Synthesis of (1-Substituted Piperidin-4-yl)-1*H*-benzimidazoles and (1-Substituted Piperidin-4-yl)-3,4-dihydroquinazolines as Possible Antihypertensive Agents

Hiroyuki Obase*, Haruki Takai and Masayuki Teranishi

Tokyo Research Laboratory, Kyowa Hakko Kogyo Co., Ltd., Asahimachi 3-6-6, Machida-shi, Tokyo 194 Japan

Nobuhiro Nakamizo

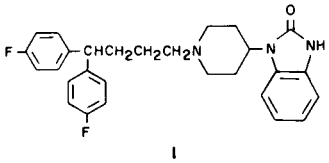
Pharmaceutical Research Laboratories, Fuji, Kyowa Kakko Kogyo Co., Ltd., Shimotogari 1188, Nagaizumi-cho, Shizuoka 411, Japan

Received July 13, 1982

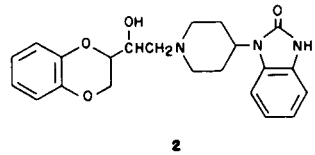
Structural modifications of 4-piperidylbenzimidazolinones (I) by replacing the benzimidazolinone group with other heterocycles (2-cyanoamino, 2-ethoxy, and 2-methylbenzimidazole and 2-cyanoamino-3,4-dihydroquinazoline) has been made and a number of new piperidines (II) were synthesized as potential antihypertensive agents.

J. Heterocyclic Chem., **20**, 565 (1983).

Compounds incorporating the piperidyl benzimidazol-2-one group show interesting biological activity. Pimozide (**1**) is a clinically useful neuroleptic, for example. In

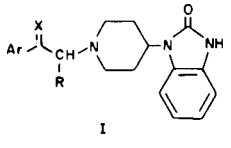


1



2

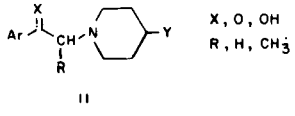
addition R-28935 (**2**) has been reported to show pronounced central hypotensive activity in various animal species (1,2). We have recently reported the synthesis and pharmacological activity of a series of 4-piperidylbenzimidazol-2-ones, of formula I. Most of the compounds showed potent antihypertensive activity in various animal models with



X, O, OH
R, H, CH_3

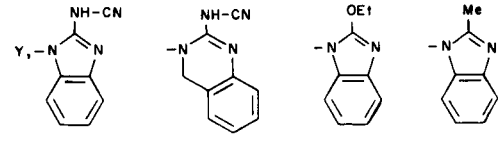
I

long duration of action (3-5). These findings prompted us to carry out the structural modification of I by replacing the benzimidazol-2-one group with other heterocycles, 2-cyanoamino-1*H*-benzimidazole, 2-cyanoamino-3,4-dihydro-quinazoline, 2-ethoxy-1*H*-benzimidazole, 2-methyl-1*H*-benzimidazole. The present paper describes the synthesis of derivatives with general formula II.



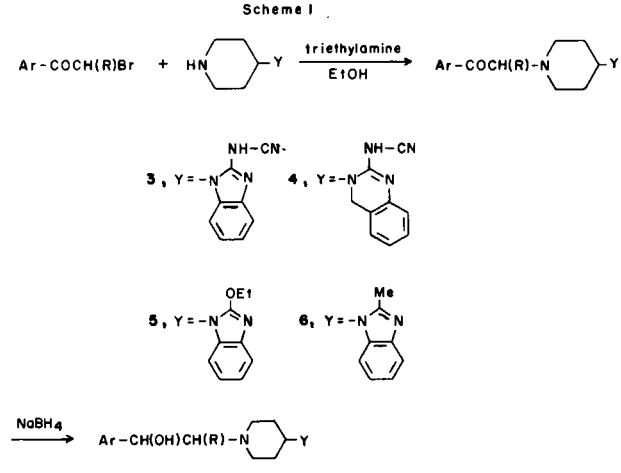
X, O, OH
R, H, CH_3

II



The compounds listed in Table I were generally prepared by reaction of a arylbromoketone with 4-substituted piperidine **3-6**. Arylethanolamines summarized in Table II were obtained by the reduction of corresponding aminoketones with sodium borohydride (Scheme I). As reported previously (3), arylethanolamines with threo configuration were yielded when aminoketones carrying a methyl group adjacent to the amino group were reduced with sodium borohydride. Therefore, our effects were

Scheme I

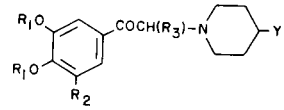


focussed on synthesizing key intermediates, 4-substituted piperidines **3-6** (Scheme I).

The synthesis of 2-cyanoaminobenzimidazole **3** which are considered as an bioisostere of benzimidazol-2-thione (6) was first investigated. The conversion of 1,3-dihydro-2*H*-benzimidazol-3-thiones **7a,b** or 2-one **8** to

Table I

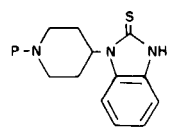
Aminoketone II (X:O)

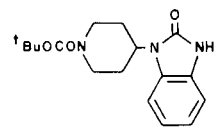


No.	R_1	R_2	R_3	Y (a)	Form	Yield (%)	Mp, °C (Crystallization solvent)	Formula	Analyses % Calcd./Found C	H	N
28	CH_3	H	H	2-cyanoamino-1*H*-benzimidazol-1-yl	base	54	137 – 139 (MeOH)	$C_{23}H_{25}N_5O_3$	65.85 65.65	6.01 6.40	16.70 16.52
29	CH_2<	H	H		base	57	196 – 198 (MeOH)	$C_{22}H_{21}N_5O_3$	65.49 65.44	5.25 5.42	17.36 17.33
30	CH_3	H	H	2-cyanoamino-3,4-dihydroquinazolin-3-yl	base	72	202 – 204 (MeOH)	$C_{24}H_{27}N_5O_3$	66.49 66.88	6.28 6.33	16.16 16.14
31	CH_3	H	CH_3		base	55	195 – 198 (MeOH)	$C_{25}H_{29}N_5O_3$	67.09 67.01	6.53 6.46	15.69 15.29
32	CH_3	OCH_3	CH_3		base	56	193 – 195 (MeOH)	$C_{26}H_{31}N_5O_4$	65.39 15.31	6.54 6.58	14.67 14.42
33	CH_3	OCH_3	H		base	53	185 – 187 (MeOH)	$C_{25}H_{29}N_5O_4 \cdot 0.5H_2O$	64.78 64.68	6.31 6.52	15.11 14.94
34	CH_2<	H	H		base	73	200 – 202 (MeOH)	$C_{23}H_{23}N_5O_3$	66.17 66.09	5.55 5.43	16.78 16.53
35	CH_3	H	H	2-ethoxy-1*H*-benzimidazol-1-yl	fumarate	53	166.2 – 167.3 (*i*-PrOH)	$C_{24}H_{29}N_3O_4 \cdot C_4H_4O_4$	62.32 62.35	6.16 6.19	7.79 7.60
36	CH_3	H	CH_3		fumarate	74	169 – 171.5 (*i*-PrOH)	$C_{25}H_{31}N_3O_4 \cdot C_4H_4O_4$	62.91 63.11	6.37 6.45	7.59 7.40
37	CH_2<	H	H		base	55	135.5 – 137 (EtOH)	$C_{23}H_{25}N_3O_4$	67.79 67.77	6.18 6.30	10.31 10.20
38	CH_3	H	H	2-methyl-1*H*-benzimidazol-1-yl	base	61	153 – 155 (*i*-PrOH)	$C_{23}H_{27}N_3O_3$	70.20 70.22	6.92 6.99	10.63 10.56
39	CH_3	H	CH_3		base	80	oil	$C_{24}H_{29}N_3O_3$	70.73 71.03	7.17 7.42	10.31 10.38
40	CH_2<	H	H		base	76	174 – 177 (EtOH)	$C_{22}H_{23}N_3O_3$	70.01 70.04	6.14 6.23	11.13 11.07

(a) Where there is a blank space in this column, the Y group is the preceding group.

2-cyanoaminobenzimidazole were tried. Lead cyanamide has been used to convert thioureas to cyanoguanidines (6), but the application of this reagent to **7a,b** resulted in recovery of starting materials. The reaction using silver cyanamide which is a softer metal cyanamide also gave





7a,b (a, P=CH_2Ph; b, P=COO^tBu)

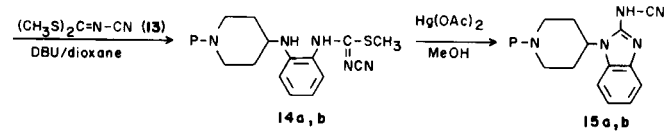
disappointing results. Treatment of **8** with diethyl azodicarboxylate/triphenylphosphine (7,8), followed by the reaction of cyanamide, led to the formation of phosphinimine **9** (9). Therefore, efforts along these lines were abandoned

$$Ph_3P=N-CN$$

9

and another approach shown in Scheme II was studied. 1-Ethoxycarbonyl-4-(2-aminophenyl)aminopiperidine (**12a**) was prepared from 1-ethoxycarbonyl-4-aminopiperidine (**10a**) essentially according to the method reported previously (10). Wittenbrook reported the preparation of

2-cyanoaminobenzimidazole *via* base-catalyzed reaction of *o*-phenylenediamine with dimethyl cyanoimidodithiocarbonate (**13**) (11). However, when **12a** was reacted with **13** under the reaction conditions described (using triethylamine as base, in ethanol), none of the desired



Scheme II

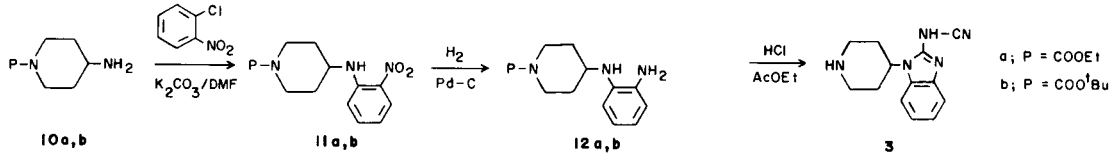
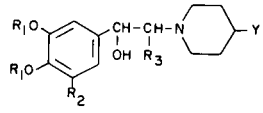


Table II

Ethanolamino II (X:O)



No.	R_1	R_2	R_3	Y (a)	Form	Yield (%)	Mp, °C (Crystallization solvent)	Formula	Analyses % Calcd./Found C	H	N
41	CH_3	H	H	2-cyanoamino-1*H*-benzimidazol-1-yl	base	93	218–219 (MeOH)	$C_{23}H_{27}N_5O_3$	65.54 65.44	6.46 6.34	16.62 16.37
42	CH_2<	H	H		base	88	232–233.5 (MeOH)	$C_{22}H_{23}N_5O_3$	65.17 65.54	5.72 5.62	17.28 16.92
43	CH_3	H	H	2-cyanoamino-3,4-dihydroquinazolin-3-yl	base	84	249–251 (EtOH)	$C_{24}H_{29}N_5O_3$	66.18 66.00	6.71 6.81	16.08 16.25
44	CH_3	H	CH_3		base	85	247–249 (EtOH)	$C_{25}H_{31}N_5O_3$	66.79 66.77	6.95 7.13	15.58 15.29
45	CH_3	OCH_3	CH_3		base	65	252–254 (EtOH)	$C_{26}H_{33}N_5O_4$	65.11 65.07	6.94 7.23	14.61 14.55
46	CH_3	OCH_3	H		base	77	218–220 (EtOH)	$C_{25}H_{31}N_5O_4$	64.49 64.32	6.71 6.89	15.04 15.04
47	CH_2<	H	H		base	86	239–241 (EtOH)	$C_{23}H_{25}N_5O_3$	65.85 65.77	6.01 6.02	16.70 16.34
48	CH_3	H	H	2-ethoxy-1*H*-benzimidazol-1-yl	fumarate	85	185–186.5 (*i*–PrOH)	$C_{24}H_{31}N_3O_4 \cdot C_4H_4O_4$	62.09 62.11	6.51 6.27	7.76 7.50
49	CH_3	H	CH_3		fumarate	57	172.5–174 (*i*PrOH)	$C_{25}H_{33}N_3O_4 \cdot C_4H_4O_4$	62.69 62.49	6.71 6.70	7.56 7.58
50	CH_2<	H	H		base	86	124–125 (*i*–PrOH)	$C_{23}H_{27}N_3O_4$	67.46 67.48	6.65 6.43	10.26 10.10
51	CH_3	H	H	2-methyl-1*H*-benzimidazol-1-yl	difumarate	57	214–215.2 (MeOH)	$C_{23}H_{29}N_3O_3 \cdot C_8H_8O_8$	59.32 59.11	5.94 6.15	6.69 6.60
52	CH_3	H	CH_3		difumarate	72	179–181 (EtOH)	$C_{24}H_{31}N_3O_3 \cdot C_8H_8O_8$	59.90 60.12	6.13 6.23	6.55 6.25
53	CH_2<	H	H		difumarate	65	167–169 (MeOH)	$C_{22}H_{25}N_3O_3 \cdot C_8H_8O_8$	58.92 59.18	5.44 5.51	6.87 6.73

(a) Where there is a blank space in this column, the Y group is the preceding structure.

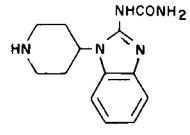
2-cyanoaminebenzimidazole (**15a**) could be detected and unchanged starting materials were recovered. Carrying out the reaction in dioxane in the presence of 1,5-diazabicyclo[5.4.0]undecene-5 (DBU) at 80° gave an uncyclized compound **14a** mainly, instead of **15a**. So, cyclization of **14a** to **15a** was examined extensively. Compound **14a** was not cyclized to **15a** with sodium hydroxide which had been used in the quinazoline series (12). In order to activate the methylthio group as a leaving group, attempts to oxidize **14a** to the corresponding sulfoxide or sulphone were undertaken. However, oxidation using several oxidants, such as *m*-chloroperbenzoic acid, sodium periodate, manganase dioxide gave disappointing results; in many instances intractable products were obtained. The desired cyclization was finally realized by a metal ion promoted reaction (13,14). Thus, **14a** was treated with mercuric

Table III

IR and NMR Spectral Data for **28—40**

Compound		IR (cm^{-1})		NMR (δ, ppm)	
28	Potassium bromide	2300, 1680 1626, 1601	Deuteriochloroform	1.5—4.9 (piperidine ring H), 3.88 (s, 2H, $COCH_2N$), 3.95, 3.97 (s, 6H, OCH_3), 6.8—8.0 (m, 7H, aromatic)
29	Potassium bromide	2300, 1674 1625, 1601	Deuteriochloroform	1.5—4.9 (piperidine ring H), 3.83 (s, 2H, $COCH_2N$), 6.06, (s, 2H, OCH_2O), 6.84—7.70 (m, 7H, aromatic)
30	Potassium bromide	2320, 1685 1628, 1590	Deuteriochloroform	1.3—4.15 (piperidine ring H), 3.78 (s, 2H, $COCH_2N$), 3.92, (s, 6H, OCH_3), 4.40 (s, 2H, CH_2 for quinazoline), 6.8—7.9 (m, 7H, aromatic), 8.45 (s, 1H, NH)
31	Potassium bromide	2300, 1660 1628, 1588	Deuteriochloroform	1.25 (d, 3H, $COCH(CH_3)$), 1.4—4.0 (piperidine ring H), 3.93 (s, 6H, OCH_3), 4.35 (s, 2H, CH_2 for quinazoline), 6.8—7.9 (m, 7H, aromatic), 8.45 (s, 1H, NH)
32	Potassium bromide	2300, 1670 1624, 1585	Deuteriochloroform	1.30 (d, 3H, $COCH(CH_3)$), 1.4—4.0 (piperidine ring H), 3.97 (s, 9H, OCH_3), 4.38 (s, 2H, CH_2 for quinazoline), 6.9—7.4 (m, 6H, aromatic), 8.73 (s, 1H, NH)
33	Potassium bromide	2300, 1680 1624, 1588	Deuteriochloroform	1.4—4.0 (piperidine ring H), 3.79 (s, 2H, $COCH_2N$), 3.89 (s, 9H, OCH_3), 4.38 (s, 2H, CH_2 for quinazoline), 6.8—7.4 (m, 6H, aromatic), 9.0 (s, 1H, NH)
34	Potassium bromide	2300, 1678 1623, 1588	Deuteriochloroform	1.4—4.0 (piperidine ring H), 3.75 (s, 2H, $COCH_2N$), 4.41 (s, 2H, CH_2 for quinazoline), 6.05 (s, 2H, OCH_2O), 6.7—7.7 (m, 7H, aromatic), 8.68 (s, 1H, NH)
35	Potassium bromide	1698, 1280	DMSO-d_6	1.45 (t, 3H, CH_2CH_3), 1.6—4.8 (piperidine ring H), 3.88 (s, 6H, OCH_3), 4.02 (s, 2H, $COCH_2N$), 4.60 (q, 2H, CH_2CH_3), 6.9—8.3 (m, 7H, aromatic)
36	Potassium bromide	1680, 1275	DMSO-d_6	1.20 (d, 3H, $COCH(CH_3)$), 1.35 (t, 3H, CH_2CH_3), 1.4—4.8 (piperidine ring H), 3.89 (s, 6H, OCH_3), 4.45 (q, 2H, $CHCH_3$), 6.8—7.9 (m, 7H, aromatic)
37	Potassium bromide	1695, 1255	Deuteriochloroform	1.3—4.4 (piperidine ring H), 1.49 (t, 3H, CH_2CH_3), 3.99 (s, 2H, $COCH_2N$), 4.60 (q, 2H, CH_2CH_3), 6.05 (s, 2H, OCH_2O), 6.7—7.7 (m, 7H, aromatic)
38	Potassium bromide	1673, 1255	Deuteriochloroform	1.6—4.5 (piperidine ring H), 2.63 (s, 3H, $NC(CH_3)=N$), 3.89 (s, 2H, $COCH_2N$), 3.99 (s, 6H, OCH_3), 6.8—7.8 (m, 7H, aromatic)
39	Chloroform	1667, 1256	Deuteriochloroform	1.31 (d, 3H, $COCH(CH_3)$), 1.4—4.4 (piperidine ring H), 2.60 (s, 3H, $NC(CH_3)=N$), 3.96 (s, 6H, OCH_3), 6.7—8.0 (m, 7H, aromatic)
40	Potassium bromide	1691, 1255	Deuteriochloroform	1.6—4.5 (piperidine ring H), 2.62 (s, 3H, $NC(CH_3)=N$), 3.80 (s, 2H, $COCH_2N$), 6.05 (s, 2H, OCH_2O), 6.7—7.8 (m, 7H, aromatic)

acetate in methanol to afford **15a** essentially in quantitative yield. The reaction proceeded under mild conditions and rapidly (at room temperature, within 0.5 hours). The deprotection of the ethoxycarbonyl group in **15a** was next examined in detail. Efforts to deprotect the ethoxycarbonyl group by the usual acid treatment led to mixtures that could not be characterized. It became apparent that the 2-cyanoaminobenzimidazole group was sensitive to acid hydrolytic conditions. Treatment of **15a** with trimethylsily chloride/pyridine and followed by the reaction of the resulting 3-trimethylsilylbenzimidazole with trimethylsilyl iodide (15) also gave many unrecognizable products. Consequently, another protective group, the *t*-butoxycarbonyl group was chosen and a series of reaction sequences (Scheme II) were repeated starting from 1-*t*-butoxycarbonyl-4-aminopiperidine (**10b**). 1-*t*-Butoxycarbonyl-4-(2-cyanoamino-1*H*-benzimidazol-1-yl)piperidine (**15b**) was obtained in 29% over all yields from **10b**. Thus obtained **15b** was treated with hydrochloric acid in ethyl acetate to obtain **3** as the hydrochloride. Another method to deblock the *t*-butoxycarbonyl group gave unfavorable results; treatment of **15b** with trifluoroacetic acid afforded a complex mixture of products and with 98% formic acid afforded the ureido derivative **16**.



16

Table IV

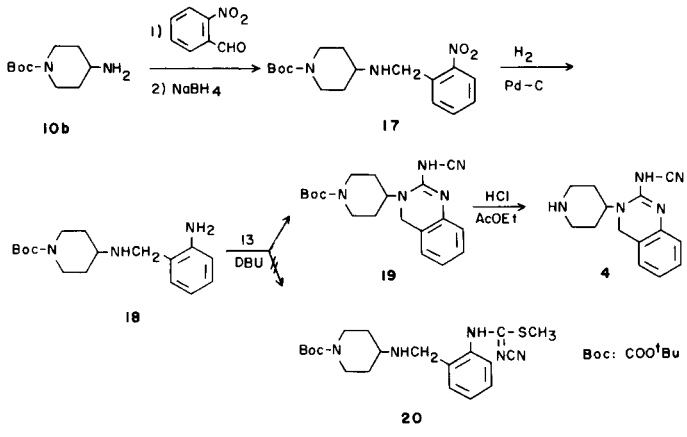
IR and NMR Spectral Data for **41**–**53**

Compound	IR (cm^{-1} Potassium bromide)			NMR (δ, ppm)	
41	2300,	1628,	1601	Deuteriochloroform	1.8–4.7 (piperidine ring H and CH_2N), 3.88, 3.91 (s, 6H, OCH_3), 4.75 (t, 1H, C*H*OH), 6.9–7.5 (m, 7H, aromatic)
42	2300,	1629,	1601	Deuteriochloroform Perdeuteriomethanol	1.8–4.7 (piperidine ring H and CH_2N), 4.75 (t, 1H, C*H*OH), 5.95 (s, 2H, OCH_2O), 6.8–7.6 (m, 7H, aromatic)
43	2300,	1630,	1589	Deuteriochloroform	1.5–4.5 (piperidine ring H and CH_2N), 3.85,3.90 (s, 2H, CH_2 for quinazoline), 4.70 (t, 1H, CHOH), 6.7–7.3 (m, 7H, aromatic), 8.85 (s, 1H, NH)
44	2301,	1628,	1590	(a)	
45	2301,	1628,	1589	Deuteriochloroform	0.81 (d, 3H, $CHCH_3$), 1.4–4.6 (piperidine ring H and CH_2N), 3.85, 3.90 (s, 9H, OCH_3), 4.44 (s, 2H, CH_2 for quinazoline), 6.6, 6.8–7.3 (m, 6H, aromatic), 9.4 (s, 1H, NH)
46	2300,	1628,	1589	Deuteriochloroform	1.5–4.7 (piperidine ring H and CH_2N), 3.8, 3.85 (s, 9H, OCH_3), 4.37 (s, 2H, CH_2 for quinazoline), 6.59, 6.8–7.3 (m, 6H, aromatic), 9.33 (s, 1H, NH)
47	2300,	1630,	1590	Deuteriochloroform DMSO-d_6	1.3–4.8 (piperidine ring H and CH_2N). 4.40 (s, 2H, CH_2 for quinazoline), 6.94 (s, 2H, OCH_2O), 6.7–7.4 (m, 7H, aromatic), 9.90 (s, 1H, NH)
48	1550,	1460,	1280	DMSO-d_6	1.43 (t, 3H, CH_2CH_3), 1.6–4.6 (piperidine ring H and CH_2N), 3.97, 3.99 (s, 6H, OCH_3), 4.57 (q, 2H, CH_2CH_3), 4.95 (t, 1H, C*H*OH), 6.8–7.7 (m, 7H, aromatic)
49	1545,	1470,	1260	DMSO-d_6	0.80 (d, 3H, $CHCH_3$), 1.45 (t, 3H, CH_2CH_3), 1.6–4.6 (piperidine ring H and CH_2N), 3.98, 4.00 (s, 6H, OCH_3), 4.60 (q, 2H, CH_2CH_3), 6.8–7.7 (m, 7H aromatic)
50	1545,	1440,	1250	Deuteriochloroform	1.49 (t, 3H, CH_2CH_3), 1.6–4.6 (piperidine ring H and CH_2N), 4.62 (q, 2H, CH_2CH_3), 5.93 (s, 2H, OCH_2O), 6.7–7.6 (m, 7H, aromatic)
51	1695,	1235		DMSO-d_6	1.7–4.8 (piperidine ring H and CH_2N), 2.64 (s, 3H, $NC(CH_3)=N$), 3.77, 3.78 (s, 6H, OCH_3), 5.07 (t, 1H, C*H*OH), 6.8–8.1 (m, 7H, aromatic)
52	1685,	1255		DMSO-d_6	0.82 (d, 3H, $CHCH_3$), 1.7–4.7 (piperidine ring H and CH_2N), 2.60 (s, 3H, $NC(CH_3)=N$), 3.98, 4.00 (s, 6H, OCH_3), 6.8–8.0 (m, 7H, aromatic)
53	1690,	1235		DMSO-d_6	1.7–4.8 (piperidine ring H and CH_2N), 2.65 (s, 3H, $NC(CH_3)=N$), 5.08 (t, 1H, C*H*OH), 6.04 (s, 2H, OCH_2O), 6.8–8.1 (m, 7H, aromatic)

(a) Compound **44** is insoluble in deuteriochloroform or DMSO-d_6.

Next the synthesis of 2-cyanoamino-3-(piperidin-4-yl)-3,4-dihydroquinazoline (**4**) was investigated and the results are illustrated in Scheme III. Reaction of **10b** with 2-nitrobenzaldehyde in methanol, followed by reduction with

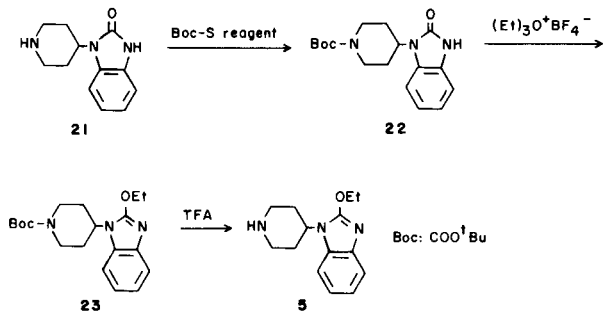
Scheme III



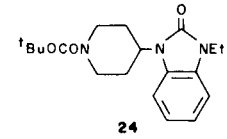
sodium borohydride gave a 68% yield of 1-*t*-butoxycarbonyl-4-(2-nitrophenyl)aminopiperidine (**17**) which was isolated as oxalate. The resulting **17** was reduced catalytically (Pd−C) to yield 1-*t*-butoxycarbonyl-4-(2-aminophenyl)methylaminopiperidine (**18**). On the basis of the foregoing observations, **18** was reacted with **13** in the presence of DBU in dioxane to produce a homogeneous product, which proved to be 2-cyanoaminoquinazoline **19**. The proton magnetic resonance spectra and elemental analyses were consistent with the proposed structure. When the reaction was carried out under similar conditions as reported by Bristol (in the absence of base, at room temperature), cyclized product **19** was also obtained. The result was surprising in view of the report of Bristol who obtained uncyclized product in 84% yield from the reaction of 2-aminobenzylamine with **13**. Finally the *t*-butoxycarbonyl group in **19** was deblocked by acid treatment (hydrochloric acid in ethyl acetate) to afford **4** in high yield.

The synthetic sequences leading to 2-ethoxy benzimidazole **5** are depicted in Scheme IV.

Scheme IV

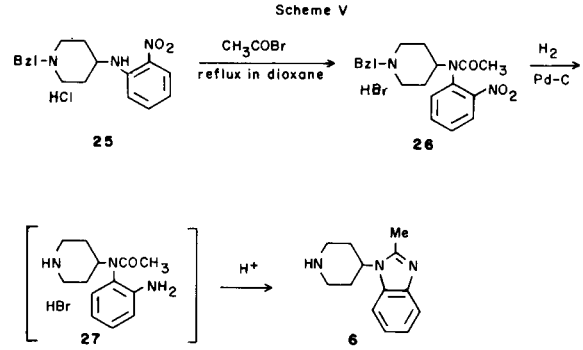


4-Piperidylbenzimidazolinone (**21**) was reacted with *S*-(4,6-dimethylpyrimidin-2-yl)thiocarbonate (Boc-S reagent) in dioxane/water in the presence of triethylamine to afford 1-(1-*t*-butoxycarbonylpiperidin-4-yl)benzimidazol-2-one (**22**) in 67% yield. Treatment of **22** with Meervein reagent gave 2-ethoxy-1*H*-benzimidazole **23**. Determination of the structure of **23** was obtained by correlation with the sample **24** which was prepared by the reaction of **22** with sodium hydride/ethyl iodide. In the infrared spectrum, **23** showed band due to C=N at 1620 cm^{-1}, while **24** exhibited band due to C=O of benzimidazol-2-one at 1690 cm^{-1}. The protective group in **23** was cleaved by usual acid treatment (trifluoroacetic acid, at 0°) to afford **5** in high yield.



2-Methyl-1-(piperidin-4-yl)-1*H*-benzimidazole (**6**) was prepared according to the route shown in Scheme V.

Scheme V



We studied first the acetylation of nitroaniline **25**. Labbezoo and coworkers (16) have reported that such a type of a nitroaniline fails to be propionylated with propionic acid anhydride or propionyl chloride even after prolonged reaction times at reflux temperature in benzene or toluene. However, heating of **25** and acetyl bromide in dioxane *N*-acetylnitroaniline **26** was obtained in fairly good yield. The resulting **26** was reduced catalytically (H_2, Pd−C) to give *O*-phenylenediamine **27** which was not isolated and the product was further stirred with a few drops of concentrated hydrochloric acid affording **6** in 87% over all yields from **26**.

The compounds **28-53** were examined for hypotensive activities which were measured after oral administration of compounds to spontaneously hypertensive rats (SHR). All of the compounds except **53** showed hypotensive activity. Amoung all of the compounds, **46** and **49** had the highest hypotensive activities. They produced a decrease in blood pressure of 40 to 50 mm Hg at a dose of 30 mg/kg. However, their hypotensive activities were not so remarkable in marked contrast to the hypotensive activity of the compound having the benzimidazolinone group:

compound **I** (Ar = 3,4,5-trimethoxyphenyl, X = OH, R = CH_3) showed the strongest hypotensive activity in the previous screening series (a decrease of 70 to 75 mm Hg/30 mg/kg) given orally, SHR (3-5).

EXPERIMENTAL

The melting points for the samples were determined with a Mitamura hot-stage apparatus and are uncorrected. Infrared spectra were recorded on a Hitachi 215 grating infrared spectrometer or a Shimadzu IR-27G grating infrared spectrometer. The ^1H nmr spectra were determined on a Varian T-60, JNM-PFT-100, or JNM-FX-100 spectrometer. Chemical shifts were reported in δ values relative to TMS as a standard. Mass spectra were run on a JEOL-JMS-O1SG-2 spectrometer at 70 eV.

1-*t*-Butoxycarbonyl-4-(2-nitrophenyl)aminopiperidine (**11b**).

A mixture of 1-*t*-butoxycarbonyl-4-aminopiperidine (**10b**) (57.5 g, 0.287 mole), 2-chloronitrobenzene (64 g, 0.41 mole), potassium carbonate (39.6 g, 0.287 mole) and potassium iodide (5 g) in 95 ml of dimethylformamide was heated at 120° for 24 hours. The reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was extracted with ethyl acetate, washed with brine and dried (anhydrous sodium sulfate). After evaporation of the solvent, the residue was purified by silica gel chromatography using ethyl acetate-*n*-hexane (3:1) as eluent giving 53.7 g (58%) of **11b**. An analytical sample was recrystallized from *n*-hexane, mp 88.5-89°, ir (potassium bromide): 1682 (C=O), 1568 (NO_2) cm^{-1}; ms: 321 (M^+), 265 (M − 56).

Anal. Calcd. for $C_{16}H_{23}N_3O_4$: C, 59.79; H, 7.21; N, 13.08. Found: C, 59.77; H, 7.35; N, 13.00.

1-*t*-Butoxycarbonyl-4-(2-aminophenyl)aminopiperidine (**12b**).

A mixture of **11b** (52.7 g, 0.164 mole) and 5.2 g of palladium on carbon in 100 ml of methanol was shaken under 50 psi hydrogen for 24 hours. The catalyst was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was crystallized with the aid of ether to give 47 g (98%) of **12b** which darkened rapidly upon exposure to air, mp 111-112° dec.

Anal. Calcd. for $C_{16}H_{25}N_3O_2$: C, 65.95; H, 8.65; N, 14.42. Found: C, 65.77; H, 8.33; N, 14.38.

1-*t*-Butoxycarbonyl-4-[2-(methylthiocyanoiminomethylamino)phenyl]aminopiperidine (**14b**).

A solution of **12b** (20.6 g, 0.07 mole), dimethyl *N*-cyanodithioimidocarbonate (**13**, 22.3 g 0.086 mole) (17), DBU (21.9 g, 0.144 mole) in 150 ml of dioxane was heated at 82° for 12 hours and concentrated. The residue was extracted with ethyl acetate and the extract was washed successively with 0.3 *N* acetic acid, 0.57 *N* hydrochloric acid and water. After drying over sodium sulfate, the solvent was removed under reduced pressure and the residue was purified by silica gel chromatography using chloroform-methanol (50:1) as eluent to afford 16.7 g (61 %) of **14b**. An analytical sample was recrystallized from isopropanol, mp 169-171°; ir (potassium bromide): 2200 (C≡N), 1690 (CO), 1604 (C≡N) cm^{-1}; nmr (DMSO-d_6): δ 1.40 (S, CH_3 for tert-butyl), 2.50 (S, SCH_3).

Anal. Calcd. for $C_{19}H_{27}N_5O_2S$: C, 58.59; H, 6.99; N, 17.98. Found: C, 58.81; H, 7.08; N, 18.00.

1-*t*-Butoxycarbonyl-4-(2-cyanoamino-1*H*-benzoimidazol-1-yl)piperidine (**15b**).

A solution of **14b** (11.0 g, 0.0282 mole) and mercuric acetate (9.5 g, 0.0298 mole) in 100 ml of methanol was stirred at 20° for 1 hour and concentrated under reduced pressure. The residue was extracted with chloroform and the extract was washed with brine, dried over sodium sulfate. After evaporation of the solvent, the residue was recrystallized from ethanol to give 8.0 g (83%) of **15b**, mp 242-243°; ir (potassium bromide): 2190 (C≡N), 1700-1690 (CO), 1635, 1615 (C=N) cm^{-1}; nmr (DMSO-d_6): δ 1.48 (s, CH_3 for *t*-butyl), 12.7 (broad s, NH).

Anal. Calcd. for $C_{18}H_{23}N_5O_2$: C, 63.32; H, 6.79; N, 20.52. Found: C, 63.47; H, 6.89; N, 20.47.

4-(2-Cyanoamino-1*H*-benzimidazol-1-yl)piperidine Hydrochloride (**3**).

To a suspension of **15b** (6.7 g, 0.0196 mole) in 200 ml of ethyl acetate was added 67 ml of 5.7 *N* hydrochloride in ethyl acetate at 20°. The suspension was stirred at the same temperature for 5 hours and filtered. The precipitates were washed with ethyl acetate and dried to give 5.3 g (97%) of **3**•hydrochloride, which was essentially a pure sample. An analytical sample was recyrstallized from ethanol-ethyl acetate, mp 273-276° dec; ir (potassium bromide): 2195 (C≡N), 1630, 16.01 (C=N) cm^{-1}.

Anal. Calcd. for $C_{13}H_{16}ClN_5$: C, 56.22; H, 5.81; N, 25.21. Found: C, 56.43; H, 5.97; N, 24.98.

1-Ethoxycarbonyl-4-[2-(methylthiocyanoiminomethyl)aminophenyl]aminopiperidine (**14a**).

This compound was prepared from **12a** by a similar procedure to that described for **14b** in 54% yield; mp 160-161° (from 2-propanol); ir (potassium bromide): 2350 (C≡N), 1690 (CO), 1605, 1570 (C=N) cm^{-1}; nmr (deuteriochloroform): δ 1.3 (t, CH_3CH_2), 2.37 (s, SCH_3), 4.18 (q, CH_3CH_2).

Anal. Calcd. for $C_{17}H_{23}N_5O_2S$: C, 56.49; H, 6.41; N, 19.38. Found: C, 56.36; H, 6.44; N, 19.19.

1-Ethoxycarbonyl-4-(2-cyanoamino-1*H*-benzimidazol-1-yl)piperidine (**15a**).

This compound was prepared from **14a** by an analogous procedure to that described for **15b** in 86% yield, mp 235-235.5° (from 2-propanol); ir (potassium bromide): 2310 (C≡N), 1682, (CO), 1629, 1608 (C=N) cm^{-1}; nmr (deuteriochloroform): δ 12.33 (broad s, NH).

Anal. Calcd. for $C_{16}H_{19}N_5O_2$: C, 61.32; H, 6.11; N, 22.35. Found: C, 61.54; H, 6.11; N, 22.18.

Attempted Deprotection of the Ethoxycarbonyl Group in **15a**.

To a solution of **15a** (100 mg, 0.32 mmole) in 10 ml of chloroform (distilled from phosphorus pentoxide) was added trimethylsilyl chloride (35 mg, 0.32 mmole) and imidazole (22 mg, 0.32 mmole) under a nitrogen atmosphere. After stirring for 1 hour at 20°, trimethylsilyliodide (96 mg, 0.48 mmole) was added to the solution. The solution was refluxed for 5 hours under an atmosphere of nitrogen. The reaction was quenched with methanol and water. The organic layer gave a mixture of several products (thin layer chromatography).

1-*t*-Butoxycarbonyl-4-(2-nitrophenylmethyl)aminopiperidine (**17**).

A solution of **10b** (36.1 g, 0.18 mole) and 2-nitrobenzaldehyde (27.3 g, 0.18 mole) in 100 ml of methanol was stirred at 20°. After stirring for 1 hour, 6.8 g (0.18 mole) of sodium borohydride was added to the solution over 1 hour. The solution was concentrated under reduced pressure and the residue was extracted with ethyl acetate. The extract was worked up as usual to afford crude **17** as a brown oil, which was converted to its oxalate in 2-propanol. The oxalate was recrystallized from 2-propanol to give 61.1 g (80%) of **17**•oxalate, mp 194-195°.

Anal. Calcd. for $C_{19}H_{27}N_3O_8$: C, 53.64; H, 6.40; N, 9.88. Found: C, 53.60; H, 6.65; N, 9.81.

The oxalate was treated with 1*N* sodium hydroxide to give 41.1 g (68%) of free **17** as an oil; ir (neat): 1668-1680 (CO), 1520 (NO_2) cm^{-1}; nmr (deuteriochloroform): δ 1.45 (s, CH_3 for *t*-butyl), 4.07 (s, $NHCH_2Ar$).

1-*t*-Butoxycarbonyl-4-(2-aminophenylmethyl)aminopiperidine (**18**).

A mixture of **17** (40 g, 0.12 mole) and 4 g of palladium on carbon in 160 ml of ethanol was shaken in parr apparatus at 20° under 50 psi hydrogen pressure for 10 hours. The catalyst was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was recrystallized from *n*-hexane to give 28.3 g (78%) of **18**, mp 79-81°.

Anal. Calcd. for $C_{17}H_{27}N_3O_2$: C, 66.85; H, 8.91; N, 13.76. Found: C, 66.99; H, 8.99; N, 13.71.

1-*t*-Butoxycarbonyl-4-(2-cyanoamino-3,4-dihydroquinazolin-3-yl)piperidine (**19**).

A solution of **18** (28.0 g, 0.092 mole), **13** (29 g, 0.111 mole) and DBU (28 g, 0.184 mole) in 150 ml of dioxane was stirred at 20° for 10 hours. The crystals were collected by filtration and recrystallized from methanol to yield 14 g (43%) of **19**, mp 249-250°; ir (potassium bromide): 2302 (C≡N), 1687 (CO), 1627, 1588 (C=N) cm^{-1}; nmr (deuteriochloroform): δ 1.43 (s, CH_3 for *t*-butyl), 4.35 (s, CH_2 for quinazoline ring protons at 4), 9.9 (broad s, NH).

Anal. Calcd. for $C_{19}H_{25}N_5O_2$: C, 64.20; H, 7.09; N, 19.71. Found: C, 64.43; H, 7.24; N, 19.69.

4-(2-Cyanoamino-3,4-dihydro-quinazolin-3-yl)piperidine Hydrochloride (**4**).

To a cooled suspension of **19** (13.0 g, 0.0366 mole) in 100 ml of ethyl acetate, 60 ml of 5.8 *N* hydrochloric acid in ethyl acetate was added at 0°. The mixture was allowed to the room temperature and filtered. The crystals were washed with ethyl acetate and dried. Crude crystals (10 g, 94%) could be used in the next reaction without further purification. An analytical sample was recrystallized from ethanol-ethyl acetate, mp 260-262°; ir (potassium bromide): 2302 (C≡N), 1623, 1587 (C=N) cm^{-1}.

Anal. Calcd. for $C_{14}H_{18}ClN_5$: C, 57.63; H, 6.22; N, 24.00. Found: C, 57.77; H, 6.48; N, 23.78.

1-*t*-Butoxycarbonyl-4-(1,3-dihydro-2-oxo-2*H*-benzimidazol-1-yl)piperidine (**22**).

A solution of 4-(1,3-dihydro-2-oxo-2*H*-benzimidazol-1-yl)piperidine (**21**; 5 g, 0.0231 mole), Boc-S (5.75 g, 0.0239 mole) and triethylamine (2.35 g, 0.0232 mole) in 50 ml of dioxane and 35 ml of water was stirred at 20° for 12 hours and concentrated under reduced pressure. The residue was extracted with ethyl acetate. The extract was worked up as usual giving 4.9 g (67%) of **22**, mp 165.5-166° (recrystallized from ethyl acetate-*n*-hexane); ir (potassium bromide): 1695 (CO) cm^{-1}; nmr deuteriochloroform): δ 1.50 (s, CH_3 for *t*-butyl).

Anal. Calcd. for $C_{17}H_{23}N_3O_3$: C, 64.33; H, 7.30; N, 13.24. Found: C, 64.58; H, 7.39; N, 13.19.

1-*t*-Butoxycarbonyl-4-(2-ethoxy-1*H*-benzimidazol-1-yl)piperidine (**23**).

A solution of **22** (0.5 g, 1.58 mmoles), triethoxonium tetrafluoroborate (0.33 g, 1.74 mmoles) in 10 ml of methylene chloride was stirred at 20° for 2.5 hours. The solution was washed successively with 1 *N* sodium carbonate and water. The organic layer was separated and dried over sodium sulfate. After removal of the solvent, the residue was recrystallized from *n*-hexane to obtain 0.3 g (55%) of **23**, mp 107-109°; ir (potassium bromide): 1695-1683 (CO), 1620 (C=N) cm^{-1}; nmr deuteriochloroform): δ 1.43, 4.6 (for ethyl), 1.50 (CH_3 for *t*-butyl).

Anal. Calcd. for $C_{19}H_{27}N_3O_3$: C, 66.06; H, 7.88; N, 12.17. Found: C, 65.97; H, 7.91; N, 12.04.

4-(2-Ethoxy-1*H*-benzimidazol-1-yl)piperidine (**5**).

To a cooled trifluoroacetic acid (1.68 g), 510 mg (1.48 mmoles) of **23** was added at 0°. After being stirred for 2 hours at the same temperature, the solution was concentrated *in vaccuo*. The residue was dissolved in water and the solution was basified to *p*H 10.6 then extracted with chloroform. The extract was worked up as usual to yield 350 mg (96.6%) of **5** as an oil, ir (neat): 1621 (C=N) cm^{-1}; nmr (deuteriochloroform): δ 1.45, 4.6 (for ethyl). Free **5** was converted to crystalline hydrochloride in ethyl acetate for analysis, mp 260-270° dec.

Anal. Calcd. for $C_{14}H_{20}ClN_3O$: C, 59.67; H, 7.15; N, 14.91. Found: C, 59.77; H, 7.26; N, 14.71.

1-*t*-Butoxycarbonyl-4-(3-ethyl-1,3-dihydro-2-oxo-2*H*-benzimidazol-1-yl)-piperidine (**24**).

A solution of **22** (1.9 g, 6.0 mmoles) in 15 ml of tetrahydrofuran (distilled from lithium aluminium hydride) was added dropwise to a cooled suspension of sodium hydride (oil free, 0.205 g, 8.9 mmoles) in 10 ml of tetrahydrofuran. The mixture was warmed to room temperature over 1 hour. Ethyl iodide (4.6 g, 29.6 mmoles) was added to the mixture and the whole was warmed at 50° for 1 hour and concentrated under reduced pressure. The residue was extracted with ethyl acetate. The extract gave crude **24** which was recrystallized from *n*-hexane to yield pure **24** (1.74 g, 84%), mp 92.5-93.5°; ir (potassium bromide): 1698 (CO) cm^{-1}; nmr (deuteriochloroform): δ 1.3, 3.9 (for ethyl), 1.48 (CH_3 for *t*-butyl).

Anal. Calcd. for $C_{19}H_{27}N_3O_3$: C, 66.06; H, 7.88; N, 12.17. Found: C, 66.00; H, 7.99; N, 12.01.

1-Benzyl-4-[N-(2-nitrophenyl)-N-acetyl]aminopiperidine Hydrobromide (**26**).

A suspension of 1.67 g (4.8 mmoles) of 1-benzyl-4-(2-nitrophenyl)aminopiperidine hydrochloride and 13 ml of acetyl bromide in 30 ml of dioxane was heated to reflux for 3 hours. The crystals were collected by filtration and recrystallized from ethanol to afford 1.4 g (64%) of **26**, mp 253-255°; ir potassium bromide): 1665-1658 (CO), 1530 (NO_2); nmr (DMSO-d_6): δ 3.8 ($PhCH_2N<$), 4.28 ($COCH_3$).

Anal. Calcd. for $C_{20}H_{24}BrN_3O_3$: C, 55.31; H, 5.57; N, 9.67. Found: C, 55.41; H, 5.54; N, 9.38.

4-(2-Methyl-1*H*-benzimidazol-1-yl)piperidine (**6**).

A suspension of **26** (2.1 g, 4.83 mmoles) and 0.3 g of palladium on carbon was stirred under a stream of hydrogen at 20° for 5 hours. The catalyst was filtered off. To the filtrate, few drops of concentrated hydrochloric acid was added and the solution was stirred for 12 hours and concentrated. The residue was diluted with water, basified to *p*H 11.0 and extracted with chloroform. The extract was worked up in the usual manner to give 0.9 g (87%) of **6**. An analytical sample was recrystallized from *n*-hexane-ethanol, mp 130-132°; ms: 215 (M^+).

Anal. Calcd. for $C_{13}H_{17}N_3$: C, 72.52; H, 7.96; N, 19.52. Found: C, 72.33; H, 8.01; N, 19.62.

Aminoketones (**28-40**).

Following the method earlier (3), equimolar quantities of 4-substituted piperidines **3-6**, appropriate aryl bromoketones and triethylamine were stirred in methanol at 20° for 5-12 hours. The solvent was removed under reduced pressure and the residue was extracted with chloroform. The extract was washed with water, dried over sodium sulfate and concentrated. Solid aminoketones were recrystallized from the appropriate solvent and syrupy ones were purified by silica gel chromatography and converted to crystalline salts. The physical constants of aminoketones are recorded in Table I. They were also characterized by their spectral (ir, nmr, Table III) and elemental analyses (Table I).

Arylethanolamines (**41-53**).

Following the method earlier (3), to the solution of aminoketones in ethanol (or methanol) was added equimolar quantities of sodium borohydride at room temperature over 0.5 hours. After additional stirring for 1 hour, the solvent was removed under reduced pressure. Crystalline arylethanolamines was collected by filtration, washed with water, dried and recrystallized from appropriate solvent. Oily ones was extracted with chloroform and the extract was washed with water, dried (sodium sulfate) and evaporated. Oily residue was converted to crystalline salt. The physical constants of arylethanolamines are shown in Table II. The structures were supported by their spectral (ir, nmr Table IV) and elemental analyses (Table II).

REFERENCES AND NOTES

(1) P. A. J. Janssen, I. van Wijngaarden and W. Soudijn, German Patent, 2,400,094 (1974); *Chem. Abstr.*, **81**, 120644g (1974).

(2) A. Scriabine and C. S. Sweet, "New Antihypertensive Drugs", Spectrum Publications Inc., New York, N.Y., 1976, p 566.

(3) H. Obase, N. Nakamizo, H. Takai, M. Teranishi, K. Kubo, K. Shuto, Y. Kasuya, H. Kato and K. Shigenobu, *Chem. Pharm. Bull.*, **30**, 462 (1982).

(4) Y. Kasuya, K. Shigenobu, M. Hashikami, N. Karashima, H. Obase, H. Takai, M. Teranishi, A. Karasawa and K. Kubo, *J. Med. Chem.*, submitted for publication.

(5) A. Karasawa, K. Shuto, K. Kubo, M. Hashikami, K. Shigenobu

and Y. Kasuya, *Arch, Int. Pharmacodyn. Ther.*, submitted for publication.

(6) G. J. Durant, J. C. Emmett, C. R. Ganellin, P. D. Miles, M. E. Passon, H. D. Prain and G. R. White, *J. Med. Chem.*, **20**, 901 (1977).

(7) O. Mitsunobu, K. Kato and F. Kakese, *Tetrahedron Letters*, 2473 (1969).

(8) O. Mitsunobu, K. Kato, and M. Tomari, *Tetrahedron*, **26**, 5731 (1970).

(9) H. J. Niclas and D. Martin, *Tetrahedron Letters*, 4031 (1978).

(10) P. A. J. Janssen, A. H. M. T. Van Heertum, J. Vandenberk and M. J. M. C. Van der Aa, German Patent, 2,527,261 (1976); *Chem. Abstr.*, **84**, 135657z (1976).

(11) L. S. Wittenbrook, *J. Heterocyclic Chem.*, **12**, 37 (1975).

(12) J. A. Bristol, *ibid.*, **15**, 1409 (1978).

(13) D. P. N. Satchell, *Chem. Soc, Rev.*, **6**, 345 (1977).

(14) The application of this interesting method has been extended to the synthesis of other heterocyclic systems and it will be reported subsequently.

(15) M. E. Jung and M. A. Lyster, *J. Chem. Soc., Chem. Commun.*, 315 (1978).

(16) M. Lobbezoo, W. Soudijn and I. van Wijngaarden, *J. Med. Chem.*, **24**, 777 (1981).

(17) R. J. Timmons and L. S. Wittenbrook, *J. Org. Chem.*, **32**, 1566 (1967).