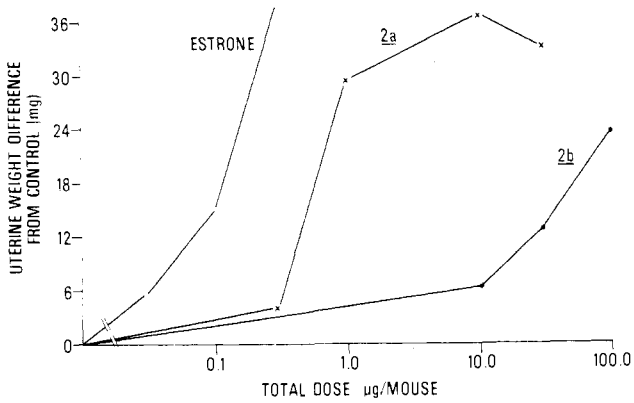

Figure 1. Uterine weight gain compared to controls of immature mice after sc injections of estrone, **2a**, and **2b**.

less exacting than for other classical hormonal activities.[15,16]

Experimental Section

Melting points were determined on a Mel-Temp apparatus. Infrared spectra, reported in reciprocal centimeters, were taken on either a Perkin-Elmer 221 or Beckman IR 12 spectrophotometer. The nmr spectra were determined on a T-60A spectrometer; chemical shifts are reported in δ from $(CH_3)_4Si$ and J values are given in Hz. Mass spectra were determined on a Hitachi RMU-6D spectrometer at 70 eV. Elemental analyses obtained were within +0.3% of the theoretical values.

3-Cyclopentyloxy-2′,3′-dihydroestra-1,3,5(10)-trieno[16α,-17α-*b*]furan-17β-ol (2a). A solution of 1.0 g (2.64 mmol) of 3-cyclopentyloxy-19-nor-17α-pregna-1,3,5(10)-trien-20-yne-16α,17β-diol (**1a**) in 250 ml of 0.05 *M* methanolic KOH was allowed to reflux for 24 hr. The methanol was then evaporated on a rotary evaporator and the resulting yellow solid was immediately chromatographed over a column of 50 g of Woelm silica gel, activity 1, using 5% EtOAc in benzene as the eluent. Alcohol **2a** was eluted as the first band, 850 mg (85%), mp 130–131°. Further elution afforded a small amount of starting diol **1a**. Both thin-layer chromatography (Brinkmann silica F_{254}, eluent 1:1 EtOAc–benzene, R_f 0.43) and glc[17] revealed **2a** to be homogeneous: mass spectrum exact mass at *m/e* 380.2358, calcd for $C_{25}H_{32}O_3$ 380.2351; ir (KBr) 3490 (OH), 2930 and 2860 (CH), no peaks from 2800–1620; nmr (pyridine-d_5) 7.4–6.8 (3 H, m, aromatics), 6.7 (1 H, d, J = 2.5 Hz, olefinic), 5.2 (1 H, d, J = 2.5 Hz, olefinic), 5.0–4.6 (2 H, m, CH adjacent to O), 3.0–1.3 (*ca.* 22 H, m), 1.2 (3 H, s, CH_3). A double resonance experiment revealed that the doublets at 6.7 and 5.2 were coupled to one another—irradiation of either doublet caused collapse of the other to a singlet. From nmr measurements in $CDCl_3$, a (δ $CDCl_3$–pyridine-d_5) value of −0.22 for the angular C_{18} methyl moiety was obtained. This is consistent[13] with a 1,3-diaxial relationship between the C_{18} methyl function and the C_{17} OH group. *Anal.* ($C_{25}H_{32}O_3$) C, H, O.

2′,3′-Dihydroestra-1,3,5(10)-trieno[16α,17α-*b*]furan-3,17β-diol (2b). This diol was generated from **1b** in 70% yield in a manner similar to the preparation of **2a** from **1a**. Purification *via* column chromatography (eluent 7% EtOAc in benzene) afforded the diol as a pale yellow solid: mp 210–212°; ir (KBr) 3400 (OH), 2950 and 2850 (CH), no peaks 2800–1670; mass spectrum exact mass at *m/e* 312.1721, calcd for $C_{20}H_{24}O_3$ 312.1725. *Anal.* ($C_{20}H_{24}O_3$) C, H.

Acknowledgment. We thank Mr. Larry Black and Mr. Ron Mincy of these laboratories for the estrogenic data described in this paper. Many thanks also go to Dr. Eugene Farkas for advice and discussions.

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Hypotensive Activity of 3-Alkyl-2-iminobenzothiazolines

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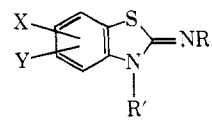
The hypotensive effects of a variety of guanidine derivatives are well documented.[1] The title compounds were investigated since they may be considered to be isosteric analogs of guanidine derivatives fused to an aromatic ring. The series of compounds investigated may be represented by formula I where R = H, aryl, aralkyl, cycloalkyl, acyl, or aroyl; R′ = alkyl; X and Y = H, alkyl, halo, or alkoxy.

The 3-alkyl-2-iminobenzothiazolines bearing an unsubstituted 2-imino moiety were synthesized by treating the appropriate phenylthiourea with bromine in chloroform solvent[2] or by alkylating the corresponding 2-aminobenzothiazole with either alkyl iodides in refluxing ethanol[3,4] or methyl fluorosulfonate in refluxing chloroform. Commerically unavailable 2-aminobenzothiazoles were synthesized by following known procedures.[5,6]



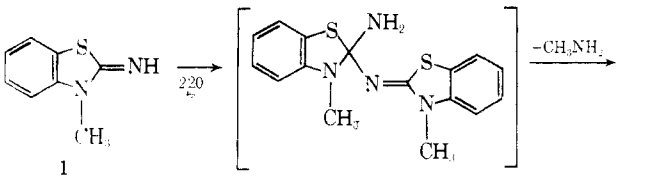
I

The displacement of the imino group of 2-imino-3-methylbenzothiazoline (1) was achieved by treating it with the appropriate primary amine at 220° under a nitrogen atmosphere.

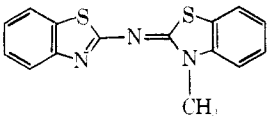
The acylation of 1 was conveniently effected by treating it with an acylating agent in pyridine.

Unexpectedly, compound **43** was isolated during the

reaction of 2,4-dimethoxyaniline with 1. Presumably, **43** arises by a self-condensation of 1 as shown below.

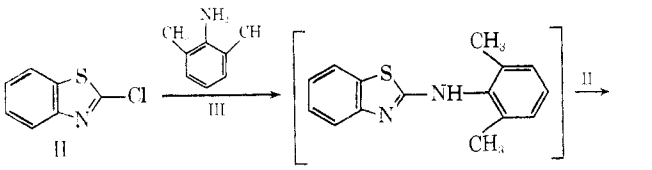


1

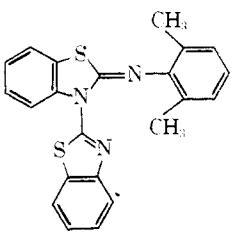


43

Compound **46** resulted when 2-chlorobenzothiazole was treated with 2,6-dimethylaniline at 170°. Apparently the ring nitrogen of presumed intermediate IV is more nucleophilic than the amino nitrogen of III under the reaction conditions employed.



II IV



46

Structure-Activity Relationships. Table I lists the hypotensive screening data obtained in the anesthetized dog for the iminobenzothiazolines unsubstituted at the imino nitrogen.

As the length of the 3-alkyl group increases, activity clearly begins to decrease (*e.g.*, compare 1 *vs.* 2 *vs.* **3**; 8 *vs.* 9 *vs.* **10**; 14 *vs.* **15**). Substitutions on the aromatic ring caused great variations in hypotensive activity. The most potent compounds were also those with a 3-methyl substituent. Compounds **5** and **21** are exceptions to this rule since both of them were inactive at 10 mg/kg. Compounds with substituents in the 4 position were particularly potent. At higher dosage levels, most of the very potent compounds had durations of action greater than 45 min. All of the active compounds listed in Table I when administered orally were inactive in the spontaneously hypertensive rat.

Table II lists compounds substituted at the nitrogen of the 2-imino moiety. All of the compounds listed were administered orally and evaluated in the spontaneously hypertensive rat. Compounds **27-31** were also evaluated in the anesthetized dog. None of these compounds reduced blood pressure sufficiently to be considered active.

The most active compound tested was **20** and it was chosen for subsequent hemodynamic evaluation in the anesthetized dog.

Hemodynamic Evaluation of 20. A comparison of the data obtained for **20** and Hydralazine is given in Table III. Analysis of the data indicates that the dramatic decrease in cardiac output seen with **20** is due to peripheral venous pooling.

Experimental Section

All melting points were determined in open capillary tubes using a Thomas-Hoover apparatus and are uncorrected. Nuclear magnetic resonance spectra were obtained at 60 MHz on a Varian A-60A spectrometer. Tetramethylsilane (TMS) was used as the internal standard and all signals are given in parts per million (δ) relative to TMS. Mass spectra were obtained on a Finnigan 1015 S/L instrument using a direct insertion probe. The electron-ionizing voltage was 70 eV at an ionizing current of 500 mA. The source temperature was 200°.

Method A. Cyclization of Phenylthioureas. A solution of 0.05 mol of the phenylthiourea in 120 ml of $CHCl_3$ was treated dropwise at ambient temperature with 10 ml of Br_2. The resultant mixture was stirred and refluxed for 1 hr, solvent was removed *in vacuo*, and crude HBr salt was converted to the free base using aqueous NaOH solution. The free base was converted to the HCl salt using Et_2O·HCl and recrystallized from the appropriate solvent.

Method B. Alkylation of 2-Aminobenzothiazoles with Alkyl Iodides. A solution of 0.1 mol of the 2-aminobenzothiazole and 0.125 mol of the alkyl iodide in 100 ml of EtOH was stirred and refluxed for 3 hr. After cooling to room temperature, the HI salt of the product was removed by filtration, suspended in 500 ml of H_2O, and converted to the free base using aqueous NaOH. Free base was extracted into $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried ($MgSO_4$), and filtered, and the filtrate was acidified to Congo Red with Et_2O·HCl. Solvent was removed *in vacuo*. The residual HCl salt obtained was purified by recrystallization from the solvent indicated.

Method C. Alkylation with Fluoromethanesulfonate. A solution of 0.1 mol of the appropriate 2-aminobenzothiazole in 1 l. of boiling $CHCl_3$ was stirred and treated dropwise with a solution of 11.4 g (0.1 mol) of fluoroethanesulfonate in 50 ml of $CHCl_3$. After stirring and refluxing for 18 hr, solvent was removed *in vacuo*. The resulting fluorosulfonate salt was converted to the HCl salt using the procedure described above for conversion of HI salts to HCl salts.

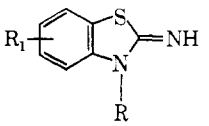
Method D. Displacement Reactions of 2-Imino-3-methylbenzothiazoline (1). Equimolar amounts of 1 and the appropriate amine were stirred and heated under an N_2 atmosphere with an oil bath at 220° until the evolution of NH_3 ceased (~0.5 hr). After cooling to room temperature, crude products were recrystallized from the indicated solvent. Free bases were converted to HCl salts using Et_2O·HCl.

Method E. Acylation of 2-Imino-3-methylbenzothiazoline (1). A mixture of 10 g (0.061 mol) of 1 and 0.061 mol of the appropriate acid chloride in 200 ml of pyridine was stirred at room temperature for 2 hr. The reaction mixture was poured into 1 l. of H_2O and crude product which precipitated was removed by filtration. Purification was accomplished by recrystallization from the appropriate solvent.

2-(2-Benzothiazolylimino)-3-methylbenzothiazoline (43). Compound **43** was isolated as a by-product in an attempt to prepare 2-[(2,4-dimethoxyphenyl)imino]-3-methylbenzothiazoline. A mixture of 10 g (0.061 mol) of 1 and 9.3 g (0.061 mol) of 2,4-dimethoxyaniline was stirred and heated under an N_2 atmosphere at ~220° for 0.5 hr. After cooling to room temperature, crude product was chromatographed on neutral alumina using $CHCl_3$ as the eluent. After removing solvent from the fraction collected, the solid residue obtained was recrystallized from CH_2Cl_2-EtOH to give 3.0 g of **43**, mp 184-186°. The structure assignment was based upon elemental analyses and ir, uv, nmr, and mass spectroscopy: ir (KBr) 2950 (aliphatic CH), 1600, 1530 cm^{-1} (C=C); uv max ($CHCl_3$) 353 nm (ϵ 46,100); nmr ($CDCl_3$) δ 7.48 (m, 8, Ar), 3.70 (s, 3, CH_3); mass spectrum 297 (M^+), 299 ($M^+ + 2$) and 301 ($M^+ + 4$) in the ratio of 500:60:1.

3-(2-Benzothiazolyl)-2-[(2,6-dimethylphenyl)imino]benzothiazoline (46). A solution of 34 g (0.2 mol) of 2-chlorobenzothiazole and 24.2 g (0.2 mol) of 2,6-dimethylaniline in 100 ml of EtOH was refluxed for 18 hr. The solvent was removed *in vacuo*, leaving a liquid residue which was then heated with an oil bath at ~170°. After ~20 min, a vigorous evolution of gas occurred and a white solid crystallized on the sides of the flask. After cooling, the residue was dissolved in $CHCl_3$. The $CHCl_3$ solution was washed with aqueous $NaHCO_3$, dried ($MgSO_4$), and filtered, and the $CHCl_3$ was removed *in vacuo*. Recrystallization from $CHCl_3$-EtOH gave 7.8 g (20%) of **46**, mp 217.5-219°. The structure assignment was based upon elemental analyses and ir, uv, nmr, and mass spectroscopy: ir (KBr) 2940 (aliphatic CH), 1600, 1530 cm^{-1} (C=C); uv max ($CHCl_3$) 313 nmr (ϵ 25,900); nmr ($CDCl_3$-TFA)

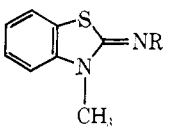
Table I

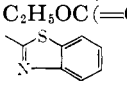


No.	R	R_1	Method[a]	Yield, %	Recrystn solvent[b]	Mp, °C	Formula	Hypotensive activity[c]
1	CH_3	H	A	80	E	123	$C_8H_8N_2S$[d]	+++
2	C_2H_5	H	A	46	E	84–85	$C_9H_{10}N_2S$[d]	+
3	*n*-C_3H_7	H	A	23	E	166	$C_{10}H_{12}N_2S$[e]	NA/10
4	*n*-C_6H_{13}	H	B	34	M–A	233–235	$C_{13}H_{18}N_2S \cdot HCl$	NA/10
5	CH_3	6-CH_3	B	55	M–A	>300	$C_9H_{10}N_2S \cdot HCl$[f]	NA/10
6	C_2H_5	6-CH_3	B	24	M–A	293–295	$C_{10}H_{12}N_2S \cdot HCl$[f]	NA/10
7	*n*-C_3H_7	6-CH_3	B	11	M–A	260–262	$C_{11}H_{14}N_2S \cdot HCl$	NA/10
8	CH_3	5,6-$(CH_3)_2$	B	42	M–A	>310	$C_{10}H_{12}N_2S \cdot HCl$	++
9	C_2H_5	5,6-$(CH_3)_2$	B	25	M–A	303–305	$C_{11}H_{14}N_2S \cdot HCl$	+
10	*n*-C_3H_7	5,6-$(CH_3)_2$	B	7	M–A	302–304	$C_{12}H_{16}N_2S \cdot HCl$	NA/10
11	CH_3	6-OCH_3	B	25	M–A	308–309	$C_9H_{10}N_2OS \cdot HCl$[g]	+++
12	C_2H_5	6-OCH_3	B	16	M–A	279–280	$C_{10}H_{12}N_2OS \cdot HCl$[h]	NA/10
13	*n*-C_3H_7	6-OCH_3	B	5	M–A	243 5–245	$C_{11}H_{14}N_2OS \cdot HCl$	NA/10
14	CH_3	6-OC_2H_5	B	26	M–A	310–312	$C_{10}H_{12}N_2OS \cdot HCl$[g]	+++
15	C_2H_5	6-OC_2H_5	B	13	M–A	273–275	$C_{11}H_{14}N_2OS \cdot HCl$	NA/10
16	*n*-C_3H_7	6-OC_2H_5	B	13	M–A	248–250	$C_{12}H_{16}N_2OS \cdot HCl$	NA/10
17	CH_3	6-Br	B	20	M–A	313–315	$C_8H_7BrN_2S \cdot HCl$[i]	+
18	C_2H_5	6-Br	B	18	M–A	263–265	$C_9H_9BrN_2S \cdot HCl$[d]	+
19	*n*-C_3H_7	6-Br	B	7	M–A	252–254	$C_{10}H_{11}BrN_2S \cdot HCl$	NA/10
20	CH_3	4-Cl	B	11	M–A	261–263	$C_8H_7ClN_2S \cdot HCl$	++++
21	CH_3	6-Cl	A	12	M	>300	$C_8H_7ClN_2S \cdot HCl$[i]	NA/10
22	CH_3	4-OCH_3	B	31	M	282–283	$C_9H_{10}N_2OS \cdot HCl$	+++
23	CH_3	5,6-$(Cl)_2$	C	11	W–M–A	>300	$C_8H_6Cl_2N_2S \cdot HCl$	++
24	CH_3	4-CH_3-7-Cl	C	12	M–A	256–258	$C_9H_9ClN_2S \cdot HCl$	+++
25	CH_3	4,6-$(OCH_3)_2$	B	44	M–A	290–292	$C_{10}H_{12}N_2O_2S \cdot HCl$	+++
26	CH_3	4-OCH_3-5-Cl	C	40	M–A	245–247	$C_9H_9ClN_2OS \cdot HCl$	+++

[a]Methods are described in the Experimental Section. All compounds analyzed within ±0.4% of theoretical for C, H, and N or Cl. [b]A, acetone; E, EtOH; M, MeOH; W, H_2O. [c]Anesthetized dog, iv: ++++, bp decrease >20% at 0.3 mg/kg; +++, bp decrease >20% at 1.0 mg/kg; ++, bp decrease >20% at 3.0 mg/kg; +, bp decrease >20% at 10 mg/kg; NA/10, inactive at 10.0 mg/kg. [d]Reference 2. [e]K. Tsuda and S. Oguri, *J. Pharm. Soc. Jap.*, **62**, 66 (1942); *Chem. Abstr.*, **45**, 1580*f* (1951). [f]Reference 4. [g]T. Takahashi and J. Okada, *J. Pharm. Soc. Jap.*, **71**, 423 (1951). [h]I. K. Ushenko and I. P. Dmitrenko, *Sb. Statei Obshch. Khim.*, **1**, 650 (1953); *Chem. Abstr.*, **49**, 1023*e* (1955). R. F. Hunter, E. R. Parken, and E. M. Short, *J. Chem. Soc.*, 784 (1959).

Table II



No.	R	Method[a]	Yield, %	Recrystn solvent[b]	Mp, °C	Formula
27	$C_6H_5CH_2$	D	65	M–A	230–233	$C_{15}H_{14}N_2S \cdot HCl$
28	$C_6H_5CH_2CH_2$	D	79	M–A	236–238	$C_{16}H_{16}N_2S \cdot HCl$
29	4-$CH_3OC_6H_4$	D	35	M–A	257–259	$C_{15}H_{14}N_2OS \cdot HCl$
30	3,4-$(CH_3O)_2C_6H_3$	D	15	E	108–110	$C_{16}H_{16}N_2O_2S$
31	3,4-$(CH_3O)_2C_6H_3CH_2CH_2$	D	45	M–A	89 5–91	$C_{18}H_{20}N_2O_2S$
32	1-Adamantanyl	D	13	M–C–E	131–133	$C_{18}H_{22}N_2S$
33	4-$(CH_3O)C_6H_4CH_2CH_2$	D	25	E	65–67	$C_{17}H_{18}N_2OS$
34	3,4-$(CH_3O)_2C_6H_3CH_2$	D	45	E	102–104	$C_{17}H_{18}N_2O_2S$
35	$C_6H_5NHCH_2CH_2$	D	42	M–A	238–240	$C_{16}H_{17}N_3S \cdot 2HCl$
36	$(C_6H_5)_2CHCH_2CH_2$	D	37	M–A	188–190	$C_{23}H_{22}N_2S \cdot HCl$
37	$C_6H_5CH_2\underset{\displaystyle CH_3}{\underset{\vert}{CH}}$	D	30	M–A	176–177	$C_{17}H_{18}N_2S \cdot HCl$
38	$C_6H_5C(=O)$	E	81	C–E	151–152 5	$C_{15}H_{12}N_2OS$
39	3,4-$(CH_3O)_2C_6H_3C(=O)$	E	50	M–A	178–179 5	$C_{17}H_{16}N_2O_3S$
40	3,4,5-$(CH_3O)_3C_6H_2C(=O)$	E	43	M–A	165–166 5	$C_{18}H_{18}N_2O_4S$
41	4-$(CH_3O)C_6H_4C(=O)$	E	81	C–E	186–188	$C_{16}H_{16}N_2O_2S$
42	$C_2H_5OC(=O)$	E	57	C–E	125–127	$C_{11}H_{12}N_2O_2S$
43		*c*	34	M–C–E	184–186	$C_{15}H_{11}N_3S_2$
44	$(CH_3)_2NC(=O)$	E	18	C–E	160–162	$C_{11}H_{13}N_3OS$
45	3-$ClC_6H_4C(=O)$	E	84	E	167–168	$C_{15}H_{11}ClN_2OS$

[a]See footnote *a*, Table *I*. [b]See footnote *b*, Table *I*; C, chloroform. [c]See Experimental Section.

Table III. Comparison of the Intravenous Effects of **20** and Hydralazine on Hemodynamic Parameters in the Pentobarbital Anesthetized Dog[a]

Compd	Dose, mg/kg iv[b]	Hemodynamic parameter, % Δ				
		MAP[c]	HR[d]	MFC[e]	CO[f]	CTPR[g]
20	0.1	−5.3	−6.3	+7.3	+10.0	−9.7
	0.3	−37.0	−5.0	+26.0	−21.0	−43.5
	1.0	−50.5	−9.3	+37.0	−23.3	−42.0
	3.0	−77.5	−10.0	+91.5	−69.0	−64.0
Hydralazine	0.1	−5.0	+6.3	+35.0	+15.8	−17.0
	0.3	−18.3	+14.0	+53.8	+25.0	−31.8
	1.0	−32.5	+9.8	+47.0	+25.5	−51.0
	3.0	−26.3	+5.3	+84.5	+91.0	−55.8
	10.0	−40.8	+29.8	+95.0	+74.5	−67.5

[a] Maximum effect occurring within 10 min after administration. [b] Four dogs per dose. [c] Mean arterial blood pressure, mm. [d] Heart rate, beats per minute. [e] Myocardial force of contraction, mm deflection. [f] Cardiac output, milliliters per minute. [g] Calculated total peripheral resistance, relative resistance units calculated by MAP/CO.

δ 7.80 (m, 11, Ar), 2.33 (s, 6, CH_3); mass spectrum 387 (M^+) and 389 ($M^+ + 2$) in the ratio of 9.8:1.

Determination of Hypotensive Activity. Compounds were evaluated in mongrel dogs and/or Wistar strain spontaneously hypertensive rats. Mongrel dogs, of either sex, were anesthetized with 35 mg/kg of sodium pentobarbital (Nembutal, Abbott Laboratories) intravenously *via* the cephalic vein. After tracheal intubation, femoral arterial blood pressure, the signal from lead II of the electrocardiogram, respiration and the blood pressure responses to bilateral common carotid occlusion, and intravenous norepinephrine were recorded on a Grass Model 7 polygraph. Aqueous solutions of the compounds to be tested were administered *via* the contralateral femoral vein. Compounds were administered to a minimum of two to four dogs and were considered active if systolic blood pressure was reduced by more than 20%.

Systolic blood pressure was recorded from the tails of spontaneously hypertensive rats. A photocell transducer was incorporated with a pneumatic pressure cuff for blood pressure measurement. The animals were warmed in a thermostatically controlled chamber (31.5 ± 0.5°) for 1 hr prior to obtaining blood pressure readings. The method for blood pressure measurement depends, essentially, on occlusion of the tail with the pneumatic cuff followed by a rapid release of the imposed pressure. The result is an abrupt rebound increase in the pressure head and blood flow in the tail. This increase is recorded as systolic blood pressure by a photocell transducer connected to a Grass Model 7 polygraph. Following 2 days of control readings, the compounds were administered orally at 25 mg/kg in 0.5% methocel (400 cps), four rats per compound, for 2 consecutive days. Blood pressure measurements were obtained 24 hr after the initial dose and 1, 2, 3, 4, and 24 hr after the second dose. Compounds were considered active if blood pressure was reduced by more than 15%.

Hemodynamic Evaluation of 20. Mongrel dogs, of either sex, were anesthetized with 35 mg/kg of sodium pentobarbital (Nembutal, Abbott Laboratories) intravenously *via* the cephalic vein. A tracheal cannula was inserted, artificial respiration applied, and the chest opened at the fifth right intercostal space. Cardiac output (CO) was obtained by affixing a Statham electromagnetic flow probe around the ascending aorta between the region of the aortic valve and the brachiocephalic artery. Right ventricular contractile force (MFC) was measured with a Walton-Brodie strain-gauge arch. Femoral arterial blood pressure (BP) was measured directly *via* a Statham P23Ac pressure transducer. The thorax was then closed and the animals were permitted to respire spontaneously. Heart rate (HR) was determined from the contractile force deflections. Relative calculated total peripheral resistance (CTPR) was calculated by the relationship of blood pressure to cardiac output. Aqueous solutions of the compounds were administered *via* the contralateral femoral vein at a rate of 2 mg/kg/min.

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Etonitazene. An Improved Synthesis

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1-(β-Diethylaminoethyl)-2-(*p*-ethoxybenzyl)-5-nitrobenzimidazole (1, etonitazene) is a potent analgesic that has value in drug addiction studies. We have developed a simple high-yield synthesis of 1 that is adaptable to large-scale preparations. The synthesis involves the condensation of 2-(β-diethylaminoethylamino)-5-nitroaniline and *p*-ethoxyphenylacetic acid in THF in the presence of EEDQ.

1-(β-Diethylaminoethyl)-2-(*p*-ethoxybenzyl)-5-nitrobenzimidazole (**1**, etonitazene) is a very potent analgesic.[1,2] However, it has a dependence potential comparable to that of morphine[3] and thus offers little advantage over morphine as an analgesic. Since experimental animals will not refuse to drink a solution of **1** as they will solutions of other analgesics, this analgesic has value in drug addiction studies.[4]

The reported synthesis of **1** involves the condensation of 2-(β-diethylaminoethylamino)-5-nitroaniline (**2**) as its hy-