ability to lower estrogen levels in laboratory animals is being pursued at the present time.

Experimental Section

All reagents and solvents were general purpose or analytical reagent grade. Proton NMR spectra (90 MHz) were determined in a Perkin-Elmer R32 spectrometer. Chemical shifts are reported in δ, parts per million, downfield from internal tetramethylsilane. Melting points were determined on an Electrothermal apparatus and are corrected. Infrared spectra were determined in KBr disks, unless otherwise stated, on either a Perkin-Elmer 681 Infrared spectrophotometer, or a Perkin-Elmer 357 Grating Infra-red spectrophotometer. Phenylethane-1,2-dicarboxylic acid (**9**) was purchased from the Aldrich Chemical Co., Gillingham, Dorset, U.K.

3-Phenylpyrrolidine-2,5-dione (10). Phenylethane-1,2-dicarboxylic acid (**9**; 19.4 g, 0.1 mol) was heated with urea (12 g, 0.3 mol) at 180–200 °C for 30 min. The residue crystallized from methanol to give **10** (10.5 g, 60% based on **9**), as a white, crystalline material: mp 79–81 °C (lit.[16] mp 79–81 °C). Further purification was carried out by dissolving the crystals in ether and washing with $NaHCO_3$ solution (2%) until effervescence ceased. The ether layer was washed with water (2 × 50 mL), dried (Na_2SO_4), and evaporated to give a white crystalline solid which crystallized from ether to give **10** as white crystals: mp 90–91 °C (lit.[9,17] mp 88–90 °C, 90 °C); IR ν_{max} 3240 (N-H str), 1790, 1780 (C=O), 1692, 1728 (C=O) cm^{-1}; ^1H NMR δ 2.8 (1 H, dd, Ha, J_{HbHa} = 18 Hz, J_{HxHa} = 6 Hz), 3.16 (1 H, dd, Hb, J_{HaHb} = 18 Hz, J_{HxHb} = 9 Hz), 4.02 (1 H, dd, Hx, J_{HaHx} = 6 Hz, J_{HbHx} = 9 Hz), 7.28 (5 H, s, Ar H), 9.37 (1 H, s, NH). Anal. ($C_{10}H_9NO_2$) C, H, N.

3-(4-Nitrophenyl)pyrrolidine-2,5-dione (11). Compound **10** (6 g, 0.034 mol) was added portionwise to fuming HNO_3 (25 mL) at −40 °C over 20 min. The resulting solution was then poured, with vigorous stirring, into ice/water (300 mL), producing a white solid. Crystallization of the solid from EtOH gave white crystals of **11** (4.74 g, 63% based on **10**): mp 148–150 °C (lit.[19] mp 131–133 °C); ν_{max} 3310 (N-H str), 1783, 1718 (C=O), 1515, 1350 (N-O) cm^{-1}; ^1H NMR δ 2.86 (1 H, dd, Ha, J_{HbHa} = 18 Hz, J_{HxHa} = 6 Hz), 3.20 (1 H, dd, Hb, J_{HaHb} = 18 Hz, J_{HxHb} = 9 hz), 4.38 (1 H, dd, Hx, J_{HaHx} = 6 Hz, J_{HbHx} = 9 Hz), 7.63 (2 H, d, Ar H, J = 9 Hz), 8.19 (2 H, d, Ar H, J = 9 Hz), 11.46 (s, 1 H, NH). Anal. ($C_{10}H_8N_2O_4$) C, H, N.

3-(4-Aminophenyl)pyrrolidine-2,5-dione (15). Compound 11 (2 g, 0.09 mol) was dissolved in EtOAc (50 mL) and shaken with gaseous H_2 and 10% Pd/C (0.2 g) until uptake of gas was complete (650 mL). The flask was cooled, the mixture filtered, and the solvent removed. The residue was crystallized from EtOH to give **15** as a pale orange solid (1.54 g, 90% based on 11): mp 171.5–173.5 °C; IR ν_{max} 3490, 3310 (N-H str), 1763, 1708 (C=O), 1265 (C-N str) cm^{-1}; ^1H NMR δ 2.56 (1 H, dd, Ha, J_{HbHa} = 18 Hz, J_{HxHa} = 6 Hz), 3.03 (1 H, dd, Hb, J_{HaHb} = 18 Hz, J_{HxHb} = 9 Hz), 3.84 (1 H, dd, Hx, J_{HaHx} = 6 Hz, J_{HbHx} = 9 Hz), 4.41 (2 H, s, NH_2), 6.47 (2 H, d, Ar H, J = 9 Hz), 6.83 (2 H, d, Ar H, J = 9 Hz), 11.12 (1 H, s, NH). Anal. ($C_{10}H_{10}N_2O_2$) C, H, N.

3-(4-Nitrophenyl)propionamide (13). The diacid **9** was nitrated as described previously.[13] The attempted ring closure of the product **12** (4 g, 0.167 mol) by fusion with molten urea at 170 °C led to charring and the production of CO_2. Extraction of the residue with chloroform (2 × 25 mL), removal of the solvent, and crystallization of the residue from EtOH gave **13** (1.09 g, 33% based on **12**) as light brown crystals: mp 175–176 °C (lit.[26] mp 175–176 °C); IR ν_{max} 3440 (amide N-H), 2850, 2940 (alkane C-H), 1660 (C=O), 1505, 1350 (N-O) cm^{-1}; ^1H NMR (Me_2SO) δ 2.44 (m, 2 H, CH_2CH_2CO, J = 7 Hz), 2.98 (m, 2 H, CH_2CO, J = 7 Hz), 6.84 (br s, 1 H, NH), 7.34 (br s, 1 H, NH), 7.53 (d, 2 H, Ar H, J = 9 Hz), 8.19 (d, 2 H, Ar H, J = 9 Hz). Anal. ($C_9H_{10}N_2O_3$) C, H, N.

3-(4-Aminophenyl)propionamide (14). Compound **13** (1 g, 0.0051 mol) was hydrogenated by the general method described.[13] Crystallization from EtOH (95%) gave 14 (170 mg, 20% based on **13**) as light brown crystals: mp 136.5–137 °C; IR ν_{max} 3400 (N-H primary amine) 1695 (C=O) cm^{-1}; ^1H NMR (Me_2SO) δ 2.22 (m, CH_2CH_2CO, J_{HaHb} = 18 Hz, CH_2CH_2CO, J = 7 Hz), 4.72 (s, 2 H, NH_2), 6.45 (2 H, d, Ar H, J = 9 Hz), 6.82 (2 H, d, Ar H, J = 9 Hz), 6.66 (br s, 1 H, HNH), 7.18 (s, 1 H, HNH). Anal. ($C_9H_{12}N_2O$) C, H, N.

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Registry No. **5**, 59512-13-9; **6**, 59512-15-1; **7**, 91351-05-2; **8**, 91567-07-6; **9**, 635-51-8; **10**, 3464-18-4; **11**, 32856-95-4; **12**, 21021-53-4; **13**, 98953-18-5; 14, 38710-60-0; **15**, 32856-49-8; **16**, 99948-56-8; urea, 57-13-6; adrenal CSCC enzyme, 37292-81-2; aromatase, 9039-48-9.

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Thromboxane Synthetase Inhibitors and Antihypertensive Agents. 1. *N*-[(1*H*-Imidazol-1-yl)alkyl]aryl Amides and *N*-[(1*H*-1,2,4-Triazol-1-yl)alkyl]aryl Amides

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The title compounds were prepared to investigate their potential as thromboxane synthetase inhibitors as well as antihypertensive agents. Imidazoles VIII and triazoles X were prepared to examine the effects of aromatic substitution, chain length, and heterocycle substitution upon biological activity. Imidazoles VIII and triazoles X were thromboxane synthetase inhibitors that did not inhibit prostacyclin formation. The most interesting thromboxane synthetase inhibitors prepared were 4-chloro-, 4-(trifluoromethyl)-, and 4-bromobenzamide derivatives of (1*H*-imidazol-1-yl)alkylamines with C_5–C_8 alkyl chains separating the heterocycle from the amide moiety, while the most active antihypertensive agents were 3- or 4-chloro, -bromo, or -(trifluoromethyl)benzamides with C_3 alkyl chains. The best thromboxane synthetase inhibitors in this study were up to 10 times more potent than the standard, dazoxiben (UK 37,248).

Prostaglandins (PGs) have been the subject of intense research efforts both biologically because of their ubiquitous role in physiological processes[2] as well as chemically because of their challenging structural requirements.

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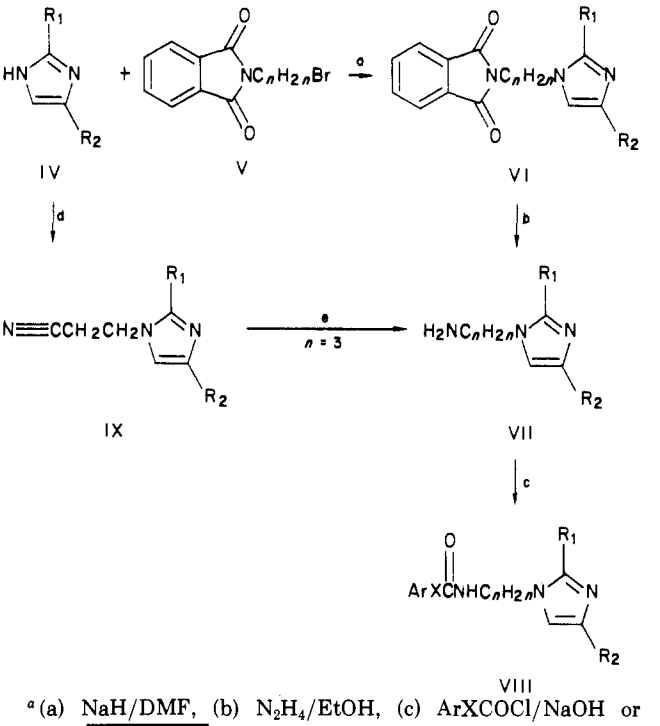
Recent studies of the arachidonic acid cascade have led to the discovery of thromboxane A_2 (TXA_2)[3] and prostacyclin (PGI_2),[4] which play important roles in the cardiovascular system and the regulation of platelet functions.[5]

It has been known that drugs such as aspirin and indomethacin exhibit their antiinflammatory properties as a result of inhibition of the enzyme cyclooxygenase, which consequently shuts down the arachidonic acid cascade.[6] We became interested in agents that might selectively interfere with enzymes farther along the cascade and might be potential drugs useful in the treatment of cardiovascular disease. In particular, TXA_2 appears to be an interesting target for selective inhibition without inhibiting PGI_2 synthesis since TXA_2 causes seemingly adverse cardiovascular effects such as vasoconstriction,[7] platelet aggregation,[5] atherosclerosis,[8] ischemia,[9] and sudden death.[10] Since thromboxane (TX) has been shown to be the most potent endogenous vasoconstrictor known, it was hoped that some TX inhibitors might have antihypertensive activity in certain forms of hypertension wherein TX maintains blood pressure.

Other laboratories have also investigated the selective inhibition of thromboxane synthetase as evidenced by clinical reports of dazoxiben (I, UK 37,248)[11] used for the treatment of ischemia and fibrillation.[12] Clinical use of OKY 1581 (II)[13] and OKY 046[14] as well as preclinical studies of OKY 025,[15] 4′-imidazol-1-ylacetophenone,[16] UK 38,485,[17] 4-[(2-pyridylmethyl)amino]benzoic acid,[18] and CGS 13080[19] as thromboxane synthetase inhibitors have all been reported since the initiation of our investigations. These agents were developed from an early observation that imidazole was a selective (if not potent) inhibitor of human platelet thromboxane synthetase.[20] In general, all of these compounds have a carboxylic acid group at one end of the molecule and a pyridyl or imidazolyl moiety at the other. These compounds, in general, have no antihypertensive effects. Alternative approaches toward thromboxane synthetase inhibition have involved preparing prostaglandin-like compounds such as AH 19437,[21] ONO 11105,[22] and others.[23-25]

Our approach to this problem involved the attachment of highly polar but neutral moieties such as aryl amides[27]

Scheme I[a]



[a] (a) NaH/DMF, (b) N_2H_4/EtOH, (c) ArXCOCl/NaOH or ArXCONCH=NCHCH/THF, (d) CH_2=CHCN/80 °C, (e) RaNi/NH_4OH/MeOH/H_2.

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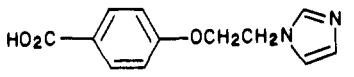

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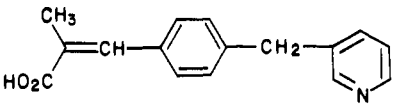

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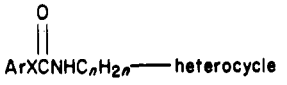


III

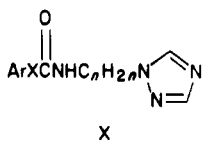
to an imidazole or selected other heterocyclic nucleus by a varying length alkyl or substituted alkyl chain to give III. Previous reports[11,13-18] suggested that derivatives with five to six atom separation between a polar moiety and heterocycle (III, n = 4, 5) were reasonable synthetic targets for potential TX synthetase inhibition. A target structure such as III would also allow simple molecular modification wherein the effects of increased or decreased lipophilicity (chain length, chain and amide substitution), polarity (amide substitution) as well as typical aromatic and heterocyclic substitution could be examined. In addition we were particularly interested in discovering agents that have antihypertensive effects that might possibly arise as a consequence of lowering the vasoconstrictor TX levels.

Chemistry

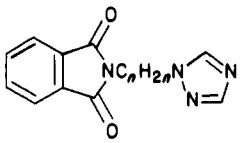
The imidazole derivatives for this study were prepared according to Scheme I. In the more general route using a routine Gabriel synthesis,[26] the appropriately substituted imidazole IV was reacted with various (bromoalkyl)-phthalimides V to give VI in moderate to good yield.[28] Hydrazinolysis of VI gave amines VII, which were isolated and distilled or could be stored as their corresponding dihydrochloride salts. Conversion to the desired derivatives VIII was accomplished by reaction of VII with either the appropriate aroyl chlorides or aryl carboxylic acids activated by 1,1'-carbonyldiimidazole. In either case VIII formed in good yield and was isolated as a crystalline solid or a suitable salt.

Alternatively, for the preparation of *N*-[3-(1*H*-imidazol-1-yl)propyl]amides (VIII, n = 3), imidazole VI was reacted with acrylonitrile via a Michael type reaction to give nitriles IX, which were reduced in a Parr apparatus using Raney nickel catalyst to give VII (n = 3) in high yields. Conversion as above gave VIII (n = 3).

During the course of these investigations into various heterocyclic derivatives, replacement of the imidazole moiety of VIII by triazole was also found to produce potent selective thromboxane synthetase inhibitors X.



X



XI

Preparation of X was accomplished similarly to VIII by using analogous procedures. Thus 1,2,4-triazole reacted with (bromoalkyl)phthalimides V to give XI. Hydrazinolysis and subsequent aroylation of the resultant amine gave X. Alternatively, 1,2,4-triazole also reacted with acrylonitrile and the product could be reduced and aroylated.

Biology: Results and Discussion

A. Thromboxane Synthetase Inhibition Activity. These compounds have highly selective activity to inhibit thromboxane synthetase as measured by determination of TXB_2 (the stable metabolite of TXA_2) levels in platelets drawn from spontaneously hypertensive rats (SHR). SHR platelets were chosen for this study since SHR were also used to evaluate the antihypertensive effects of the test compounds and comparison of data from the same species was then possible. Platelet suspensions were treated with either saline, standard (UK 37,248), or test compound, and the resultant supernatant was analyzed for TXB_2 content by direct radioimmunoassay (RIA) methods using the RIA kits from New England Nuclear (Boston, MA). Selectivity for enzyme inhibition was determined by analysis for PGI_2 production of incubates with guinea pig aortic rings by RIA of the stable 6-keto-$PGF_{1\alpha}$ metabolite. Since platelets mainly produce TX while blood vessels produce PGI_2, measurements in both tissues were required for meaningful evaluation. For all members of this series of compounds, only thromboxane synthetase was inhibited in rat platelets without inhibiting PGI_2 in pig aortic rings, suggesting that phospholipase A_2 and cyclooxygenase were not inhibited, therefore indicating specific TX synthetase inhibition. As summarized in Tables I–V, effects of aromatic substitution, chain-length variation, chain branching, imidazole substitution, and imidazole replacement by 1,2,4-triazole were investigated. The effects of aromatic substitution for the (imidazolylpropyl)benzamides (Table I) are surprisingly modest. The least active thromboxane synthetase inhibitors (**10** and **26**) suggest that ortho substitution is least desirable for activity, but clearly **3**, **7**, and **27** demonstrate the limitations of this generalization. It also may be inferred that electron-deficient aryl derivatives such as the 4-substituted compounds **5**, **12**, **15**, **20**, **21**, **23**, and **32** have better activity than their electron-rich 4-substituted counterparts **2**, **16**, and **17**. The 3,4,5-trimethoxy (**18**) and the 4-methylthio (**19**) derivatives clearly are extremely active and again weaken attempts to generalize SAR. The most interesting compounds for TXA_2 synthetase inhibition from this series are unsubstituted (**1**), 2-chloro (**3**), 4-chloro (**5**), 3,4-dichloro (**6**), 3-fluoro (**8**), 4-iodo (**13**), 3-trifluoromethyl (**14**), 3,4,5-trimethoxy (**18**), 4-phenyl (**22**), 4-benzoyl (**24**), and 4-acetamido (**31**) derivatives.

Similar conclusions concerning aromatic substitution effects on triazole derivatives may be made from data in Table IV. As a group, these compounds are less active than their imidazole counterparts (compare **81** to **14**, **80** to **12**, **79** to **11**, **78** to **9**, **77** to **8**, **75** to **5**, **74** to **4** for electron-deficient derivatives and **84** to **18**, **83** to **17**, and **82** to **16** for electron-rich derivatives), and little correlation between substituent and activity seems to exist. The best compounds in this series are 4-*tert*-butyl (**73**), 3-chloro (**74**), 3-fluoro (**77**), and 3-bromo (**79**).

Variations in chain length alter TXA_2 inhibition activity with larger separation (greater n) increasing activity within the scope of compounds prepared for this study. Thus for the imidazole series, as n increases from 2 to 4 for the 3,4-dichloro derivatives (**33**, **6**, and **36**) or from 3 to 8 for 4-chloro and 4-bromo derivatives (**5**, **35**, **39**, **42**, **43** and **12**, **37**, **40**, **44**, respectively), 100% inhibition of TXA_2 synthetase is achieved. A similar increase is observed for the triazole series for 3-chloro (**74** and **91**), 4-chloro (**75**, **92**, and **97**), and 4-bromo (**80**, **93**, and **98**) derivatives, but inhibition is never greater than 90% for this series in our test procedures. Interestingly, branching seems to have

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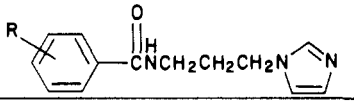
Table I. *N*-[3-(1*H*-Imidazol-1-yl)propyl]benzamides



compd	R	procedure	yield, %	mp, °C	thromb formation inhib[a]	anti-hypertensive act.[b]	formula
1	H	A	78	134–136	96	I	$C_{13}H_{15}N_3O$
2	4-CH_3	A	60	107–109	83	I	$C_{14}H_{17}N_3O$
3	2-Cl	A	61	98–101	100	I	$C_{13}H_{14}ClN_3O$
4	3-Cl	A	49	124–126	75	A	$C_{13}H_{14}ClN_3O$
5	4-Cl	A	56	141–143[c]	95	A	$C_{13}H_{14}ClN_3O$
6	3,4-Cl_2	A	44	158–160[c]	93	I	$C_{13}H_{13}Cl_2N_3O$
7	2-F	A	40	73–75	84	I	$C_{13}H_{14}FN_3O$
8	3-F	A	72	136–138	96	I	$C_{13}H_{14}FN_3O$
9	4-F	A	63	73–75	87	I	$C_{13}H_{14}FN_3O$
10	2-Br	A	65	95–98	50	I	$C_{13}H_{14}BrN_3O$
11	3-Br	A	66	113–115[c]	91	A	$C_{13}H_{14}BrN_3O$
12	4-Br	A	54	156–159[c]	85	A	$C_{13}H_{14}BrN_3O$
13	4-I	B	50	156–159	97	I	$C_{13}H_{14}IN_3O$
14	3-CF_3	C	32	82–84[d]	100	A	$C_{14}H_{14}F_3N_3O$
15	4-CF_3	A	52	107–109	93	A	$C_{14}H_{14}F_3N_3O$
16	4-CH_3O	B	70	132–135	89	I	$C_{14}H_{17}N_3O_2$
17	4-C_4H_9O	B	67	82–84	75	I	$C_{17}H_{23}N_3O_2$
18	3,4,5-$(CH_3O)_3$	B	88	155–158	100	I	$C_{16}H_{21}N_3O_4$
19	4-CH_3S	B	80	132–134	100	I	$C_{14}H_{17}N_3OS$
20	4-CH_3SO_2	B	35	174–176	80	I	$C_{14}H_{17}N_3O_3S$
21	4-CN	A	45	154–156	91	I	$C_{14}H_{14}N_4O$
22	4-C_6H_5	B	70	138–140	100	I	$C_{19}H_{19}N_3O$
23	4-CH_3CO	B	77	132–134[c]	90	I	$C_{15}H_{17}N_3O_2$
24	4-C_6H_5CO	B	80	107–109	100	I	$C_{20}H_{19}N_3O_2$
25	2-NH_2	E	60	107–109	89	A	$C_{13}H_{16}N_4O$
26	2-CH_3NH	D	64	140–143	57	I	$C_{14}H_{18}N_4O$
27	2-C_2H_5NH	D	76	115–117[d]	86	I	$C_{15}H_{20}N_4O$
28	4-$(CH_3)_2N$	B	25	133–135[d]	93	I	$C_{15}H_{20}N_4O$
29	2-NH_2-5-Cl	D	77	155–157[d]	96	A	$C_{13}H_{15}ClN_4O$
30	2-allyl-NH, 5-Cl	D	51	102–104[d]	95	A	$C_{16}H_{19}ClN_4O$
31	4-CH_3CONH	B	86	230–232	99	I	$C_{15}H_{18}N_4O_2$
32	2-COOH	F	71	162–164	82	I	$C_{14}H_{15}N_3O_3$

[a] Inhibition of thromboxane formation at a concentration of 10^{-4} M. UK 37,248 = 98%. [b] Spontaneously hypertensive rats at 100 mg/kg po/day for 2 days. A, active; I, inactive. [c] Recrystallized from ethanol. [d] Recrystallized from ethyl acetate.

little effect upon activity for the limited number of cases studied. For example, in the imidazole series with 4-chlorophenyl, 4-bromophenyl, or 4-(trifluoromethyl)phenyl substitution, branching retains or slightly enhances activity (**44–49**) as compared to the *n*-propyl (**5, 12, 15**) and *n*-butyl (**35, 37**) derivatives. Unsaturation in the chain also seems to produce small positive enhancements in activity (**51–54**).

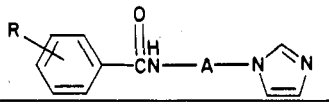
Effects of substitution on imidazole also significantly altered activity (Table III). With the use of the (imidazolylpropyl)benzamide system to study these effects, 2-methyl substitution on imidazole greatly altered TXA_2 synthetase activity while 4-methyl substitution had marginal effects (**4, 55, 62**; **5, 56, 63**; **6, 57, 66**; **11, 58, 64**; **12, 59, 65**; and **15, 61, 67**).

Finally, effects of altering the aroyl amide attachment were examined (Table V). Clearly the best activity for these compounds results when the aromatic moiety is conjugated either by an alkene (**108**) or cyclopropane (**110**) for the imidazole series while, for the triazoles, even this conjugation has little beneficial effect (**109**). When the aryl moiety is separated from the amide carbonyl by methylene (**99–102**), ethyl (**103**), or methyleneoxy (**104–106**), activity is significantly reduced.

Concentration–response studies were run on the most active compounds prepared in the series, and IC_{50} values for selected compounds are reported in Table VI. The IC_{50} was determined by plotting the percent inhibition against log concentration of the test compound in the concentration–response studies and measuring the concentration for 50% inhibition of TX formation from the graph. Comparison of these data with activity reported in Table I–V shows some variations between potency and activity which is common in drug development. 4-Chlorobenzamide derivatives **35, 39, 42**, and **43** show potency paralleling the earlier SAR discussion. In particular, increasing chain length (**35, 39, 42**, and **43**) increases potency with octyl derivative **43** having potency 10 times that of the standard UK 37,248. This increasing potency with increasing chain length is in accord with reports for other TX synthetase inhibitors.[11,13–18] Alteration of aromatic substituents (**13, 14, 19, 41**) does not greatly affect potency any more than activity noted earlier. Overall this family of compounds has selective thromboxane synthetase inhibitory activity that compares favorably to dazoxiben (UK 37,248).

B. Antihypertensive Activity. Routine testing of these compounds in the spontaneously hypertensive rat (SHR) showed several to have interesting levels of activity. Compounds with chloro, bromo, or trifluoromethyl substitution in the 3- or 4-position of the benzamide ring with three-carbon ($n = 3$) chain separation between the imidazole and amide moieties had good antihypertensive effects. In particular, propyl imidazoles **4, 5, 11, 12, 14, 15**, butyl imidazole **37**, substituted imidazoles **56, 61–63, 65–67**, and **70** had levels of lowering of blood pressure in SHR interesting enough to pursue. As is clear from the data, SHR activity does not necessarily parallel TXA_2 activity, since most compounds with longer alkyl chains ($n > 3$) were inactive. It is not clear from these data the impor-

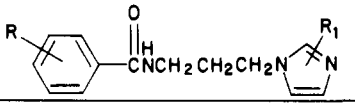
Table II. *N*-[(1*H*-Imidazol-1-yl)alkyl]benzamides



compd	R	A	procedure	yield, %	mp, °C	throm formation inhib[a]	anti-hyper-tensive act.[b]	formula
33	3,4-Cl_2	C_2H_4	A	50	137–140	59	I	$C_{12}H_{11}Cl_2N_3O$
34	H	C_4H_8	A	51	77–79[c]	91	I	$C_{14}H_{17}N_3O$
35	4-Cl	C_4H_8	A	58	70–72	95	I	$C_{14}H_{16}ClN_3O$
36	3,4-Cl_2	C_4H_8	A	31	86–88[d]	100	I	$C_{14}H_{15}Cl_2N_3O$
37	4-Br	C_4H_8	A	58	105–107	87	A	$C_{14}H_{16}BrN_3O$
38	2-COOH	C_4H_8	G	46	132–133[e]	50	I	$C_{15}H_{17}N_3O_3$
39	4-Cl	C_5H_{10}	A	82	102–104[c,f]	100	I	$C_{15}H_{18}ClN_3O$
40	4-Br	C_5H_{10}	A	80	104–106	100	I	$C_{15}H_{18}BrN_3O$
41	4-CF_3	C_5H_{10}	A	53	76–78	100	I	$C_{16}H_{18}F_3N_3O$
42	4-Cl	C_6H_{12}	A	81	72–76	100	I	$C_{16}H_{20}ClN_3O$
43	4-Cl	C_8H_{16}	A	38	61–63[c]	100	I	$C_{18}H_{24}ClN_3O$
44	4-Br	C_8H_{16}	A	77	90–92[c]	100	I	$C_{18}H_{24}BrN_3O$
45	3-Cl	$CH_2CH_2CH(CH_3)$	A	40	107–109[c]	93	I	$C_{14}H_{16}ClN_3O$
46	4-Cl	$CH_2CH_2CH(CH_3)$	A	45	159–161[c]	96	I	$C_{14}H_{16}ClN_3O$
47	4-Br	$CH_2CH_2CH(CH_3)$	A	75	122–124	91	I	$C_{14}H_{16}BrN_3O$
48	4-CF_3	$CH_2CH_2CH(CH_3)$	C	53	125–127[c]	94	I	$C_{15}H_{16}F_3N_3O$
49	4-Cl	$CH_2CH(CH_3)CH_2$	A	67	142–144[g]	100	I	$C_{14}H_{16}ClN_3O{\cdot}C_4H_4O_4$
50	3,4-Cl_2	$CH_2CH(CH_3)CH_2$	A	45	159–161[c]	86	I	$C_{14}H_{15}Cl_2N_3O$
51	4-Cl	$CH_2CH{=}CHCH_2$	A	42	124–126[h]	100	I	$C_{14}H_{14}ClN_3O$
52	4-Cl	$CH_2CH{=}CHCH_2$	A	63	112–114[i]	91	I	$C_{14}H_{14}ClN_3O$
53	4-CF_3	$CH_2CH{=}CHCH_2$	A	41	126–128[h]	93	I	$C_{15}H_{14}F_3N_3O$
54	4-CF_3	$CH_2CH{=}CHCH_2$	A	64	102–104[i]	95	I	$C_{15}H_{14}F_3N_3O$

[a] Inhibition of thromboxane formation at a concentration of 10^{-4} M. UK 37,248 = 98%. [b] Spontaneously hypertensive rats at 100 mg/kg po/day for 2 days. A, active; I, inactive. [c] Recrystallized from ethyl acetate. [d] Recrystallized from ethanol/ether. [e] Recrystallized from ethanol/ethyl acetate. [f] Hemihydrate. [g] Fumarate. [h] Cis isomer. [i] Trans isomer.

Table III. *N*-[(Substituted 1*H*-imidazol-1-yl)propyl]benzamides



compd	R	R_1	procedure	yield, %	mp, °C	thromb formation inhib[a]	anti-hyper-tensive act.[b]	formula
55	3-Cl	2-CH_3	A	65	130–132[c]	59	I	$C_{14}H_{16}ClN_3O$
56	4-Cl	2-CH_3	A	76	142–144	0	A	$C_{14}H_{16}ClN_3O$
57	3,4-Cl_2	2-CH_3	A	65	135–138	82	I	$C_{14}H_{15}Cl_2N_3O$
58	3-Br	2-CH_3	A	71	136–138	64	I	$C_{14}H_{16}BrN_3O$
59	4-Br	2-CH_3	A	70	154–156[c]	66	I	$C_{14}H_{16}BrN_3O$
60	3-CF_3	2-CH_3	C	51	145–147[d]	75	I	$C_{15}H_{16}F_3N_3O$
61	4-CF_3	2-CH_3	A	66	124–126	36	A	$C_{15}H_{16}F_3N_3O$
62	3-Cl	4-CH_3	A	75[e]	109–111[f]	84	A	$C_{14}H_{16}ClN_3O$
63	4-Cl	4-CH_3	A	75[e]	126–130[f]	93	A	$C_{14}H_{16}ClN_3O$
64	3-Br	4-CH_3	A	78[e]	115–123[f]	93	I	$C_{14}H_{16}BrN_3O$
65	4-Br	4-CH_3	A	74[e]	125–127[f]	80	A	$C_{14}H_{16}BrN_3O$
66	3,4-Cl_2	4-CH_3	A	77[e]	127–132[f]	90	A	$C_{14}H_{15}Cl_2N_3O$
67	4-CF_3	4-CH_3	A	71[e]	127–135[f]	92	A	$C_{15}H_{16}F_3N_3O$
68	4-I	4-CH_3	C	86[e]	124–131[f]	99	I	$C_{14}H_{16}IN_3O$
69	4-Cl	2-C_2H_5	A	72	120–122	32	I	$C_{15}H_{18}ClN_3O$
70	4-Cl	4-C_6H_5	A	82	118–120	69	A	$C_{19}H_{18}ClN_3O$

[a] Inhibition of thromboxane formation at a concentration of 10^{-4} M. UK 37,248 = 98%. [b] Spontaneously hypertensive rats at 100 mg/kg po/day for 2 days. A, active; I, inactive. [c] Recrystallized from ethyl acetate. [d] Recrystallized from ethanol. [e] Crude yield. [f] Mixture of 4-methyl and 5-methyl isomers. Melting point after recrystallization once or twice from ethyl acetate.

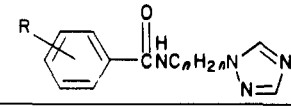
tance (if any) of TX synthetase inhibition activity vis-a-vis antihypertensive effects. Therefore, the antihypertensive effect may be independent of TX synthetase inhibition. Further elaboration of this SHR activity is the subject of a future report from these laboratories.[28]

In conclusion, the imidazolyl and triazolyl series of derivatives reported herein represent a novel class of selective TXA_2 synthetase inhibitors that may lead to an interesting clinical agent. It is interesting that such inhibitors do not require carboxylic acid moieties as might be concluded from other reported agents.[11,13–18] Several of these derivatives also have interesting antihypertensive properties. Further development of these series as TXA_2 synthetase inhibitors and/or antihypertensive agents is the subject of future papers.[28]

Experimental Section

Although there was some variation in the procedures used in the preparation of these compounds, the general procedures described below are representative. Yields and melting points are recorded in the tables. Analyses for C, H, N, S, and halogen were within 0.4% of theoretical values, and ^1H NMR spectra were obtained for all compounds on a Varian Associates HA100A

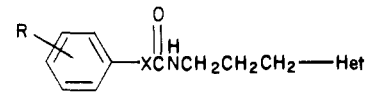
Table IV. *N*-[(1*H*-1,2,3-Triazol-1-yl)alkyl]benzamides



compd	R	*n*	procedure	yield, %	mp, °C	thromb formation inhib[a]	anti-hyper-tensive act.[b]	formula
71	4-Br	2	B	38	160–162	0	I	$C_{11}H_{11}BrN_4O$
72	H	3	A	58	75–78	77	A	$C_{12}H_{14}N_4O$
73	4-*t*-C_4H_9	3	A	51	90–91[c]	86	I	$C_{16}H_{22}N_4O$
74	3-Cl	3	A	60	57–60[c]	86	I	$C_{12}H_{13}ClN_4O$
75	4-Cl	3	A	70	110–112	16	I	$C_{12}H_{13}ClN_4O$
76	2-F	3	A	47	166–168[d]	25	I	$C_{12}H_{13}FN_4O\cdot HCl$
77	3-F	3	A	43	94–96[c]	82	I	$C_{12}H_{13}FN_4O$
78	4-F	3	A	12	100–101[c]	67	I	$C_{12}H_{13}FN_4O$
79	3-Br	3	C	62	70–73[c]	85	I	$C_{12}H_{13}BrN_4O$
80	4-Br	3	A	75	115–117	40	I	$C_{12}H_{13}BrN_4O$
81	3-CF_3	3	C	50	160–162	71	I	$C_{13}H_{13}F_3N_4O\cdot HCl$
82	4-CH_3O	3	C	41	120–122[c]	70	I	$C_{13}H_{16}N_4O_2$
83	4-C_4H_9O	3	C	76	83–85[c]	71	I	$C_{16}H_{22}N_4O_2$
84	3,4,5-$(CH_3O)_3$	3	C	25	128–129[c]	64	I	$C_{15}H_{20}N_4O_4$
85	4-C_6H_5CO	3	C	45	143–145[c]	65	I	$C_{19}H_{18}N_4O_2$
86	4-CH_3CONH	3	C	20	186–187[e]	75	I	$C_{14}H_{17}N_5O_2$
87	4-$(CH_3)_2N$	3	C	76	132–133[c]	64	A	$C_{14}H_{19}N_5O$
88	3-NO_2	3	A	47	101–103[c]	72	I	$C_{12}H_{13}N_5O_3$
89	2-C_6H_5	3	A	41	50–53[f]	65	I	$C_{18}H_{18}N_4O\cdot C_2H_2O_2$
90	2-COOH	3	F	83	165–167[e]	23	I	$C_{13}H_{14}N_4O_3$
91	3-Cl	4	B	78	67–68	87	I	$C_{13}H_{15}ClN_4O$
92	4-Cl	4	B	81	87–88	52	I	$C_{13}H_{15}ClN_4O$
93	4-Br	4	B	81	125–127	88	I	$C_{13}H_{15}BrN_4O$
94	4-CF_3	4	A	58	118–120[c]	38	I	$C_{14}H_{15}F_3N_4O$
95	3,4-Cl_2	4	B	70	97–99	82	I	$C_{13}H_{14}Cl_2N_4O$
96	2-C_6H_5	4	B	48	110–112[e,f]	89	I	$C_{19}H_{20}N_4O\cdot C_2H_2O_2$
97	4-Cl	5	A	82	68–70	79	I	$C_{14}H_{17}ClN_4O$
98	4-Br	5	A	89	93–95	81	I	$C_{14}H_{17}BrN_4O$

[a] Inhibition of thromboxane formation at a concentration of 10^{-4} M. UK 37,248 = 98%. [b] Spontaneously hypertensive rats at 100 mg/kg po/day for 2 days. A, active; I, in active. [c] Recrystallized from ethyl acetate. [d] Hydrochloride. [e] Recrystallized from ethanol. [f] Hemifumarate.

Table V. Miscellaneous *N*-[3-(1*H*-Imidazol-1-yl)propyl]aryl Amides and *N*-[3-(1*H*-1,2,4-Triazol-1-yl)propyl]aryl Amides



compd	R	X	Het[c]	procedure	yield, %	mp, °C	thromb formation inhib[a]	anti-hyper-tensive act.[b]	formula
99	4-F	CH_2	Im	B	55	101–103[d]	33	I	$C_{14}H_{16}FN_3O\cdot C_4H_4O_4$
100	3-Cl	CH_2	Im	B	55	109–111[d]	75	A	$C_{14}H_{16}FN_3O\cdot C_4H_4O_4$
101	3-Cl	CH_2	Tr	C	67	146–152[e]	0	I	$C_{13}H_{15}ClN_4O\cdot HCl$
102	4-CH_3	CH_2	Im	B	48	79–81[f]	58	A	$C_{15}H_{19}N_3O\cdot C_2H_2O_2$
103	H	C_2H_4	Im	B	50	90–92[g]	64	I	$C_{15}H_{19}N_3O\cdot C_6H_6O_6$
104	H	OCH_2	Im	B	82	91–93	86	I	$C_{14}H_{17}N_3O_2$
105	4-Cl	OCH_2	Im	B	82	116–119	85	I	$C_{14}H_{16}ClN_3O_2$
106	4-Cl	OCH_2	Tr	C	59	74–76	56	I	$C_{13}H_{15}ClN_4O_2$
107	H	CO	Im	B	35	95–105[d]	80	I	$C_{14}H_{15}N_3O_2\cdot C_4H_4O_4$
108	4-Cl	CH=CH	Im	C	40	151–153	98	A	$C_{15}H_{16}ClN_3O$
109	4-Cl	CH=CH	Tr	C	36	124–126	47	I	$C_{14}H_{15}ClN_4O$
110	H		Im	C	79	62–64[m]	100	I	$C_{16}H_{19}N_3O$

[a] Inhibition of thromboxane formation at a concentration of 10^{-4} M. UK 37,248 = 98%. [b] Spontaneously hypertensive rats at 100 mg/kg po/day for 2 days. A, active; I, in active. [c] Im = imidazolyl, Tr = triazolyl. [d] Fumarate. [e] Hydrochloride. [f] Hemifumarate. [g] 1.5 fumarate. [h] Crude yield. [i] Recrystallized from ethanol.

nuclear magnetic resonance spectrometer and were consistent with assigned structures. Melting points were determined on a Mel-Temp apparatus in open capillaries and are uncorrected.

Procedure A. Reaction of a (1*H*-Imidazol-1-yl)alkanamine or a (1*H*-1,2,4-Triazol-1-yl)alkanamine with an Acid Chloride. A mixture of 0.01 mol of the amine, 0.01 mol of 1 N NaOH (10 mL), and 50 mL of CH_2Cl_2 was stirred and 0.01 mol of the acid chloride was added. The reaction mixture was stirred overnight and treated with more CH_2Cl_2 and 5 mL of 1 N NaOH. The layers were separated, and the organic layer was washed with H_2O, dried over $MgSO_4$, and concentrated. The residue generally crystallized upon trituration with Et_2O and was isolated by filtration. Satisfactory microanalyses were generally obtained without recrystallization. When necessary, recrystallization from EtOH or EtOAc was usually satisfactory. If crystallization did not occur, attempts were made to prepare HCl or fumarate salts.

Table VI. Thromboxane Synthetase Inhibition IC_{50} Values for Selected Imidazole Derivatives

compd	IC_{50}, M	compd	IC_{50}, M
UK 37,248	1.5×10^{-6}	**39**	5×10^{-6}
13	5.5×10^{-7}	**41**	7×10^{-7}
14	4×10^{-6}	**42**	8×10^{-7}
19	5×10^{-7}	**43**	1×10^{-7}
35	5×10^{-6}		

In some cases a crystalline derivative would not form.

In some of the early reactions, the dihydrochloride of the amine and 0.03 mol of 1 N NaOH were used.

Procedure B. Reaction of a (1*H*-Imidazol-1-yl)alkanamine Dihydrochloride or a (1*H*-1,2,4-Triazol-1-yl)alkanamine Dihydrochloride with an Acid and 1,1′-Carbonyldiimidazole. A mixture of 0.01 mol of the acid and 0.01 mol of 1,1′-carbonyldiimidazole in 50 mL of THF was stored at room temperature for 2 h and 0.01 mol of the amine *dihydrochloride* was added. The reaction mixture was then stirred at room temperature for 18–24 h, refluxed for 2–5 h, treated with 5 mL of H_2O, and again heated for 1 h. The solvent was removed in vacuo and the residue was treated with CH_2Cl_2 and 0.03 mol of 1 N NaOH. The layers were separated, and the organic layer was washed with H_2O, dried over $MgSO_4$, and concentrated to give the desired product, which was washed onto a filter with Et_2O or recrystallized from a suitable solvent.

Procedure C. Reaction of a (1*H*-Imidazol-1-yl)alkanamine or a (1*H*-1,2,4-Triazol-1-yl)alkanamine with an Acid and 1,1′-Carbonyldiimidazole. A mixture of 0.01 mol of the acid and 0.01 mol of 1,1′-carbonyldiimidazole in 25–50 mL of THF was stored at room temperature for 2 h and 0.01 mol of the amine was added. The reaction mixture was allowed to stand at room temperature for 18–24 h, refluxed for 2 h, treated with 5 mL of H_2O, and again heated for 1 h and concentrated.

The residue was shaken with a mixture of CH_2Cl_2 and 10 mL of 1 N NaOH, and the layers were separated. The organic layer was washed with H_2O, dried over $MgSO_4$, and concentrated to obtain the desired product.

Procedure D. Reaction of a (1*H*-Imidazol-1-yl)alkanamine with an Isatoic Anhydride. A mixture of 0.02 mol of the isatoic anhydride and 0.018 mol of the (1*H*-imidazol-1-yl)alkanamine in 30 mL of toluene was stirred at 90–95 °C for 30–60 min and cooled. The precipitate that separated was collected by filtration, washed with Et_2O, and dried. With compounds **25** and **30** a taffeylike material separated and was dissolved in CH_2Cl_2, washed with 1 N NaOH, H_2O, dried over $MgSO_4$, and reconcentrated to give a satisfactory crystalline product, which was washed onto a filter with Et_2O.

Procedure E. Reaction of a (1*H*-Imidazol-1-yl)alkanamine or a (1*H*-1,2,4-Triazol-1-yl)alkanamine with an isatoic Anhydride. A mixture of 0.1 mol of the amine, 0.1 mol of the isatoic anhydride, and 100 mL of EtOH was stirred at room temperature for 4 h and concentrated. The residue was recrystallized from EtOAc.

Procedure F. 2-[[[3-(1*H*-Imidazol-1-yl)propyl]amino]carbonyl]benzoic Acid. A solution of 3.75 g (0.03 mol) of 3-(1*H*-imidazol-1-yl)propanamine in 25 mL of CH_2Cl_2 was added to a solution of 4.44 g (0.03 mol) of phthalic anhydride in 75 mL of CH_2Cl_2 with stirring. After 2 h, the precipitate was collected by filtration, washed with CH_2Cl_2 and then Et_2O, and dried in a vacuum oven, yield 7.3 g (89%), mp 152–155 °C. The above product was heated with 70 mL of EtOH, and the insoluble material was removed by filtration, yield 5.8 g, mp 162–164 °C. A small amount of crystalline product from the mother liquid had the same melting point.

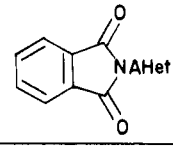
Procedure G. 2-[[[4-(1*H*-Imidazol-1-yl)butyl]amino]carbonyl]benzoic Acid. A mixture of 0.269 g (0.001 mol) of 2-[4-(1*H*-imidazol-1-yl)butyl]-1*H*-isoindole-1,3(2*H*)-dione, 1 mL of EtOH, and 1 mL of 1 N NaOH was stirred for 1.5 h and then neutralized with 0.08 mL of 12.4 N HCl. The solution was evaporated to a gum, which was heated with a mixture of EtOAc/EtOH and filtered hot. The filtrate was concentrated, and the residue was recrystallized from EtOAc to obtain 0.176 g (46%) of product, mp 132–133 °C dec.

Procedure H. Preparation of 2-[(1*H*-Imidazol-1-yl)alkyl]-1*H*-isoindole-1,3(2*H*)-diones and 2-[(1*H*-1,2,4-Triazol-1-yl)alkyl]-1*H*-isoindole-1,3(2*H*)-diones (Table VII). A mixture of 0.2 mol of the amine and 0.2 mol of 50% NaH (in oil) in 300 mL of DMF was stirred for 1–2 h, and 0.19 mol of the *N*-(bromoalkyl)phthalimide was added. The reaction mixture was heated on the steam bath for 8 h and concentrated to remove DMF. The residue was extracted with hot toluene, and the toluene layer was concentrated to remove the solvent. The residue was triturated with Et_2O or EtOAc, and the desired product was removed by filtration. If precipitation did not occur, the product was further purified by HPLC (EtOAc on silica column).

Procedure I. As above but the reaction mixture after the removal of the DMF was treated with a mixture of CH_2Cl_2 and H_2O, the layers were separated, the organic layer was dried over $MgSO_4$ and concentrated, and the product was obtained by trituration with Et_2O or recrystallization from a suitable solvent.

Procedure J. Preparation of (1*H*-Imidazol-1-yl)alkanamines and (1*H*-1,2,4-Triazol-1-yl)alkanamines from Isoindole-1,3(2*H*)-diones. A mixture of 0.1 mol of the isoindole-1,3(2*H*)-diones (Table VI), 0.11 mol of hydrazine hydrate, and 230 mL of EtOH was heated at reflux temperature for 8 h, cooled, treated with 335 mL of 4 N HCl, and refluxed for 6 h. The white precipitate (phthalhydrazide) was removed by filtration, and the mother liquor was concentrated to low volume and filtered again. The filtrate was concentrated, treated with 20 mL of H_2O and 11 g NaOH, and extracted with 400 mL of CH_2Cl_2 in four portions. The organic layer was dried over $MgSO_4$, concentrated, and distilled in a Kugelrohr apparatus. In some reactions, the residue

Table VII. 2-[*w*-(1*H*-Imidazol-1-yl)alkyl]-1*H*-isoindole-1,3(2*H*)-dione and 2-[*w*-(1*H*-1,2,4-Triazol-1-yl)alkyl]-1*H*-isoindole-1,3(2*H*)-dione Derivatives



compd	A	Het[a]	procedure	yield, %	mp, °C	formula
111	C_2H_4	Im	H[b]	30	165–167[c,d]	$C_{13}H_{11}N_3O_2$
112	C_2H_4	Tr	H	50	171–173[e-g]	$C_{12}H_{10}N_4O_2$
113	C_3H_6	2-EtIm	H	74	104–106[e]	$C_{16}H_{17}N_3O_2$
114	C_4H_8	Im	H	66	79–81[e]	$C_{15}H_{15}N_3O_2$
115	C_4H_8	Tr	I	83	139–141[g]	$C_{14}H_{14}N_4O_2$
116	C_5H_{10}	Im	I	78	194–196[g,h]	$C_{16}H_{17}N_3O_2$·HCl
117	C_5H_{10}	Tr	I	68	185–188[g,h]	$C_{15}H_{16}N_4O_2$·HCl
118	C_6H_{12}	Im	H	39	83–85[i]	$C_{17}H_{19}N_3O_2$
119	C_8H_{16}	Im	I	62	43–45[j]	$C_{19}H_{23}N_2O_2$
120	$CH_2CH{=}CHCH_2$	Im	I	51	80–82[k]	$C_{15}H_{13}N_3O_2$

[a] Im = imidazolyl, Tr = triazolyl. [b] Reaction run in toluene. [c] Recrystallized from 2-propanol. [d] Literature[30] mp 157 °C. [e] Recrystallized from ethyl acetate. [f] Literature[31] mp 169–170 °C. [g] Recrystallized from ethanol. [h] Hydrochloride. [i] Recrystallized from ether. [j] Purified by HPLC (ethyl acetate/silica gel column). [k] Prepared from *cis*-2-(4-chloro-2-butenyl)-1*H*-isoindole-1,3(2*H*)-dione.

after removal of the H_2O was treated with EtOH to obtain a crude, generally hygroscopic, dihydrochloride.

The following compounds were prepared in this way and used as intermediates without further purification: 2-(1*H*-imidazol-1-yl)ethanamine, 2-(1*H*-1,2,4-triazol-1-yl)ethanamine, 3-(2-ethyl-1*H*-imidazol-1-yl)propanamine, 4-(1*H*-imidazol-1-yl)butanamine, 4-(1*H*-1,2,4-triazol-1-yl)butanamine, 5-(1*H*-imidazol-1-yl)pentanamine, 5-(1*H*-1,2,4-triazol-1-yl)pentanamine, 6-(1*H*-imidazol-1-yl)hexanamine, and 8-(1*H*-imidazol-1-yl)octanamine. The crude *cis*-4-(1*H*-imidazol-1-yl)-2-butenamine and *trans*-4-(1*H*-imidazol-1-yl)-2-butenamine were similarly prepared and used as intermediates without distillation.

Procedure K. Preparation of Heterocyclic Propanamines from an Amine and Acrylonitrile. A mixture of 25 mL of acylonitrile and 0.1 mol of the amine was heated on the steam bath for 8 h and concentrated to remove the excess acrylonitrile. The residual oil was dissolved in 150–200 mL of MeOH, Raney nickel catalyst and 75 mL of NH_4OH were added, and the mixture was reduced in a Parr apparatus until 32–33 lb of hydrogen was absorbed. The catalyst was removed by filtration, and the mother liquor was concentrated and distilled in a Kugelrohr apparatus. The following intermediates were prepared in this way: 3-(1*H*-imidazol-1-yl)propanamine, 3-(1*H*-1,2,4-triazol-1-yl)propanamine, 3-(2-methyl-1*H*-imidazol-1-yl)propanamine, 3-(4-methyl-1*H*-imidazol-1-yl)propanamine, 3-(2-phenyl-1*H*-imidazol-1-yl)-propanamine, and 3-(4-phenyl-1*H*-imidazol-1-yl)propanamine.

Similar reactions of imidazole with crotanonitrile and methacrylonitrile gave 3-(1*H*-imidazol-1-yl)butanamine and 3-(1*H*-imidazol-1-yl)-2-methylpropanamine, respectively.

Preparation of *cis*-2-(4-Chloro-2-butenyl)-1*H*-isoindole-1,3(2*H*)-dione. A solution of 100 g (0.8 mol) of *cis*-1,4-dichloro-2-butene in 1500 mL of DMF was stirred at room temperature, and 74 g (0.4 mol) of potassium phthalimide was added. The mixture was stirred for 18 h, concentrated to remove the solvent, and extracted with four 500-mL portions of hexane. The residue was treated with CH_2Cl_2 and H_2O, and the layers were separated. The organic layer was dried with $MgSO_4$ and concentrated, and the residue was recrystallized from large volumes of hexane to obtain *cis*-2-(4-chloro-2-butenyl)-1*H*-isoindole-1,3-(2*H*)-dione, mp 78–80 °C. Anal. Calcd for $C_{12}H_{10}NO_2Cl$: C, 61.15; H, 4.28; N, 5.94; Cl, 15.05. Found: C, 61.28; H, 4.19; N, 5.96; Cl, 14.40. *trans*-2-(4-Chloro-2-butenyl)-1*H*-isoindole-1,3(2*H*)-dione was prepared from *trans*-1,4-dichloro-2-butene by using the same procedure, mp 100–101 °C. Anal. Calcd for $C_{12}H_{10}NO_2Cl$: C, 61.15; H, 4.28; N, 5.94; Cl, 15.05. Found: C, 61.53; H, 4.58; N, 6.22; Cl, 14.02.

Thromboxane Synthetase Inhibition and Prostacyclin Synthetase Inhibition. Under urethane anesthesia, 10 mL of arterial blood was collected in 1 mL of 3.2% sodium citrate in a polystyrene tube from Okamoto-Aoki spontaneously hypertensive rats (SHR) (Taconic Farms, Germantown, NY) between 19 and 24 weeks of age. The blood was diluted with 3 mL of cold saline and centrifuged at room temperature for 15 min at 460*g*. The platelet-rich plasma (PRP) was separated. The platelets were isolated by centrifuging the PRP at 4 °C for 10 min at 1060*g* and were washed in 4 mL of cold oxygenated Krebs phosphate buffer, pH 7.4. The chilled platelets recovered from centrifuging at 800*g* for 10 min were resuspended in oxygenated Krebs phosphate buffer and diluted to contain 4.5–6.0 × 10^4 platelets/μL. Platelets prepared by this procedure did not aggregate.

The inhibition of thromboxane (TX) formation was studied by determining the concentration of thromboxane B_2(TXB_2), the stable hydrolysis product of TXA_2. Assay samples, prepared on ice, contained 200 μL of platelet suspension, 50 μL of saline, and 50 μL of vehicle or drug under study. The samples were incubated for 10 min at 37 °C in a metabolic shaker. The reaction was terminated by immersing the tubes in an ice bath and adding 50 μL of 0.5 M citric acid. The samples were centrifuged for 10 min in a refrigerated centrifuge, and the supernatants thus obtained were decanted and stored at −20 °C. Controls wherein platelets, vehicle, and incubation buffer were inactivated in boiling water for 3 min prior to 37 °C incubation were run in parallel. The TXB_2 content for each sample was determined by a direct radioimmunoassay (RIA) utilizing a TXB_2 specific RIA kit purchased from New England Nuclear, Boston, MA, and instructions contained therein and expressed as picograms of TXB_2 formed $minute^{-1}$ $sample^{-1}$, from which the percent inhibition of TXB_2 formation was calculated. The small amount of TXB_2 measured in the controls was considered released before incubation and was subtracted from the test samples before this calculation. The results of this test are summarized in Tables I–VI.

The inhibition of PGI_2 was similarly determined on guinea pig aortic ring preparations with use of $^3H_6$-keto-$PGF_{1\alpha}$ (the stable hydrolysis product of PGI_2) levels as measured with a RIA method obtained from New England Nuclear. None of the test compounds altered levels from control values.

Antihypertensive Activity in Spontaneously Hypertensive Rats (SHR). The test compounds were tested for antihypertensive activity by the published methods.[29] Male, 16 week old, spontaneously hypertensive rats of the Okamoto strain, from Taconic Farms, Germantown, NY, having an average mean arterial blood pressure of 170 ± 1.5 mm of mercury are used in the test. One to three rats are used per test compound. A rat is dosed by gavage with a test compound, suspended in 2% preboiled starch at a concentration of 50 mg/mL, at a dose of 100 mg/kg of body weight or less, with 0.9% sodium chloride loading at a dose of 25 mL/kg of body weight. A second identical dose of the test compound, without sodium chloride loading, is given 24 h later. At 28 h after the initial dose, the mean arterial blood pressure is measured by the method of Chan and Poorvin vide supra.[29] The procedure is repeated in a second and third rat when activity is determined. Compounds are considered active when blood pressure in one test SHR has been reduced to ≤116 mmHg or when the average of two test SHR has been reduced to ≤122 mmHg.

The results of this test are summarized in Table I-V.

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