-$CH_3OC_6H_4$	5.2 (s)	6.85 (d, 2H, J = 7) 7.45 (d, 2H)	7.8-8.2 (m, 6H)	3.68 (s, 3H)
6g	3,4-$CH_2O_2C_6H_3$	5.0 (s)	6.82 (d, 1H, J = 9) 7.02 (d, 1H) 7.20 (s, 1H)	7.9-8.9 (m, 6H)	5.8 (s, 2H)

Footnotes [a] All spectra were recorded in a Perkin Elmer R-24B (60 MHz) spectrometer. Except when stated, DMSO was used as the solvent and TMS as internal standard. Chemical shifts in ppm and coupling constants in Hz. [b] TFA was used as the solvent.

As a conclusion, association of phase transfer catalysis with ultrasound can be of interest either in the synthesis of Reissert derivatives as well as in substitution of Reissert anions. In the synthesis, although there is no general improvement effects on yield, reaction time is appreciably reduced. In reactions of Reissert anions, at least with isoquinoline derivatives, there are significant improvements in yield, reaction time and there is a considerable simplification of work-up, specially when using the one step procedure. It is unclear how advantageous would be the technique with other systems.

Table VIII

^{1}H NMR of Compounds **7** [a]

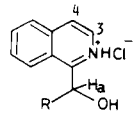


Compound	R	Ha (coupl)	H Phenyl	H Isoquinoline [b]	Others
7a	C_6H_5	7.9 (s)	7.2-7.8 (m, 12H)	8.1-8.5 (m, 3H), 8.6 (d, 1H, J = 6)	
7b	3-ClC_6H_4	7.85 (s)	7.3-7.8 (m, 11H)	8.0-8.5 (m, 3H), 8.6 (d, 1H, J = 6)	
7c	4-ClC_6H_4	7.9 (s)	7.25-7.8 (m, 11H)	8.0-8.5 (m, 3H), 8.6 (d, 1H, J = 6)	
7d	4-$CH_3C_6H_4$	7.9 (s)	7.1-7.5 (m, 11H)	8.15-8.5 (m, 3H), 8.1 (d, 1H, J = 6)	2.3 (s, 3H)
7e	3-$CH_3OC_6H_4$	7.9 (s)	7.3-7.75 (m, 9H), 6.9 (d, 2H, J = 9)	8.2-8.5 (m, 3H), 8.15 (d, 1H, J = 6)	3.7 (s, 3H)
7f	3,4-$CH_2O_2C_6H_3$	7.8 (s)	7.0-7.8 (m, 8H), 6.75 (d, 2H, J = 8)	8.1-8.4 (m, 3H), 8.55 (d, 1H, J = 6)	5.85 (s, 2H)
7g	2-Thienyl [c]	7.7 (s)	6.9-7.9 (m, 9H)	8.1-8.6 (m, 4H), 8.7 (d, 1H, J = 6)	
7h	2-Furyl [d]	8.0 (s)	7.35-8.1 (m, 9H)	8.1-8.6 (m, 3H), 8.75 (d, 1H, J = 6)	6.5 (dd, 1H)

Footnotes [a] All spectra were recorded in a Perkin Elmer R-24B (60 MHz) spectrometer. Deuteriochloroform was used as the solvent and TMS as the internal standard. Chemical shifts in ppm and coupling constants in Hz. [b] Two protons from the isoquinoline system appear overlapped with the phenyl area. [c] Three protons from the thiophene ring appear overlapped with the phenyl and isoquinoline areas. [d] Two protons from the furan ring appear overlapped with the phenyl area.

Table IX

^{1}H NMR of Compounds **8** [a]

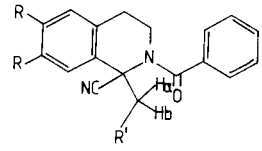


Compound	R	Ha (coupl)	H Phenyl	H Isoquinoline	Others
8a	C_6H_5	7.1 (s)	7.3-7.8 (m, 5H)	7.9-8.4 (m, 4H), 8.55 (dd, 1H, J = 7), 8.77 (d, 1H)	
8b	3-ClC_6H_4	7.1 (s)	7.45 (bs, 3H), 7.75 (bs, 1H)	7.9-8.4 (m, 4H), 8.52 (d, 1H, J = 7), 8.75 (d, 1H)	
8c	4-ClC_6H_4	7.1 (s)	7.7 (d, 2H, J = 9), 7.4 (d, 2H)	7.9-8.5 (m, 4H), 8.54 (d, 1H, J = 6), 8.77 (d, 1H)	
8d	4-$CH_3C_6H_4$	7.1 (s)	7.22 (d, 2H, J = 9), 7.52 (d, 2H)	7.8-8.4 (m, 4H), 8.55 (d, 1H, J = 6), 8.75 (d, 1H)	2.22 (s, 3H)
8e	4-CH_3OC_6H4	7.1 (s)	6.92 (d, 2H, J = 9), 7.56 (d, 2H)	7.8-8.4 (m, 4H), 8.55 (d, 1H, J = 7), 8.75 (d, 1H)	3.7 (s, 3H)
8f	3,4-$CH_2O_2C_6H_3$	7.0 (s) [b]	6.87 (d, 1H, J = 9), 7.12 (d, 1H), 7.2 (s, 1H)	7.8-8.9 (m, 4H), 8.56 (d, 1H, J = 6), 8.78 (d, 1H)	6.0 (s, 2H)
8g	2-Thienyl	7.43 (s)		8.0-8.9 (m, 4H), 8.55 (d, 1H, J = 6) b, 8.74 (d, 1H) b	7.0 (dd, 1H), 7.55 (d, 1H, J = 4), 7.85 (d, 1H, J = 3)
8h	2-Furyl	7.25 (s)		7.8-8.4 (m, 4H), 8.5 (d, 1H, J = 6), 8.65 (d, 1H)	6.55 (m, 1H), 6.75 (d, 1H, J = 4), 7.65 (d, 1H, J= 2)

Footnotes [a] ALl spectra were recorded in a Perkin Elmer R-24B (60 MHz). DMSO was used as the solvent and TMS as the internal standard. Chemical shfits in ppm and coupling constants in Hz. [b] Overlapped signal.

Table X

^{1}H NMR of Compounds **2**, **3** [a]

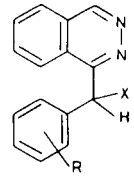


Compound	R	R'	-CH_2CH_2N=	Ha (coupl $J_{a,b}$)	Hb (coupl)	Others
2a	H	H	1.7-2.5 (m, 4H)	4.5 (d, 12)	3.3 (d)	6.5 (bd, 2H, J = 9), 7.05 (m, 2H), 7.2-7.8 (m, 5H), 7.3 (s, 5H)
2b	H	4-Cl	1.9-2.7 (m, 2H) 3.0-3.7 (m, 2H)	4.5 (d, 2H)	3.3 (d)	7.2-7.8 (m, 4H), 7.45 (s, 5H), 6.4 (d, 2H, J = 9), 7.0 (d, 2H)
3a	CH_3O	H	1.8-2.4 (m, 2H) 2.7-3.7 (m, 2H)	4.4 (d, 12)	3.5 (d)	6.4-6.7 (m, 2H), 6.75 (s, 1H), 6.65 (s, 1H), 3.9 (s, 6H)

Footnotes [a] All spectra were recorded in a Perkin Elmer R-24B (60 MHz) spectrometer. Deuteriochloroform was used as the solvent and TMS as the internal standard. Chemical shifts in ppm and coupling constants in Hz.

Table XI

^{1}H NMR of Compounds **4** [a]



Compound	R	X	Phthalazine H		Others
4a	2-Cl	H	10.4 (s, 1H), 8.8-8.2 (m, 4H)	7.7-7.1 (m, 4H)	5.05 (s, 2H)
4b	H	OH	9.7 (s, 1H), 8.7-7.8 (m, 4H)	7.7-7.2 (m, 6H)	6.6 (s, 1H)
4c	4-CH_3O	OH	9.7 (s, 1H), 8.7-7.8 (m, 4H)	7.5 (d, 2H, J = 6) 6.95 (d, 2H, J = 6)	6.9 (s, 1H) 3.8 (s, 3H)

Footnotes [a] All spectra were recorded in a Perkin Elmer R-24B (60 MHz) spectrometer. DMSO was used as the solvent and TMS as the internal standard. Chemical shifts in ppm and coupling constants in Hz.

EXPERIMENTAL

Melting points were determined in open capillary tubes and are uncorrected. Spectra were recorded with a Perkin-Elmer 577 grating ir spectrophotometer. The benzyl halides and aldehydes were used as obtained from commercial sources when purity was 97% as indicated by ^{1}H nmr. Lower purity reagents were distilled or recrystallized to 97% purity. Some halides were prepared from the appropriate alcohols by action of thionyl chloride and pyridine in dry toluene, according to the procedure of Grice and Owen [31].

The sonicator was a Branson 220 Ultrasound Laboratory Cleaner (150W, 50/60 Hz). Reaction time was checked by ^{1}H nmr.

Elemental analysis of all new compounds are presented in Table V. The ^{1}H nmr data are given in Tables VI to X.

Synthesis of Reissert Derivatives **1-4**.

A mixture of the corresponding heterocycle (50 mmoles), 9.8 g of potassium cyanide (150 mmoles) and 0.3 g of triethylbenzylammonium chloride was suspended in 200 ml of water in a flask equipped with a mechanical stirrer, reflux condenser, addition funnel and immersed into the sonicating bath. Stirring and sonication started, and 400 ml of dichloromethane were added. The bath was refrigerated to prevent the temperature from rising above 20°, and when the mixture was homogeneous, 12 ml of benzoyl chloride (100 mmoles) was added within 20 minutes. Then, the mixture was stirred and sonicated for an additional 20 minutes to complete the process. The mixture was then filtered and the solid residue was washed with 20 ml of water and 20 ml of dichloromethane.

The organic layers were separated and washed with 30 ml of water, 3 × 2 ml of 2*N* sodium hydroxide solution, 30 ml of 2*N* hydrochloric acid and finally again with 20 ml of water. The organic extract was dried and concentrated, yielding the Reissert derivative which was crystallized from ethanol (Table I).

Reaction of **1** with Alkyl Halides. Step by Step procedure.

Synthesis of **5**. Method A.

A mixture of Reissert compound (5.7 mmoles) and triethylbenzylammonium chloride (13 mg) was suspended in 2.5 ml of aqueous 50% sodium hydroxide solution. The mixture was mechanically stirred and sonicated at room temperature for 20-25 minutes [29] and filtered. The solid was washed with water and crystallized from methanol.

Synthesis of **5**. Method B.

A mixture of the Reissert Compound (5.7 mmoles), the halide (86 mmoles), cetyltrimethylammonium bromide (33 mg) and aqueous 50% sodium hydroxide solution (3.3 ml) was mechanically stirred and sonicated for 20-25 minutes at room temperature [29]. After acidification to *p*H 6 (5% sulfuric acid) the product was extracted with toluene, the dried solution was concentrated, and the residue crystallized from methanol.

Hydrolysis of **5**.

The alkylated Reissert compound **5** (3.9 mmoles) was suspended in a mixture of 4 ml of dichloromethane, 5 ml of ethanol and 1.5 ml of aqueous 50% sodium hydroxide solution. The mixture was mechanically stirred and sonicated for 40 minutes. The product was poured into 20 ml of water. The suspension was extracted with 3 × 10 ml portions of dichloromethane, and the combined organic fractions were dried and concentrated to *ca.* 10 ml. This solution was saturated with dry hydrochloric acid and the product was precipitated by addition of dry ether.

Reaction of **1** with Alkyl Halides. One Step Procedure.

A mixture of Reissert compound (4.6 mmoles), the halide (6.6 mmoles) and triethylbenzylammonium chloride (10 mg) was suspended in dichloromethane (2.4 ml) and aqueous 50% sodium hydroxide solution (1.8 ml). The mixture was mechanically stirred and sonicated at room temperature for 20 minutes. Then, 6 ml of ethanol was added and the mixture was sonicated for an additional 30 minutes. The product was poured into 20 ml of water. The suspension was extracted with 3 × 10 ml portions of dichloromethane, and the combined fractions were dried and concentrated to *ca.* 10 ml. This solution was saturated with dry hydrochloric acid and the product precipitated by addition of dry ether.

Reaction of **1** with Aldehydes. Step by Step Procedure.

Synthesis of **7**.

A mixture of the Reissert compound (5.7 mmoles), the aldehyde (7.1 mmoles) and triethylbenzylammonium chloride (13 mg) was suspended in 2.3 ml of aqueous 50% sodium hydroxide and 3 ml of acetonitrile. The mixture was mechanically stirred and sonicated at room temperature, for 5 minutes. The suspension was filtered, the solid washed with 5 ml of water and crystallized from ethanol.

Hydrolysis of **7**.

To a suspension of 4 mmoles of **7** in 15 ml of dichloromethane and 4 ml of 3*N* potassium hydroxide solution was added 8 ml of ethanol, and the mixture was sonicated for 1 hour. After the addition of 10 ml of water, the organic layer was removed and the aqeous layer was extracted with 2 × 5 ml portions of dichloromethane. The combined organic extracts were dried and concentrated to *ca.* 10 ml, saturated with anhydrous hydrochloric acid and diluted with ether to precipitate the product which was filtered and crystallized from ethanol/ether.

Reaction of **1** with Aldehydes. One Step Procedure.

A mixture of the Reissert compound (5.7 mmoles), the corresponding aldehyde (7.1 mmoles) and triethylbenzylammonium chloride (13 mg) was suspended in dichloromethane (3 ml) and aqueous 50% sodium hydroxide solution (2.5 ml). The mixture was mechanically stirred and sonicated at room temperature for 5 minutes. Then, 8 ml of ethanol and 15 ml of dichloromethane was added, and the mixture was again sonicated for 85 minutes. Finally, the mixture was poured into 20 ml of water, the organic layer was separated and the aqueous phase was extracted with 3 × 10 portions of dichloromethane. The combined extracts were dried and concentrated to *ca.* 10 ml, saturated with anhydrous hydrochloric acid and the product was precipitated by addition of dry ether. All compounds were recrystallized from ethanol/ether.

Reaction of Compounds **2** and **3** with Alkyl Halides.

A mixture of the Reissert compound (2 mmoles), the halide (2.8 mmoles) and triethylbenzylammonium chloride (10 mg) was suspended in dichloromethane (1 ml) and aqueous 50% sodium hydroxide solution (0.8 ml). The mixture was mechanically stirred and sonicated for 20 minutes as described above. The suspension was filtered, the solid washed with water and recrystallized (Table IV).

Synthesis of 1-(*o*-Chlorobenzyl)phthalazine **4a**.

A mixture of 0.5 g of Reissert compound **4** (1.9 mmoles), *o*-chlorobenzyl chloride (0.29 ml, 2.3 mmoles) and triethylbenzylammonium chloride (10 mg) was suspended in dichloromethane (1 ml) and aqueous 50% sodium hydroxide solution (0.8 ml). The mixture was mechanically stirred and sonicated for 20 minutes at room temperature, 2.5 ml of ethanol was added and the mixture was sonicated for an additional 30 minutes. The crude product was poured into 10 ml of water. The suspension was extracted with 3 × 5 ml portions of dichloromethane, and the combined organic extracts were dried and concentrated to *ca.* 5 ml, saturated with anhydrous hydrochloric acid and the product was precipitated by addition of dry ether and recrystallized from methanol/ether yielding 0.37 g, (67%) of **4a** with a mp of 195-197°.

Synthesis of Phthalazinecarbinols **4b** and **4c**.

A mixture of the 0.5 g of Reissert compound **4** (1.9 mmoles), 0.23 ml of benzaldehyde (2.3 mmoles) and triethylbenzyl ammonium chloride (10 mg) was suspended in 1 ml of dichloromethane and 0.8 ml of aqueous 50% sodium hydroxide solution. The mixture was stirred and sonicated for 90 minutes at room temperature with addition, after the first five minutes of 3 ml of ethanol and 5 ml of dichloromethane. The reaction mixture was poured into 10 ml of water, and the suspension was extracted with 3 × 5 ml portions of dichloromethane, the organic fractions were combined, dried, concentrated and the residue crystallized, yielding 0.44 g of **4b** (98%); mp 175-175° (ethanol) lit [28] mp 172-175° (ethanol).

The same procedure, using 0.27 ml of anisaldehyde (2.3 mmoles) produced, after crystallization, 0.46 g of **4c** (90%), mp 172-174°.

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