The Chemistry of *N*-Substituted Benzotriazoles; Part 11.[1] The Preparation of Tertiary Amines Containing Tertiary-Alkyl Groups from Ketones, Secondary Amines, and Organometallic Reagents

Alan R. Katritzky,* Zbigniew Najzarek,[2] Zofia Dega-Szafran[3]

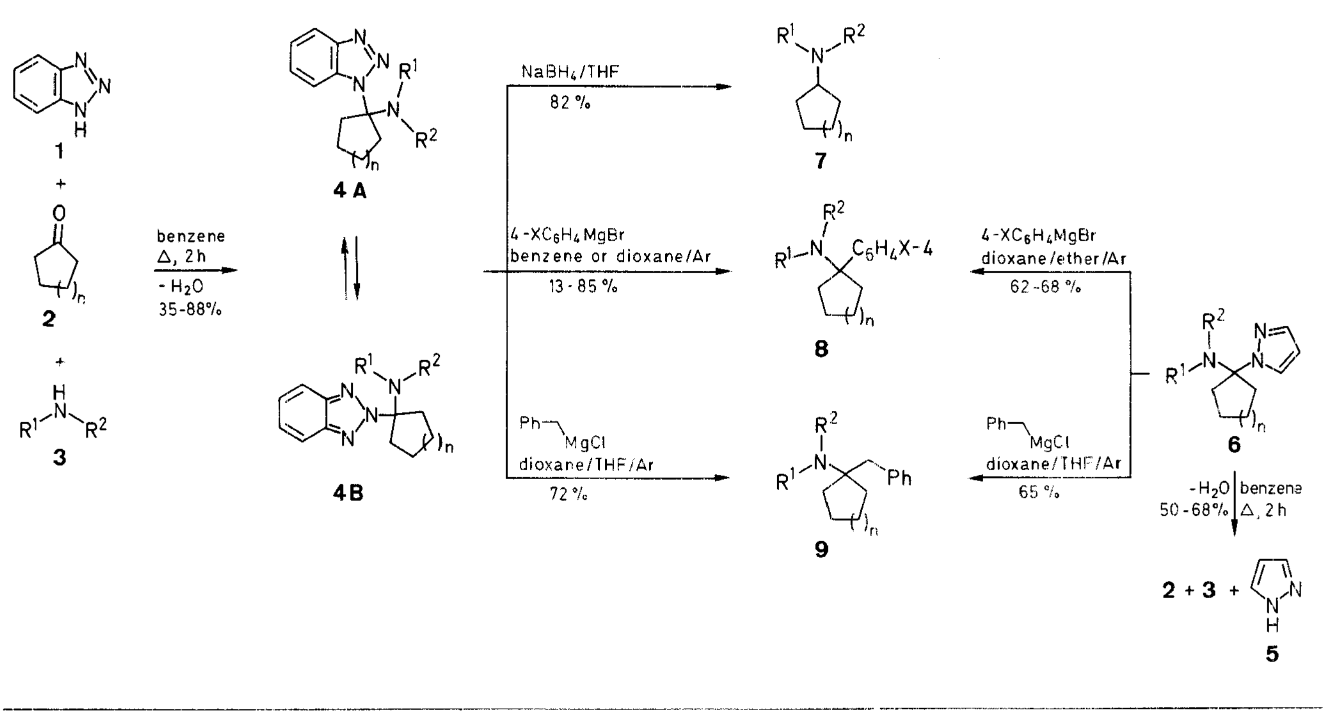
Department of Chemistry, University of Florida, Gainesville, FL 32611, USA

The preparation of important pharmaceutically active highly branched tertiary amines by the reaction of Grignard reagents with adducts of cyclic ketones, benzotriazole (or pyrazole) and secondary amines is far superior to previously available routes.

In continuation of our studies on the synthetic uses of *N*-substituted benzotriazoles, we report here some transformations of the reaction products of benzotriazole, and of pyrazole with cyclic ketones and heterocyclic amines. We have previously shown that benzotriazole reacts with a variety of aldehydes plus a primary or secondary amine, to form the mono- and bis-*N*-[1-(1-benzotriazolyl)alkyl] derivatives of the amines.[4,5] However, the carbonyl groups of ketones were generally much less studied in these condensations with benzotriazole and primary amines in contrast to aldehydes.[6]

Now we report that an azole [benzotriazole (**1**) or pyrazole (**5**)], a cyclic ketone **2**, [cyclopentanone (**2a**), cyclohexanone (**2b**), or cycloheptanone (**2c**)], and an amine **3** [pyrrolidine (**3a**), piperidine (**3b**), morpholine (**3c**), or benzylamine (**3d**)] do react under suitable conditions to produce the corresponding 1-amino-1-(1-benzotriazolyl)cycloalkanes **4** or 1-amino-1-(1-pyrazolyl)cycloalkanes **6**, frequently in good yields (Scheme A).

Adducts **4a–e** were obtained from cyclopentanone and cyclohexanone in 50–88% yield, but adduct **4f** was isolated from cycloheptanone in lower yield (35%); cyclooctanone and morpholine gave the enamine as the major product. The adducts **6** from pyrazole were obtained in slightly lower yields (50–68%) (Table 1). All these adducts were very sensitive to water, and they decompose to the keto-enamine and benzotriazole particularly readily in acidic or in alkaline media. Hence, their purification is difficult, and completely good analyses could not always be obtained. However they were stable in the crystalline state at 10 °C for several weeks.



2	n	3	R¹	R²	4, 6	n	R¹	R²
a	1	a	$-(CH_2)_4-$		a	2	$-CH_2CH_2OCH_2CH_2-$	
b	2	b	$-(CH_2)_5-$		b	1	$-CH_2CH_2OCH_2CH_2-$	
c	3	c	$-CH_2CH_2OCH_2CH_2-$		c	2	$-(CH_2)_4-$	
		d	H	CH_2Ph	d	2	$-(CH_2)_5-$	
					e	2	H	CH_2Ph
					f	3	$-CH_2CH_2OCH_2CH_2-$	

7, 9	n	R¹	R²	8	n	R¹	R²	X
a	2	$-CH_2CH_2OCH_2CH_2-$		a	2	$-(CH_2)_4-$		H
b	1	$-CH_2CH_2OCH_2CH_2-$		b	2	$-(CH_2)_5-$		H
c	2	$-(CH_2)_4-$		c	2	$-CH_2CH_2OCH_2CH_2-$		H
d	2	$-(CH_2)_5-$		d	2	$-CH_2CH_2OCH_2CH_2-$		CH_3
e	2	H	CH_2Ph	e	2	$-CH_2CH_2OCH_2CH_2-$		Cl
f	3	$-CH_2CH_2OCH_2CH_2-$		f	3	$-CH_2CH_2OCH_2CH_2-$		H

Scheme A

The ^1H-NMR spectra of the 1-amino-1-(benzotriazolyl) cycloalkanes **4** show two multiplets in the aromatic region (Table 1). These signals remain relatively unchanged as the ketone and amine were varied. The benzotriazole proton chemical shifts of the adducts differ slightly from those of unsubstituted benzotriazole (**1**).[7] The spectra in the aliphatic region are more complicated: the four protons attached to the carbons α to the nitrogen atom are observed at the lowest field, the others are overlapped by the cycloalkane ring proton signals. Some broadening of signals is observed, indicative of the exchange process postulated below.

The ^{13}C-NMR spectra (Table 2) of the Mannich bases **4** each show just three aromatic carbon signals for the benzotriazole ring.[8] The quaternary carbons, approximately in the $\delta = 85$ region, are in some cases difficult to observe. Signals for the morpholine, pyrrolidine, piperidine, and cycloalkyl rings are in the expected regions.

The three signal pattern in the aromatic ^{13}C-region for these benzotriazoles suggest either (i) that they exist solely in the 1-benzotriazolyl form **4A**, or (ii) that the tautomeric equilibria **4A** ⇄ **4B** are rapid on the NMR time scale. To settle this ambiguity, the ^{13}C-NMR spectrum of the morpholine adduct **8c** was measured at low temperature (−30 °C). In the aromatic region six additional new signals then appeared at $\delta = 113.6$, 115.5, 120.3, 124.0, 126.0, and 128.0. This shows that the equilibrium between the 1- and 2-substituted benzotriazoles **4** is fast on the NMR time scale at room temperature, and also that this equilibrium favors the 2-substituted product **4B**, as could be expected on steric grounds.

The mass spectra of adducts **4a**, **4c**, **4d**, **4e**, and **6a** show that the initial fragmentation from the molecular ion is loss of the benzotriazole or pyrazole moieties ($M^+ - 119$), ($M^+ - 68$), respectively. The molecular ion (M^+) was not observed.

These new 1:1:1 Mannich type adducts **4** and **6** showed the expected reactivity towards nucleophiles. Thus, reactions of **4** and **6** with sodium borohydride or with Grignard reagents gave cycloalkylamines **7** and (1-substituted cycloalkyl)amines **8** and **9**, respectively, in good yields (Scheme B) (Table 3). The reaction of the benzotriazole and pyrazole adducts **4** and **6**, respectively, with Grignard reagents provides an easy route to physiologically active compounds of types **8** and **9**, respectively. However, when the adducts **4b** and **4e** are treated with Grignard reagents, enamines are obtained as the major products. 1-(1-Phenylcyclohexyl)piperidine (**8b**) is the well known used and abused drug, phencyclidine (PCP).[9] A series of structural analogues have displayed similar biological activity.[10-12]

Table 1. Compounds **4a–f** and **6a**, **b** Prepared

Product	Yield (%)	mp (°C)[a]	Appearance	Molecular Formula[b]	^1H-NMR ($CDCl_3$/TMS) δ, J(Hz)
4a	85	132–134	prisms	$C_{16}H_{22}N_4O$ (286.4)	1.43–1.85 (m, 6H); 2.57 (m, 8H); 3.65 (t, 4H); 7.35 (m, 2H_{arom}); 7.89 (q, 2H_{arom})
4b	66	115–117	plates	$C_{15}H_{20}N_4O$ (272.3)	1.73 (br s, 4H); 2.63 (t, 4H); 2.78 (br s, 4H); 3.68 (t, 4H); 7.40 (q, 2H_{arom})
4c	88	71–74	microcrystals	$C_{16}H_{22}N_4$ (270.4)	1.59 (br s, 10H); 2.58 (br s, 4H); 2.85 (s, 4H); 7.34 (m, 2H_{arom}); 7.90 (m, 2H_{arom})
4d	50	108–112	microcrystals	$C_{17}H_{24}N_4$ (284.4)	1.25–1.77 (m, 12H); 2.48 (t, 4H); 2.57 (t, 4H); 7.34 (m, 2H_{arom}); 7.91 (m, 2H_{arom})
4e	85	73–75	needles	$C_{19}H_{22}N_4$ (306.4)	1.47–1.59 (br m, 6H); 2.47 (t, 4H, $J = 000$); 3.81 (br s, CH_2); 7.24 (s, 5H_{arom}); 7.35 (m, 2H_{arom}); 7.85 (m, 2H_{arom})
4f	35	41–43	needles	$C_{17}H_{24}N_4O$ (300.4)	1.43–1.66 (m, 8H); 2.58–2.64 (m, 8H); 3.65 (t, 4H); 7.41 (q, 2H_{arom}); 7.91 (q, 2H_{arom})
6a	68	77–75	prisms	$C_{13}H_{21}N_3O$ (235.3)	1.45 (m, 4H); 1.70 (m, 2H); 2.22 (m, 4H); 2.40 (t, 4H); 3.60 (t, 4H); 6.25 (m, 1H_{arom}); 7.50 (m, 2H_{arom})
6b	50	47–53	plates	$C_{12}H_{19}N_3O$ (221.3)	1.82 (m, 4H); 2.51 (t, 4H); 2.82 (m, 4H); 3.60 (m, 4H); 6.26 (m, 1H_{arom}); 7.55 (m, 2H_{arom})

[a] All products are recrystallized from petroleum ether. Compound **4a** can also be recrystallized from cyclohexane and **4d** from benzene/THF (2:1).

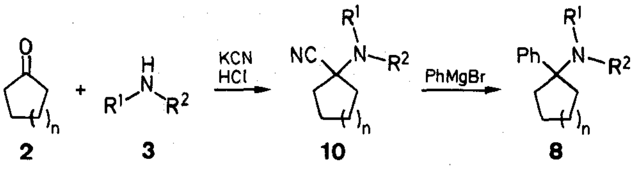
[b] Satisfactory microanalyses obtained: C ±0.27, H ±0.27, N ±0.27.

Table 2. ^{13}C-NMR Chemical Shifts (δ) of Compounds **4a–d** and **6a**, **b** ($CDCl_3$/TMS)

Product	Aromatic ring			Amine ring			Cycloalkyl ring			
	C-3a, 7a	C-5,6	C-4,7	C_α	C_β	C_γ	C-1′	C-2′	C-3′	C-4′
4a	142.9	125.9	118.1	67.3	45.4	–	84.9	33.5	22.5	25.0
4b	140.7	125.7	116.7	67.6	48.2	–	98.2	36.0	22.3	–
4c	142.1	125.0	117.0	45.3	25.0	–	–	35.5	22.5	24.0
4d	142.2	124.9	117.0	45.5	24.8	26.7	86.2	34.2	22.5	23.7
4e	139.6	125.5	116.6	48.6	(CH_2)	–	46.1	35.5	25.2	24.1
	128.3	126.8	127.9							
4f	140.5	125.5	11.3	67.3	46.3	–	49.8	35.7	26.6	22.3
6a	126.9[a]	104.2[b]	–	67.4	45.2	–	78.2	33.3	22.1	–
6b	137.5[a]	127.2[b]	–	66.6	45.5	–	89.3	35.4	21.5	–

[a] C-3/5.

[b] C-4.



Scheme B

The (1-substituted cycloalkyl)amines prepared have the expected spectral features. The ^{1}H-NMR spectra (Table 3) show cycloalkyl and aromatic protons in the usual regions.[14] The ^{13}C-NMR spectra possess the correct number of carbon resonances (Table 4), and are in general agreement with previously reported data for similar compounds.[16-19]

Cycloalkylamines **7** have been previously satisfactorily obtained by the reduction of enamines using, e.g. formic acid or $Na_2[ZnCl_2(BH_3CN)_2]$ with yields of 73–85%.[20-22]

Previous routes to (1-substituted cycloalkyl)amines **8** and **9** are less satisfactory.[11] Ketones reacted with amines to give enamines (80–90% yields for cyclic ketone),[23] which were treated with potassium cyanide (or alternatively either acetone cyanohydrin or diethyl phosphorocyanidate) to give 1-amino-1-cyanocycloalkanes **10** (48–92%).[11,24,25] In the third step, 1-amino-1-cyanocycloalkanes **10** were reacted with Grignard reagents to afford the desired products **8** (22–63%).[10] The overall yield in this 3-step method (Scheme **B**) usually does not exceed 35%. In solution the carbonitrile intermediates **10** degraded rapidly with loss of hydrogen cyanide.[26,27] Moreover, Wall and Clark[28] showed by liquid chromatography that PCP-type compounds prepared in this way are often contaminated by toxic unreacted nitrile. Other methods afford low (or unstated) yields; thus Bailey et al.[14] obtained analogues of phencyclidine from the corresponding cyclohexanone enamines via the *p*-toluenesulfonic acid salts and the appropriate aryl Grignard reagent: no yields were quoted.

Table 3. 1-Substituted cycloalkylamines Prepared

Product	Starting Materials		Yield (%)	mp (°C)[a]	Appearance	Molecular Formula[b] or Lit. mp (°C)	^{1}H-NMR (CDCl$_3$/TMS) δ, J(Hz)
	Adduct	Reagent					
7a	**4a**	$NaBH_4$	82	256–258[c]	microcrystals	257–258[c,13]	0.75–2.18 (br m, 11H); 2.55 (m, 4H); 3.78 (m, 4H)[d]
8a	**4c**	PhMgBr	13	221–223[c]	microcrystals	221–222[c,14]	1.20–1.93 (m, 14H); 2.41 (q, 4H); 7.34 (m, 5H$_{arom}$)
8b	**4d**	PhMgBr	73	44–45	plates	44–45[11]	1.24–1.56 (m, 10H); 1.69 (m, 2H); 1.98–2.09 (m, 4H); 2.25 (t, 4H); 7.28 (m, 5H$_{arom}$)
8c	**4a**	PhMgBr	74	63–64	needles	–	1.22–2.15 (m, 10H); 2.37 (t, 4H); 3.63 (t, 4H); 7.31 (m, 5H$_{arom}$)
				181–182[c]	microcrystals	188–189[c,14]	–
	6a	PhMgBr	62	63–64	needles		
8d	**4a**	$4\text{-}CH_3C_6H_4MgBr$	85	54–56	needles	$C_{17}H_{25}NO$ (259.4)	1.28–2.13 (m, 10H); 2.29–2.33 (m, 7H); 3.62 (t, 4H); 7.16 (m, 4H$_{arom}$)
	6a	$4\text{-}CH_3C_6H_4MgBr$	71	53–56	needles		
8e	**4a**	$4\text{-}ClC_6H_4MgBr$	86	65–67	microcrystals	$C_{16}H_{22}ClNO$ (279.8)	1.21–2.11 (m, 10H); 2.29 (t, 4H); 3.61 (t, 4H); 7.29 (d, 2H$_{arom}$); 7.32 (d, 2H$_{arom}$)
	6a	$4\text{-}ClC_6H_4MgBr$	68	63–67	microcrystals		
8f	**4f**	PhMgBr	13	42–44	needles	$C_{17}H_{25}NO$ (259.4)	1.37–1.76 (m, 8H); 2.03 (m, 4H); 2.42 (t, 4H); 3.57 (t, 4H); 7.35 (m, 5H$_{arom}$)
9a	**4a**	$PhCH_2MgCl$	72	77–78	plates	77[15]	0.78–1.80 (m, 10H); 2.46–2.68 (m, 6H); 3.70 (t, 4H); 7.72 (s, 5H$_{arom}$)
	6a	$PhCH_2MgCl$	65				

[a] Solvents used for recrystallization: Petroleum ether for **8b–8f**, **9a**; EtOH/ether (1:1) for **7a** · HCl, **8a** · HCl; *i*-PrOH for **8c** · HCl.

[b] Satisfactory microanalyses obtained: C ±0.20, H ±0.07, N ±0.25.

[c] Melting point of hydrochloride salt.

[d] Recorded as hydrochloride salt in DMSO-d_6/TMS.

Table 4. ^{13}C-NMR Chemical Shifts (δ) of 1-Substituted cycloalkylamines (CDCl$_3$/TMS)

Product	Aromatic ring				Amine ring			Cycloalkyl ring			
	C-1″	C-2″	C-3″	C-4″	C_α	C_β	C_γ	C-1′	C-2′	C-3′	C-4′
7a[a]	–	–	–	–	48.1	63.5	–	64.5	25.9	24.5	24.8
8a	138.1	127.9	128.2	126.0	44.6	22.8	–	60.0	34.8	22.5	26.3
8b	139.8	127.3	127.3	125.9	46.4	27.0	24.9	61.0	33.5	22.4	26.3
8c	139.2	127.6	128.3	126.3	45.8	67.8	–	60.6	32.8	22.2	26.3
8d[b]	136.8	127.9	128.9	136.3	46.5	68.4	–	61.1	33.5	22.9	26.9
8e	138.1	128.7	127.7	132.1	45.7	67.7	–	60.4	32.7	22.1	26.1
8f	147.4	127.3	127.6	125.9	46.9	68.0	–	66.5	34.4	30.4	24.2
9a	139.2	127.7	130.7	125.6	68.1	44.5	–	58.0	31.9	20.6	25.8
								39.4	(CH_2)		

[a] Recorded as hydrochloride salt in DMSO-d_6/TMS.

[b] Signal for CH_3 appears at δ = 21.5.

All melting points are uncorrected and were taken in open glass capillary tubes with a Thomas-Hoover melting point apparatus. ^{1}H-NMR spectra were obtained at 200 MHz on a Varian XL-200 NMR spectrometer with TMS as internal standard. ^{13}C-NMR spectra were obtained at 50 MHz on a Varian XL-200 spectrometer, referenced to solvent $CDCl_3$ ($\delta = 77.0$). Mass spectra were obtained on an AEI-Ms 30 mass spectrometer. Microanalyses were performed on a Carlo Erba 1106 elemental analyzer.

Commercially available amines and ketones were purified. Solvents were dried by standard methods.

1-Amino-1-(1-benzotriazolyl)cycloalkanes 4 and 1-Amino-1-(1-pyrazolyl)cycloalkanes 6; General Procedure:
Benzotriazole (**1**; 5.96 g, 0.05 mol) or pyrazole (**5**; 3.4 g, 0.05 mol), the cyclic ketone **2** (0.05 mol), and the amine **3** (0.05 mol) are heated under reflux in dry benzene (10 mL) for 2 h, with azeotropic removal of water using a Dean-Stark apparatus. The solvent is then evaporated under reduced pressure. The residue solidifies and is used in the reaction with Grignard reagents or $NaBH_4$ without further purification. Analytical samples of Mannich adducts **4** and **6** are prepared by recrystallization of the crude products from the solvents given in Table 1.

Reaction of Adducts with $NaBH_4$: *N*-Cyclohexylmorpholine Hydrochloride (7a); Typical Procedure:
1-(1-Benzotriazolyl)-1-(4-morpholino)cyclohexane (**4a**; 1.43 g, 5 mmol) and $NaBH_4$ (0.30 g, 5 mmol) and dry THF (20 mL) are heated under reflux with stirring for 3 h. The reaction is monitored by TLC on silica gel (acetone/EtOAc, 1:1; R_f 0.42). The solvent is evaporated under reduced pressure, and the residue is poured into ice-water (75 mL) and extracted with benzene (100 mL). The organic layer is washed with water (2 × 30 mL) and dried ($MgSO_4$). The solvent is evaporated (to 20 mL), and the solution is then saturated with dry HCl to give **7a**; yield: 0.84 g (82 %) (Table 3).

Reaction of Adducts 4 and 6 with Grignard Reagents; General Procedure:
To an aryl- or aralkylmagnesium halide (0.02 mol) in ether or THF (10 mL), is added the adduct **4** (0.015 mol) in dry benzene (40 mL) or in a mixture of dry benzene (8 mL) and dioxane (12 mL). The mixture is stirred at 20 °C for 2–6 h under argon [the reaction is monitored by TLC on silica gel (acetone/EtOAc, 1:1], then 10 % aq. HCl is added till pH = 1, and the mixture is evaporated to dryness at 50 °C. The residue is dissolved in water (10 mL), and 10 % NaOH solution is added till pH = 10, and the solution is extracted with benzene (3 × 20 mL). The organic layer is collected, and dried ($MgSO_4$). The solvent is evaporated to give the *(1-phenylcycloalkyl)amines* **8** or the *(1-benzylcycloalkyl)amines* **9**, which are recrystallized from the solvents given in Table 3.

Hydrochloride salts are obtained by precipitation from the ethereal solution with HCl gas.

We thank IREX-Foundation for a fellowship to Z. N.

Received: 9 May 1988; revised: 15 August 1988

(1) For part 10, see: Katritzky, A.R., Yannakopoulou, K., Lue, P., Rasala, D., and Urogdi, L. *J. Chem. Soc. Perkin Trans. 1*, submitted.
(2) On leave from Technical University, Opole, Poland.
(3) On leave from Department of Chemistry, A. Mickiewicz University, Poznam, Poland.
(4) Katritzky, A.R., Rachwal, S., Rachwal, B. *J. Chem. Soc. Perkin Trans. 1* **1987**, 805.
(5) Katritzky, A.R., Yannakopoulou, K. *J. Chem. Soc. Perkin Trans. 1*, submitted.
(6) Katritzky, A.R., Rachwal, S., Rachwal, B. *J. Chem. Soc. Perkin Trans. 1* **1987**, 799.
(7) Rondeau, R.E., Rosenberg, H.M., Dunbar, D.J. *J. Mol. Spectrosc.* **1969**, *29*, 305.
(8) Begtrup, M., Claramunt, R.M., Elguero, J. *J. Chem. Soc. Perkin Trans. 2* **1978**, 99.
(9) *Phencyclidine (PCP) Abuse: An Appraisal*, Petersen, R.C., Stillman, R.C. (eds.), NIDA Research Monograph 21, 1978.
(10) McQuinn, R.L., Cone, E.J., Shannon, H.E., Su, T.-P. *J. Med. Chem.* **1981**, *24*, 1429.
(11) Kalir, A., Edery, H,, Pelah, Z., Balderman, D., Porath, G. *J. Med. Chem.* **1969**. *12*. 473.
(12) Aguayo, L.G., Albuquerque, E.X. *J. Pharmacol. Exp. Ther.* **1986**, *239*, 15.
(13) Metayer, M. *Bull. Soc. Chim. Fr.* **1950**, 1048.
(14) Bailey, K., Gagne, D.R., Pike, R.K. *J. Assoc. Off. Anal. Chem.* **1976**, *59*, 81.
(15) Abdel-Rahman, M.O., Aboul-Enein, M.N., Tammam, G.H. *Egypt. J. Chem.* **1975**, *18*, 581; *C.A.* **1978**, *89*, 197017.
(16) Bailey, K., Legault, D. *Anal. Chim. Acta* **1980**, *113*, 375.
(17) Geneste, P., Kamenka, J.M. *Org. Magn. Reson.* **1975**, *2*, 579.
(18) Brine, G.A., Williams, E.E., Boldt, K.G., Carroll, F.I. *J. Heterocycl. Chem.* **1979**, *16*, 1425.
(19) Brine, G.A., Boldt, K.G., Coleman, M.L., Carroll, F.I. *J. Heterocycl. Chem.* **1984**, *21*, 71.
(20) Nilsson, A. Carlson, R. *Acta Chem. Scand. Ser. B* **1985**, *39*, 187.
(21) Carlson, R., Nilsson, A., Stromquist, M. *Acta Chem. Scand. Ser. B* **1983**, *37*, 7.
(22) Kim, S., OH, C.H., Ko, J.S., Ahn, K.H., Kim, Y.J. *J. Org. Chem.* **1985**, *50*, 1927.
(23) Hickmott, P.W. *Tetrahedron* **1982**, *38*, 1975.
(24) Nomura, Y., Shimura, T., Takeuchi, Y. *Bull. Chem. Soc. Jpn.* **1964**, *37*, 892.
(25) Harusawa, S., Hamada, Y., Shioiri, T. *Synthesis* **1979**, 716.
(26) Soine, W.H., Brady, K.T., Balster, R.L., Underwood, J.Q. *Res. Commun. Chem. Pathol. Pharmacol.* **1980**, *30*, 59.
(27) Vaupel, D.B., McCoun, D.,Cone, E.J. *J. Pharmacol. Exp. Ther.* **1984**, *230*, 20.
(28) Wall, G.M., Clark, C.R. *J. Assoc. Off. Anal. Chem.* **1981**, *64*, 1431.