# Studies on Agents with Vasodilator and β-Blocking Activities. II[1)]

Toshimi SEKI,* Takayuki TAKEZAKI, Rikio OHUCHI, Hiroshi OHUYABU, Yoshitaka TANIMOTO, Takashi YAMAGUCHI, Morinobu SAITOH, Tsutomu ISHIMORI, and Kikuo YASUDA

*Research Division, Teikoku Hormone Manufacturing Co., Ltd., 1604 Shimosakunobe Takatsu-ku, Kawasaki, Kanagawa 213, Japan.* Received August 2, 1994; accepted October 26, 1994

**A series of phenoxypropanolamines having a hydrazinopyridazinyl moiety was synthesized. Their hypotensive and β-blocking activities were evaluated after intravenous administration of the compounds to anesthetized rats. Some of them exhibited both activities. In particular, compound 20k is a candidate for clinical use due to its hypotensive activity, equal to that of hydralazine, and its β-blocking activity, 2.7-fold more potent than that of propranolol.**

**Key words** phenoxypropanolamine; hydrazinopyridazine; antihypertensive agent; hypotensive activity; β-blocking activity; $\beta_1$-selectivity

Though various vasodilators are available as effective antihypertensive agents, most of them also cause tachycardia. In an attempt to avoid this unfavorable effect, we have hybridized a vasodilator with a β-blocker.[1)] Both activities were observed in some phenoxypropanolamine derivatives (**1**—**3**) having a hydrazinopyridazinyl moiety at the *ortho*-position of their phenyl ring, but not at the *meta*- or *para*-position.

It was reported that branching in the alkyl group on the α-carbon atom (*e.g.*, isopropyl and *tert*-butyl) was essential for potent β-blocking activity.[2)] Furthermore, as exemplified by bevantolol (**5**) and tolamolol (**6**), a substituent on nitrogen of phenoxypropanolamine was essential for cardioselective activity.[3)] Such a preference was also observed in some thioether analogues (general formula **7**).[4)] In the present study, therefore, another series of novel phenoxypropanolamine compounds having a hydrazinopyridazinyl moiety as an *N*-alkyl substituent, as shown by general formula **4** was synthesized with the aim of obtaining a better combination of hypotensive and β-blocking activities.

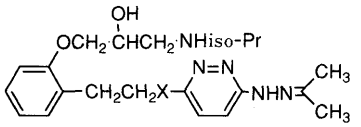
## Chemistry

A series of phenoxypropanolamines (**20**—**22**) having a hydrazinopyridazinyloxy or hydrazinopyridazinylthio moiety was synthesized by the procedure shown in Chart 2.

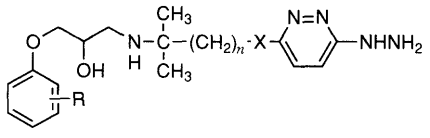
Monosubstitution of 3,6-dichloropyridazine (**8**) with 2-amino-2-methyl-1-propanol (**9**) in the presence of sodium hydride in *tert*-butanol proceeded rapidly at room temperature to afford the amino-ether (**12**), which was gradually isomerized at room temperature through the Smiles rearrangement[5)] to 3-chloro-6-(1,1-dimethyl-2-hydroxyethylamino)pyridazine (**15**). Heating of **8** with the aminoalcohol (**9**) without sodium hydride directly gave **15**. Ring opening of the glycidyl ethers (**16**) with the amine (**12**) provided the corresponding propanolamines (**17**). Reaction of the chlorides (**17**) with hydrazine hydrate afforded the hydrazino compounds (**20**) in low yields, followed by treatment with acetone or diethyl pyrocarbonate to give the hydrazones (**23**) or carbazates (**24**), respectively. In a similar way, compounds **21** and **22** were prepared by the reaction of **8** with the corresponding aminoalcohol (**10**) or aminothiol (**11**).

The alternative route *via* the thioxo-derivative (**25**) was employed as follows.[6)] The hydrochloride of **17** readily reacted with thiourea to give **25** in good yields, though the free base **17** did not react in a usual manner.[7)] Conversion of **25** to **20** easily proceeded on treatment with hydrazine hydrate.

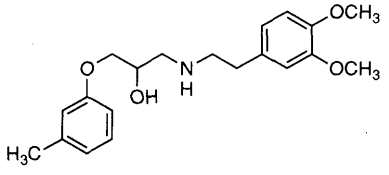
In this nucleophilic substitution, the reaction was



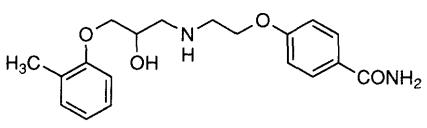
1: X=O
2: X=S
3: X=NCH$_3$



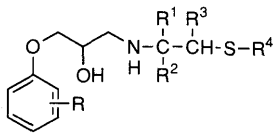
4



bevantolol (5)



tolamolol (6)



7

Chart 1

* To whom correspondence should be addressed.

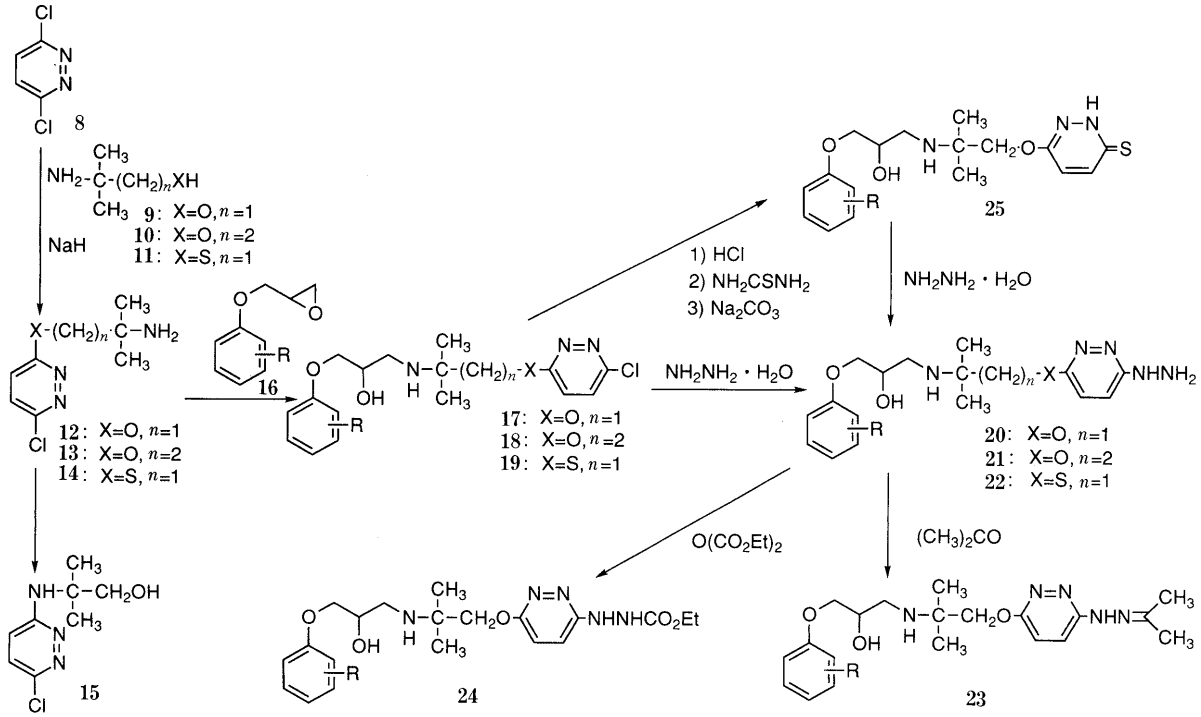


Chart 2

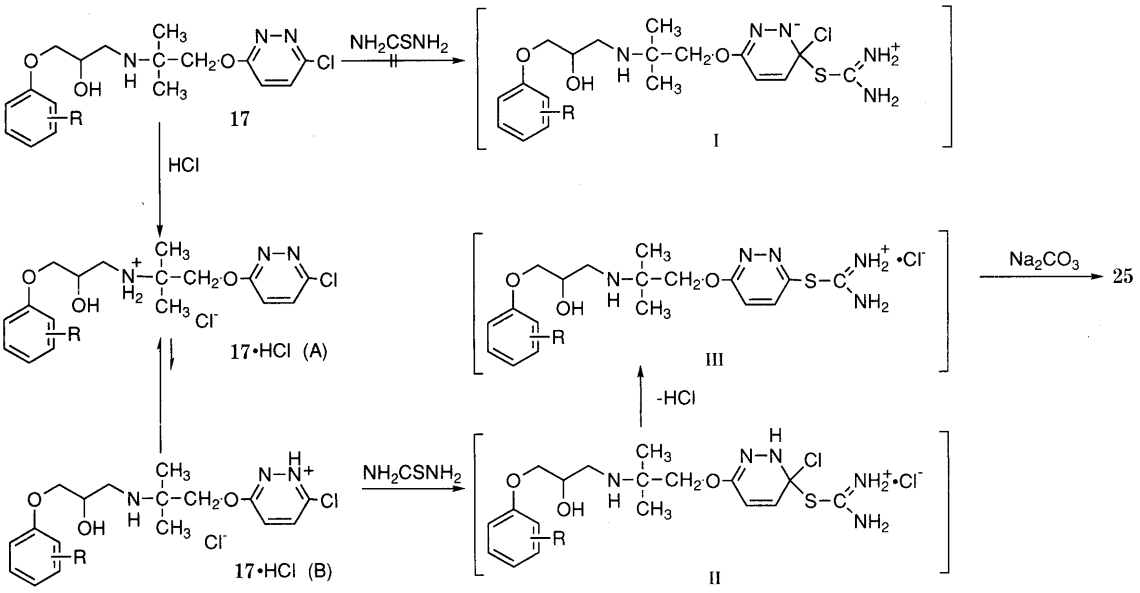


Chart 3

expected to proceed as follows (Chart 3): the hydrochloride of **17** in solution exists in equilibrium between the ammonium salt (A), the preferred form, and the pyridazinium salt (B). As in the case of chloropyridine,[8] the chlorine atom in the salt (B) allows smooth conversion to the thiuronium salt (III) *via* the intermediate (II), followed by hydrolysis to **25**. On the other hand the free base (**17**) hardly forms the thiuronium salt (III). Thus, the formation of the salt (B) is essential for this nucleophilic substitution.

Aminothiol (**11**) was synthesized according to the method described in the literature,[9] and aminobutanol (**10**) was prepared as follows: the Ritter reaction of 3-methyl-1,3-butanediol[10] with acetonitrile in sulfuric acid provided 2,4,4-trimethyl-4,5-dihydro-1,3-oxazine.[11] After hydrolysis the corresponding aminobutanol (**10**)[12] was obtained.

Synthesis of the pyridazine compounds having an amino or a carbamoyl group at the 3-position is shown in Chart 4. According to the method of Coleman and Callen,[13] ring opening of 2,2-dimethylethyleneimine (**26**)[14] by *N*,*N*-dibenzylamine in the presence of aluminum chloride afforded the diamine (**27**). The diaminopropanol (**29**) was obtained by the reaction of the glycidyl ether (**16**) with the diamine (**27**), followed by hydrogenolysis of the benzyl group using 10% palladium on charcoal as a catalyst.

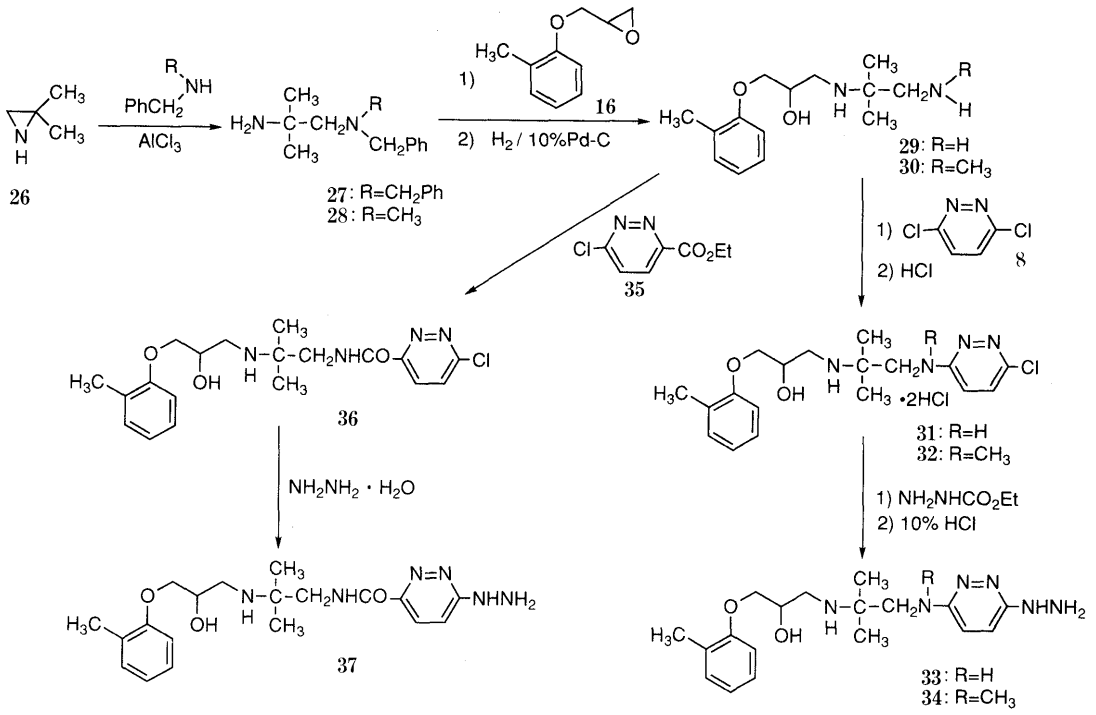


Chart 4

Reaction of **29** with **8** yielded the aminopyridazine (**31**). Steric hindrance to the adjacent amino group due to α-*gem*-dimethyl substitution apparently resulted in the selective attack of **8** at the terminal amino group. Compound **31** was converted to the hydrochloride to activate the chlorine atom[1] and then treated with ethoxycarbonylhydrazine,[15] followed by hydrolysis with 10% hydrochloric acid to give the final product **33**. The *N*-methyl analogue **34** was similarly obtained from **26** and *N*-methylbenzylamine.

Reaction of **29** with 3-chloro-6-ethoxycarbonylpyridazine (**35**)[16] yielded the carboxamide (**36**), followed by treatment with hydrazine hydrate to give the hydrazino compound **37**. The results are summarized in Tables I—III.

## Pharmacology

The hypotensive and β-blocking activities of **4** were examined in anesthetized rats using the procedures previously described.[1] Hydralazine and propranolol were used as reference drugs for hypotensive and β-blocking activities, respectively. The results are shown in Table IV.

The unsubstituted phenoxy compound **20m** showed both activities; it was one-fourth as active as hydralazine in terms of hypotensive activity and its β-blocking activity was half that of propranolol. These potencies were approximately the same as those of **1** (one-third of the hypotensive activity of hydralazine and one-third of the β-blocking activity of propranolol). These results encouraged us to make further modifications of **20**.

Monosubstitution on the phenyl ring at the *ortho*-position (**20a—l**) gave rise to potent hypotensive and β-blocking activities in comparison with those of **20m**, except in the case of the 2-fluoro derivative (**20l**), which showed no hypotensive activity.

It was reported that the lipophilicity of certain β-blockers was closely related to their β-blocking potency.[17] Therefore the partition coefficients of **20** were measured in order to see whether lipophilicity might be involved in the two activities (Table V). The order of lipophilicity was as follows: $CH_2CH=CH_2 > Cl > Et > Me > CH_2OMe > CN$. On the other hand, the order of hypotensive activity was as follows: $Cl > Me > CF_3$, $C\equiv CH$, CN, Et, $CH_2OMe > Br$, *n*-Pr, $CH_2CH_2OMe$, $CH_2CH=CH_2$. From these results, the hypotensive activity of this series of compounds seemed to depend not on the lipophilicity but rather on the bulkiness of the substituent on the phenyl ring.[18] For β-blocking activity as well, the less bulkier the *ortho*-substituent, the more potent was the activity.

The hypotensive and β-blocking activities of **20b** were one-half as active as that of hydralazine and 1.3 times more potent than that of propranolol, respectively and those of **20k** were equal to that of hydralazine and 2.7 times more potent than that of propranolol. In comparison with **1**, both activities of **20k** were much improved. Thus, introduction of a hydrazinopyridazinyl moiety into 1-aryloxy-3-isopropylamino-2-propanol at its nitrogen was effective in enhancing hypotensive activity.

In general the *ortho*-substitution of 1-aryloxy-3-isopropylamino-2-propanol led to an increase of β-blocking activity, as reported by Crowther *et al.*[19] However, in the case of 3-aryloxyethylamino- (**6**) and 3-arylthioethylamino-2-propanol (**7**), the *ortho*-substituent to the aminopropoxy moiety of the phenyl ring decreased the potencies.[3] In the case of 3-hydrazinopyridazinyloxyethylamino-2-propanol (**20**), the *ortho*-substitution gave rise to potent β-blocking activity accompanied by an increase of the hypotensive activity, while substitution at another position on the phenyl ring rather decreased both activities. Thus monosubstitution of the phenyl ring at the

TABLE I. Physical Properties of Chloropyridazines

| Compd.[a] No. | R | Yield (%) | mp (°C) | Formula | Analysis (%) Calcd C | Calcd H | Calcd N | Found C | Found H | Found N |
|---|---|---|---|---|---|---|---|---|---|---|
| **17a** | 2-CN | 74.6 | 168—170 | $C_{18}H_{21}ClN_4O_3 \cdot HCl$ | 52.31 | 5.37 | 13.56 | 52.40 | 5.40 | 13.78 |
| **17b** | 2-Me | 83.6 | 132—134 | $C_{18}H_{24}ClN_3O_3 \cdot HCl$ | 53.73 | 6.26 | 10.44 | 53.97 | 6.32 | 10.40 |
| **17c** | 2-Et | 51.2 | 129—131 | $C_{19}H_{26}ClN_3O_3 \cdot C_4H_4O_4$[b] | 55.70 | 6.10 | 8.47 | 55.68 | 6.15 | 8.58 |
| **17d** | 2-*n*-Pr | 74.5 | 128—130 | $C_{20}H_{28}ClN_3O_3 \cdot C_4H_4O_4$ | 56.52 | 6.33 | 8.24 | 56.57 | 6.48 | 8.14 |
| **17e** | 2-$CH_2CH=CH_2$ | 36.3 | 123—125 | $C_{20}H_{26}ClN_3O_3 \cdot C_4H_4O_4$ | 56.75 | 5.95 | 8.27 | 56.48 | 5.90 | 8.40 |
| **17f** | 2-C≡CH | 51.3 | 85—89 | $C_{19}H_{22}ClN_3O_3 \cdot HCl \cdot 0.5H_2O$ | 54.16 | 5.74 | 9.97 | 54.41 | 5.51 | 10.11 |
| **17g** | 2-$CH_2OMe$ | 82.0 | 182—183 | $C_{19}H_{26}ClN_3O_4 \cdot C_4H_4O_4$ | 53.96 | 5.91 | 8.21 | 54.22 | 5.83 | 8.47 |
| **17n** | 2-$CH_2CH_2OMe$ | 76.8 | 126—128 | $C_{20}H_{28}ClN_3O_4 \cdot C_4H_4O_4$ | 54.80 | 6.13 | 7.99 | 54.62 | 6.00 | 8.26 |
| **17i** | 2-$CF_3$ | 62.4 | 97—100 | $C_{18}H_{21}ClF_3N_3O_3$ | 51.49 | 5.04 | 10.01 | 51.57 | 5.02 | 10.02 |
| **17j** | 2-Br | 56.2 | 167—169 | $C_{17}H_{21}BrClN_3O_3 \cdot C_4H_4O_4$ | 46.12 | 4.61 | 7.68 | 45.97 | 4.57 | 7.58 |
| **17k** | 2-Cl | 88.2 | 97—99 | $C_{17}H_{21}Cl_2N_3O_3 \cdot HCl$ | 48.30 | 5.25 | 9.94 | 48.55 | 5.31 | 9.91 |
| **17l** | 2-F | 59.7 | 72—73 | $C_{17}H_{21}ClFN_3O_3$ | 55.21 | 5.72 | 11.36 | 55.26 | 5.81 | 11.61 |
| **17m** | H | 65.1 | 186—188 | $C_{17}H_{22}ClN_3O_3 \cdot C_4H_4O_4$ | 53.90 | 5.60 | 8.98 | 53.87 | 5.66 | 9.11 |
| **17n** | 3-Me | 79.5 | 84—86 | $C_{18}H_{24}ClN_3O_3$ | 59.09 | 6.61 | 11.49 | 58.96 | 6.48 | 11.32 |
| **17o** | 3-$CF_3$ | 39.2 | 89—91 | $C_{18}H_{21}ClF_3N_3O_3$ | 51.49 | 5.04 | 10.01 | 51.38 | 4.95 | 10.03 |
| **17p** | 3-Br | 61.6 | 83—85 | $C_{17}H_{21}BrClN_3O_3$ | 47.40 | 4.91 | 9.76 | 47.55 | 5.00 | 9.70 |
| **17q** | 3-Cl | 66.3 | 87—89 | $C_{17}H_{21}Cl_2N_3O_3$ | 52.86 | 5.48 | 10.88 | 52.89 | 5.56 | 11.00 |
| **17r** | 3-F | 52.6 | 82—85 | $C_{17}H_{21}ClFN_3O_3$ | 55.21 | 5.72 | 11.36 | 55.26 | 5.74 | 11.32 |
| **17s** | 2-CN-3-Me | 81.1 | 157—159 | $C_{19}H_{23}ClN_4O_3 \cdot HCl$ | 53.40 | 5.66 | 13.11 | 53.43 | 5.66 | 13.07 |
| **17t** | 2,3-$Me_2$ | 66.7 | 148—151 | $C_{19}H_{26}ClN_3O_3 \cdot HCl$ | 54.81 | 6.54 | 10.09 | 54.66 | 6.67 | 10.04 |
| **17u** | 2,3-$Cl_2$ | 83.6 | 189—190 | $C_{17}H_{20}Cl_3N_3O_3 \cdot C_4H_4O_4$ | 46.98 | 4.51 | 7.83 | 46.86 | 4.37 | 7.68 |
| **17v** | 2-Cl-3-Me | 76.9 | 175—177 | $C_{18}H_{23}Cl_2N_3O_3 \cdot HCl$ | 49.50 | 5.54 | 9.62 | 49.58 | 5.66 | 9.65 |
| **17w** | 2-CH=CH-CH=CH-3 | 83.9 | 156—158 | $C_{21}H_{24}ClN_3O_3 \cdot C_4H_4O_4$ | 57.97 | 5.45 | 8.11 | 57.83 | 5.35 | 8.18 |
| **17x** | 2-CN-5-Me | 70.5 | 175—176 | $C_{19}H_{23}ClN_4O_3 \cdot HCl$ | 53.40 | 5.66 | 13.11 | 53.48 | 5.68 | 13.11 |
| **17y** | 2-CN-5-Cl | 73.6 | 185—187 | $C_{18}H_{20}Cl_2N_4O_3 \cdot HCl$ | 48.28 | 4.73 | 12.51 | 48.44 | 4.81 | 12.21 |
| **17z** | 2,5-$Me_2$ | 76.9 | 174—176 | $C_{19}H_{26}ClN_3O_3 \cdot HCl$ | 54.81 | 6.54 | 10.09 | 54.88 | 6.60 | 9.94 |
| **17aa** | 2,5-$Cl_2$ | 85.4 | 155—156 | $C_{17}H_{20}Cl_3N_3O_3 \cdot HCl$ | 44.66 | 4.63 | 9.14 | 44.69 | 4.65 | 9.14 |
| **17ab** | 2-Cl-5-Me | 85.4 | 150—152 | $C_{18}H_{23}Cl_2N_3O_3 \cdot C_4H_4O_4$ | 51.17 | 5.27 | 8.14 | 51.20 | 5.22 | 8.22 |
| **17ac** | 3,5-$Me_2$ | 75.8 | 164—165 | $C_{19}H_{26}ClN_3O_3 \cdot HCl$ | 54.81 | 6.54 | 10.09 | 54.81 | 6.64 | 10.24 |
| **18a** | 2-CN | 59.2 | 176—178 | $C_{19}H_{23}ClN_4O_3 \cdot HCl$ | 53.40 | 5.66 | 13.11 | 53.57 | 5.53 | 13.17 |
| **18b** | 2-Me | 78.9 | 185—187 | $C_{19}H_{26}ClN_3O_3 \cdot HCl$ | 54.81 | 6.54 | 10.09 | 54.64 | 6.71 | 10.07 |
| **18c** | 2-Cl | 56.7 | 172—174 | $C_{18}H_{23}Cl_2N_3O_3 \cdot HCl$ | 49.50 | 5.54 | 9.62 | 49.39 | 5.42 | 9.49 |
| **18d** | 2-Cl-3-Me | 63.1 | 149—150 | $C_{19}H_{25}Cl_2N_3O_3 \cdot HCl$ | 50.62 | 5.81 | 9.32 | 50.62 | 5.93 | 9.32 |
| **18e** | 2-Cl-5-Me | 74.5 | 190—192 | $C_{19}H_{25}Cl_2N_3O_3 \cdot HCl$ | 50.62 | 5.81 | 9.32 | 50.73 | 5.87 | 9.44 |
| **19a** | 2-Me | 84.6 | 170—172 | $C_{18}H_{24}ClN_3O_2S \cdot 0.5(CO_2H)_2$ | 53.45 | 5.90 | 9.84 | 53.47 | 6.07 | 9.64 |
| **19b** | 2-Cl | 84.3 | 177—178 | $C_{17}H_{21}Cl_2N_3O_2S \cdot 0.5(CO_2H)_2$ | 48.32 | 4.96 | 9.39 | 48.47 | 4.92 | 9.41 |
| **19c** | 2-Cl-3-Me | 97.9 | 186—188 | $C_{18}H_{23}Cl_2N_3O_2S \cdot 0.5(CO_2H)_2$ | 49.46 | 5.24 | 9.11 | 49.44 | 5.22 | 8.92 |
| **19d** | 2-Cl-5-Me | 93.2 | 166—169 | $C_{18}H_{23}Cl_2N_3O_2S \cdot 0.5(CO_2H)_2$ | 49.46 | 5.24 | 9.11 | 49.32 | 5.20 | 9.21 |
| **31** | 2-Me | 67.8 | 165—167 | $C_{18}H_{25}ClN_4O_2 \cdot 2HCl$ | 49.38 | 6.22 | 12.80 | 49.48 | 6.26 | 12.58 |
| **32** | 2-Me[c] | 68.3 | Oil | | | | | | | |
| **36** | 2-Me | 53.0 | 170—172 | $C_{19}H_{25}ClN_4O_3 \cdot (CO_2H)_2$ | 52.23 | 5.64 | 11.60 | 52.37 | 5.72 | 11.49 |

*a*) The structures are shown in Charts 2 and 4. *b*) Maleate. *c*) Elemental analysis was not performed.

TABLE II. Physical Properties of Thioxopyridazines

| Compd.[a] No. | Recrystn. Solvent | Yield (%) | mp (°C) | Formula | Analysis (%) Calcd. C | Calcd. H | Calcd. N | Found C | Found H | Found N |
|---|---|---|---|---|---|---|---|---|---|---|
| **25a** | iso-PrOH–$H_2O$ | 84.8 | 78—81 | $C_{18}H_{22}N_4O_3S$ | 57.73 | 5.92 | 14.96 | 57.71 | 6.13 | 14.92 |
| **25b** | EtOH | 63.5 | 114—115 | $C_{18}H_{25}N_3O_3S$ | 59.47 | 6.93 | 11.56 | 59.46 | 7.03 | 11.53 |
| **25d** | iso-PrOH | 77.2 | 121—123 | $C_{20}H_{29}N_3O_3S$ | 61.35 | 7.47 | 10.73 | 61.31 | 7.61 | 11.02 |
| **25f** | iso-PrOH | 85.2 | 127—128 | $C_{19}H_{23}N_3O_3S$ | 61.10 | 6.21 | 11.25 | 61.05 | 6.18 | 11.34 |
| **25i** | EtOH | 63.3 | 144—145 | $C_{18}H_{22}F_3N_3O_3S$ | 51.79 | 5.31 | 10.07 | 51.90 | 5.36 | 9.99 |
| **25j** | iso-PrOH | 77.2 | 126—128 | $C_{17}H_{22}BrN_3O_3S \cdot 0.2H_2O$ | 47.27 | 5.23 | 9.72 | 47.06 | 5.27 | 9.81 |
| **25k** | EtOH | 96.0 | 141—143 | $C_{17}H_{22}ClN_3O_3S$ | 53.18 | 5.78 | 10.95 | 53.41 | 5.88 | 10.88 |
| **25m** | iso-PrOH | 65.6 | 126—128 | $C_{17}H_{23}N_3O_3S$ | 58.43 | 6.63 | 12.03 | 58.47 | 6.63 | 12.28 |
| **25s** | iso-PrOH | 75.9 | 153—155 | $C_{19}H_{24}N_4O_3S \cdot 0.1H_2O$ | 58.47 | 6.25 | 14.36 | 58.35 | 6.28 | 14.48 |
| **25t** | iso-PrOH | 41.5 | 169—171 | $C_{19}H_{27}N_3O_3S$ | 60.45 | 7.21 | 11.13 | 60.19 | 7.44 | 11.07 |
| **25u** | MeOH | 62.3 | 150—152 | $C_{17}H_{21}Cl_2N_3O_3S$ | 48.80 | 5.06 | 10.04 | 48.91 | 4.95 | 10.24 |
| **25w** | EtOH | 94.0 | 167—169 | $C_{21}H_{25}N_3O_3S \cdot C_4H_4O_4$[b] | 58.24 | 5.67 | 8.15 | 58.15 | 5.76 | 8.15 |
| **25y** | MeOH | 66.8 | 171—172 | $C_{18}H_{21}ClN_4O_3S$ | 52.87 | 5.18 | 13.70 | 52.84 | 5.17 | 13.68 |
| **25aa** | MeOH | 72.7 | 160—162 | $C_{17}H_{21}Cl_2N_3O_3S$ | 48.80 | 5.06 | 10.04 | 48.82 | 4.99 | 10.12 |
| **25ab** | MeOH | 88.8 | 137—139 | $C_{18}H_{24}ClN_3O_3S$ | 54.33 | 6.08 | 10.56 | 54.17 | 6.12 | 10.46 |

*a*) The structures are shown in Chart 2. *b*) Maleate.

TABLE III. Physical Properties of Hydrazinopyridazines and Their Derivatives

| Compd.[a] No. | Yield (%) | mp (°C) | Formula[b] | Analysis (%) Calcd C | Calcd H | Calcd N | Found C | Found H | Found N |
|---|---|---|---|---|---|---|---|---|---|
| **20a** | (51.8)[c] | 183—188 | $C_{18}H_{24}N_6O_3 \cdot 2HCl$ | 48.54 | 5.88 | 18.87 | 48.31 | 5.81 | 19.05 |
| **20b** | (70.3) | 181—182 | $C_{18}H_{27}N_5O_3 \cdot 2HCl$ | 49.77 | 6.73 | 16.12 | 49.87 | 6.91 | 15.94 |
| **20c** | 14.8 | 184—186 | $C_{19}H_{29}N_5O_3 \cdot 2HCl$ | 50.89 | 6.97 | 15.62 | 50.97 | 6.86 | 15.61 |
| **20d** | (65.8) | 184—187 | $C_{20}H_{31}N_5O_3 \cdot 2HCl$ | 51.95 | 7.19 | 15.15 | 51.85 | 7.34 | 15.10 |
| **20e** | 17.9 | 170—172 | $C_{20}H_{29}N_5O_3 \cdot 2HCl \cdot 0.2H_2O$ | 51.77 | 6.82 | 15.09 | 51.77 | 6.72 | 14.86 |
| **20f** | 4.6 | 188—189 | $C_{19}H_{25}N_5O_3 \cdot 2HCl \cdot 0.2H_2O$ | 50.94 | 6.17 | 15.64 | 50.71 | 6.31 | 15.46 |
| **20g** | 29.5 | 174—177 | $C_{19}H_{29}N_5O_4 \cdot 2HCl$ | 49.14 | 6.73 | 15.08 | 49.14 | 6.81 | 15.18 |
| **20h** | 2.9 | 183—184 | $C_{20}H_{31}N_5O_4 \cdot 2HCl$ | 50.21 | 6.95 | 14.64 | 50.21 | 6.78 | 14.68 |
| **20i** | 25.2 | 191—194 | $C_{18}H_{24}F_3N_5O_3 \cdot 2HCl$ | 44.27 | 5.37 | 14.34 | 44.03 | 5.41 | 14.43 |
| **20j** | (66.7) | 181—184 | $C_{17}H_{24}BrN_5O_3 \cdot 2HCl \cdot 0.1H_2O$ | 40.75 | 5.27 | 13.98 | 40.54 | 5.07 | 14.15 |
| **20k** | (71.0) | 186—188 | $C_{17}H_{24}ClN_5O_3 \cdot 2HCl$ | 44.89 | 5.76 | 15.40 | 44.96 | 5.64 | 15.31 |
| **20l** | 26.0 | 178—180 | $C_{17}H_{24}FN_5O_3 \cdot 2HCl$ | 46.58 | 5.98 | 15.98 | 46.50 | 6.16 | 16.26 |
| **20m** | (49.6) | 177—178 | $C_{17}H_{25}N_5O_3 \cdot 2HCl$ | 48.57 | 6.48 | 16.66 | 48.42 | 6.21 | 16.73 |
| **20n** | (61.4) | 172—175 | $C_{18}H_{27}N_5O_3 \cdot 2HCl$ | 49.77 | 6.73 | 16.12 | 49.84 | 6.80 | 16.26 |
| **20o** | 25.0 | 183—185 | $C_{18}H_{24}F_3N_5O_3 \cdot 2HCl$ | 44.27 | 5.37 | 14.34 | 44.27 | 5.37 | 14.59 |
| **20p** | 5.5 | 180—183 | $C_{17}H_{24}BrN_5O_3 \cdot 2HCl$ | 40.90 | 5.25 | 14.03 | 40.98 | 5.30 | 14.11 |
| **20q** | (47.9) | 174—177 | $C_{17}H_{24}ClN_5O_3 \cdot 2HCl$ | 44.89 | 5.76 | 15.40 | 44.97 | 5.80 | 15.62 |
| **20r** | 24.3 | 175—176 | $C_{17}H_{24}FN_5O_3 \cdot 2HCl$ | 46.58 | 5.98 | 15.98 | 46.52 | 6.01 | 16.16 |
| **20s** | (47.3) | 189—191 | $C_{19}H_{26}N_6O_3 \cdot 2HCl$ | 49.67 | 6.14 | 18.30 | 49.81 | 6.29 | 18.25 |
| **20t** | (65.8) | 187—189 | $C_{19}H_{29}N_5O_3 \cdot 2HCl$ | 50.89 | 6.97 | 15.62 | 50.70 | 7.26 | 15.64 |
| **20u** | (78.8) | 191—193 | $C_{17}H_{23}Cl_2N_5O_3 \cdot 2HCl$ | 41.73 | 5.15 | 14.32 | 41.75 | 5.13 | 14.25 |
| **20v** | 18.8 | 192—194 | $C_{18}H_{26}ClN_5O_3 \cdot 2HCl$ | 46.11 | 6.02 | 14.94 | 46.26 | 5.87 | 15.12 |
| **20w** | (58.9) | 192—194 | $C_{21}H_{27}N_5O_3 \cdot 2HCl$ | 53.62 | 6.21 | 14.89 | 53.50 | 6.14 | 14.87 |
| **20x** | 16.2 | 190—191 | $C_{19}H_{26}N_6O_3 \cdot 2HCl$ | 49.67 | 6.14 | 18.30 | 49.50 | 6.31 | 18.05 |
| **20y** | (49.7) | 189—191 | $C_{18}H_{23}ClN_6O_3 \cdot 2HCl$ | 45.06 | 5.25 | 17.52 | 44.92 | 5.25 | 17.31 |
| **20z** | (58.3) | 187—190 | $C_{19}H_{29}N_5O_3 \cdot 2HCl$ | 50.89 | 6.97 | 15.62 | 50.87 | 7.06 | 15.74 |
| **20aa** | (68.4) | 190—191 | $C_{17}H_{23}Cl_2N_5O_3 \cdot 2HCl$ | 41.73 | 5.15 | 14.32 | 41.64 | 5.13 | 14.30 |
| **20ab** | (65.8) | 183—186 | $C_{18}H_{26}ClN_5O_3 \cdot 2HCl$ | 46.11 | 6.02 | 14.94 | 45.99 | 6.13 | 14.73 |
| **20ac** | 14.1 | 183—186 | $C_{19}H_{29}N_5O_3 \cdot 2HCl$ | 50.89 | 6.97 | 15.62 | 50.73 | 7.15 | 15.77 |
| **21a** | 20.4 | 157—160 | $C_{19}H_{26}N_6O_3 \cdot 2HCl$ | 49.67 | 6.14 | 18.30 | 49.40 | 6.18 | 18.04 |
| **21b** | 20.5 | 182—185 | $C_{19}H_{29}N_5O_3 \cdot 2HCl$ | 50.89 | 6.97 | 15.62 | 51.02 | 7.19 | 15.59 |
| **21c** | 20.9 | 143—144 | $C_{18}H_{26}ClN_5O_3 \cdot 2HCl$ | 46.11 | 6.02 | 14.94 | 46.10 | 5.98 | 14.90 |
| **21d** | 24.1 | 172—175 | $C_{19}H_{28}ClN_5O_3 \cdot 2HCl$ | 47.26 | 6.26 | 14.51 | 47.04 | 6.23 | 14.68 |
| **21e** | 30.4 | 191—194 | $C_{19}H_{28}ClN_5O_3 \cdot 2HCl$ | 47.26 | 6.26 | 14.51 | 47.48 | 6.43 | 14.25 |
| **22a** | 86.2 | 207—210 | $C_{18}H_{27}N_5O_2S \cdot 2HCl$ | 47.99 | 6.49 | 15.55 | 48.06 | 6.47 | 15.25 |
| **22b** | 84.3 | 211—212 | $C_{17}H_{24}ClN_5O_2S \cdot 2HCl$ | 43.36 | 5.57 | 14.88 | 43.21 | 5.52 | 14.64 |
| **22c** | 93.8 | 198—200 | $C_{18}H_{26}ClN_5O_2S \cdot 2HCl$ | 44.58 | 5.82 | 14.44 | 44.49 | 5.87 | 14.36 |
| **22d** | 44.4 | 201—202 | $C_{18}H_{26}ClN_5O_2S \cdot 2HCl$ | 44.58 | 5.82 | 14.44 | 44.43 | 5.81 | 14.26 |
| **23a** | 76.1 | 124—127 | $C_{21}H_{28}N_6O_3$ | 61.14 | 6.84 | 20.38 | 61.01 | 6.91 | 20.38 |
| **23c** | 88.4 | 139—142 | $C_{22}H_{33}N_5O_3 \cdot 2HCl$ | 54.09 | 7.22 | 14.34 | 54.03 | 7.26 | 14.61 |
| **23i** | 89.6 | 140—142 | $C_{21}H_{28}F_3N_5O_3 \cdot 2HCl \cdot 0.5H_2O$ | 46.93 | 5.81 | 13.03 | 46.89 | 5.86 | 13.00 |
| **23k** | 98.3 | 164—166 | $C_{20}H_{28}ClN_5O_3 \cdot 2HCl$ | 48.54 | 6.11 | 14.15 | 48.41 | 6.29 | 14.28 |
| **24k** | 49.1 | 156—157 | $C_{20}H_{28}ClN_5O_5 \cdot 2HCl$ | 45.59 | 5.74 | 13.29 | 45.32 | 5.76 | 13.20 |
| **33** | 18.4 | 172—174 | $C_{18}H_{28}N_6O_2 \cdot 3HCl$ | 46.01 | 6.65 | 17.89 | 45.81 | 6.76 | 17.72 |
| **34** | 29.5 | 135—137 | $C_{26}H_{34}N_6O_2 \cdot 0.5H_2O$[d] | 66.21 | 7.48 | 17.82 | 66.26 | 7.40 | 17.67 |
| **37** | 77.7 | 178—180 | $C_{19}H_{28}N_6O_3 \cdot 2HCl$ | 49.46 | 6.55 | 18.22 | 49.41 | 6.80 | 18.07 |

*a*) The structures are shown in Charts 2 and 4. *b*) Recrystallization from EtOH, except for **23**, **24** and **34**, which were done from EtOH–acetone. *c*) Yields from thioxopyridazines (**25**). *d*) Benzylidenehydrazone.

*meta*-position (**20n—r**) led to a great reduction of both potencies in comparison with the corresponding *ortho*-monosubstituted compound and none of the compounds was superior to **20m**. Moreover, the 3,5-disubstituted compound (**20ac**) showed less potent $\beta$-blocking activity than those of the corresponding 2,3- and 2,5-disubstituted compounds (**20t** and **z**), and each of them was inferior to the corresponding *ortho*-monosubstituted one. As for the hypotensive activity, the 2,5-disubstituted phenoxy compounds (**20x—ab**) were better than the corresponding 2,3- or 3,5-disubstituted derivatives (**20s—v** and **ac**) and some of them were more potent than **20m**. No hypotensive activity was observed in the case of the $\alpha$-naphthyloxy derivative (**20w**).

The effect of methylene chain length ($n$) between the nitrogen atom and the pyridazine ring was next examined. Lengthening of the methylene chain of **20** ($n=1$), which showed potent and long-lasting hypotensive activity, resulted in retention of the hypotensive activity, though it became transient. On the other hand, $\beta$-blocking activity was remarkably reduced in comparison with that of the corresponding **20**. This result is compatible with those obtained from non-branched derivatives.[4,20] Thus when the hypotensive activity is weak, the $\beta$-blocking

TABLE IV. Pharmacological Properties of Hydrazinopyridazines and Their Derivatives

| Compd.[a] No. | Hypotensive activity[b] | β-Blocking activity[c] |
|---|---|---|
| **20a** | +++ | 1.0 |
| **20b** | +++ | 1.3 |
| **20c** | +++ | 0.4 |
| **20d** | +++ | 0.12 |
| **20e** | +++ | 0.25 |
| **20f** | +++ | 1.0 |
| **20g** | +++ | 0.75 |
| **20h** | +++ | 0.25 |
| **20i** | +++ | 0.75 |
| **20j** | +++ | NT[d] |
| **20k** | +++ | 2.7 |
| **20l** | ± | NT |
| **20m** | ++ | 0.5 |
| **20n** | ++ | 0.2 |
| **20o** | ++ | 0.05 |
| **20p** | ++ | 0.05 |
| **20q** | ++ | 0.08 |
| **20r** | ++ | 0.33 |
| **20s** | ± | 0.5 |
| **20t** | + | 0.14 |
| **20u** | + | 0.2 |
| **20v** | ++ | 0.25 |
| **20w** | ± | 0.25 |
| **20x** | +++ | 0.4 |
| **20y** | ++ | 0.17 |
| **20z** | +++ | 0.17 |
| **20aa** | + | 0.1 |
| **20ab** | +++ | 0.14 |
| **20ac** | ++ | 0.08 |
| **21a** | +++ | 0.5 |
| **21b** | +++ | 0.4 |
| **21c** | +++ | 0.2 |
| **21d** | ++ | 0.1 |
| **21e** | ++ | 0.07 |
| **22a** | ++ | 0.5 |
| **22b** | ++ | 0.25 |
| **22c** | + | 0.17 |
| **22d** | + | 0.14 |
| **23a** | ++ | 0.1 |
| **23c** | + | NT[d] |
| **23i** | +++ | NT |
| **23k** | +++ | NT |
| **24k** | + | 1.3 |
| **33** | + | 4.0 |
| **34** | + | NT |
| **37** | ± | 0.04 |
| **1** | +++ | 0.33 |
| Hydralazine | +++ | NT |
| Propranolol | NT | 1.0 |

Each compound was injected intravenously into anesthetized rats. *a*) The structures are shown in Charts 1, 2 and 4. *b*) Degree of hypotension induced at 1 mg/kg: +++, ≧35 mmHg; ++, 25—34 mmHg; +, 15—24 mmHg; ±, <15 mmHg. *c*) Potency relative to the $ID_{50}$ value of propranolol. *d*) NT = not tested.

activity is also weak, suggesting that appearance of both activities is linked.

In our previous study,[1] the conversion of the hydrazino group to the acetone hydrazone as in the case of **1** resulted in potentiation of both activities. Hydrazonization seemed effective for protection of the hydrazino group from metabolic inactivation. However, in the case of **20**, the hypotensive activities of the corresponding acetone hydrazones (**23**) decreased. The β-blocking activity of **23a** was also very weak. Therefore, the steric effect of the hydrazinopyridazinyloxy moiety may have an important influence on both activities.

TABLE V. Hydrophobicities of Hydrazinopyridazines

| Compd.[a] No. | R | $\lambda_{max}$[b] (nm) | log $P$[c] |
|---|---|---|---|
| **1** | | 265 | 1.43 |
| **20a** | 2-CN | 266 | 0.48 |
| **20b** | 2-Me | 269 | 0.98 |
| **20c** | 2-Et | 269 | 1.03 |
| **20e** | $2\text{-}CH_2CH{=}CH_2$ | 267 | 1.39 |
| **20g** | $2\text{-}CH_2OMe$ | 267 | 0.49 |
| **20k** | 2-Cl | 267 | 1.06 |
| **20s** | 2-CN-3-Me | 268 | 0.88 |
| **20x** | 2-CN-5-Me | 269 | 0.73 |

*a*) The structures are shown in Charts 1 and 2. *b*) Wavelength for UV detection. *c*) Logarithm of *n*-octanol/McIlvaine's buffer pH 7.4 partition coefficient determined by the shaken flask method at 28—30°C.

Conversion of **20k** to the carbazate (**24k**) remarkably decreased the hypotensive activity, probably owing to slow elimination of the ethoxycarbonyl group.

It was reported that 3-substituted-6-hydrazinopyridazines possessed potent and long-lasting hypotensive activities, and the 3-alkylamino compounds were superior to the 3-alkoxy compounds.[21] We changed the 3-alkoxy moiety to 3-alkylthio, 3-alkylamino and 3-alkylaminocarbonyl and examined the change of activity. The results are shown in Table VI as relative potencies between **1** and **20b**, **k**, **v**, **ab** when the pyridazine ether oxygen of **20** was replaced with sulfur, nitrogen, or a carbamoyl group.

In our previous study,[1] replacement of the pyridazine ether oxygen of **1** with sulfur and nitrogen atoms resulted in retention of the potencies. On the other hand the conversion of **20** to the corresponding thioether (**22**) reduced both activities (**22a**, one-fourth as active as hydralazine and one-half as active as propranolol). In the case of the amine (**33**) the hypotensive activity was remarkably reduced but the β-blocking activity was enhanced about 3 times over the corresponding **20**. Thus **33** showed 7 times less potent hypotensive activity than hydralazine and 4 times more potent β-blocking activity than propranolol.

6-Hydrazino-3-pyridazinecarboxamide (**38**, hydracarbazine), a potent vasodilator, was taken up as another lead compound.[22] The carboxamide derivative (**37**), however, had no hypotensive activity and only a slight β-blocking activity (25 times less potent than propranolol).

Table VII gives the doses of compounds **20b** and **20k** causing 50% inhibition of the tachycardia and hypotension produced by isoproterenol. The ratio of these two values gives an indication of the selectivity for $\beta_1$ (cardiac) over $\beta_2$ (vascular) receptors. Such cardioselectivity, *i.e.*, $\beta_1$-selectivity, was observed when the aryloxypropanolamine has a *para*-substituent on its aryl ring[23] or a suitably substituted phenoxyalkyl group on its amino group, such as **6**.[3] Though the *para*-isomer of **1**, resembling metoprolol, one of the $\beta_1$-blockers, was previously found to have no β-blocking activity at all but a potent hypotensive activity.[1] *gem*-Dimethyl compounds **20b** (TZC-1365) and **20k** (TZC-1370) showed more potent

TABLE VI. Pharmacological Activities of Pyridazine Derivatives (4)[a]

| R | X=O | | | X=S | | | X=NH | | | X=CONH | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Compd. No. | HA[b] | β-BA[c] | Compd. No. | HA | β-BA | Compd. No. | HA | β-BA | Compd. No. | HA | β-BA |
| | **1** | 0.33 | 0.33 | **2** | 0.33 | 0.2 | **3**[d] | 0.33 | 0.8 | **38**[e] | 1.5 | NT[f] |
| 2-Me | **20b** | 0.5 | 1.3 | **22a** | 0.25 | 0.5 | **33** | 0.15 | 4.0 | **37** | —[g] | 0.04 |
| 2-Cl | **20k** | 1.0 | 2.7 | **22b** | 0.22 | 0.25 | | | | | | |
| 2-Cl-3-Me | **20v** | 0.25 | 0.25 | **22c** | 0.17 | 0.17 | | | | | | |
| 2-Cl-5-Me | **20ab** | 0.3 | 0.17 | **22d** | 0.17 | 0.14 | | | | | | |

*a*) The structures are shown in Chart 1. *b*) HA = hypotensive activity. (Potency relative to hydralazine). *c*) β-BA = β-blocking activity. (Potency relative to propranolol). *d*) X = NMe. *e*) Hydracarbazine. *f*) NT = not tested. *g*) No hypotensive activity at the dose of 1 mg/kg i.v.

TABLE VII. β-Blocking Activities of Hydrazinopyridazines

| Compd.[a] No. | $n$[b] | $\beta_1$-BA[c] | $\beta_2$-BA[d] | Ratio[e] |
|---|---|---|---|---|
| Propanolol | 10 | 20.6 | 38 | 1.8 |
| Atenolol | 5 | 46.0 | >1000[f] | >22 |
| **20b** | 5 | 15.7 | 460 | 29 |
| **20k** | 5 | 7.5 | 300 | 40 |

β-Blocking activities were evaluated in terms of antagonism of isoproterenol (0.1 μg/kg i.v.)-induced tachycardia and hypotension in anesthetized rats. *a*) The structures are shown in Chart 2. *b*) Number of experiments. *c*) $\beta_1$-BA = $\beta_1$-blocking activity. Dose (μg/kg i.v.) giving 50% inhibition of tachycardia. *d*) $\beta_2$-BA = $\beta_2$-blocking activity. Dose (μg/kg i.v.) giving 50% inhibition of hypotension. *e*) $\beta_2/\beta_1$. *f*) 44% inhibition of hypotension.

$\beta_1$-blocking activities than atenolol, a known $\beta_1$-blocker, and unexpectedly their $\beta_1$-selectivities were comparable to that of atenolol. In particular, **20k** was 6 times more potent than atenolol and had a similar degree of $\beta_1$-selectivity to atenolol. According to Tucker's report on a series of thioether derivatives (**7**),[4] *gem*-dimethylation at the α-position to the nitrogen atom decreased the $\beta_1$-selectivity. It is noteworthy, however, that in the case of both **20b** and **20k** cardioselectivity remained irrespective of α-*gem*-dimethyl substitution.

## Conclusion

In the present study, a series of novel hydrazinopyridazine derivatives was synthesized with the aim of finding a hybrid compound with both vasodilator and β-blocking activities. Compounds **20a—k**, having an *ortho*-monosubstituted phenyl group, exhibited potent dual activities. In particular, **20b** (*ortho*-methyl) and **20k** (*ortho*-chloro) exhibited the most potent hypotensive and $\beta_1$-selective blocking activities, and were selected for further study as candidate antihypertensives.

### Experimental

Melting points were determined with a Mettler FP-2 melting point apparatus and are uncorrected. NMR spectra were taken at 60 MHz on a Hitachi R-20A with tetramethylsilane (TMS) or sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) as an internal standard. Mass spectra were determined with a Shimadzu GCMS-QP 1000 instrument. UV spectra were measured with a Hitachi U-3210 spectrophotometer. Elemental analysis results were within ±0.3% of the theoretical values.

**3-(2-Amino-2-methylpropoxy)-6-chloropyridazine (12)** A solution of an aminoalcohol (**9**) (31.3 g, 0.352 mol) in *tert*-BuOH (50 ml) was added dropwise to a mixture of **8** (50 g, 0.336 mol), 60% NaH in oil (16.1 g, 0.403 mol) and dry $C_6H_6$ (300 ml), with stirring at 25—35 °C. Stirring was continued for 1 h, then the precipitates were removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was dissolved in EtOH (100 ml) and acidified with 20% ethanolic HCl. The resulting precipitates were collected by filtration to give **12** (57.05 g, 71.4%) as a colorless hydrochloride. mp 195—197 °C. NMR ($D_2O$) δ: 1.58 (6H, s), 4.50 (2H, s), 7.40 (1H, d, $J$=9 Hz), 7.79 (1H, d, $J$=9 Hz). MS *m/z*: 202 ($M^+$+1), 201 ($M^+$), 58 (base peak). *Anal.* Calcd for $C_8H_{12}ClN_3O \cdot HCl$: C, 40.35; H, 5.50; N, 17.65. Found: C, 40.34; H, 5.39; N, 17.94.

The hydrochloride (57.0 g) was dissolved in $H_2O$ (120 ml) and made alkaline with $Na_2CO_3$. The separated oily material was extracted with $CHCl_3$. The organic layer was dried over $MgSO_4$, and the solvent was removed under reduced pressure to afford **12** (42.15 g, 87.3%) as colorless crystals. NMR ($CDCl_3$) δ: 1.22 (6H, s), 1.49 (2H, s), 4.23 (2H, s), 7.03 (1H, d, $J$=9 Hz), 7.42 (1H, d, $J$=9 Hz).

**3-(3-Amino-3-methylbutoxy)-6-chloropyridazine (13)** $CH_3CN$ (4.0 g, 97.6 mmol) was added dropwise to $H_2SO_4$ (18 ml) under ice-cooling with stirring. 3-Methyl-1,3-butanediol (8.6 g, 82.7 mmol) was added to this mixture over a period of 2 h. Stirring was continued for 2 h under ice-cooling, then the reaction mixture was poured onto ice (70 g). The whole was made alkaline with 10% NaOH and extracted with $Et_2O$. The organic layer was dried over $Na_2SO_4$ and concentrated under reduced pressure. The residue was purified by distillation to give 2,4,4-trimethyl-4,5-dihydrooxazine (5.92 g, 56.4%) as a colorless oil. bp 65—72 °C (40 mmHg).

A mixture of the oxazine (2.8 g, 22 mmol) and 10% NaOH (12 ml) was refluxed for 20 h. After cooling, the reaction mixture was extracted with $Et_2O$. The organic layer was dried over KOH and concentrated. The residue was purified by distillation to give aminobutanol (**10**) (1.33 g, 58.5%) as a colorless oil. bp 69—73°C (10 mmHg). [lit.[9] bp 71 °C (9 mmHg)].

A solution of **10** (17.8 g, 0.173 mol) in *tert*-BuOH (40 ml) and dry $C_6H_6$ (60 ml) was added dropwise to a mixture of **8** (25.8 g, 0.173 mol), 60% NaH in oil (8.4 g, 0.21 mol) and dry $C_6H_6$ (135 ml), with stirring at 25—35 °C. Stirring was continued for 1 h, then the reaction mixture was poured into ice-water. The organic layer was separated and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was recrystallized from $C_6H_6$–*n*-hexane to yield **13** (32.08 g, 86.0%) as colorless crystals. mp 63—65 °C. NMR ($CDCl_3$) δ: 1.20 (6H, s), 1.32 (2H, br s), 1.90 (2H, t, $J$=7 Hz), 4.61 (2H, t, $J$=7 Hz), 6.88 (1H, d, $J$=9 Hz), 7.33 (1H, d, $J$=9 Hz). An analytical sample was recrystallized from EtOH as a hydrochloride. mp 234—236 °C. MS *m/z*: 216 ($M^+$+1), 215 ($M^+$), 58 (base peak). *Anal.* Calcd for $C_9H_{14}ClN_3O \cdot HCl$: C, 42.87; H, 6.00; N, 16.67. Found: C, 42.94; H, 5.99; N, 16.94.

**3-(2-Amino-2-methylpropylthio)-6-chloropyridazine (14)** *tert*-BuOH (28 ml, 0.295 mol) was added dropwise to a mixture of 2-amino-2-methylpropanethiol hydrochloride (**11**) (14.15 g, 0.1 mol), **8** (14.9 g, 0.1 mol), 60% NaH in oil (8.2 g, 0.205 mol) and dry $C_6H_6$ (135 ml), with stirring at 25—35 °C. Stirring was continued for 1 h, then the reaction mixture was treated as described above. Recrystallization from $C_6H_6$–*n*-hexane gave **14** (19.91 g, 91.5%) as pale yellow crystals. mp 67—69 °C. NMR ($CDCl_3$) δ: 1.24 (6H, s), 1.42 (2H, s), 3.51 (2H, s), 7.15 (1H, d, $J$=9 Hz), 7.35 (1H, d, $J$=9 Hz). MS *m/z*: 218 ($M^+$+1), 217 ($M^+$), 58 (base peak). *Anal.* Calcd for $C_8H_{12}ClN_3S$: C, 44.13; H, 5.56; N, 19.30. Found: C, 44.25; H, 5.47; N, 19.22.

**3-Chloro-6-(1,1-dimethyl-2-hydroxyethylamino)pyridazine (15)** A mixture of **8** (300 mg, 2.01 mmol) and aminoalcohol (**9**) (1 ml) was heated

at 160 °C for 2 h. After cooling, $H_2O$ was added to the reaction mixture and the whole was extracted with $CHCl_3$. The organic layer was dried over $Na_2SO_4$ and concentrated under reduced pressure. The residue was recrystallized from acetone–ether to give **15** (152 mg, 37.4%) as pale yellow needles. mp 131—133 °C NMR ($CDCl_3$) $\delta$: 1.39 (6H, s), 3.67 (2H, s), 5.25 (1H, br s), 5.78 (1H, br s), 6.76 (1H, d, $J$=9 Hz), 7.14 (1H, d, $J$=9 Hz). MS $m/z$: 201 ($M^+$). *Anal.* Calcd for $C_8H_{12}ClN_3O$: C, 47.65; H 6.00; N, 20.84. Found: C, 47.60; H 6.06; N, 21.14.

**1-(2-Chlorophenoxy)-3-[1,1-dimethyl-2-(3-chloro-6-pyridazinyloxy)-ethylamino]-2-propanol (17k)** A solution of **12** (3.08 g, 15.3 mmol) and 1-(2-chlorophenoxy)-2,3-epoxypropane (2.82 g, 15.3 mmol) in *tert*-BuOH (40 ml) was stirred for 8 h at 60 °C. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography to give **17k** (4.87 g, 88.2%) as a colorless oil. NMR ($CDCl_3$) $\delta$: 1.21 (6H, s), 2.50—3.04 (4H, m), 4.00 (3H, br s), 4.33 (2H, s), 6.70—7.45 (4H, m), 6.90 (1H, d, $J$=9 Hz), 7.31 (1H, d, $J$=9 Hz). **17k** (4.87 g, 12.6 mmol) was dissolved in EtOH (25 ml) and treated with 20% ethanolic HCl (5 g, 27.4 mmol). This solution was kept overnight at room temperature, and the resulting precipitates were collected by filtration to give **17k** (5.01 g, 94.0%) as a colorless hydrochloride. mp 97—99 °C. NMR ($CD_3OD$) $\delta$: 1.58 (6H, s), 3.27—3.60 (2H, m), 4.00—4.55 (3H, m), 4.64 (2H, s), 6.80—7.60 (4H, m), 7.29 (1H, d, $J$=9 Hz), 7.69 (1H, d, $J$=9 Hz). MS $m/z$: 386 ($M^+$+1), 385 ($M^+$), 242 (base peak). *Anal.* Calcd for $C_{17}H_{21}Cl_2N_3O_3 \cdot HCl$: C, 48.30; H, 5.25; N, 9.94. Found: C, 48.55; H, 5.31; N, 9.91.

Compounds **17**—**19** were prepared from the corresponding amines (**12**—**14**) and glycidyl ethers (**16**), as described above.

**1-(2-Chloro-5-methylphenoxy)-3-[1,1-dimethyl-2-(3-hydrazino-6-pyridazinylthio)ethylamino]-2-propanol Dihydrochloride (22d)** A solution of **19d** (550 mg, 1.32 mmol) and hydrazine hydrate (5 ml) in EtOH (5 ml) was refluxed for 5 h with stirring. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in $CHCl_3$. The solution was washed twice with $H_2O$ and dried over $MgSO_4$. The solvent was then removed under reduced pressure and the residue was dissolved in EtOH (100 ml) and treated with 20% ethanolic HCl. The solvent was removed under reduced pressure and the residue was recrystallized from EtOH to give **22d** (601 mg, 93.8%) as colorless crystals. mp 201—202 °C. NMR ($D_2O$) $\delta$: 1.61 (6H, s), 2.36 (3H, s), 3.51 (2H, d, $J$=5 Hz), 3.72 (2H, s), 4.08—4.57 (3H, m), 6.70—7.60 (3H, m), 7.15 (1H, d, $J$=9 Hz), 7.41 (1H, d, $J$=9 Hz). MS $m/z$: 412 ($M^+$+1), 411 ($M^+$), 256 (base peak). *Anal.* Calcd for $C_{18}H_{26}ClN_5O_2S \cdot 2HCl$: C, 44.58; H, 5.82; N, 14.44. Found: C, 44.43; H, 5.81; N, 14.26.

Compounds **20**—**22** were prepared from the corresponding chlorides (**17**—**19**) and hydrazine hydrate, as described above.

**1-(2-Chlorophenoxy)-3-[1,1-dimethyl-2-[3(2*H*)-thioxo-6-pyridazinyl-oxy]ethylamino]-2-propanol (25k)** A solution of **17k** (10 g, 23.7 mmol) and thiourea (2.16 g, 28.4 mmol) in MeOH (50 ml) was stirred for 4 h at 60 °C. The solvent was removed under reduced pressure. Then, 10% $Na_2CO_3$ (30 ml) was added to the residue and the mixture was stirred for 3 h. The resulting yellow solid was collected by filtration, washed with $H_2O$ and dried. Recrystallization from EtOH gave **25k** (7.29 g, 80.3%) as yellow crystals. mp 141—142 °C. NMR ($CD_3OD$) $\delta$: 1.21 (6H, s), 2.69—2.99 (2H, m), 4.05 (3H, br s), 4.08 (2H, s), 6.83—7.40 (4H, m), 6.83 (1H, d, $J$=9 Hz), 7.50 (1H, d, $J$=9 Hz). MS $m/z$: 383 ($M^+$), 242 (base peak). *Anal.* Calcd for $C_{17}H_{22}ClN_3O_3S$: C, 53.18; H, 5.78; N, 10.95. Found: C, 53.41; H, 5.88; N, 10.88.

Compounds **25** were similarly obtained from the corresponding **17** and thiourea as described above.

**1-(2-Chlorophenoxy)-3-[1,1-dimethyl-2-(3-hydrazino-6-pyridazinyl-oxy)ethylamino]-2-propanol Dihydrochloride (20k)** A solution of **25k** (30 g, 78.3 mmol) and hydrazine hydrate (50 ml) in EtOH (150 ml) was refluxed for 3 h with stirring under a nitrogen stream. The solution was treated as described above to give **20k** (27.5 g, 77.3%) as colorless crystals. mp 186—188 °C. NMR ($D_2O$) $\delta$: 1.60 (6H, s), 3.31—3.59 (2H, m), 4.15—4.50 (3H, m), 4.46 (2H, s), 6.89—7.56 (4H, m), 7.24 (2H, s). MS $m/z$: 381 ($M^+$), 242 (base peak). *Anal.* Calcd for $C_{17}H_{24}ClN_5O_3 \cdot 2HCl$: C, 44.89; H, 5.76; N, 15.40. Found: C, 44.96; H, 5.64; N, 15.31.

Compounds **25** were converted to the corresponding **20** as described above.

**1-(2-Chlorophenoxy)-3-[1,1-dimethyl-2-(3-isopropylidenehydrazino-6-pyridazinyloxy)ethylamino]-2-propanol Dihydrochloride (23k)** A solution of **20k** (1.0 g, 2.2 mmol) in EtOH (10 ml) and acetone (10 ml) was refluxed for 3 h. The solvent was removed under reduced pressure, and the residue was recrystallized from EtOH–acetone to give **23k** (1.07 g, 98.3%) as pale yellow crystals. mp 164—166 °C. NMR ($CD_3OD$) $\delta$: 1.59 (6H, s), 2.17 (3H, s), 2.21 (3H, s), 3.18—3.60 (2H, m), 3.90—4.60 (3H, m), 4.53 (2H, s), 6.80—7.50 (4H, m), 7.64 (1H, d, $J$=9 Hz), 7.89 (1H, d, $J$=9 Hz). MS $m/z$: 421 ($M^+$), 84 (base peak). *Anal.* Calcd for $C_{20}H_{28}ClN_5O_3 \cdot 2HCl$: C, 48.54; H, 6.11; N, 14.15. Found: C, 48.41; H, 6.29; N, 14.28.

Compounds **23** were similarly prepared from the corresponding **20**, as described above.

**1-(2-Chlorophenoxy)-3-[1,1-dimethyl-2-(3-ethoxycarbonylhydrazino-6-pyridazinyloxy)ethylamino]-2-propanol Dihydrochloride (24k)** Diethyl pyrocarbonate (1.16 g, 7.16 mmol) was added dropwise to a solution of **20k** (2.60 g, 7.1 mmol) in EtOH (20 ml), with stirring at room temperature. Stirring was continued for 10 min, then the reaction mixture was concentrated under reduced pressure. The residue was dissolved in EtOH and treated with 20% ethanolic HCl, and the solvent was removed under reduced pressure. Recrystallization from EtOH–acetone yielded **24k** (1.837 g, 49.1%) as colorless crystals. mp 156—157 °C. NMR ($CD_3OD$) $\delta$: 1.33 (3H, t, $J$=7 Hz), 1.58 (6H, s), 3.25—3.70 (2H, m), 4.00—4.70 (3H, m), 4.30 (2H, q, $J$=7 Hz), 4.51 (2H, s), 6.80—7.60 (4H, m), 7.69 (2H, s). MS $m/z$: 308, 84 (base peak). *Anal.* Calcd for $C_{20}H_{28}ClN_5O_5 \cdot 2HCl$: C, 45.59; H, 5.74; N, 13.29. Found: C, 45.32, H, 5.76; N, 13.20.

**1-(2-Methylphenoxy)-3-[1,1-dimethyl-2-(3-chloro-6-pyridazinylamino)-ethylamino]-2-propanol Dihydrochloride (31)** Compound **26** was treated with *N*,*N*-dibenzylamine in the presence of $AlCl_3$ according to the method of Coleman and Callen,[13] to give *N*,*N*-dibenzyl-2-methyl-1,2-propanediamine (**27**) as a colorless oil. bp 145—148 °C (0.6 mmHg). Yield: 66.6%.

Compound **27** was reacted with 1-(2-methylphenoxy)-2,3-epoxypropane followed by hydrogenolysis using 10% Pd–C as a catalyst to give **29** as a colorless oil. Yield: 58.5%.

A mixture of **8** (800 mg, 5.37 mmol) and **29** (1.25 g, 4.96 mmol) was stirred for 1 h at 110 °C. The reaction mixture was dissolved in $CHCl_3$. The solution was washed with saturated $NaHCO_3$ and dried over $MgSO_4$. The solvent was then removed under reduced pressure, and the residue was purified by silica gel column chromatography to yield **31** (1.225 g, 67.8%) as a pale brown oily free base. NMR ($CDCl_3$) $\delta$: 1.24 (6H, s), 2.13 (3H, s), 2.77—3.03 (2H, m), 3.44 (2H, d, $J$=6 Hz), 3.69—4.32 (6H, m), 6.62—7.32 (4H, m), 6.73 (1H, d, $J$=9 Hz), 7.00 (1H, d, $J$=9 Hz). MS $m/z$: 365 ($M^+$+1), 222 (base peak). The free base was treated with excess 20% ethanolic HCl and the solvent was evaporated under reduced pressure. The residue was recrystallized from EtOH to yield **31** as colorless crystals. mp 165—167 °C. *Anal.* Calcd for $C_{18}H_{25}ClN_4O_2 \cdot 2HCl$: C, 49.38; H, 6.22; N, 12.80. Found: C, 49.48; H, 6.26; N, 12.58.

Compound **32** was similarly prepared from **26** as described above.

**1-(2-Methylphenoxy)-3-[1,1-dimethyl-2-(3-hydrazino-6-pyridazinyl-amino)ethylamino]-2-propanol Trihydrochloride (33)** A mixture of **31** (170 mg, 0.39 mmol) and ethoxycarbonylhydrazine (80 mg, 0.77 mmol) was stirred for 2 h at 140—150 °C. The reaction mixture was dissolved in $CHCl_3$. The solution was washed with 5% $Na_2CO_3$ and dried over $MgSO_4$. The solvent was then removed under reduced pressure, and the residue was purified by silica gel column chromatography to afford the carbazate (66 mg, 39.7%).

A solution of the carbazate (50 mg) in 10% HCl (3 ml) was refluxed for 5 h and then concentrated under reduced pressure. The residue was recrystallized from EtOH to give **33** (25 mg, 46.3%) as colorless crystals. mp 172—174 °C. NMR ($D_2O$) $\delta$: 1.53 (6H, s), 2.21 (3H, s), 3.48 (2H, d, $J$=5 Hz), 3.75 (2H, br s), 4.13 (2H, d, $J$=5 Hz), 4.20—4.60 (1H, m), 6.70—7.35 (4H, m), 7.09 (1H, d, $J$=9 Hz), 7.29 (1H, d, $J$=9 Hz). MS $m/z$: 361 ($M^+$+1), 360 ($M^+$), 222 (base peak). *Anal.* Calcd for $C_{18}H_{28}N_6O_2 \cdot 3HCl$: C, 46.01; H, 6.65; N, 17.89. Found: C, 45.81; H, 6.76; N, 17.72.

Compound **34** was prepared from the corresponding chloride (**32**) as described above.

**1-(2-Methylphenoxy)-3-[1,1-dimethyl-2-(3-chloro-6-pyridazinylcarbon-ylamino)ethylamino]-2-propanol (36)** A solution of **35** (550 mg, 2.95 mmol) and **29** (600 mg, 2.38 mmol) in EtOH (10 ml) was stirred overnight at room temperature. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography to afford **36** (495 mg, 53.0%) as a pale brown viscous oil. NMR ($CDCl_3$) $\delta$: 1.20 (6H, s), 2.19 (3H, s), 2.28 (2H, br s), 2.75—3.00 (2H, m), 3.44 (2H, d, $J$=6 Hz), 4.04 (3H, br s), 6.60—7.20 (4H, m), 7.56 (1H, d, $J$=9 Hz), 8.15 (1H, d, $J$=9 Hz), 8.30—8.70 (1H, m). MS $m/z$: 377 ($M^+$−15), 222 (base peak). An analytical sample was recrystallized

from EtOH as the oxalate. mp 170—172 °C. *Anal.* Calcd for $C_{19}H_{25}ClN_4O_3 \cdot (CO_2H)_2$: C, 52.23; H, 5.64; N, 11.60. Found: C, 52.37; H, 5.72; N, 11.49.

**1-(2-Methylphenoxy)-3-[1,1-dimethyl-2-(3-hydrazino-6-pyridazinylcarbonylamino)ethylamino]-2-propanol Dihydrochloride (37)** A solution of **36** (324 mg, 0.83 mmol) and hydrazine hydrate (350 mg, 7 mmol) in EtOH (10 ml) was refluxed for 1 h with stirring. The reaction mixture was treated as described for the preparation of **22d** to give **37** (296 mg, 77.7%) as colorless crystals. mp 178—180 °C. NMR ($D_2O$) $\delta$: 1.52 (3H, s), 1.57 (3H, s), 2.16 (3H, s), 3.47—3.70 (2H, m), 3.56 (1H, d, $J$=15 Hz), 3.97 (1H, d, $J$=15 Hz), 4.10—4.60 (3H, m), 6.73—7.30 (4H, m), 7.29 (1H, d, $J$=9 Hz), 7.80 (1H, d, $J$=9 Hz). MS $m/z$: 389 ($M^+ + 1$), 222 (base peak). *Anal.* Calcd for $C_{19}H_{28}N_6O_3 \cdot 2HCl$: C, 49.46; H, 6.55; N, 18.22. Found: C, 49.41; H, 6.80; N, 18.07.

## References


1) T. Seki, T. Takezaki, R. Ohuchi, H. Ohuyabu, T. Ishimori, K. Yasuda, *Chem. Pharm. Bull.*, **42**, 1609 (1994).
2) A. M. Barrett, "Drug Design," Vol. III, ed. by E.J. Ariens, Academic Press, New York and London, 1972, Chapter 4; A.F. Crowther, L.H. Smith, *J. Med. Chem.*, **11**, 1009 (1968).
3) J. Augstein, D. A. Cox, A. L. Ham, P. R. Leeming, M. Snarey, *J. Med. Chem.*, **16**, 1245 (1973); M. L. Hoefle, S. G. Hastings, R. F. Meyer, R. M. Corey, A. Holmes, C.D. Stratton, *ibid.*, **18**, 148 (1975).
4) H. Tucker, J. F. Coope, *J. Med. Chem.*, **21**, 769 (1978).
5) W. E. Truce, E. M. Kreider, W. W. Brand, "Organic Reactions," Vol. 18, John Wiley and Sons, Inc., New York, 1970, p. 99
6) S. Sato, *Yakugaku Zassi*, **82**, 1085 (1962); J.A. Elvidge, J.A. Pickett, *J. Chem. Soc., Perkin Trans. 1*, **1972**, 1483.
7) M. Kumagai, *Nippon Kagaku Zassi*, **81**, 1604 (1960); R.N. Castle, K. Kaji, *J. Heterocyclic Chem.*, **2**, 463 (1965).
8) G. R. Newkome, W. W. Paudler, "Contemporary Heterocyclic Chemistry: Syntheses, Reactions, and Applications," John Wiley and Sons, Inc., New York, 1982, Chapter 18; M. Liveris, J. Miller, *J. Chem. Soc.*, **1963**, 3486.
9) G. R. Handrick, E. R. Atkinson, F.E. Granchelli, R. J. Bruni, *J. Med. Chem.*, **8**, 762 (1965); J. R. Piper, C. R. Stringfellow Jr, T. P. Johnston, *ibid.*, **9**, 911 (1966).
10) H. M. Walborsky, C. Colombini, *J. Org. Chem.*, **27**, 2387 (1962).
11) A. A. Gevorkyan, G. G. Tokmadzhyan, L.A. Saakyan, *Arm. Kim. Zh.*, **30**, 693 (1977) [*Chem. Abstr.*, **88**, 170053*d* (1978)].
12) F. J. Soday, U.S.Patent 2393483 (1946) [*Chem. Abstr.*, **40**, 3129 (1946)].
13) G. H. Coleman, R. E. Callen, *J. Amer. Chem. Soc.*, **68**, 2006 (1946).
14) T. L. Cairns, *J. Amer. Chem. Soc.*, **63**, 871 (1941).
15) O. Diels, *Chem. Ber.*, **47**, 2183 (1914).
16) S. Mitsui, H. Saito, *Nippon Kagaku Zassi*, **78**, 577 (1957).
17) L. H. Smith, *J. Med. Chem.*, **19**, 1119 (1976); L.H. Smith, *ibid.*, **20**, 705 (1977).
18) B. G. Main, *J. Chem. Tech. Biotechnol.*, **32**, 617 (1982).
19) A. F. Crowther, D. J. Gilman, B. J. McLoughlin, L. H. Smith, R. W. Turner, T. M. Wood, *J. Med. Chem.*, **12**, 638 (1969).
20) L. H. Smith, H. Tucker, *J. Med. Chem.*, **20**, 1653 (1977).
21) G. Pifferi, F. Parravicini, C. Carpi, L. Dorigotti, *J. Med. Chem.*, **18**, 741 (1975).
22) D. Libermann, A. Rouaix, *Bull. Soc. Chim. France*, **1959**, 1793 [*Chem. Abstr.*, **55**, 18737*b* (1961)].
23) A. F. Crowther, R. Howe, L. H. Smith, *J. Med. Chem.*, **14**, 511 (1971); L.H. Smith, *ibid.*, **20**, 1254 (1977).