yielded three fractions of bp (0.3 mm) 79–91, 134–142, and 145–158°. The second fraction was redistilled [bp 132–136° (0.3 mm), 31 g] and then crystallized from pentane at −40° to afford pure 3-benzylindene as colorless prisms, mp 31.5–33° (lit.[34] mp 33–34°), yield 27.1 g (27%).

The last fraction solidified in the condenser and was recrystallized from petroleum ether to yield 15.2 g (15%) of colorless, prismatic needles, mp 75–77°, identified as *trans*-**1-benzalindane.**

trans-**1-Benzalindane (XVI).**—Benzyltriphenylphosphonium chloride (45 g, 0.11 mole) was added to sodium ethoxide (from 2.3 g, 0.1 g-atom of Na) in 250 ml of dry ethanol under N_2. 1-Indanone (13.2 g, 0.1 mole) was then added to the yellow solution. The reaction mixture was stirred at 20° in the dark under N_2 for 60 hr, poured into 250 ml of 10% aqueous HBr, and filtered. The buff-colored residue was washed with 1:1 ethanol–water and crystallized (after being treated with active charcoal) first from ethanol, then from petroleum ether (bp 60–80°) to afford XVI, mp 75–76.5° (lit.[19] mp 73–74.5°), yield 6.6 g (32%).

Anal. Calcd for $C_{16}H_{14}$: C, 93.2; H, 6.84. Found: C, 93.4; H, 7.02.

The ultraviolet spectrum (typical *trans*-stilbene absorptions) had λ_{max}^{EtOH} 229 mμ (log ε 4.12), 236 (4.06), 244 (3.79), 275 (infl), 284.5 (4.31), 296 (4.34), 306 (infl), 317 (4.46), and 331 (4.29).

2-(Indan-1′-ylidene)-1-indanone (0.2 g) crystallized from the ethanolic mother liquor, and, after recrystallization from petroleum ether, had mp 142–144° (lit.[35] mp 142°).

1(3)-Benzyl-3(1)-(2-diethylaminoethyl)indene Hydrogen Oxalate (26).—3-Benzylindene (20.6 g, 0.1 mole), NaH (4.45 g, 0.1 mole), and dry toluene (200 ml) were heated under reflux for 6 hr under N_2. Then, 1-chloro-2-diethylaminoethane (from 0.14 mole of hydrochloride) in 50 ml of dry toluene was added to the resulting suspension of buff solid sodium derivative. Reaction was rapid and exothermic, and a white precipitate formed. After being stirred under gentle reflux for 12 hr, the mixture was extracted with dilute HCl, and the amine was isolated in the usual manner. Distillation *in vacuo* yielded 19 g of pale yellow oil, bp 158–178° (0.4 mm), which, with oxalic acid in ethanol, afforded 6.1 g (15%) of the hydrogen oxalate after dilution with ether. Three crystallizations from water furnished the product, mp 139–145°.

Anal. Calcd for $C_{22}H_{27}N \cdot C_2H_2O_4$: C, 72.9; H, 7.39; N, 3.54; acid equiv, 198. Found: C, 72.8; H, 7.45; N, 3.80; acid equiv, 196.

The ultraviolet absorption spectrum showed several low-intensity maxima at 292–330 mμ which suggest the presence of 1% of an impurity containing a 1-benzalindane chromophore: λ_{max}^{EtOH} 257 mμ (log ε 3.95), 282 (2.47), 292 (2.46), 303 (2.44), 315 (2.42), shoulders at 296 and 330; nmr (D_2O at 75°), τ 8.55 (triplet, CH_3), 8.0–6.0 (complex, aliphatic), 3.57 (doublet, vinylic), 3.1–2.2 (complex, aromatic) in the ratio 5.9:11.4:1.1:9.

1-Benzal-3-(2-diethylaminoethyl)indene Hydrochloride (27).—Indene (87 g, 0.75 mole) was treated with NaH (33.6 g, 0.75 mole) in dry DMF (650 ml) at 20° under N_2. After 2.5 hr, 1-chloro-2-diethylaminoethane (from 344 g, 2 mole of hydrochloride) in 250 ml of dry toluene was added. After being stirred at 40–50° for 15 hr, the mixture was diluted with water (750 ml), and the toluene layer was separated, washed with water, and extracted with 5 *N* HCl. **3-(2-Diethylaminoethyl)indene**, which was isolated by basification of the acidic extract, was distilled twice *in vacuo* and obtained as a colorless mobile oil (62 g, 39%), bp 148–150° (0.2 mm), $n^{21}D$ 1.5356 [lit.[3] bp 140° (0.4 mm)].

Anal. Calcd for $C_{15}H_{21}N$: C, 83.7; H, 9.83; N, 6.51. Found: C, 83.6; H, 9.97; N, 6.48.

To 3-(2-diethylaminoethyl)indene (10 g, 0.046 mole) and benzaldehyde (5.35 g, 0.05 mole) in 100 ml of ethanol was added ethanolic KOH (85 ml containing 3.85 g, 0.068 mole). The mixture was stirred at 21° for 4 hr, then concentrated to 50 ml, diluted with water (100 ml), and extracted with ether. The ether solution was extracted with 5 *N* HCl, and the acid extract was basified to liberate the oily amine (13.4 g) which was converted to the hydrochloride. After recrystallization from 2-propanol–ether, it was obtained as bright yellow needles: mp 189–191°; yield 11.8 g (76%); λ_{max}^{EtOH} 240–242 mμ (log ε 3.96), 283–284 (4.12), and 341 (4.17).

Anal. Calcd for $C_{22}H_{25}N \cdot HCl$: C, 77.7; H, 7.71; N, 4.12; Cl, 10.4. Found: C, 77.9; H, 7.87; N, 3.93; Cl, 10.4.

Acknowledgment.—The authors are indebted to Dr. D. K. Vallance and Mr. G. H. Hall, formerly of these laboratories, for the pharmacological investigations. We thank Mr. S. G. Garnish and Mr. C. S. Stolz for technical assistance and Dr. E. S. Pepper for the measurement and helpful discussion of the nmr spectra.

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(35) F. S. Kipping, *J. Chem. Soc.*, **65**, 480 (1894).

Sympathetic Nervous System Blocking Agents. III. Derivatives of Benzylguanidine[1-3]

JAMES H. SHORT AND THOMAS D. DARBY

Organic Chemistry Department and Pharmacology Department, Research Division, Abbott Laboratories, North Chicago, Illinois 60064

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A series of 25 derivatives of benzylguanidine and related compounds was synthesized and investigated for sympathetic nervous system blocking activity by their effect on the nictitating membrane of the unanesthetized cat. Selected members were also screened for hypotensive activity in the anesthetized cat by the intravenous route. The most active compounds, *p*-trifluoromethylbenzylguanidine sulfate (Table I, **14**) and α-methyl-*p*-trifluoromethylbenzylguanidine sulfate (**23**), were subjected to extensive pharmacological evaluation. Both effectively lower the blood pressure in both renal and neurogenic hypertensive dogs. Compound **23** is notable for its lack of side effects.

The first two drugs found capable of blocking the sympathetic nervous system without concomitantly blocking the parasympathetic system, thus making them superior to the ganglionic blocking agents for the treatment of hypertension, were guanethidine[4] (I) and bretylium tosylate[5] (II).

Inevitably the attractive possibility of combining the *o*-bromobenzyl portion of bretylium with the guanidine moiety of guanethidine was undertaken by medicinal chemists. Boura, *et al.*,[6] was the first to report compounds of this sort. The most active mem-

(1) Paper I: J. H. Short and U. Biermacher, *J. Pharm. Sci.*, **51**, 881 (1962).
(2) Paper II: J. H. Short, U. Biermacher, D. A. Dunnigan, and T. D. Leth, *J. Med. Chem.*, **6**, 275 (1963).
(3) Presented before the Division of Medicinal Chemistry at the 153rd National Meeting of the American Chemical Society, Miami Beach, Fla., April 1967.
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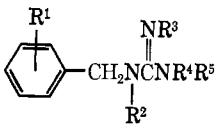
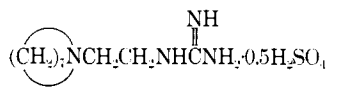
(5) A. L. A. Boura and A. F. Green, *Brit. J. Pharmacol.*, **14**, 536 (1959).
(6) A. L. A. Boura, F. C. Copp, A. F. Green, H. F. Hodson, G. K. Ruffell, M. F. Sim, and E. Walton, *Nature*, **191**, 1312 (1961).

TABLE I
BENZYLGUANIDINES

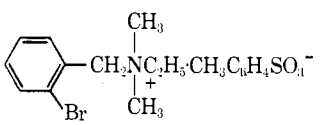


No.	R^1	R^2	R^3	R^4	R^5	Salt mp, °C	Method	Formula	% C Calcd	% C Found	% H Calcd	% H Found	% N Calcd	% N Found
1	2-F	H	H	H	H	189–189.5	A[a]	$C_8H_{10}FN_3 \cdot 0.5H_2SO_4$	44.43	44.49	5.13	5.21	19.44	19.33
2	4-F	H	H	H	H	167–168	A[b]	$C_8H_{10}FN_3 \cdot 0.5H_2SO_4$	44.43	44.66	5.13	5.42	19.44	19.35
3	3-Cl	H	H	H	H	144–145	B[c,d]	$C_8H_{10}ClN_3 \cdot HCl$	43.65	43.58	5.04	5.02	19.09	19.15
4	2-Br	H	H	H	H	245–247	A	$C_8H_{10}BrN_3 \cdot 0.5H_2SO_4$	34.67	34.79	4.00	3.92	15.16	15.20
5	4-Br	H	H	H	H	230–232	A[e]	$C_8H_{10}BrN_3 \cdot 0.5H_2SO_4$	34.67	34.71	4.00	4.04	15.16	15.09
6	2-I	H	H	H	H	229–231	A[a]	$C_8H_{10}IN_3 \cdot 0.5H_2SO_4$	29.64	29.98	3.42	3.78	12.96	13.03
7	4-I	H	H	H	H	258–260	A	$C_8H_{10}IN_3 \cdot 0.5H_2SO_4$	29.64	29.80	3.42	3.41	12.96	12.91
8	2,4-Cl_2	H	H	H	H	225–227	A[e]	$C_8H_9Cl_2N_3 \cdot 0.5H_2SO_4$	35.97	35.78	3.78	3.63	15.73	15.65
9	3,4-Cl_2	H	H	H	H	241–242	A[e]	$C_8H_9Cl_2N_3 \cdot 0.5H_2SO_4$	35.97	36.03	3.78	3.90	15.73	15.94
10	2,6-Cl_2	H	H	H	H	270–272	A	$C_8H_9Cl_2N_3 \cdot 0.5H_2SO_4$	35.97	35.95	3.78	3.77	15.73	15.64
11	4-CN	H	H	H	H	233–235	A[e]	$C_9H_{10}N_4 \cdot 0.5H_2SO_4$	48.42	48.63	4.97	5.10	25.10	25.16
12	2-CF_3	H	H	H	H	262–264	A	$C_9H_{10}F_3N_3 \cdot 0.5H_2SO_4$	40.60	40.59	4.17	4.12	15.79	15.75
13	3-CF_3	H	H	H	H	193.5–195.5	A[e]	$C_9H_{10}F_3N_3 \cdot 0.5H_2SO_4$	40.60	40.81	4.17	4.13	15.79	15.65
14	4-CF_3	H	H	H	H	258	A[e]	$C_9H_{10}F_3N_3 \cdot 0.5H_2SO_4$	40.60	40.82	4.17	4.15	15.79	15.68
15	4-CF_3	H	CH_3	CH_3	H	246–247	A[d]	$C_{11}H_{14}F_3N_3 \cdot HCl$	46.90	46.70	5.37	5.48	14.92	15.10
16	2-Cl-5-CF_3	H	H	H	H	267–269	A[e]	$C_9H_9ClF_3N_3 \cdot 0.5H_2SO_4$	35.95	35.60	3.35	3.68	13.98	13.73
17	4-Cl	H	H	CH_3	H	158–159	A[b,f]	$C_9H_{12}ClN_3 \cdot 0.5H_2SO_4$	43.81	43.68	5.32	5.15	17.03	17.09
18	4-Cl	CH_3	H	H	H	275.5–276	A,B[e,g]	$C_9H_{12}ClN_3 \cdot 0.5H_2SO_4$	43.81	43.68	5.32	5.40	17.03	16.98
19	4-Cl	H	CH_3	CH_3	H	281.5–282.5	A[e,h]	$C_{10}H_{14}ClN_3 \cdot 0.5H_2SO_4$	46.07	45.87	5.80	5.85	16.12	16.02
20	4-Cl	H	H	CH_3	CH_3	178.5–179	B[d,i]	$C_{10}H_{14}ClN_3 \cdot HCl$	48.40	48.39	6.09	5.92	16.94	17.01
21	4-ClC_6H_4	H	H	H	H	200–202	A[e]	$C_{14}H_{14}ClN_3 \cdot HCl$	56.77	56.46	5.10	4.93	14.19	14.22
22	*p*-Chlorophenethylguanidine					232–234	A[e]	$C_9H_{12}ClN_3 \cdot 0.5H_2SO_4$	43.81	43.89	5.32	5.26	17.03	17.24
23	α-Methyl-*p*-trifluoromethylbenzylguanidine					253–255	B[e,j]	$C_{10}H_{12}F_3N_3 \cdot 0.5H_2SO_4$	42.85	43.01	4.67	4.58	15.00	14.86
24	α,α-Dimethyl-*p*-trifluoromethylbenzylguanidine					215–215.5	B[j]	$C_{11}H_{14}F_3N_3 \cdot HCl$	46.90	46.96	5.37	5.33	14.92	15.00
25	4-Chloro-1-naphthylmethylguanidine					271.5–272.5	A[a]	$C_{12}H_{12}ClN_3 \cdot 0.5H_2SO_4$	50.98	51.01	4.64	4.70	14.86	15.08

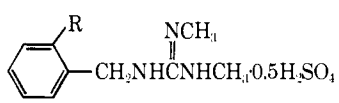
[a] Recrystallized from methanol. [b] Recrystallized from ethanol. [c] *m*-Chlorobenzylamine hydrochloride was prepared from the amine and ethereal HCl, and it has been described by J. v. Braun, M. Kühn, and J. Weismantel, *Ann.*, **449**, 249 (1926). [d] Recrystallized from ethanol–acetone–ethyl acetate. [e] Recrystallized from aqueous ethanol. [f] This compound was prepared from the amine and 2,3-dimethyl-2-thiopseudourea hydriodide,[2] and it was converted to the sulfate with silver sulfate. [g] The yield by method A was 24%, by method B 77%. *p*-Chloro-N-methylbenzylamine hydrochloride was prepared from the amine and ethereal HCl, and it has been reported previously by J. v. Braun, M. Kühn, and J. Weismantel in footnote *c*. [h] This compound was prepared from the amine and 2-thio-1,2,3-trimethylpseudourea hydrochloride, and it was converted to the sulfate with silver sulfate. [i] *p*-Chlorobenzylamine hydrochloride was prepared from the amine and ethereal HCl, and it has been described by K. Kindler, *Arch. Pharm.*, **265**, 402 (1927). [j] For preparation see Experimental Section.



I



II



III, R = H
IV, R = Cl

bers of his series were 1-benzyl-2,3-dimethylguanidine sulfate (III) and its *o*-chloro analog (IV). The former is known as "bethanidine."

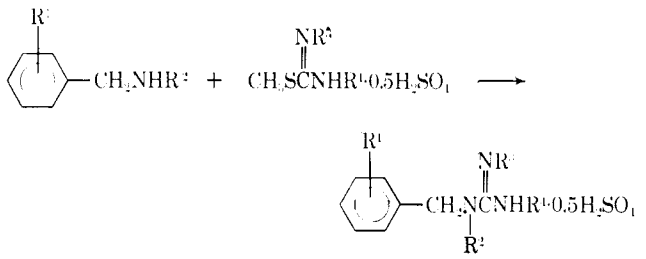
The next report of benzylguanidines came from our laboratories.[2] This paper was concerned chiefly with dialkylaminoalkylguanidines, but among some miscellaneous compounds reported were *o*- and *p*-chlorobenzylguanidine sulfates. Both effectively blocked the sympathetic nervous system and constituted a lead which we felt was worth exploiting. The purpose of this paper is to report our studies with this series of compounds.

Chemistry.—Most of the compounds described in Table I were prepared by allowing the appropriate benzylamine to react with 2-methyl-2-thiopseudourea sulfate (method A). Excellent yields of the guanidines were generally obtained when the reactants were primary amines and 2-methyl-2-thiopseudourea sulfate itself, but yields were lower when the amine was secondary (*p*-chloro-N-methylbenzylamine) or when the pseudourea was substituted with one or more methyl groups. Method A was unsuccessful if the amine was substituted with a methyl group on the carbon atom next to the nitrogen atom.

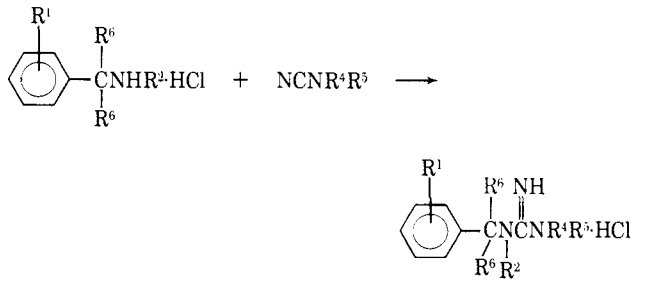
A by-product of method A was the formation of some salt (hydrochloride or sulfate) of the starting amine. Usually the amine salt was more soluble than the guanidine salt and one or two crystallizations were sufficient to remove the amine salt. However, the opposite proved true with *m*- and *p*-chlorobenzylamine, and separation of the guanidine salt from the less soluble amine salt sometimes was difficult.

Reaction of N,N′-dimethylthiourea with dimethyl sulfate gave the expected 2-thio-1,2,3-trimethylpseudourea, but as the acid sulfate salt instead of the neutral sulfate salt. The product obtained failed to react with amines unless the acid was at least partially neutralized. We found it more convenient, therefore, to use this thiopseudourea in the form of its hydrochloride.

An alternative method involved the reaction of a benzylamine hydrochloride with cyanamide or dimethylcyanamide (method B).



method A



method B

The reaction between α-methyl-*p*-trifluoromethylbenzylamine and cyanamide gave, in addition to the desired guanidine, a small amount of a different compound. Elemental analyses, the infrared spectrum, and the nmr spectrum indicated that this material was N,N′-bis(α-methyl-*p*-trifluoromethylbenzyl)urea. Its identity was confirmed by its preparation from the amine hydrochloride and urea, which is a known method for preparing symmetrically disubstituted ureas.[7]

The corresponding urea was also obtained from α,α-dimethyl-*p*-trifluoromethylbenzylamine hydrochloride and cyanamide in addition to the desired guanidine.

Most of the amines were available from commercial sources. The isomeric trifluoromethylbenzylamines were prepared by catalytic reduction of the appropriate nitriles, and have been described in a previous publication from these laboratories.[8]

p-Trifluoromethylbenzylamine was also prepared by reduction of the nitrile with $LiAlH_4$. Yields were similar by both methods. $LiAlH_4$ reduction was also used to obtain 2-chloro-5-trifluoromethylbenzylamine and 4-chloro-1-naphthalenemethylamine. The nitrile required for the latter reaction was obtained from 4-chloro-1-naphthylamine *via* a Sandmeyer reaction. α-Phthalimido-*p*-tolunitrile was prepared from α-chloro-*p*-tolunitrile and potassium phthalimide. Cleavage with hydrazine gave the desired α-amino-*p*-tolunitrile.

Preparation of 4-(*p*-chlorophenyl)benzylamine started with 4′-nitro-4-biphenylcarboxylic acid. Catalytic reduction gave the amino acid and the Sandmeyer reaction was utilized to convert the latter to 4′-chloro-4-biphenylcarboxylic acid. This acid was converted to the amide *via* the acid chloride, and $LiAlH_4$ was used to reduce the amide to the desired amine.

α-Methyl-*p*-trifluoromethylbenzylamine was obtained by catalytic reduction of the corresponding oxime, and also by reduction with $LiAlH_4$, but the yield was poor in the latter case.

The Ritter reaction was utilized to obtain α,α-dimethyl-*p*-trifluoromethylbenzylamine. The reaction between *p*-trifluoromethylphenylmagnesium bromide and acetone gave the desired carbinol, which was allowed to react with HCN to give N-(α,α-dimethyl-*p*-trifluoromethylbenzyl)formamide. Hydrolysis of the latter with HCl gave the desired amine.

Structure–Activity Relationships.—Our first efforts were directed toward establishing whether or not chlorine was the optimum halogen substituent in this type of compound. Both *o*- and *p*-fluorobenzylguanidine sulfates (Table I, 1 and **2**) were inactive. In the case of the bromo analogs the *ortho* isomer (**4**) (analog of bretylium) was active but the *para* isomer (**5**) was not. The iodo analogs were prepared and the *para* isomer (**7**) proved to be active but not the *ortho* isomer (**6**). These results indicated that other halogens showed no superiority over the chloro substituent. The *p*-chloro isomer was slightly more active than the *ortho* isomer,[2] while the *meta* isomer (**3**) was inactive.

The two N-methyl derivatives (**17** and **18**) and two of the three possible N,N-dimethyl derivatives (**19** and **20**) of *p*-chlorobenzylguanidine were prepared and all proved to be inactive. We found it particularly interesting that **19** was inactive since it is the *p*-chloro analog of bethanidine. The reduction in activity caused by the methyl groups in this series of compounds parallels our experience in the dialkylaminoalkylguanidine series.[2]

p-Chlorophenethylguanidine (**22**) was found to be less active than its benzyl homolog.

Of three dichlorobenzylguanidines (**8**–**10**) the 2,4- and 2,6-dichloro isomers were active, but neither was more active than *p*-chlorobenzylguanidine sulfate. Replacement of the *p*-chloro atom by the cyano group gave a compound (**11**) with only weak activity. The naphthalene (**25**) and biphenyl (**21**) analogs were inactive.

p-Trifluoromethylbenzylguanidine (**14**) was prepared and found to be more active than *p*-chlorobenzylguanidine sulfate. As in the chloro series the optimum position for the substituent was in the *para* position. The *ortho* isomer (**12**) was less active, while the *meta* isomer (**13**) was active only at a very high dose. As in the chloro series, the bethanidine analog, 2,3-dimethyl-1-(*p*-trifluoromethylbenzyl)guanidine hydrochloride (**15**), was inactive. A compound containing both chloro and trifluoromethyl substituents (**16**) was only slightly active.

A remarkable increase in activity occurred when **14** was modified by introduction of an α-methyl group to give α-methyl-*p*-trifluoromethylbenzylguanidine sulfate (**23**). The compound containing a second α-methyl group, α,α-dimethyl-*p*-trifluoromethylbenzylguanidine hydrochloride (**24**), much to our surprise proved to be inactive.

Pharmacology. Effect on the Nictitating Membrane. Methods.—The compounds in Table I were examined for their ability to cause relaxation of the nictitating membrane in the unanesthetized cat when administered orally. Relaxation (prolapse) of the nictitating membrane of the cat was suggested by McLean, *et al.*,[9]

(7) T. L. Davis and K. C. Blanchard, *J. Am. Chem. Soc.*, **45**, 1816 (1923).
(8) M. Freifelder and Y. H. Ng, *J. Pharm. Sci.*, **54**, 1204 (1965).
(9) R. A. McLean, R. J. Geus, R. J. Mohrbacher, P. A. Mattis, and G. E. Ullyot, *J. Pharmacol. Exptl. Therap.*, **129**, 11 (1960).

TABLE II
COMPOUNDS SHOWING AN EFFECT ON THE NICTITATING MEMBRANE OF THE CAT

Comod[a]	Dose, mg/kg	Effect on nictitating membrane[b]	Duration, hr
4	15	++	30
	30	+	7
7	15	+	30
	30	++	24
8	30	++	30
10	15	++	30
	30	++	24
11	30	+	5
12	10	++	6
	20	++	7
	30	++	30
13	60	++	30
14	15	++	8
	30	+++	72
16	30	+	7
22	30	+	25
23	15	++	144
	30	++	168
Bethanidine	30	++	72

[a] The numbers refer to the compounds in Table I. Compounds not listed here were inactive at 30 mg/kg. [b] The degree of prolapse is indicated as follows: +, one-fourth of the eye covered by the membrane; ++, one-half; +++, three-fourths.

as a test for sympathetic nervous system inhibition. Observations were made at regular intervals over a period of 24 hr and then daily readings were taken until prolapse was absent. The degree of prolapse was recorded as follows: +, one-fourth of the eye was covered by the membrane; ++, one-half of the eye was covered; and +++, three-fourths of the eye was covered. Effects on the pupil size in semidarkness and the reaction to light were measured.

Results.—The results are shown in Table II. Emesis proved to be a problem with many of these compounds. All were tested at 30 mg/kg, but only those showing activity are reported in the table. Failure to absorb the drug because of emesis may have been the reason for the lack of activity of some of the compounds.

Effect on Cat Blood Pressure. Methods.—Twelve of the compounds listed in Table I were examined for their effect on mean arterial blood pressure of the anesthetized cat following intravenous administration. Measurements were obtained from the femoral artery. A polyethylene catheter was connected to a Statham transducer and all recordings were made on a Grass Model 5 polygraph. Respiration and the electrocardiogram were also monitored. The response to a test dose of epinephrine was determined before and after the compound was given. The pressor response elicited by 30 sec of bilateral carotid occlusion was also determined before and after administering the test compound.

Results.—The data obtained by this test are summarized in Table III. The initial blood pressure responses were variable. The pressor response to bilateral carotid artery occlusion was reduced, but the response to the test dose of epinephrine was usually increased.

Symptomatology in Dogs. Methods.—Oral doses of **14** were administered to eight dogs for 3 days. The doses used were 15 (two dogs), 30 (two dogs), and 60 mg/kg (four dogs). Comparable studies were carried out with **23** on three dogs at 60 mg/kg, and the same three dogs at 30 mg/kg 6 weeks later. Observations were made at 0.5, 1, 2, 3, 4, 6, and 24 hr. Heart rate, respiration, relaxation of the nictitating membrane, and pupil changes were measured. The general condition of the dog was determined.

Results.—Emesis occurred in all dogs receiving **14** at all dose levels. Relaxation of the nictitating membrane was seen at the end of the first hour following administration of 60 mg/kg of **14**. Heart rate decreased, but the pulse was very strong. These changes occurred despite the emesis at the end of the first 0.5 hr. Dry mouth and listlessness were also observed. Administration of the drug in coated capsules decreased the incidence of emesis. Diarrhea also proved to be a serious problem with this drug even at the lowest dose.

The main symptom observed following administration of **23** was a ++ or +++ prolapse of the nictitating membrane lasting up to 9 days following the last dose of the drug. At the lower dose no other symptoms were observed. At the higher dose one dog suffered emesis, and another dog had diarrhea during the first 2 days of drug administration.

Effect on Hypertensive Dogs. Methods.—Mean arterial blood pressure of trained unanesthetized dogs was obtained by direct needle puncture of the femoral artery. Experimental renal hypertension was produced by reduction in renal blood flow. Bilateral constriction of the renal arteries similar to the procedure described by Goldblatt, *et al.*,[10] was performed approximately 2 years prior to the test.

Neurogenic hypertensive dogs were prepared by the method of Nowak,[11] and had been in our colony for about 2 years prior to test.

The electrocardiogram, lead II, and respiration were recorded concomitantly with the mean arterial blood pressure on a Grass polygraph.

Results.—Oral doses of 30 mg/kg of **14**, administered in coated capsules, initially increased blood pressure but later decreased blood pressure in both types of hypertensive dogs. A more marked reduction in blood pressure was seen with the neurogenic hypertensive dogs than with the renal hypertensive dogs. The results obtained with a single oral dose are shown in Table IV. The average and the range of the mean arterial blood pressure are shown for four dogs with each type of hypertension. The blood pressure was reduced for at least 50 hr. Coating the capsules reduced the incidence of emesis. At this dose level diarrhea was observed, but with lower doses no GI symptoms were noted and the dogs appeared alert and ate well. The blood pressure lowering effects of the drug could be maintained over extended periods of time. Following the initial 30-mg/kg dose, the animals could be maintained at a relatively normal blood pressure by daily doses as low as 5 mg/kg. No adverse effects occurred despite the long period of treatment.

A slightly different type of study was done with **23**. The drug was given orally at a dose of 10 mg/kg and 4 hr later, the point at which maximum blood pressure decrease occurred, blood pressure measurements were taken and are given in Table V. The same procedure

(10) H. Goldblatt, J. Lynch, R. F. Hanzal, and W. W. Summerville, *Am. J. Pathol.*, **9**, 942 (1933).
(11) S. J. G. Nowak, *Ann. Surg.*, **111**, 102 (1940).

TABLE III

INTRAVENOUS ADMINISTRATION OF THE COMPOUNDS TO ANESTHETIZED CATS

Compd[a]	Dose, mg/kg	Effect on mean arterial blood pressure[b]	Duration, min	Carotid occlusion[b] Before	Carotid occlusion[b] After	Epinephrine[b] Before	Epinephrine[b] After	Heart rate[b]	Respiration[b]
2	2	−62	3					0	−
	5	−44	63	+33	+10	+18	+24	+	−
	5	+67	85	No change		+25	+11	+	−
4	2, 5, 10	0		No change		No change		0	0
5	2	−15	83	No change		+24	+15	−	−
	2	+28	85	+17	+24	+11	+15	+	−
7	2	+22	14						
	2	+17	27						
	5	+25	20	+11	+4	+33	+65	+	−
	10	+23	20	+14	+3	+34	+68	+	−
8	2	−17	28						
	10	+34	23	+32	+9	+30	+40	+	−
10	2	+54	30						
	10	+56	40	+8	+5	+33	+70	+	−
12	2	−45	10	+30	+10	+15	+30	−	−
	5	+25	20	+32	+12	+8	+25	+	−
	10	−26	120	+35	+8	+15	+30	−	−
13	2	+12	5						
	5	+47	10	+11	+4	No change		0	0
14	2	−30	10					0	0
	5	−40	15	+5	−1	+30	+9	−	−
	10	−55	15	+20	+6	+25	+5	−	−
	10	+30	25	+15	+5	+20	+10	+	+
20	2	−25	10	+34	+20	+16	+24	−	−
	5	−12	15	+30	+10	+20	+30	0	−
23[c]	2	−4	4					0	0
		+3	5						
	10	−30	6	+7	+2	+28	+65	+	+
		+4	8						
	10	−5	4	+20	+7	+17	+35	+	+
		+20	120						
24	5	0							

[a] The numbers refer to compounds in Table I. [b] + = increase; − = decrease; 0 = no change. [c] The drug caused an initial fall in blood pressure, followed by a subsequent rise.

was repeated with the same dogs on a subsequent day with 5 mg/kg of the drug, and finally the drug was given at 2.5 mg/kg at a later date. A good dose–response relationship is apparent. Again the neurogenic dogs exhibited a better response than did the renal dogs.

Hemodynamic Studies. Methods.—Arterial blood pressure was measured from the femoral artery in the manner described above. Isometric systolic tension of ventricular muscle was recorded by means of a strain gauge arch.[12] Lead II of the electrocardiogram was also recorded. The drug was administered intravenously.

TABLE IV

EFFECT OF COMPOUND **14** ON NEUROGENIC AND RENAL HYPERTENSIVE DOGS

Control blood pressure, mm	Dose, mg/kg	Mean arterial blood pressure, mm[a] 4 hr	24 hr	51 hr	72 hr
Neurogenic Hypertension					
210[b]	30	110	125	160	
240–185[c]		130–90	140–100	180–130	
Renal Hypertension					
190[b]	30	140	145		160
220–170[c]		170–110	175–120		200–130

[a] Measurements were made 4, 24, 51, and 72 hr after administration of the drug. [b] The figures on these lines represent the average of blood pressure measurements of four dogs. [c] The figures on these lines represent the range of blood pressure measurements for four dogs.

Results.—Compound **14**, 5 mg/kg, increased isometric systolic tension, heart rate, and arterial blood pressure for a period of 0.25 hr. The initial increases were followed by decreases in all parameters measured. Larger doses, 20 mg/kg, elicited a longer period of increase in these parameters. The blood pressure and isometric systolic tension remained above control values for over 8 hr. Vagotomy or administration of atropine did not alter the initial responses. During the hypotensive period there was a slight increase in right atrial pressure accompanying the decrease in heart rate and isometric systolic tension.

Comparable studies were not done with **23**.

Toxicity Studies.—In the mouse **14** had an LD_{50} of 150 mg/kg following intraperitoneal administration, and with oral administration the LD_{50} was 475 mg/kg. The deaths were delayed except at the high dose levels. Ataxia was noted at 20 mg/kg ip and at 100 mg/kg *po*. Other symptoms included increased muscle tone, decreased activity, jerks, squinting, decreased respiration, and cyanosis prior to death.

The LD_{50} for each route of administration was slightly higher in rats. All other aspects of the toxicity were similar.

(12) M. deV. Cotten and E. Bay, *Am. J. Physiol.*, **187**, 122 (1956).

TABLE V
EFFECT OF COMPOUND 23 ON NEUROGENIC AND RENAL HYPERTENSIVE DOGS

Dog[a]	Control blood pressure, mm[b]	Dose, mg/kg[c]	Blood pressure, mm[d]
1	275	10 (1)	170
		5 (7)	190
		2.5 (5)	210
2	215	10 (1)	155
		5 (7)	175
		2.5 (5)	190
3	190	10 (1)	145
		5 (7)	150
		2.5 (5)	160
4	180	10 (1)	145
		5 (7)	145
		2.5 (5)	145

[a] Dogs 1 and 2 were neurogenic and dogs 3 and 4 were renal. [b] Measurements of arterial blood pressure were taken on four different days for each dog and averaged. [c] The figure in parenthesis indicates the number of measurements made. Each measurement represents an experiment carried out on a different day. The drug was given and the blood pressure was measured 4 hr later, at which time the maximum fall in blood pressure occurred. [d] The figure represents an average value in those cases where more than one measurement was made.

At a dose of 150 mg/kg two of five rabbits died; at 250 mg/kg three of five died; and at 300, 350, and 500 mg/kg none survived. At 400 mg/kg only four of five rabbits died. Marked respiratory depression occurred in all rabbits.

The toxicity to mice of **23** was comparable to that seen with **14**. Toxicity was not studied in other species.

Sleeping Time Studies.—Compound **14** was administered to mice at 200 mg/kg ip for a period of 3 days. A standard sleeping time study using pentobarbital as the standard was performed.[13] There was no significant difference in the sleeping time of the control group and the group receiving **14**. Some compounds with halogen substituents effect biotransformation by the liver, but **14** apparently does not alter this function, at least as far as detoxification of pentobarbital is concerned.

Experimental Section[14]

Preparation of Guanidines. Method A.—A solution of 0.1 mole of the appropriate amine and 13.9 g (0.05 mole) of 2-methyl-2-thiopseudourea sulfate (or derivative thereof) in 100 ml 50% ethanol was heated under reflux for 4 hr. The solvent was removed if the product did not precipitate on chilling, and the residue was crystallized from an appropriate solvent.

Method B.—A solution of 0.05 mole of the appropriate amine hydrochloride and 2.5 g (0.06 mole) of cyanamide (or an equivalent quantity of dimethylcyanamide) in 25 ml of water was heated in an oil bath to 180° during 1 hr and held at that temperature for 2–3 hr. The residue, usually a glasslike solid, was crystallized from an appropriate solvent.

2-Thio-1,2,3-trimethylpseudourea Hydrochloride.—A solution of 50 g (0.48 mole) of N,N'-dimethylthiourea and 50.5 g (1.0 mole) of CH_3Cl in 100 ml of ethanol was heated at 110° in a bomb for 8 hr. The solvent was removed and the residue was crystallized from ethanol–acetone to give 67.5 g (91%) of the desired product, mp 172–172.5°.

Anal. Calcd for $C_4H_{10}N_2S \cdot HCl$: C, 31.06; H, 7.17; N, 18.11. Found: C, 31.24; H, 7.23; N, 17.99.

2-Thio-1,2,3-trimethylpseudourea Hydrogen Sulfate.—The reaction between 104 g (1.0 mole) of N,N'-dimethylthiourea and 70 g (0.55 mole) of dimethyl sulfate was effected in the customary manner.[15] The desired product did not precipitate as the neutral sulfate salt but only as the acid sulfate salt. Recrystallization from ethanol gave 50 g (23%) of white crystals, mp 177–178.5°.

Anal. Calcd for $C_4H_{10}N_2S \cdot H_2SO_4$: C, 22.12; H, 5.94; N, 12.90. Found: C, 22.05; H, 5.82; N, 13.03.

α-Phthalimido-*p*-tolunitrile.—The procedure is a modification of the one described by Reinglass[16] for the corresponding *meta* isomer. To a solution of 42.5 g (0.28 mole) of α-chloro-*p*-tolunitrile in 250 ml of dimethylformamide (DMF) was added 55.5 g (0.3 mole) of potassium phthalimide. The reaction mixture was stirred and heated at 130–135° for 2 hr, then allowed to cool to 100°, and 250 ml of water was added. The white solid which precipitated on chilling was collected. The yield was 61.5 g (87%), mp 170–175°. Recrystallization from aqueous DMF raised the melting point to 182–183°.

Anal. Calcd for $C_{16}H_{10}N_2O_2$: C, 73.28; H, 3.82; N, 10.68. Found: C, 73.22; H, 3.91; N, 10.84.

α-Amino-*p*-tolunitrile.—The procedure described by Goldberg and Kelly[17] for the preparation of 3-aminopropionitrile was modified. To a suspension of 73.7 g (0.28 mole) of α-phthalimido-*p*-tolunitrile in 400 ml of 95% ethanol was added 36 g (0.56 mole) of 50% hydrazine. The reaction mixture was shaken occasionally until the solid dissolved. The solution was left on the steam bath for 0.5 hr during which time the contents of the flask solidified. The cooled reaction mixture was triturated with 200 ml of 3 *N* HCl and the solid was collected on a filter. The filtrate was evaporated and the residue was dissolved in 100 ml of water. The free base was liberated with 50% NaOH, taken up in $CHCl_3$, dried, and distilled to give 23.6 g (54%) of colorless oil, bp 147.5–148° (10 mm), $n^{25}D$ 1.5644. Blackwell, *et al.*,[18] reported bp 107° (0.5 mm).

Anal. Calcd for $C_8H_8N_2$: C, 72.70; H, 6.10; N, 21.20. Found: C, 72.65; H, 6.06; N, 21.16.

The hydrochloride was prepared and crystallized from methanol–ethanol. It melted at 290–291°, lit.[19] mp 274°.

***p*-Trifluoromethylbenzylamine.**—A solution of 19 g (0.05 mole) of $LiAlH_4$ in 500 ml of dry ether was stirred as 100 g (0.584 mole) of *p*-trifluoromethylbenzonitrile (Pierce Chemical Co.) in 500 ml of dry ether was added dropwise. The reaction mixture was heated under reflux for 2 hr and decomposed by the dropwise addition of 20 ml of water, 20 ml of 15% NaOH, and 60 ml of water. The product was purified *via* distillation to give 73.2 g (70.5%) of colorless oil boiling at 105–113° (40 mm), $n^{25}D$ 1.4636. The recorded physical constants[8] are bp 114–120° (50–52 mm), $n^{25}D$ 1.4630.

2-Chloro-5-trifluoromethylbenzylamine.—From 100 g (0.487 mole) of 2-chloro-5-trifluoromethylbenzonitrile (Pierce Chemical Co.), reduced in the manner described above for *p*-trifluoromethylbenzonitrile, was obtained 80 g (78.5%) of colorless oil, bp 100–106° (14 mm), $n^{25}D$ 1.4856.

Anal. Calcd for $C_8H_7ClF_3N$: C, 45.84; H, 3.37; N, 6.68. Found: C, 45.79; H, 3.60; N, 6.65.

4'-Amino-4-biphenylcarboxylic Acid.—A suspension of 24.3 g (0.1 mole) of 4'-nitro-4-biphenylcarboxylic acid[20] and 2.5 g of 5% Pd–C in 250 ml of Methyl Cellosolve was reduced with an initial hydrogen pressure of 8.8 kg/cm². Uptake was complete within 1 hr. The catalyst was removed and the solution was concentrated and chilled to give 13.9 g (65%) of the amino acid, mp 242–243°, lit.[21] mp 243–246°.

4'-Chloro-4-biphenylcarboxylic Acid.—A suspension of 21 g (0.1 mole) of 4'-amino-4-biphenylcarboxylic acid in 200 ml of glacial acetic acid and 100 ml of water was stirred and cooled in

(13) J. D. Taylor, E. M. Swenson, J. C. Davin, and R. K. Richards, *Proc. Soc. Exptl. Biol. Med.*, **95**, 462 (1957).

(14) Melting points below 300° are corrected.

(15) P. R. Shildneck and W. Windus in "Organic Syntheses," Coll. Vol. 11, A. H. Blatt, Ed., John Wiley and Sons, Inc., New York, N. Y., 1943, p 411.

(16) P. Reinglass, *Ber.*, **24**, 2418 (1891).

(17) A. A. Goldberg and W. Kelly, *J. Chem. Soc.*, 1369 (1947).

(18) L. F. Blackwell, A. Fischer, I. J. Miller, R. D. Topsom, and J. Vaughan, *ibid.*, 3588 (1964).

(19) F. Ehrlich, *Ber.*, **34**, 3368 (1901).

(20) The acid, mp 334–336°, was obtained from the sodium salt (Du Pont Organic Chemicals Department). R. L. Danuley and M. Sternfeld [*J. Am. Chem. Soc.*, **76**, 4543 (1954)] reported mp 339–340°.

(21) J. Colonge and E. Fichet, *Bull. Soc. Chim. France*, 415 (1955).

an ice bath to 5°. A solution of 10.4 g (0.15 mole) of $NaNO_2$ in 100 ml of water was added below the surface at such a rate that the temperature remained at 5°. The dark brown solution was added dropwise to a stirred, boiling solution of 15 g (0.15 mole) of CuCl in 100 ml of concentrated HCl. Refluxing was continued for 0.5 hr after completion of the addition. The crude product was collected after chilling and was crystallized from *n*-butyl alcohol to give 12 g (52%) of the acid, mp 282–287°. Recrystallization of a small portion from AcOH raised the melting point to 287.5–289.5°, lit.[22] mp 289.8–290.8°.

4'-Chloro-4-biphenylcarboxamide.—A suspension of 11.6 g (0.05 mole) of 4'-chloro-4-biphenylcarboxylic acid in 200 ml of $CHCl_3$ and 16 ml (0.2 mole) of $SOCl_2$ was heated under reflux for 4 hr. The solvent was removed under reduced pressure. A 50-ml portion of $CHCl_3$ was added and removed. A second portion was added and removed. The residual oil was dissolved in 100 ml of $CHCl_3$, liquid NH_3 was added, and the solution was left at room temperature overnight. The solvent was removed. The residue was boiled with 100 ml of glacial acetic acid, diluted with 200 ml of water, and chilled. The tan solid was collected and weighed 11 g (95%), mp 253–254°, lit.[23] mp 254°.

4-(*p*-Chlorophenyl)benzylamine.—A Soxhlet extractor containing 11.8 g (0.05 mole) of 4'-chloro-4-biphenylcarboxamide was placed above a flask containing 3.8 g (0.1 mole) of $LiAlH_4$ and 500 ml of dry THF. The reaction mixture was heated under reflux for 16 hr and then was worked up in the usual manner. The crude product was crystallized from *n*-butyl alcohol to give 9.5 g (87%) of the amine, mp 119–122°.

Anal. Calcd for $C_{13}H_{12}ClN$: C, 71.72; H, 5.56; N, 6.44. Found: C, 72.00; H, 5.67; N, 6.60.

***p*-Trifluoromethylacetophenone Oxime.**—A solution of 68 g (0.36 mole) of *p*-trifluoromethylacetophenone (Pierce Chemical Co.) and 50 g (0.72 mole) of hydroxylamine hydrochloride in 700 ml of ethanol was heated under reflux for 4 hr. The hot solution was diluted with 700 ml of water and chilled to obtain 68.4 g (93%) of white solid, mp 105–106°.

Anal. Calcd for $C_9H_8F_3NO$: C, 53.20; H, 3.97; N, 6.89. Found: C, 53.03; H, 3.94; N, 6.97.

α-Methyl-*p*-trifluoromethylbenzylamine.—The reduction of 16.3 g (0.08 mole) of *p*-trifluoromethylacetophenone oxime was effected in 250 ml of 75% ethanol containing 0.24 mole of HCl and 6.5 g of 5% Pd–C, containing 50% by weight of water (Englehard Industries). The initial hydrogen pressure was 2.79 kg/cm² and uptake was complete in 18 hr. The catalyst was removed and the alcohol solution was evaporated. The residue was dissolved in water and extracted with ether. The aqueous solution was made alkaline and the free base was extracted with ether. A total of four runs gave 38.5 g (64%) of amine, bp 80–86° (10 mm), $n^{25}D$ 1.4580.

Anal. Calcd for $C_9H_{10}F_3N$: C, 57.13; H, 5.32; N, 7.40. Found: C, 56.99; H, 5.45; N, 7.36.

A portion of the amine was converted to the hydrochloride and crystallized from acetone–ethyl acetate to give a white solid melting at 204.5–205°.

Anal. Calcd for $C_9H_{10}F_3N \cdot HCl$: C, 47.90; H, 4.91; N, 6.21. Found: C, 47.93; H, 4.98; N, 6.31.

α-Methyl-*p*-trifluoromethylbenzylguanidine Sulfate and N,N'-Bis(α-methyl-*p*-trifluoromethylbenzyl)urea.—Cyanamide, 5.5 g (0.13 mole), and 25.8 g (0.104 mole) of α-methyl-*p*-trifluoromethylbenzylamine hydrochloride were allowed to react as described above (method B). The residue was taken up in 75 ml of hot water and filtered to remove 2.7 g of white solid. The filtrate was heated on the steam bath for 1 hr after adding 75 ml of ethanol and 18 g (0.058 mole) of Ag_2SO_4. The hot solution was filtered, concentrated, and chilled to give 21 g of the desired guanidine (Table I, **23**). The 2.7 g of solid was recrystallized once from aqueous ethanol and twice from 1-butanol to give 0.2 g of white, crystalline solid, mp 195.5–197°. The same substance was obtained when the reaction was carried out as above but with 0.05 mole of urea in place of the cyanamide. Infrared spectrum showed 3438 (ν_{NH}), 1670 (amide I), 1508 (amide II), 1615 cm^{-1} (aromatic ring); nmr spectrum, doublet, 78, 84, quintet centered at 290, doublet 384, 392 (exchanged with D_2O), quartet centered at 458 cps. The peaks are in the ratio, respectively, 3:1:1:4 and represent CH_3, CH, NH, and aromatic H.

Anal. Calcd for $C_{19}H_{18}F_6N_2O$: C, 56.43; H, 4.49; N, 6.93; mol wt, 404.35. Found: C, 56.03; H, 4.26; N, 7.25, 7.11; mol wt (Rast method), 405.

α,α-Dimethyl-*p*-trifluoromethylbenzyl Alcohol.—The Grignard reagent was formed from 45 g (0.2 mole) of *p*-bromobenzotrifluoride (Pierce Chemical Co.) and 4.8 g (0.2 g-atom) of Mg turnings in 50 ml of dry ether. A solution of 11.6 g (0.22 mole) of acetone in 25 ml of ether was added, and the reaction mixture was heated under reflux for 2 hr. Hydrolysis was effected by the dropwise addition of 20 ml of saturated NH_4Cl. The mixture was filtered and the filtrate was evaporated. The residue was distilled twice to give 25 g (62%) of the alcohol, bp 64–65° (1.2 mm), $n^{25}D$ 1.4531. The distillate slowly solidified, mp 36–37.5°.

Anal. Calcd for $C_{10}H_{11}F_3O$: C, 58.82; H, 5.42. Found: C, 58.67; H, 5.63.

N-(α,α-Dimethyl-*p*-trifluoromethylbenzyl)formamide.—Glacial acetic acid (80 ml) was cooled in an ice bath and the temperature was kept below 20° as 16.7 g (0.34 mole) of NaCN was added followed by a solution of 40 ml of H_2SO_4 and 32 ml of AcOH. The solution was stirred as 60 g (0.29 mole) of α,α-dimethyl-*p*-trifluoromethylbenzyl alcohol was added. The reaction mixture was allowed to warm up to room temperature during 1 hr, then was heated at 65–75° for 2 hr, and finally left at room temperature for 3 days. Solid $NaHCO_3$ was added to neutralize the acid, and the mixture was filtered. The solid was washed with water. The filtrate was extracted with two 75-ml portions of ether, and the solid was dissolved in the ether. The ether solution was dried (Drierite). The drying agent and solvent were removed, and the solid residue was washed with a small amount of cold Skellysolve B. The yield was 34.2 g (50%), mp 104–105°.

Anal. Calcd for $C_{11}H_{12}F_3NO$: C, 56.94; H, 5.56; N, 6.04. Found: C, 57.06; H, 5.44; N, 6.24.

α,α-Dimethyl-*p*-trifluoromethylbenzylamine Hydrochloride.—A solution of 34.5 g (0.15 mole) of N-(α,α-dimethyl-*p*-trifluoromethylbenzyl)formamide in 175 ml of ethanol was diluted with 175 ml of 6 *N* HCl and heated on the steam bath for 2 hr. The solution was taken to dryness under reduced pressure. The solid residue was crystallized twice from 50 ml of water, once with the aid of charcoal, to give 18.3 g of white leaflets, mp 250.5–252°. The combined filtrates were concentrated and chilled to give an additional 9.7 g of product. The total yield was 28 g (78%).

Anal. Calcd for $C_{10}H_{12}F_3N \cdot HCl$: C, 50.11; H, 5.46; N, 5.85. Found: C, 50.20; H, 5.45; N, 5.90.

α,α-Dimethyl-*p*-trifluoromethylbenzylguanidine Hydrochloride and N,N'-Bis(α,α-dimethyl-*p*-trifluoromethylbenzyl)urea.—A solution of 7.2 g (0.03 mole) of α,α-dimethyl-*p*-trifluoromethylbenzylamine hydrochloride and 1.7 g (0.04 mole) of cyanamide in 15 ml of water was allowed to react in the manner of method B. The viscous oil was dissolved in 50 ml of hot water and filtered to obtain 0.8 g of white solid. The filtrate was taken to dryness and the residue was dissolved in 150 ml of 1:1 acetone–ethanol. The solution was passed through a column packed with Florisil. Fractions of 25 ml each were collected and evaporated. The residues were dissolved in boiling ethyl acetate and on standing several solutions precipitated white solid; total yield was 1.1 g, mp 214–215°. The guanidine was recrystallized from acetone–ethyl acetate (Table I, **24**).

The 0.8 g of solid was crystallized from 1-butanol and from aqueous ethanol to obtain 0.4 g of material which melted at 263.5–264°. The same substance was obtained when the reaction was carried out as above but with 0.015 mole of urea in place of the cyanamide. Infrared spectrum showed 3336 (ν_{NH}), 1640 (amide I), 1556 (amide II), 1613 cm^{-1} (aromatic ring); nmr, singlet 89, singlet 389 (exchanged with D_2O), singlet 453 cps. The peaks are in the ratio, respectively, 6:1:4 and represent CH_3, NH, and aromatic H.

Anal. Calcd for $C_{21}H_{22}F_6N_2O$: C, 58.33; H, 5.13; N, 6.48. Found: C, 58.55; H, 5.18; N, 6.55.

4-Chloro-1-naphthonitrile.—The procedure described by Gomberg and Blicke[24] for the preparation of 4-bromo-1-naphthonitrile was followed. From 62.5 (0.35 mole) of 4-chloro-1-naphthylamine was obtained 48 g (73%) of the nitrile, which melted at 95–96°, lit.[25] mp 110°.

(22) E. Berliner and E. A. Blommers, *J. Am. Chem. Soc.*, **73**, 2482 (1951).
(23) C. Musante and V. Parrini, *Gazz. Chim. Ital.*, **79**, 453 (1949).
(24) M. Gomberg and F. F. Blicke, *J. Am. Chem. Soc.*, **45**, 1773 (1923).
(25) P. Friedlander and J. Weisberg, *Ber.*, **28**, 1838 (1895).

Anal. Calcd for $C_{10}H_6ClN$: C, 70.41; H, 3.22; N, 7.47. Found: C, 70.51; H, 3.13; N, 7.66.

4-Chloro-1-naphthalenemethylamine.—Reduction of 47 g (0.25 mole) of 4-chloro-1-naphthonitrile was accomplished with $LiAlH_4$. The nitrile was dissolved in 1.0 l. of 1:1 ether–THF and added to 9.5 g (0.25 mole) of the hydride in 500 ml of ether. Two distillations of the product gave 17.6 g (37%) of yellow oil, bp 113–115° (0.2 mm) $n^{25}D$ 1.6446.

Anal. Calcd for $C_{11}H_{10}ClN$: C, 68.92; H, 5.26; N, 7.31. Found: C, 69.17; H, 5.54; N, 7.13.

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Hypotensive 1,2-Benzisothiazole 1,1-Dioxides. I. Pyrazole and Pyrazoline Derivatives

JOHN J. TRAVERSO, CALVERT W. WHITEHEAD, JAMES F. BELL, HAROLD E. BOAZ, AND PAUL W. WILLARD

The Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana

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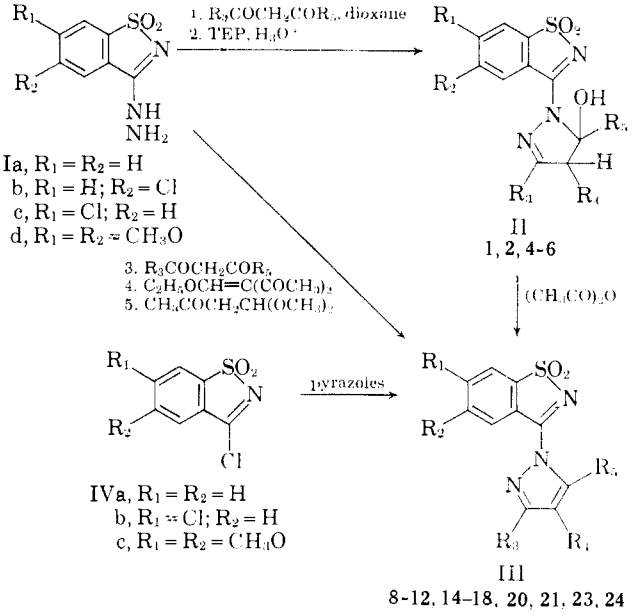
Pyrazolyl- and pyrazolinyl-1,2-benzisothiazole 1,1-dioxides were prepared by the condensation of 3-hydrazinobenzisothiazole 1,1-dioxides with 1,3-diketones, keto esters, ketoacetaldehyde acetals, diacetals, and unsaturated ketones. Hydroxypyrazolines were obtained under certain conditions and these were dehydrated to pyrazoles. The hypotensive activities were determined in the Goldblatt rat preparation.

In our search for hypotensive agents 3-(3,5-dimethylpyrazol-1-yl)-1,2-benzisothiazole 1,1-dioxide was prepared and subsequently was found to lower blood pressure in the Goldblatt rat preparation. Additional substituted pyrazolyl and pyrazolinyl derivatives were synthesized and studied to confirm the hypotensive activity of this series. Condensation of 1,3-diketones with 3-hydrazino-1,2-benzisothiazole 1,1-dioxide[1] (I) in refluxing Ethyl Cellosolve yielded 3-(3,5-disubstituted pyrazol-1-yl)-1,2-benzisothiazol 1,1-dioxides (Scheme I). The corresponding 3-(3,5-disubstituted 5-hydroxypyrazolin-1-yl)-1,2-benzisothiazole 1,1-dioxides were obtained when the reaction was carried out in dioxane. This indicates that hydroxypyrazolines are intermediates in the Cellosolve reaction and undergo dehydration to the pyrazoles *in situ* at the boiling temperature of the solvent.

Dehydration of the hydroxypyrazolines was also accomplished with acetic anhydride. Acylation of the hydroxy group occurred in the case of 3-(5-hydroxy-3-methyl-5-phenyl-2-pyrazolin-1-yl)-1,2-benzisothiazole 1,1-dioxide. Dehydration of the 3,5-dialkyl-5-hydroxypyrazolines always occurred under the mildest conditions required for reaction with acetic anhydride. An alternate method was used when substituted 3-hydrazino-1,2-benzisothiazole 1,1-dioxides were not easily accessible. Pyrazole, 4-chloropyrazole, and 3,5-dimethylpyrazole were fused with substituted 3-chloro-1,2-benzisothiazole 1,1-dioxides[2] to yield the corresponding substituted 3-pyrazolyl-1,2-benzisothiazole 1,1-dioxides.

Tetraethoxypropane (TEP) reacted with 3-hydrazino-1,2-benzisothiazole 1,1-dioxide[1] (I) in dilute H_2SO_4 to give a crystalline product, $C_{10}H_9N_3O_3S$

SCHEME I



(Scheme I). Upon treatment with acetic anhydride, this compound gave 3-(pyrazol-1-yl)-1,2-benzisothiazole 1,1-dioxide (**11**) identical with that obtained from the fusion of pyrazole and I. The cyclic pyrazolinyl structure for the $C_{10}H_9N_3O_3S$ product was established as 3-(5-hydroxypyrazolin-1-yl)-1,2-benzisothiazole 1,1-dioxide.

The reaction of I with mesityl oxide gave 3-(3,5,5-trimethylpyrazolin-1-yl)-1,2-benzisothiazole 1,1-dioxide (**3**). Condensation of 3-ketobutyraldehyde 1-dimethyl acetal yielded 3-(3-methylpyrazol-1-yl)-1,2-benzisothiazole 1,1-dioxide (**12**). Ethoxymethyleneacetylacetone reacted with I to furnish 3-(4-acetyl-3-methylpyrazol-1-yl)-1,2-benzisothiazole 1,1-dioxide (**17**).

(1) E. Schrader, *J. Prakt. Chem.*, [2] **95**, 312 (1917).
(2) J. R. Meadow and E. E. Reid, *J. Am. Chem. Soc.*, **65**, 457 (1943).