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Studies on Benzoheterocyclic Derivatives. XVI.[1] Synthesis and Analgesic Action of Benzofuran Derivatives

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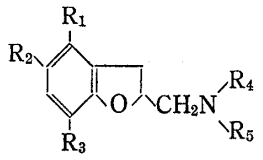
A series of 2-(N-substituted amino)methyl-2,3-dihydrobenzofurans were synthesized in order to examine the effect of the N-substituent on their analgesic activity. Some of these compounds demonstrated a good analgesic activity when tested by the acetic acid writhing method in mice. 2-(3-Phenylpropylamino)methyl-7-methoxy-2,3-dihydrobenzofuran (**4i**) showed the most potent activity in this series.

In the previous articles[3-5] the synthesis and screening tests of 2-(N-substituted amino)-methyl-2,3-dihydrobenzofuran derivatives (I) were reported; a marked adrenergic α-blocking effect was observed in them as expected. Contrary to our expectation, however, it was found that 2-(alkylamino)methyl-2,3-dihydrobenzofurans (Ia) possessed a potent analgesic activity and the 2-(methylamino)methyl analog showed the best activity, being about 1/2 times that of codeine.

In order to examine the effect on the analgesic potency produced by changing the substituent (R_1, R_2, and R_3) in the aromatic ring and the N-substituent (R_4) of Ia, the compounds indicated by the general formula (II) were prepared and tested for their analgesic potency in mice. As to the effect of substituents in the aromatic ring, introduction of a substituent CH_3, OCH_3, or Cl at 5-position (R_2) decreased the analgesic potency markedly as compared with Ia, and chlorine atoms at R_1, R_2, and R_3 or at R_2 and R_3 also diminished the potency. On the contrary, introduction of a substituent CH_3, OCH_3, or Cl at 7-position (R_3) markedly increased the analgesic potency as compared with Ia, and a methoxyl group at 7-position produced a marked increase of the activity.

On the other hand, the structural requirement for analgesic activity in this series seems to be the presence of a primary or a secondary amino group and, as regards the N-substituents (R_4 and R_5), hydrogen and methyl group were chosen which produced the best activity. The activity tended to diminish with increasing length of the N-alkyl chain (CH_3, C_2H_5, iso-C_3H_7, . .).



I: R_1,R_2,R_3=H R_4,R_5=alkyl, alkoxyalkyl *etc.*
Ia: R_1,R_2,R_3,R_4=H R_5=alkyl
II: R_1,R_2,R_3=CH_3,OCH_3,Cl R_4,R_5=H, alkyl
III: R_1,R_2,R_4=H R_3=OCH_3 R_5=CH_3
IV: R_1,R_2,R_4=H R_3=OCH_3 R_5=alkyl, alkenyl, aralkyl *etc.*

Chart 1

1) Part XV: N. Hirose, S. Kuriyama, and S. Sohda, *Yakugaku Zasshi*, **94**, 905 (1974).
2) Location: *Koishikawa 4-6-10, Bunkyo-ku, Tokyo 112, Japan.*
3) S. Toyoshima, N. Hirose, T. Ohgoh, and A. Sugii, *Yakugaku Zasshi*, **88**, 503 (1968).
4) T. Ohgoh, N. Hirose, N. Hashimoto, A. Kitahara, and K. Miyao, *Japan. J. Pharmacol.*, **21**, 119 (1971).
5) T. Ohgoh, N. Hirose, S. Sohda, and S. Toyoshima, *Yakugaku Zasshi*, **91**, 603 (1971).

7-Methoxy-2-(methylamino)methyl-2,3-dihydrobenzofuran (III) was selected as the most potent of this series; its effective dose 50% (ED_{50}) value was 6.3 mg/kg in electric stimulation method (mouse, *i.p.*), and 3.2 mg/kg in acetic acid writhing method (mouse, *i.p.*). However, it was found that III produced undesirable actions for analgesia, namely, restlessness and increase of spontaneous motility in mice (suggestive of central nervous system stimulation) and reddening of eyelids, ears, tail, and limbs in mice (suggestive of peripheral vasodilation). An attempt to find a compound possessing a potent analgesic activity without undesirable activities by means of transformation of the N-substituent was planned.

Analgesic benzomorphan derivatives (Pentazocine or Cyclazocine) can be viewed as cyclized versions of 3-(3-hydroxyphenyl)propylamine (V) bearing a relatively bulky N-substituent and, similarly, 2-(N-substituted amino)methyl-7-methoxy-2,3-dihydrobenzofuran analogs (IV) can be regarded as a cyclized type of V. From this point of view, an introduction of relatively bulky group such as alkyl, alkenyl, alkinyl, aralkyl, alkoxyalkyl, and cycloalkyl group as the N-substituents (R_5) in IV was attempted.

In this paper the synthesis of IV and the results of screening test for their analgesic potency are described.

Chemistry

The synthetic route used in the preparation of these compounds is illustrated in Chart 2. The synthesis was carried out by the procedure described by Adams[6] and in our previous

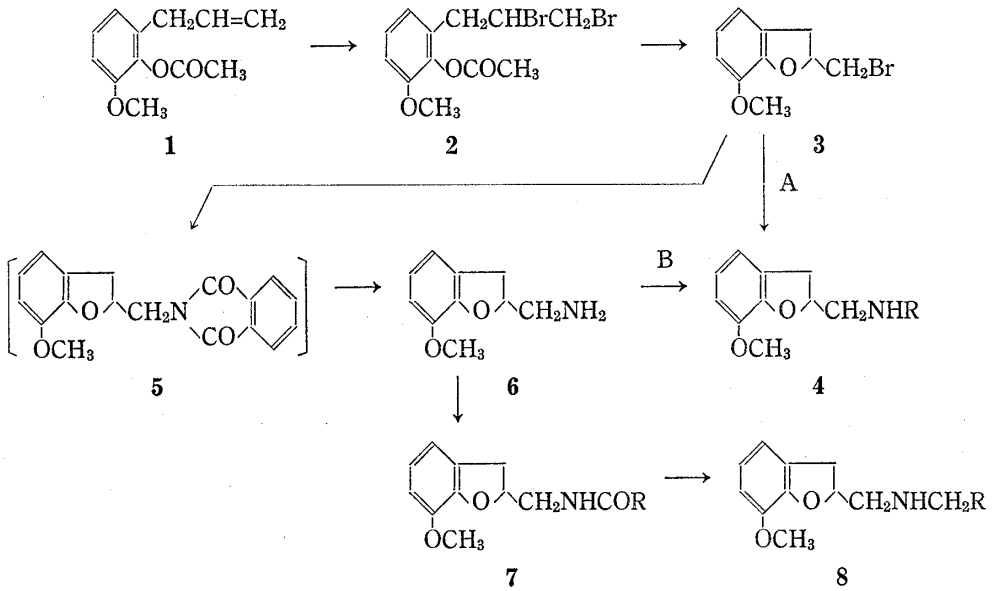


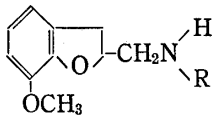
Chart 2

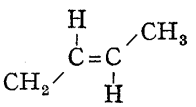
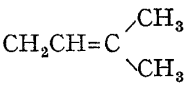
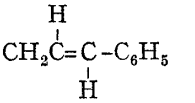
report.[5] 2-(2,3-Dibromopropyl)-6-methoxyphenol acetate (2) was prepared by bromination of 2-allyl-6-methoxyphenol acetate (1) with bromine in carbon disulfide solution under cooling. Then, 2 was treated with equimolar sodium ethoxide in ethanol to give 2-bromomethyl-7-methoxy-2,3-dihydrobenzofuran (3) by cyclization. 7-Methoxy-2-(alkylamino)methyl-2,3-dihydrobenzofurans (4) were obtained by treatment of 3 with the appropriate monoalkylamines in an autoclave (method A).

The intermediate bromide (3) was converted to 2-aminomethyl-7-methoxy-2,3-dihydrobenzofuran (6) *via* the phthalimide derivative (5) by the Gabriel method.[7] Compounds 4 were also obtained by alkylation of 6 with the appropriate alkyl halide (method B). An

6) R. Adams and R.E. Rindfutz, *J. Am. Chem. Soc.*, **41**, 648 (1919).
7) *a*) S. Gabriel, *Chem. Ber.*, **20**, 2224 (1887); *b*) J.C. Sheehan and W.A. Bolhofer, *J. Am. Chem. Soc.*, **72**, 2786 (1950).

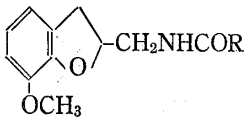
TABLE I. 2-(N-Substituted amino)methyl-7-methoxy-2,3-dihydrobenzofurans (**4a—v**)



Compd. No.	R	bp (°C/mmHg)	Yield (%) (method)	mp (salt, °C)	Formula[a]	*Anal.* (%) Calcd. (Found) C	H	N
4a	n-C_3H_7	132—134/0.4	63(A)	179.5—180	$C_{13}H_{19}O_2N \cdot HCl$	60.56 (60.37)	7.83 (7.70)	5.43 (5.65)
4b	$CH_2CH(OH)CH_3$	176—180/0.6	54(A)	154 —155	$C_{13}H_{19}O_3N \cdot M$	57.77 (57.47)	6.57 (6.63)	3.96 (3.69)
4c	n-C_4H_9	130—136/0.6	68(A)	165.5—167	$C_{14}H_{21}O_2N \cdot M$ 1/2 H_2O	59.96 (60.23)	7.28 (7.10)	3.87 (3.91)
4d	n-C_5H_{11}	140—142/0.3	65(A)	168 —169	$C_{15}H_{23}O_2N \cdot M$	62.44 (62.60)	7.46 (7.43)	3.83 (3.82)
4e	n-C_6H_{13}	156—160/0.6	59(A)	150 —151	$C_{16}H_{25}O_2N \cdot M$ 1/2 H_2O	61.83 (62.06)	7.79 (7.59)	3.61 (3.67)
4f	$CH_2C_6H_5$	175—180/0.4	72(A)	169 —169.5	$C_{17}H_{19}O_2N \cdot M$	65.43 (65.24)	6.03 (6.06)	3.64 (3.66)
4g	$CH(CH_3)C_6H_5$	160—163/0.3	65(A)	152.5—154	$C_{18}H_{21}O_2N \cdot M$	66.14 (65.82)	6.32 (6.37)	3.51 (3.60)
4h	$(CH_2)_2C_6H_5$	182—184/0.6	53(A)	180(decomp.)	$C_{18}H_{21}O_2N \cdot M$	66.14 (66.08)	6.32 (6.22)	3.51 (3.52)
4i	$(CH_2)_3C_6H_5$	—	49(A)	158 —160	$C_{19}H_{23}O_2N \cdot HCl$	68.34 (68.16)	7.25 (7.22)	4.19 (4.46)
4j	$(CH_2)_2OC_2H_5$	150—155/0.5	64(A)	140 —142	$C_{14}H_{21}O_3N \cdot M$	58.83 (58.62)	6.87 (6.94)	3.81 (3.67)
4k	$(CH_2)_3OCH_3$	147—150/0.3	61(A)	149.5—150	$C_{14}H_{21}O_3N \cdot M$	58.83 (58.50)	6.87 (6.94)	3.81 (3.59)
4l	$(CH_2)_3OC_2H_5$	146—150/0.3	59(A)	127 —128	$C_{15}H_{23}O_3N \cdot M$	59.82 (59.69)	7.15 (6.92)	3.67 (3.50)
4m	$(CH_2)_3OCH(CH_3)_2$	151—155/0.2	51(A)	140 —141	$C_{16}H_{25}O_3N \cdot M$	60.73 (60.51)	7.41 (7.25)	3.54 (3.51)
4n	$(CH_2)_3OCH_2C_6H_5$	198—202/0.2	65(A)	112 —114	$C_{20}H_{25}O_3N \cdot M$	64.99 (64.71)	6.60 (6.57)	3.16 (3.19)
4o	$(CH_2)_3OCH_2$- 	198—200/0.2	63(A)	104 —105	$C_{18}H_{27}O_4N \cdot M$	60.39 (60.24)	7.15 (7.12)	3.20 (3.33)
4p	$CH_2CH=CH_2$	128—136/0.8	68(B)	158 —159	$C_{13}H_{17}O_2N \cdot M$	60.88 (60.89)	6.39 (6.18)	4.18 (4.25)
4q	$CH_2C(CH_3)=CH_2$	145—148/0.8	74(B)	162 —163	$C_{14}H_{19}O_2N \cdot M$	61.86 (61.62)	6.64 (6.50)	4.00 (4.01)
4r	$CH(CH_3)$-$CH=CH_2$	139—140/0.3	70(B)	152 —153	$C_{14}H_{19}O_2N \cdot M$	61.86 (61.74)	6.64 (6.56)	4.00 (4.06)
4s		141—145/0.2	64(B)	151 —152	$C_{14}H_{19}O_2N \cdot M$	61.86 (61.68)	6.64 (6.61)	4.00 (3.84)
4t		146—150/0.6	53(B)	152 —152.5	$C_{15}H_{21}O_2N \cdot M$	62.80 (62.69)	6.93 (6.94)	3.85 (3.93)
4u		198—202/0.4	75(B)	165 —165.5	$C_{19}H_{21}O_2N \cdot M$	67.14 (67.37)	6.12 (6.05)	3.40 (3.32)
4v	$CH_2C{\equiv}CH$	155—158/0.9	61(B)	145 —147	$C_{13}H_{15}O_2N \cdot M$ 1/2 H_2O	59.63 (59.55)	5.89 (5.56)	4.09 (4.25)

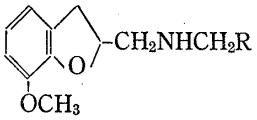
a) In Tables I, II, and III, letter M in formula column signifies maleic acid ($C_4H_4O_4$), and the compounds listed in formula column were used for microanalysis and pharmacological screening tests.

Table II. 2-(Cycloalkylcarbonylamino)methyl-7-methoxy-2,3-dihydrobenzofurans (**7a**—**c**)



Compd. No.	R	Yield (%)	mp (°C)	Formula	*Anal.* (%) Calcd. (Found) C	H	N
7a		72	115—115.5	$C_{14}H_{17}O_3N$	67.99 (67.88)	6.94 (7.02)	5.67 (5.76)
7b		98	127.5—128	$C_{16}H_{21}O_3N$	69.78 (69.79)	7.70 (7.60)	5.09 (5.11)
7c		96	146—146.5	$C_{17}H_{23}O_3N$	70.55 (70.41)	8.03 (7.87)	4.84 (4.93)

Table III. 2-(Cycloalkylmethylamino)methyl-7-methoxy-2,3-dihydrobenzofurans (**8a**—**c**)



Compd. No.	R	bp (°C/mmHg)	Yield (%)	mp (°C, maleate)	Formula	*Anal.* (%) Calcd. (Found) C	H	N
8a		141—142/0.4	53	170—170.5	$C_{14}N_{19}O_2N \cdot M$	61.87 (61.57)	6.65 (6.55)	4.01 (4.26)
8b		140—142/0.4	58	173.5—175	$C_{16}H_{23}O_2N \cdot M$	63.63 (63.50)	7.22 (7.21)	3.71 (3.68)
8c		163—164/0.6	56	160.5—161	$C_{17}H_{25}O_2N \cdot M$	64.62 (64.72)	7.48 (7.38)	3.58 (3.66)

attempt to react **6** with cyclopropylmethyl bromide failed to afford 2-(cyclopropylmethylamino)methyl-7-methoxy-2,3-dihydrobenzofuran (**8a**) directly. Thus the cycloalkylcarbonyl derivatives (**7**) were obtained by acylation of **6** with the appropriate cycloalkylcarbonyl chlorides, and then **7** were reduced with sodium dihydro-bis(2-methoxyethoxy)aluminate to afford 2-(cycloalkylmethylamino)methyl-7-methoxy-2,3-dihydrobenzofurans (**8**).

The compounds prepared were converted into the corresponding maleates or hydrochlorides, which were used for microanalysis and pharmacological screening tests. Their physical constants and the results of microanalysis are summarized in Tables I, II, and III.

Pharmacology

Twenty-seven compounds synthesized in this study were screened for their inhibitory action against acetic acid-induced stretching or writhing syndrome as a preliminary test for their analgesic activity.

Analgesic Activity (Acetic Acid Method)[8]

Mice were injected intraperitoneally with 10 ml/kg of 0.5% acetic acid solution to produce a typical writhing reaction. This dose caused stretching or writhing more than 10 times during 10 min in all the mice. A group of 5 mice (dd strain) weighing 17—23 g were used

8) P.J. Costa and D.D. Bonnycastle, *J. Pharmacol. Exptl. Therap.*, **113**, 310 (1955).

TABLE IV. Analgesic Activity of 2-(N-Substituted amino)methyl-7-methoxy-2,3-dihydrobenzofurans

Compd. No.	R	Inhibition (%) dose (mg/kg, *i.p.*) 25.0	12.5
4a	$CH_2CH_2CH_3$	40	40
4b	CH_2CHCH_3 (OH)	40	20
4c	$CH_2(CH_2)_2CH_3$	0	0
4d	$CH_2(CH_2)_3CH_3$	40	40
4e	$CH_2(CH_2)_4CH_3$	60	40
4f	$CH_2C_6H_5$	0	0
4g	CHC_6H_5 (CH_3)	0	0
4h	$(CH_2)_2C_6H_5$	80	0
4i	$(CH_2)_3C_6H_5$	100	70
4j	$(CH_2)_2OC_2H_5$	40	0
4k	$(CH_2)_3OCH_3$	60	0
4l	$(CH_2)_3OC_2H_5$	60	0
4m	$(CH_2)_3OCH(CH_3)_2$	60	20
4n	$(CH_2)_3OCH_2C_6H_5$	60	0
4o	$(CH_2)_3OCH_2$-(O)	0	0
4p	$CH_2CH{=}CH_2$	100	40
4q	$CH_2C{=}CH_2$ (CH_3)	40	20
4r	$CHCH{=}CH_2$ (CH_3)	60	40
4s	CH_2, H, CH_3, H	100	20
4t	$CH_2CH{=}C(CH_3)(CH_3)$	60	20
4u	$CH_2CH{=}CHC_6H_5$	100	0
4v	$CH_2C{\equiv}CH$	60	20
7a	CO-(cyclopropyl)	20	0
7b	CO-(cyclobutyl)	60	20
7c	CO-(cyclohexyl)	40	0
8a	CH_2-(cyclopropyl)	80	20
8b	CH_2-(cyclobutyl)	0	0
8c	CH_2-(cyclohexyl)	20	0
9a[a]	H	100	60 (20)[b]
9b[a]	CH_3	100	100 (80)[b]
9c[a]	C_2H_5	100	80 (60)[b]
Pentazocine		100	40 (10)[b]

a) quoted from the previous report[5]
b) 6.3 mg/kg (*i. p.*)

for each dosage level. The test chemical was administered intraperitoneally to each group at doses of 25 and 12.5 mg/kg, and 15 min later each mouse was injected with acetic acid. Each mouse was then placed in a cage, and was observed for 10 min. The test chemical was considered effective at a specific dose, when stretching or writhing syndrome did not appear during this observation period. Pentazocine was used as a reference standard for comparison.

Results

The results of the screening tests are summarized in Table IV, and anti-writhing activity was observed in almost all the compounds tested. Compounds **4i**, **4p**, **4s**, and **4u** showed a significant analgesic potency, and **4h** and **8a** also showed a relatively potent activity at 25 mg/kg. It seemed that the activity of these derivatives is affected by the type of the N-substituents significantly. As can be seen in Table IV, lengthening of the N-alkyl chain (CH_3: **9a**, C_2H_5: **9b**, C_3H_7: **4a**) reduced the analgesic potency, and an introduction of C_4H_9 (**4c**) extinguished the potency completely. However, further lengthening of the alkyl chain (C_5H_{11}: **4d**, C_6H_{13}: **4e**) restored the potency. As to the aralkyl moiety, the lower homolog (**4f**) bearing a benzyl group did not show any analgesic activity, whereas a significant potent activity was observed in its higher homologs (**4h** and **4i**) bearing a phenethyl and a phenylpropyl group. However, the α-methylbenzyl homolog (**4g**) containing a branched CH_3 on the benzyl function showed no potency. The analgesic activity increased with increasing size of the methylene moiety in the aralkyl group. When the N-substituents are alkenyl or alkinyl group (**4p**—**v**), a relatively high analgesic activity was observed in all the compounds. The allyl homolog (**4p**) exhibited a significant potency, but a methyl substitution in the α(**4r**), β(**4q**), or γ position (**4s**) of the allyl function reduced the potency. When the allyl of **4p** is further substituted with γ,γ-dimethyl (**4t**) or γ-phenyl group (**4u**), the activity is diminished.

On the other hand, the alkoxyalkyl analogs (**4j**—**o**) also showed the activity with the exception of the 3-(tetrahydrofurfuryloxy)propyl analog (**4o**). Lengthening of the alkoxyl or alkylene chain in the alkoxyalkyl moiety had little or no influence on the analgesic potency. The cycloalkylcarbonyl (**7a**—**c**) and cycloalkylmethyl (**8a**—**c**) derivatives also retained analgesic activity, but were generally less potent than the others, except the cyclopropylmethyl analog (**8a**). It is interesting that the similar effects of changing the N-substituents on the analgesic activity were reported for benzomorphan derivatives.[9,10]

It seems that **4i**, **4p**, **4s**, and **4u** have approximately the same potency as Pentazocine, and **4h** and **8a** have a slightly weaker potency than Pentazocine. In particular, **4i** bearing a phenylpropyl moiety as the N-substituent is the most active of this series. Although the compounds prepared in this study were less potent than the parent compounds (**9a**—**c**) prepared in our previous work,[5] most of them did not produce no restlessness and reddening of eyelids, ears, tail, *etc.* (suggestive of central nervous system—stimulating and peripheral vasodilating activities) which are undesirable in analgesics. Compound **4i** rather exerted slight central nervous system depressant activity. Some of these compounds are worth further investigation for their analgesic activity.

Experimental

Boiling points and melting points are uncorrected. Infrared (IR) spectra were determined on Hitachi-215 spectrometer and nuclear magnetic resonance (NMR) spectra on a JEOL JNM-PS 100 spectrometer using tetramethylsilane as the internal standard.

2-(2,3-Dibromopropyl)-6-methoxyphenol Acetate (2)——To a solution of 5.2 g (0.25 mol) of 2-allyl-6-methoxyphenol acetate (**1**) in 200 ml of CS_2, a solution of 44.8 g (0.28 mol) of Br_2 in 50 ml of CS_2 was added dropwise with stirring at 0°. The reaction mixture was evaporated to dryness, and the resulting oily residue

9) N.B. Eddy, H. Beisendorf, and B. Pellmont, *Bull. Narcotics*, **10**, 23 (1958).
10) S. Archer, N.F. Albertson, L.S. Harris, A.K. Pierson, and J.G. Bird, *J. Med. Chem.*, **7**, 123 (1964).

was distilled to give a colorless viscous liquid **2**, bp 161—166° (6.0 mmHg); Yield, 62.2 g (68%). *Anal.* Calcd. for $C_{12}H_{14}O_3Br_2$: C, 39.34; H, 3.86. Found: C, 39.67; H. 3.75.

2-Bromomethyl-7-methoxy-2,3-dihydrobenzofuran (**3**)——To a solution of 5.1 g (0.22 mol) of Na in 300 ml of anhyd. EtOH, 73.2 g (0.2 mol) of **2** was added while being cooled, and the mixture was refluxed for 2 hr with stirring. The brownish reaction mixture was concentrated and diluted with water. The oil that separated was extracted with ether and the extract was washed, dried, and evaporated. The oily residue was purified by distillation to give a colorless viscous liquid **3**, bp 132—137° (1.0 mmHg); Yield, 25.3 g (52%). NMR ($CDCl_3$) δ: 6.8 ppm (3H, m, aromatic H), 5.00 (1H, m, C_2–H), 3.80 (3H, s, OCH_3), 3.7—3.0 (4H, m, C_3-*gem*-2H and CH_2Br). *Anal.* Calcd. for $C_{10}H_{11}O_2Br$: C, 49.38; H, 4.57. Found: C, 49.13; H, 4.76.

7-Methoxy-2-(alkylamino)methyl-2,3-dihydrobenzofurans (**4**)——Method A: (1) A mixture of 4.9 g (0.02 mol) of **3**, 0.03 mol of an appropriate amine, and 4.1 g (0.04 mol) of Et_3N in 100 ml of toluene was heated in an autoclave for 20 hr at 120°. The reaction mixture was diluted with dil. HCl, and the acidic extract was made alkaline with 10% NaOH. The separated amine was extracted with ether and the extract was dried and evaporated to give a crude product, which was purified by distillation and converted into the salt indicated in Table I (**4a—h** and **4j—o**).

(2) A mixture of 4.0 g (0.02 mol) of **3**, 4.1 g (0.03 mol) of 3-phenylpropylamine, and 3.2 g (0.03 mol) of Na_2CO_3 in 200 ml of iso-PrOH was stirred and refluxed for 20 hr. After the reaction mixture was filtered, the filtrate was concentrated, and the residual oil was treated with 10% HCl. After washing with ether, the acidic layer was made alkaline with NaOH solution. The crude amine that separated was extracted with ether, and the extract was dried ($MgSO_4$) and evaporated to give a free amine (**4i**), which was converted into a maleate, mp 158—160° (needles from iso-PrOH).

Method B: (1) A suspension of 5.4 g (0.03 mol) of **6**, 4.6 g (0.03 mol) of cinnamyl chloride, and 4.2 g (0.04 mol) of Na_2CO_3 in 70 ml of iso-PrOH was refluxed for 15 hr under stirring and filtered. The filtrate was concentrated to dryness, and the residual oil was distilled and converted into a maleate, mp 165—165.5° (needles from iso-PrOH) (**4u**).

(2) A mixture of 3.6 g (0.02 mol) of **6**, 0.02 mol of an appropriate alkyl halide, and 4.1 g (0.04 mol) of Et_3N in 100 ml of toluene was heated in an autoclave for 20 hr at 120°. The reaction mixture was treated similarly as in method A (**4p—t** and **4v**).

2-Aminomethyl-7-methoxy-2,3-dihydrobenzofuran (**6**)——A stirred suspension of 48.6 g (0.2 mol) of **3** and 44.4 g (0.24 mol) of potassium phthalimide in 200 ml of Me_2NCHO was heated for 3 hr at 140°. When cooled, the reaction mixture was poured into ice-water, and the white solid that separated was filtered, washed with EtOH, and dried. The crude phthalimide derivative (**5**) obtained was used for the next process without purification. A suspension of crude **5** and 20 ml of $NH_2NH_2 \cdot H_2O$ (80%) in 200 ml of EtOH was refluxed for 2 hr, and 30 ml of 6 N HCl was added to it. The acidic mixture was refluxed for 2 hr, then the solid material that separated was filtered off, the filtrate was made alkaline with NaOH solution, and the oil that separated was extracted with ether. The extract was dried and concentrated to give a crude product (**6**), which was purified by distillation, bp 81—83° (0.3 mmHg); Yield, 16.1 g (45%). IR $\nu_{max}^{liq.\ film}$ cm^{-1}: 3380, 3300 (NH_2). NMR ($CDCl_3$) δ: 6.8 ppm (3H, m, aromatic H), 4.90 (1H, m, C_2–H), 3.75 (3H, s, OCH_3), 3.7—3.0 (4H, m, C_3-*gem*-2H and $CH_2N\langle$). *Anal.* Calcd. for $C_{10}H_{13}O_2N$: C, 67.00; H, 7.33; N, 7.82. Found: C, 67.29; H, 7.35; N, 8.05.

2-(Cycloalkylcarbonylamino)methyl-7-methoxy-2,3-dihydrobenzofurans (**7**)——To a stirred solution of 3.6 g (0.02 mol) of **6** and 2.5 g (0.025 mol) of Et_3N in 100 ml of benzene, 0.02 mol of an appropriate cycloalkylcarbonyl chloride in 10 ml of dry benzene solution was added dropwise while being cooled. After the addition was completed, the reaction mixture was stirred for 1 hr at 60°, washed, dried, and evaporated. The resulting residue was recrystallized from hexane–iso-PrOH to give **7a—c** (Table II).

2-(Cyclopropylcarbonylamino)methyl Analog (**7a**): IR ν_{max}^{Nujol} cm^{-1}: 3300 (NH), 1640 (C=O). NMR (DMSO-d_6) δ: 8.30 ppm (1H, t, CONH, D_2O exchangeable), 6.8 (3H, m, aromatic H), 3.78 (3H, s, OCH_3), 3.7—3.0 (4H, m, C_3-*gem*-2H and $CH_2N\langle$), 0.7 (5H, m, cyclopropane H).

2-(Cycloalkylmethylamino)methyl-7-methoxy-2,3-dihydrobenzofurans (**8**)——To a solution of 10 g of sodium dihydro-bis(2-methoxyethoxy)aluminate (64%, benzene solution) in 100 ml of dry benzene, 0.01 mol of **7** in 25 ml of dry benzene was added dropwise at room temperature, and stirring was continued for 1 hr at 60°. After being cooled, 5 ml of acetone was added to the mixture to decompose the excess reagent, then 10% NaOH was added, and the mixture was extracted with ether. The ether extract was dried and concentrated to give a crude product, which was purified by distillation. The free amines obtained were converted into their maleates indicated in Table III.

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