Minoo Khazan, Farzin Hadizadeh, and Abbas Shafiee*

Department of Chemistry, Faculty of Pharmacy, The Medical Sciences University of Tehran, Tehran, Iran

Received December 12, 1996
Revised May 22, 1997

Reaction of methyllithium with 1-methyl-2-imidazolecarboxaldehyde afforded the corresponding alcohol **2**. Oxidation of compound **2** with manganese dioxide gave 2-acetyl-1-methylimidazole (**3**). Using compound **3** and substituted isatins **4**, the corresponding quinoline-4-carboxylic acids (**5**) were prepared. The reaction of acid imidazolides of **5** with appropriate amines yielded the amides **6**. Carbamic acid esters **10** were prepared by the Curtius rearrangement in good yield. Substituted quinolin-4-amines **13** were obtained by the acid hydrolysis of compound **10** (R_1 = *t*-Bu). Alkylation of amines **13** with diakylaminoalkyl chlorides gave compounds **14**.

J. Heterocyclic Chem., **34**, 1543 (1997).

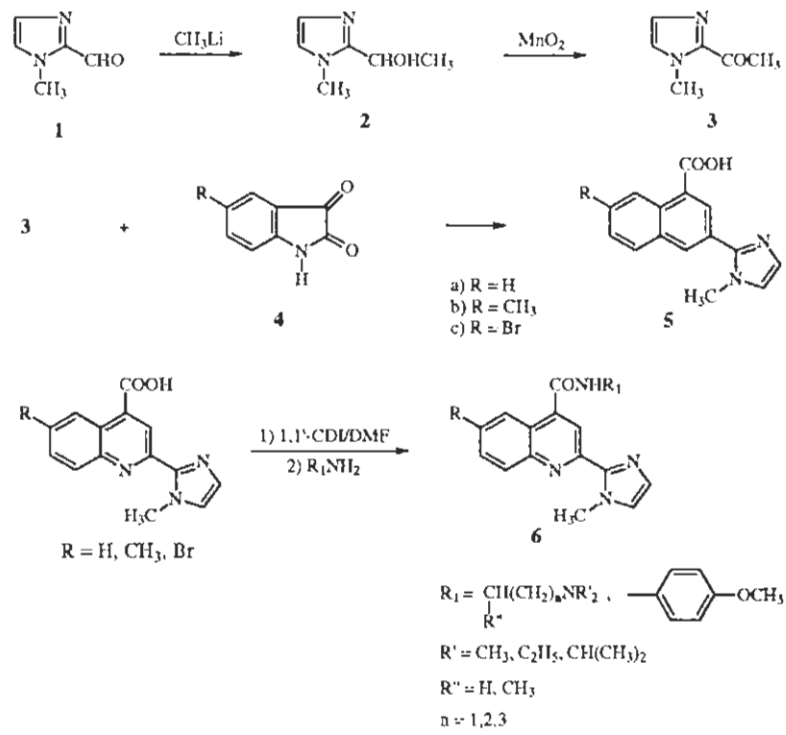
In view of the potential biological activity of 2-phenylquinoline-4-carboxamides as analgesic, tranquillizer, antitumor and antitubercular [1,4], carbamic acid esters as antibacterial, antifungal and local anesthetic [5,8]; 2-aryl(or 2-heteroaryl)quinolin-4-amines as anti-HIV-1 [9] and qninolin-4-amines as antimalarial [10] and in continuation of our research interest on the chemistry and biological activities of 2-arylquinolines [11,13], we now report the syntheses of the title compounds.

The most common approach employed for the synthesis of 2-(1-methyl-2-imidazolyl)quinoline-4-carboxylic acid (**5**), the key intermediate for the preparation of the desired compounds, was the condensation of aryl ketones with isatic acid in alcoholic potassium hydroxide solution (Pfitzinger reaction) [14].

The usual method for the preparation of 1-(1-methyl-2-imidazolyl)ethanol (**2**), namely the reaction of *n*-butyllithium with 1-methylimidazole and acetaldehyde did not give compound **2**. However the latter could be prepared from the reaction of methyllithium with 1-methyl-2-imidazolecarboxaldehyde (**1**) [15]. Oxidation of compound **2** with manganese dioxide gave 2-acetyl-1-methylimidazole (**3**). Using compound **3** and substituted isatins **4** the corresponding quinoline-4-carboxylic acids were prepared (Scheme 1).

The usual method for the preparation of the carboxamide **6**, namely the reaction of acid **5** with thionyl chloride

Scheme 1



and the subsequent reaction of the acid halide with an amine did not give the desired compound **6**. However, compounds **6** could be synthesized by treating the corresponding acid imidazolides with the appropriate amines [16] (Scheme 1).

Carbamic acid esters **10** were prepared by the reaction of 4-quinolinylisocyanate intermediates **9** with the corresponding alcohols (Scheme 2). The intermediate isocyanate **9**, conld be prepared by different methods, namely, the thermal Curtius rearrangement of aroyl azides in toluene [17], the Hofmann reaction of amides [18] the Lossen rearrangement of hydroxamic acids [19], the Schmidt degradation [20] and finally the Neber rearrangement in which the leaving group from nitrogen is *p*-toluenesulphonate or hydrogen sulphate ion, using hydroxylamine-*O*-sulphonic acid [21]. In our case the Neber rearrangement of compound **7** gave the desired compound **10** in low yield. However, we could obtain compound **10** by the Curtius rearrangement in good yield.

Quinolin-4-amines **13** could be prepared by different methods, such as acid or base catalayzed hydrolysis of isocyanate intermediate **10** [22], direct amine substitution of 4-haloquinolines [23] and condensation of 2-(trifluoromethyl)aniline with aryl ketone and subsequent cyclization by lithium amide [24]. In this work all the above methods failed. However, we could prepare the desired amines **13** through acid hydrolysis of *tert*-butyl carbamilate (**10**, R_1 = *t*-Bu) [22]. Subsequent alkylation of amines **13** with dialkylaminoalkyl chlorides [25] gave compounds **14** (Scheme 2). The physical constants of the compounds prepared are summarized in Tables 1 and 2.

Scheme 2

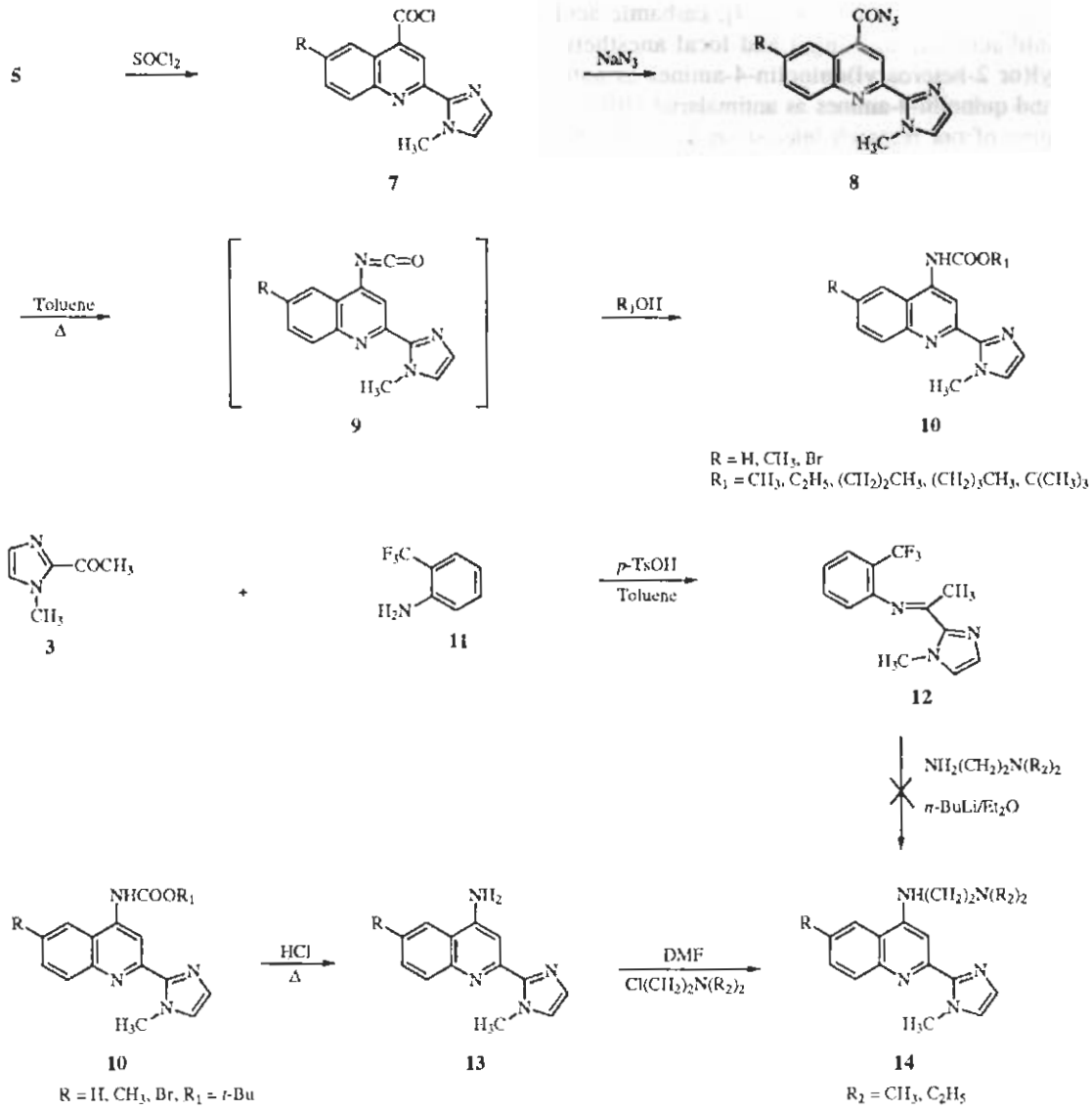
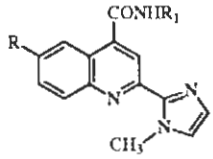


Table 1

Melting Points, Yields and Crystallization Solvents for 2-(1-Methyl-2-imidazolyl)quinoline-4-carboxamides **6**

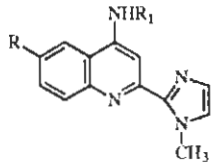


Compound	R	R_1	mp (°C)	Yield (%)	Crystallization solvent	Formula	Calcd. C%	Found C%	Calcd. H%	Found H%	Calcd. N%	Found N%
6a	H	$(CH_2)_2N(CH_3)_2$	130-131	55	Et_2O	$C_{18}H_{21}N_5O$	66.87	66.69	6.50	6.57	21.67	21.34
6b	H	$(CH_2)_2N(C_2H_5)_2$	112-118	52	Et_2O	$C_{20}H_{25}N_5O$	68.38	68.25	7.12	7.19	19.94	19.66
6c	H	$(CH_2)_3N(CH_3)_2$	116-120	53	Acetone-hexane	$C_{19}H_{23}N_5O$	67.66	67.73	6.82	6.43	20.77	20.49
6d	H	$(CH_2)_3N(C_2H_5)_2$	113-115	54	Et_2O	$C_{21}H_{27}N_5O$	69.04	69.32	7.40	7.37	19.18	19.27
6e	H	$CH(CH_3)CH_2N(CH_3)_2$	[a]	50	[b]	$C_{19}H_{23}N_5O$	67.66	67.48	6.82	6.54	20.77	20.91
6f	H	$(CH_2)_2N[CH(CH_3)_2]_2$	116-118	52	Hexane	$C_{22}H_{29}N_5O$	69.66	69.79	7.65	7.95	18.47	18.63
6g	H	$CH(CH_3)(CH_2)_3N(C_2H_5)_2$	[a]	53	[b]	$C_{23}H_{31}N_5O$	70.23	70.41	7.89	7.67	17.81	17.57
6h	H	*p*-C_6H_4-OCH_3	207-210	66	EtOH	$C_{21}H_{18}N_4O_2$	70.39	70.43	5.03	5.37	15.64	15.47
6i	CH_3	$(CH_2)_2N(CH_3)_2$	164-167	56	Acetone-hexane	$C_{19}H_{23}N_5O$	67.66	67.37	6.82	6.91	20.77	20.63
6j	CH_3	$(CH_2)_2N(C_2H_5)_2$	117-119	47	Hexane	$C_{21}H_{27}N_5O$	69.04	69.31	7.40	7.66	19.18	19.23
6k	CH_3	$(CH_2)_3N(CH_3)_2$	146-148	54	Acetone-Et_2O	$C_{20}H_{25}N_5O$	68.38	68.49	7.12	7.32	19.94	19.71
6l	CH_3	$(CH_2)_3N(C_2H_5)_2$	129-131	29	Hexane	$C_{22}H_{29}N_5O$	69.66	69.42	7.65	7.43	18.47	18.29
6m	CH_3	$CH(CH_3)CH_2N(CH_3)_2$	147-149	49	Et_2O	$C_{20}H_{25}N_5O$	68.38	68.42	7.12	7.08	19.94	19.76
6n	CH_3	$(CH_2)_2N[CH(CH_3)_2]_2$	109-110	52	Hexane	$C_{23}H_{31}N_5O$	70.23	70.11	7.89	7.95	17.81	17.93
6o	CH_3	$CH(CH_3)(CH_2)_3N(C_2H_5)_2$	133-137	30	Et_2O	$C_{24}H_{33}N_5O$	70.76	70.85	8.11	8.33	17.20	17.14
6p	CH_3	*p*-C_6H_4-OCH_3	251-253	30	Et_2O	$C_{22}H_{20}N_4O_2$	70.97	70.83	5.38	5.41	15.05	15.25
6q	Br	$(CH_2)_2N(CH_3)_2$	193-195	65	MeOH	$C_{18}H_{20}N_5OBr$	53.73	53.51	4.98	4.67	17.41	17.63
6r	Br	$(CH_2)_2N(C_2H_5)_2$	110-112	43	Hexane	$C_{20}H_{24}N_5OBr$	55.81	55.97	5.58	5.47	16.28	16.16
6s	Br	$(CH_2)_3N(CH_3)_2$	156-159	43	Acetone	$C_{19}H_{22}N_5OBr$	54.81	54.61	5.29	5.31	16.83	16.70
6t	Br	$(CH_2)_3N(C_2H_5)_2$	133-138	41	Hexane	$C_{21}H_{26}N_5OBr$	56.76	56.79	5.86	5.63	15.77	15.49
6u	Br	$CH(CH_3)CH_2N(CH_3)_2$	171-174	30	Acetone	$C_{19}H_{22}N_5OBr$	54.81	54.89	5.29	5.34	16.83	16.61
6v	Br	$(CH_2)_2N[CH(CH_3)_2]_2$	55-60	41	Petroleum ether	$C_{22}H_{28}N_5OBr$	57.64	57.43	6.11	6.32	15.28	15.39
6w	Br	$CH(CH_3)(CH_2)_3(C_2H_5)_2$	150-154	26	Acetone	$C_{23}H_{30}N_5OBr$	58.47	58.69	6.36	6.17	14.83	14.91
6x	Br	*p*-C_6H_4-OCH_3	262-264	33	EtOH	$C_{21}H_{17}N_4O_2Br$	57.67	57.34	3.89	3.92	12.81	12.74

[a] This compound was separated as an oil. [b] This compound was purified by thin layer chromatography.

Table 2

Melting Point, Yields and Crystallization Solvents for Compounds **10**, **13** and **14**



Compound	R	R_1	mp (°C)	Yield (%)	Crystallization Solvent	Formula	Calcd. C%	Found C%	Calcd. H%	Found H%	Calcd. N%	Found N%
10a	H	$COOCH_3$	[a]	35	[b]	$C_{15}H_{14}N_4O_2$	63.83	63.68	4.96	4.76	19.86	19.54
10b	H	$COOC_2H_5$	[a]	32	[b]	$C_{16}H_{16}N_4O_2$	64.86	64.97	5.41	5.63	18.92	18.64
10c	H	$COO(CH_2)_2CH_3$	[a]	29	[b]	$C_{17}H_{18}N_4O_2$	65.81	65.61	5.81	5.70	18.06	18.21
10d	H	$COO(CH_2)_3CH_3$	[a]	12	[b]	$C_{18}H_{20}N_4O_2$	66.67	66.69	6.17	6.19	17.28	17.43
10e	H	$COOC(CH_3)_3$	165-168	7	Acetone-Et_2O	$C_{18}H_{20}N_4O_2$	66.67	66.73	6.17	6.23	17.28	17.16
10f	CH_3	$COOCH_3$	179-182	29	Acetone-hexane	$C_{16}H_{16}N_4O_2$	64.86	64.55	5.41	5.67	18.92	18.74
10g	CH_3	$COOC_2H_5$	141-143	21	EtOH	$C_{17}H_{18}N_4O_2$	65.81	65.69	5.81	5.51	18.06	18.26
10h	CH_3	$COOC(CH_3)_3$	96-100	75	Et_2O	$C_{19}H_{22}N_4O_2$	67.46	67.26	6.51	6.22	16.57	16.71
10i	Br	$COOCH_3$	183-186	27	[b]	$C_{15}H_{13}N_4O_2Br$	49.86	49.73	3.60	3.25	15.51	15.78
10j	Br	$COOC(CH_3)_3$	191-195	99	Et_2O	$C_{18}H_{19}N_4O_2Br$	53.60	53.81	4.71	4.44	13.90	13.95
13a	H	H	150-152	95	Acetone-Et_2O	$C_{13}H_{12}N_4$	69.64	69.94	5.36	5.63	25.00	25.31
13b	CH_3	H	150	89	Acetone	$C_{14}H_{14}N_4$	70.59	70.29	5.88	5.67	23.53	23.72
13c	Br	H	200-205	99	MeOH	$C_{13}H_{11}N_4Br$	51.49	51.39	3.63	3.82	18.48	18.61
14a	H	$CH_2CH_2N(CH_3)_2$	[a]	11.5	[b]	$C_{17}H_{21}N_5$	69.15	69.18	7.12	7.31	23.73	23.95

Table 2 (continued)

Compound	R	R_1	mp (°C)	Yield (%)	Crystallization Solvent	Formula	Calcd. C%	Found C%	Calcd. H%	Found H%	Calcd. N%	Found N%
14b	CH_3	$CH_2CH_2N(CH_3)_2$	[a]	12	[b]	$C_{18}H_{23}N_5$	69.90	69.97	7.44	7.23	22.65	22.93
14c	CH_3	$CH_2CH_2N(C_2H_5)_2$	113-115	25	[b]	$C_{20}H_{27}N_5$	71.22	71.15	8.01	8.21	20.77	20.54

[a] This compound was separated as an oil. [b] This compound was purified by thin layer chromatography.

EXPERIMENTAL

Melting points were determined on a Kofler hot stage apparatus and are uncorrected. The ir spectra were obtained using a Perkin-Elmer Model 267 spectrograph (potassium bromide disks). The ^{1}H-nmr spectra were recorded on a Bruker FT-80 or Varian 400 unity plus spectrometers and chemical shifts (δ) are in ppm relative to internal tetramethylsilane. Mass spectra were run on a Finnigan TSQ-70 spectrometer at 70 eV. All compounds gave satisfactory C, H, N analyses within ±0.4%.

1-(1-Methyl-2-imidazolyl)ethanol **2**.

To a stirring solution of 1-methyl-2-imidazolecarboxaldehyde (**1**, 5 g, 40 mmoles) [26] in 250 ml of anhydrous diethyl ether was added dropwise 50 ml of methyllithium (1.5 *M* in hexane). During the addition the reaction mixture was maintained under a nitrogen atmosphere and the temperature was maintained below 5°. After stirring for 4 hours at 0°, the mixture was allowed to warm to room temperature, stirred for one hour, and then quenched with 150 ml of water. The aqueous phase was continuously extracted with ethyl acetate for 16 hours. Evaporation of the ethyl acetate extract under vacuum yielded **2** as a yellow oil which crystallized on standing. Recrystallization from benzene-hexane yielded **2** (4.24 g, 74%) of colorless prisms, mp 82-83.5° (lit [15], mp 82-83.5°).

2-Acetyl-1-methylimidazole **3**.

To a stirring solution of compound **2** (11.5 g, 93 mmoles) in 200 ml of chloroform was added manganese dioxide (58 g). The mixture was refluxed for 2 hours and filtered. The solvent was removed under reduced pressure to afford 9.6 g (85%) of compound **3**, bp 104-105°/15 mm (lit [26], bp 61° at 1 mmg Hg); ir: ν_{max} 1680 cm^{-1} (C=O); ^{1}H-nmr (deuteriochloroform): 2.60 (s, 3H, CH_3), 3.90 (s, 3H, MeN), 7.01 ppm (s, 1 H, imidazole).

2-(1-Methyl-2-imidazolyl)quinoline-4-carboxylic Acids **5a-c**.

Compounds **5a-c** were prepared by the following general procedure: A mixture of compound **3** (6.2 g, 50 mmoles) and substituted isatin **4** (50 mmoles) in 50% aqueous ethanol (65 ml) containing potassium hydroxide (12.88 g, 0.23 mole) was heated under reflux for 2 hours and then diluted with 50% aqueous ethanol to obtain a homogeneous mixture. This was filtered and acidified with acetic acid and the precipitate was collected, washed with 30% aqueous ethanol, and recrystallized from dimethylformamide to give compounds **5** (yield 33-84%), the spectral data for **5a** (R = H) is given as an example; ir: 3120 (aromatic), 1690 cm^{-1} (C=O); ms: m/z (%) 253 (M$^+$, 70), 208 (100), 128 (10), 101 (8), 57 (8), 43 (11).

2-(1-Methyl-2-imidazolyl)quinoline-4-carboxamides **6a-x**.

Compounds **6a-x** were prepared by the following general procedure: **5** (1 mole) was suspended in dry dimethylformamide (10 ml/g) and treated with 1,1'-carbonyldiimidazole (1.5 moles) at 20-40° for 20 minutes. The homogeneous mixture was then cooled to 5° and treated with the appropriate amine (2.5 moles at 20° for 15 minutes). The solvent was removed under reduced pressure, and the residue was partitioned between dichloromethane and diluted aqueous sodium bicarbonate. The organic layer yielded **6** (yield 26-66%). Purification of each product was obtained by crystallization from the appropriate solvent. The spectral data for **6a** is given as an example; ir (potassium bromide): 3240 (NH), 3060 (aromatic), 1670 cm^{-1} (C=O); ^{1}H-nmr (deuteriochloroform): 2.29 (s, 6H, $N(CH_3)_2$), 2.60 (t, 2H, CH_2-N), 3.65 (q, 2H, CH_2NH), 4.30 (s, 3H, N-CH_3 imidazole), 6.80 (bs, 1H, NH), 7.04 (d, 1H, H_5-imidazole, J = 0.8 Hz), 7.16 (d, 1H, H_4 imidazole, J = 0.8 Hz), 7.60 (m, 2H, $H_{6,7}$-quinoline), 8.06 (dd, 1H, H_8-quinoline, $J_{7,8}$ = 8.4 Hz, $J_{6,8}$ = 1.2 Hz), 8.30 (dd, 1H, H_5-quinoline, $J_{5,6}$ = 8.4 Hz, $J_{5,7}$ = 1.2 Hz), 8.40 (s, 1H, H_3-quinoline), ms: m/z (%), 323 (M$^+$, 70), 280 (12), 265 (23), 253 (65), 237 (12), 208 (90), 71 (92), 58 (100).

Anal. Calcd. for $C_{18}H_{21}N_5O$: C, 66.87; H, 6.50; N, 21.67. Found: C, 66.69; H, 6.57; N, 21.34.

2-(1-Methyl-2-imidazolyl)quinoline-4-carbonylazides **8**.

To a stirring mixture of 2-(1-methyl-2-imidazolyl)quinoline-4-carbonyl chloride **7** (0.1 mole), which was in turn synthesized by treating the corresponding acid **5** with thionyl chloride, in acetone (30 ml) at 0° was added dropwise a solution of sodium azide (6.5 g, 0.1 mole) in 15 ml of water. The reaction mixture was stirred for an additional hour. The precipitate was filtered, washed with water and dried at room temperature under reduced pressure to give **8** in 80% yield, mp 210-215°; ir (potassium bromide): 3100 (aromatic), 2150 (azide), 1695 cm^{-1} (C=O).

2-(1-Methyl-2-imidazolyl)quinoline-4-carbamic Acid Esters **10a-j**.

These compounds **10a-j** were prepared by the following general methods.

Method A.

A solution of 2-(1-methyl-2-imidazolyl)quinoline-4-carbonyl azide **8** (0.01 mole) with the corresponding alcohol (20 ml) was refluxed for 12 hours. The solvent was evaporated and the residue was crystallized from the appropriate slovent or purified by thin layer chromatography.

Method B.

A solution of **8** (0.01 mole) in 30 ml of dry benzene was refluxed for 4 hours. The corresponding alcohol (0.01 mole) was added to the reaction mixture and refluxing was continued for 3 hours. The solvent was evaporated and the residue was purified by thin layer chromatography. The spectral data for compound **10a** (R = H, R_1 = CH_3) is given as an example; ir (potassium bromide): 1740 cm^{-1} (C=O); ^{1}H-nmr (deuteriochloroform): 3.82 (s, 3H, O-CH_3), 4.22 (s, 3H, N-CH_3), 6.99 (d, 1H, H_5-imidazole, J = 1 Hz), 7.16 (d, 1H, H4-imidazole, J = 1 Hz), 8.05-7.43 (m,

4H, $H_{5,6,7,8}$-quinoline), 8.78 (s, 1H, H_3-quinoline); ms: m/z (%) 282 (M^+, 40), 249 (100), 223 (28), 208 (43), 196 (30).

Anal. Calcd. for $C_{15}H_{14}N_4O_2$: C, 63.83; H, 4.96; N, 19.86. Found: C, 63.68; H, 4.76; N, 19.54.

2-(1-Methyl-2-imidazolyl)quinolin-4-amines 13a-c.

Compounds **13a-c** were prepared by the following general procedure.

A solution of 2-(1-methyl-2-imidazolyl)quinoline-4-carbamic acid *t*-butyl ester, **10e,h,j**, in excess concentrated hydrochloric acid was heated for 2 days. The hydrochloric acid was evaporated under reduced pressure and the residue was made alkaline by sodium hydroxide solution and extracted with chloroform. The organic extract was evaporated and crystallized from methanol. The spectral data of compound **13a** is given as an example; ir (potassium bromide): 3408, 3330 (NH_2), 3240 (NH), 1650 cm^{-1} (NH_2); ^{1}H-nmr (deuteriochloroform): 4.28 (s, 3H, N-CH_3 imidazole), 7.00 (d, 1H, H_5-imidazole, J = 1.1 Hz), 7.13 (d, 1H, H_4-imidazole, J = 1.1 Hz), 7.59 (s, 1H, H_3-quinoline), 8.02-7.35 (m, 4H, $H_{5,6,7,8}$-quinoline); ms: m/z (%), 224 (M^+, 70), 223 (100), 170 (14).

Anal. Cacld. for $C_{13}H_{12}N_4$: C, 69.64; H, 5.36; N, 25.00. Found: C, 69.94; H, 5.63; N, 25.31.

N-[2-(Dialkylamino)ethyl]-2-(1-methyl-2-imidazolyl)quinoline-4-amines 14a-c.

Compounds **14a-c** were prepared by the following procedure: To a stirring solution of **13a-c** (2 mmoles) in dimethylformamide (10 ml) was added freshly distilled 2-(dialkylamino)ethyl chloride (10 ml). The mixture was kept at 120° for 14 hours. The mixture was made alkaline with aqueous sodium hydroxide and continuously extracted with chloroform. The organic extract was evaporated and the residue was purified by thin layer chromatography to give **14a-c** (yield 12-25%). The spectral data for compound **14c** is given as an example; ir (potassium bromide): 3320 (NH), 3210 (NH), 3120 (aromatic), 1645 cm^{-1} (NH-bending); ^{1}H-nmr (deuteriochloroform): 0.89 (t, 6H, CH_3), 2.46 (q, 4H, CH_2), 2.58 (s, 3H, CH_3-quinoline), 2.80 (t, 2H, CH_2NEt_2), 4.05 (s, 3H, CH_3-imidazole), 4.34 (t, 2H, CH_2NH), 7.35 (d, 1H, H_5-imidazole; J = 2 Hz), 7.55 (dd, 1H, H7-quinoline; $J_{7,8}$ = 8.4 Hz, $J_{5,7}$ = 2 Hz), 7.62 (d, 1H, H4-imidazole, J = 2 Hz), 7.65 (s, 1H, H_5-quinoline), 7.78 (d, 1H, H_8-quinoline, $J_{7,8}$ = 8.4 Hz), 7.96 (s, 1H, H_3-quinoline); ms: m/z (%) 251 (8), 237 (100), 224 (70), 184 (18), 99 (10), 86 (95), 58 (10).

Anal. Calcd. for $C_{20}H_{27}N_5$: C, 71.22; H, 8.01; N, 20.77. Found: C, 71.15; H, 8.21; N, 20.54.

Acknowledgment

This research was partially supported by a grant from IOCD.

REFERENCES AND NOTES

* To whom correspondence should be addressed. This work was a part of M. Khazan's dissertation for the Ph.D. degree.

[1] A. Kar, *J. Pharm. Sci.*, **72**, 1082 (1983).

[2] M. C. Dubroeucq, G. Lefur and C. Renault, *European Patent Appl Ep.*, 112,776 (1984); *Chem. Abstr.*, **101**, 191716z (1984).

[3] G. J. Atwell, C. D. Bos, B. C. Baguley and W. A. Denny, *J. Med. Chem.*, **31**, 1048 (1988).

[4] R. Medvecky, M. Hornackova and Z. Odlerova, *Acta Fac. Pharm. Univ. Comenianae*, **43**, 15 (1991); *Chem. Abstr.*, **115**, 228126z (1991).

[5] A. Shafiee, I. Lalezari, S. Yazdani and A. Pournorouz, *J. Pharm. Sci.*, **62**, 839 (1973).

[6] A. Shafiee, I. Lalezari, S. Yazdani, F. M. Shahbazian and T. Partovi, *J. Pharm. Sci.*, **65**, 304 (1976).

[7] F. Ghabgharan, H. Kooshkabadi, M. Emami, A. Rashidbaigi and A. Shafiee, *J. Pharm. Sci.*, **65**, 1085 (1976).

[8] A. Shafiee, F. Savabi, A. Rezvani, M. Farrokhsiar and A. Khoyi, *J. Pharm. Sci.*, **67**, 125 (1978).

[9] L. Streckowski, J. L. Mokrosz, V. A. Honkan, A. Czarny, M. T. Cegla and R. L. Wydra, S. E. Patterson and R. F. Schinzi, *J. Med.Chem.*, **34**, 1739 (1991).

[10] W. E. Wolff, Burger's Medicinal Chemistry: Antimalarials, 4th Ed, Part II, John Wiley and Sons, New York, 1979, pp 333-415.

[11] A. Shafiee, K. Parang, M. Khazan and F. Ghasemian, *J. Heterocyclic Chem.*, **29**, 1859 (1992).

[12] A. Shafiee, N. Tavasoli, K. H. Abdolahnegat and F. Kamal, *J. Sci. I. R. Iran*, **4**, 118 (1993).

[13] A. Shafiee, H. Rezaeifar, and R. Miri, *J. Sci. I. R. Iran*, **6**, 25 (1995).

[14] J. Fillipi, *Bull. Soc. Chim. France*, 268 (1968).

[15] D. S. Noyce and G. T. Stowe, *J. Org. Chem.*, **38**, 3762 (1973).

[16] G. J. Atwell, B. C. Baguley and W. A. Denny, *J. Med. Chem.*, **32**, 396 (1989).

[17] P. A. S. Smith, *Org. React.*, **3**, 337 (1946).

[18] E. S. Wallis and J. F. Lane, *Org. React.*, **3**, 267 (1946).

[19] W. Lossen, *Liebgis Ann. Chem.*, **161**, 347 (1872).

[20] H. Wolff, *Org. React.*, **3**, 307 (1946).

[21] R. G. Wallace, J. M. Barker and M. L. Wood, *Synthesis*, 1143 (1990).

[22] P. A. S. Smith, *Org. React.*, **3**, 387 (1946).

[23] J. C. Craig, H. N. Bhargava, T. Everhart, B. Labelle, U. Ohnsorge and R. V. Webster, *J. Org. Chem.*, **53**, 1167 (1988).

[24] L. Strekowski, R. L. Wydra, M. T. Cegla, A. Czarny, D. B. Harden, S. E. Patterson, M. A. Battiste and J. M. Coxon, *J. Org. Chem.*, **55**, 4777 (1990).

[25] J. Berlot and J. Renault, *Bull. Soc. Chim. France*, 2860 (1973).

[26] D. H. Davies, J. Hall, and E. H. Smith, *J. Chem. Soc., Perkin Trans. 1*, 2691 (1991).