$CDCl_3$ using TMS as an internal standard) was compatible with the assigned structure. Nmr signals were observed at δ 7.31 (1 H doublet, $J_{5,6}$ = 8 Hz, C_5-H), 6.82 and 6.75 (overlapping H doublet, 1 H quartet, $J_{2,6}$ = 2.8 Hz, C_2-H and C_6-H, respectively), 4.62 (2 H singlet, $-CH_2O-$), 3.14 and 2.97 (10 H, unresolved singlets, OH, NH, and $(CH_2N)_4$). There was *no* CH_3 signal. The mixture melting points with samples prepared by the other routes showed no depression. The ir spectra of these samples were essentially superimposable.

Microbiological Oxidation of N-(3-Chloro-4-methylphenyl)-N',N'-diethylethylenediamine Hydrochloride (III).—Essentially the same procedure was used here. A total of 161 g (0.58 mole) of substrate was converted over an 8-day period. The substance was extracted and concentrated as in the above procedure. However, tlc examination of the residue indicated that there was a minor component which furnished a positive test with 2,4-DNP. Accordingly, the residual oil was dissolved in 200 ml of methanol and treated with 6.0 g of $NaBH_4$. After 30 min this carbonyl-positive component had disappeared as judged from tlc. The methanol was removed and the residue was dissolved in 500 ml of $CHCl_3$. The solution was washed several times with water and concentrated to a small volume. On cooling the crystals were filtered and washed with hexane. There was obtained 93 g of IV as white crystals, mp 66.0–67.5° (cor). The filtrate yielded an additional 13.5 g, making the total yield 106.5 g (0.385 mole) or 66% of the theoretical. This was identical (IR, mixture melting point, and ir spectra) with the sample prepared chemically.

Adrenergic Neurone Blocking Agents. II.[1] Some Dioxane-Substituted Derivatives of Guanoxan

A. M. MONRO, G. W. H. POTTER,

Research Division, Pfizer Ltd., Sandwich, Kent, England

AND M. J. SEWELL

School of Chemical Sciences, University of East Anglia, Norwich, Norfolk, England

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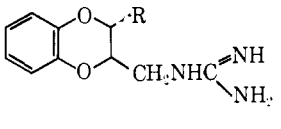
Syntheses are described of 2-methyl- and *trans*-3-methyl-2-guanidinomethyl-1,4-benzodioxan and of *syn*- and *anti*-2'-guanidinospiro(1,4-benzodioxan-2,1'-cyclopropanes) (**2a** and **b**). The stereochemistry of the compounds was determined by nmr spectroscopy, and their adrenergic neurone blocking properties were compared with those of guanoxan.

In a recent publication[1] we described the synthesis and adrenergic neurone blocking properties of a series of guanidines related to guanoxan (**1**, R = H). Although many derivatives with substituents in the aromatic



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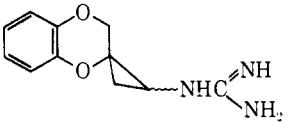
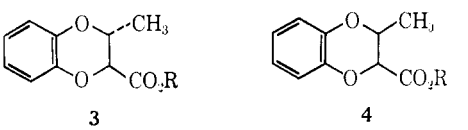


2a *syn*
b *anti*

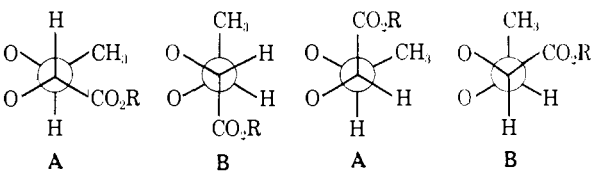
ring were described, the only reference to a substituent in the dioxane ring was to the 3-methyl derivative which was prepared and tested as a mixture of *cis* and *trans* isomers.

We have now prepared the pure *trans*-3-methyl derivative (**1**, R = CH_3) and the 2-methyl derivative of guanoxan. Following reports of the biological activity of phenoxycyclopropylamines[2,3] it seemed reasonable to synthesize the spirocyclopropyl compounds (**2**). Accordingly, both epimers (**2a** and **b**) were prepared.

Chemistry.—The 3-methyl derivative (**1**, R = CH_3) was approached *via* the mixture of esters **3** and **4** (R = C_2H_5), obtained by reaction of catechol with ethyl 2,3-dibromobutyrate in the presence of K_2CO_3 and

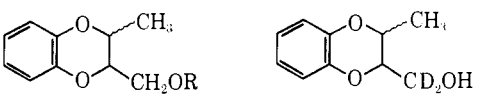


3 **4**



A **B** **A** **B**

acetone.[4] Reduction of the ester mixture ($LiAlH_4$) yielded the mixture of alcohols (**5**, R = H) from which the *trans* isomer was isolated readily by crystallization; the *cis* isomer could not be isolated in a pure state from this reaction. The *trans*-alcohol (**5a**, R = H) was converted to the tosylate (**5a**, R = Ts), which upon treatment with guanidine[1] yielded the desired product, **1** (R = CH_3).



5 **a** = *trans* **6**
b = *cis*

Initially, the *trans* series of compounds was established as such by conversion of the ester mixture with lithium aluminum deuteride to the corresponding mixture of deuterioalcohols **6**. From this mixture a pure crystalline alcohol having a relatively large vicinal

(1) Part I of this series: J. Augstein, S. M. Green, A. M. Monro, G. W. H. Potter, C. R. Worthing, and T. I. Wrigley, *J. Med. Chem.*, **8**, 446 (1965).

(2) Hoffman-La Roche and Co., A. G., Belgian Patent 613,910 (Aug 14, 1962); Smith Kline and French Laboratories, U. S. Patent 3,156,725 (Nov 10, 1964).

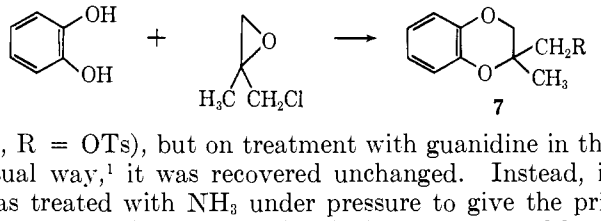
(3) (a) C. Kaiser, B. M. Lester, C. L. Zirkle, A. Burger, C. S. Davis, T. L. Delia, and L. Zirngibl, *J. Med. Pharm. Chem.*, **5**, 1243 (1962); (b) C. L. Zirkle, C. Kaiser, D. H. Tedeschi, R. E. Tedeschi, and A. Burger, *ibid.*, **5**, 1265 (1962).

(4) J. Kim, *J. Org. Chem.*, **26**, 339 (1961); this ester mixture is now available from Aldrich Chemical Co.

coupling constant[5] was isolated. Later, isolation of the pure *cis*-ester (**4**) by preparative gas–liquid partition chromatography (glpc) allowed preparation of the corresponding *cis*-deuterioalcohol (**6**),[6] which had a much smaller vicinal coupling constant.

Confirmation of these assignments was obtained by examination of the nmr spectra of the esters **3** and **4** (R = CH_3). The ethyl esters were isolated by preparative glpc and, to simplify interpretation of the spectra, these esters were converted to the corresponding methyl esters by transesterification. Details of chemical shifts and coupling constants are given in the Experimental Section.

The 2-methyl derivative of guanoxan was prepared *via* the intermediate (**7**, R = OH) obtained from the reaction of catechol with 2-methylepichlorohydrin and base. This alcohol was converted to the tosylate ester

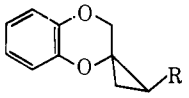


7

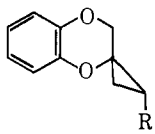
(**7**, R = OTs), but on treatment with guanidine in the usual way,[1] it was recovered unchanged. Instead, it was treated with NH_3 under pressure to give the primary amine (**7**, R = NH_2), which was converted by a standard procedure to the required guanidine [**7**, R = $NHC(=NH)NH_2$].

The spirocyclopropyl compounds were elaborated from 2-methylene-1,4-benzodioxan[7] and ethyl diazoacetate, by following previously reported procedures,[3] to give a mixture of epimers **8a** and **9a**.[8] These could be separated by preparative glpc, and each could be saponified to the corresponding carboxylic acid **8b** and **9b**. Alternatively, the ester mixture can be saponified as such, and the resultant acids can be separated by fractional crystallization.

The configurations of the acids **8b** and **9b** were determined by examination of the nmr spectra. Because these acids tended to decompose in trifluoroacetic acid, which was the only suitable solvent for nmr, the methyl esters of **8b** and **9b** were examined.



8a, R = $CO_2C_2H_5$
b, R = CO_2H
c, R = NH_2



9a, R = $CO_2C_2H_5$
b, R = CO_2H
c, R = NH_2

The acids **8b** and **9b** were subjected to the Curtius degradation, and the crude isocyanate products were hydrolyzed to give the amines **8c** and **9c**. Alkaline hydrolysis of the *anti*-isocyanate gave a moderate yield of **9c**, which was converted to the corresponding guanidine **2b** with 1-amidino-3,5-dimethylpyrazole sulfate. The *syn*-isocyanate, on alkaline hydrolysis, gave only a small yield of **8c**, the bulk of the product being the disubstituted urea.[9] This urea was converted with phthalic anhydride into the corresponding N-substituted phthalimide,[10] which was cleaved with hydrazine to give the required amine, **8c**. The production of the urea during the hydrolysis of the isocyanate could be obviated by using acidic conditions, whereupon a good yield of amine was obtained directly. Amine **8c** was converted to the guanidine **2a** by the method used for **9c**, or by reaction of the tosylate salt of the amine with cyanamide.

TABLE I

ADRENERGIC NEURONE BLOCKING PROPERTIES OF 1,4-BENZODIOXANS

Compd	R_1	R_2	R_3	Effect on NM[a] 5 mg/kg	Effect on NM[a] 20 mg/kg
	H	H	H	+	+++[b]
	H	H	CH_3	+	++[b]
1	CH_3	H	H	0	++
7	H	CH_3	H	0	+
2a	H	$-CH_2-$		0	+++[c]
2b	H	$-CH_2-$		0	0

[a] NM = nictitating membrane; percentage of eye covered: 0 (<15%), + (15–30%), ++ (30–50%), +++ (>50%). On this scale guanethidine was rated ++ (5 mg/kg) and +++ (20 mg/kg). [b] References 1 and 12. [c] Activity of short duration.

Biological Results.—The products were tested for adrenergic neurone blocking properties by the methods described previously[1] (see Table I). It was already known that methyl substitution in the side chain gave a compound of good activity.[1,12] The introduction of a 2-methyl group, however, led to considerable loss of activity. The *anti* compound **2b** was found to be almost inactive; by contrast, a marked, albeit short-lived, activity was observed in the *syn* compound **2a**.

The *trans*-3-methyl compound (**1**, R = CH_3) proved to be similar in activity to the mixture of *cis* and *trans* compounds tested previously, and thus, in the absence of data for the *cis* compound, little can be concluded about the effect of a 3-methyl group on the activity of guanoxan.

Experimental Section[13]

trans-**2-Hydroxymethyl-3-methyl-1,4-benzodioxan.**—2-Ethoxycarbonyl-3-methyl-1,4-benzodioxan[4] (25 g, 0.113 mole) in dry

(5) If "x" is the proportion of the isomer with substituents diaxial, then $xJ_{ee} + (1 - x)J_{aa} = 7.5$ cps; see **3A** ⇌ **3B**.

(6) This isomer is expected to have a small vicinal coupling constant as the ring inversion leads to an average of J_{ea} and J_{ae}; see **4A** ⇌ **4B**.

(7) A. R. Katritzky, M. J. Sewell, R. D. Topsom, A. M. Monro, and G. W. H. Potter, *Tetrahedron*, **22**, 931 (1966).

(8) The terms *syn* and *anti* refer to the configuration of the functional group with respect to the methylene group of the dioxane ring.

(9) This course of reaction has been frequently observed by other workers; see P. A. S. Smith, *Org. Reactions*, **3**, 337 (1946).

(10) R. H. F. Manske, *J. Am. Chem. Soc.*, **51**, 1202 (1929).

(11) E. S. Wallis and J. F. Lane, *Org. Reactions*, **3**, 267 (1946).

(12) M. W. Baines, D. B. Cobb, R. J. Eden, R. Fielden, J. N. Gardner, A. M. Roe, W. Tertiuk, and G. L. Willey, *J. Med. Chem.*, **8**, 81 (1965).

(13) Melting points are corrected. Infrared spectra were run as Nujol mulls or liquid films on an Infracord 137 spectrometer. Nmr spectra were obtained in CCl_4 on Perkin-Elmer R10 and Varian A-60 instruments using Me_4Si as internal standard.

ether (250 ml) was added dropwise to a slurry of $LiAlH_4$ (8.55 g, 0.225 mole) in refluxing dry ether (250 ml). The mixture was refluxed for a further 2 hr and then cooled. Water (10 ml), 5 *N* NaOH (10 ml), and more water (10 ml) were added in succession, and the precipitated solids were filtered off. The ether solution was evaporated to yield an oil (14.8 g) which partially crystallized after standing for several days. This material was separated by filtration into crystalline and liquid fractions. The former fraction (the *trans* isomer, 10.2 g, 50%) was recrystallized from petroleum ether (bp 60–80°) to mp 91–92.5°.

Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.66; H, 6.82.

The liquid fraction was shown by glpc to be a mixture of *cis* and *trans* isomers in a ratio of *ca.* 9:1.

***trans*-2-Tosyloxymethyl-3-methyl-1,4-benzodioxan** was prepared in the usual way[1] from the above alcohol (mp 91–92.5°). After recrystallization from ethanol, it had mp 118.5–119.5°.

Anal. Calcd for $C_{17}H_{18}O_5S$: C, 61.07; H, 5.43; S, 9.56. Found: C, 61.32; H, 5.42; S, 9.98.

***trans*-2-Guanidinomethyl-3-methyl-1,4-benzodioxan.**—The above *trans*-tosylate ester was treated with guanidine in the manner described previously.[1] The crude product was triturated with acetone and recrystallized from water (with charcoal) to give 22% of a product which showed a transition point at 93–98° and mp 161–163°. Drying at >100° (*in vacuo*) was necessary to obtain correct analytical figures.

Anal. Calcd for $C_{18}H_{23}N_3O_5S$: C, 54.95; H, 5.89; N, 10.68; S, 8.14. Found: C, 54.89; 5.79; N, 10.56; S, 8.25.

***cis*- and *trans*-2-Alkoxycarbonyl-3-methyl-1,4-benzodioxans (3 and 4).**—The commercially available mixture[4] of ethyl esters was separated on a Wilkens Autoprep (A 700) glpc apparatus, using a cyanosilicone (XF 1150) column at 188°. The ethyl esters were each converted to the corresponding methyl esters, by dissolving them in methanol containing a catalytic quantity of sodium methoxide, and after 1 hr working up with saturated aqueous NaCl and ether.

From Newman projections **3A** and **B**, the *trans*-ester could have the dioxane protons in a diaxial or diequatorial conformation. Similarly, for the *cis* compound conformations **4A** and **B** are possibilities. From a consideration of the dihedral angles involved and the coupling constants[14] deduced from the nmr spectra the *trans* (**3**) and *cis* (**4**) series were readily assigned. This is evident as large vicinal coupling constants (8–16 cps) may be associated with interactions between protons which are in an approximate diaxial (J_{aa}) orientation, while smaller splittings are associated with axial–equatorial (J_{ae}) or equatorial–equatorial (J_{ee}) values.

Nmr showed for the *cis* isomer: δ 6.82 (4 H complex pattern, aromatic protons), 4.63 (H_2, doublet, A part of ABX_3 spectrum[15]), 4.49 (H_3, octet, B part), 1.32 (CH_3, doublet, X part) (J_{AB} = 2.5 cps, J_{BX} = 6.7 cps, $J_{AX} \simeq 0$ cps), 3.74 (OCH_3 singlet); for the *trans* isomer: δ 6.80 (4 H complex pattern, aromatic protons), 4.30 (H_2), 4.33 (H_3), 1.37 (CH_3), ABX_3 spectrum of similar type (J_{AB} = 6.0 cps, J_{BX} = 6.4 cps, $J_{AX} \simeq 0$ cps), 3.72 (OCH_3).

***cis*-2-Hydroxydideuteriomethyl-3-methyl-1,4-benzodioxan (6b).**—The *cis*-ethyl ester (400 mg from preparative glpc) was reduced with $LiAlD_4$ in the manner of the first experiment described in this paper. The product (300 mg) was purified by dissolving it in benzene and filtering through alumina; nmr showed δ 6.70 (4 H complex pattern, aromatic protons), 4.06 (H_2), 4.22 (H_3), 1.18 (CH_3), ABX_3 spectrum (J_{AB} = 2.3 cps, J_{BX} = 6.6 cps, $J_{AX} \simeq 0$ cps), 3.47 (OH broad singlet); ν_{max} 3400 (OH), 2230 (CD), 2105 (CD) cm^{-1}.

***trans*-2-Hydroxydideuteriomethyl-3-methyl-1,4-benzodioxan (6a)** was prepared in an identical manner by $LiAlD_4$ reduction of the mixture of *cis* and *trans* esters, and separated from the *cis* product as described earlier for **5a** (R = H). Nmr showed δ 6.75 (4 H complex pattern, aromatic protons), 3.74 (H_2), 4.13 (H_3), 1.38 (CH_3), ABX_3 spectrum (J_{AB} = 7.5 cps, J_{BX} = 6.1 cps, $J_{AX} \simeq 0$ cps), 2.35 (OH broad singlet).

2-Hydroxymethyl-2-methyl-1,4-benzodioxan[16] **(7, X = OH)** was prepared from catechol and 2-methylepichlorohydrin[17] according to general procedure D.[1] The product had bp 90–100° (0.05 mm), $n^{22}D$ 1.5454, mp 64–65° from petroleum ether (bp 60–80°).

Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.99; H, 6.68.

2-Methyl-2-tosyloxymethyl-1,4-benzodioxan was prepared from the above alcohol in the usual manner; it had mp 77.5–79° (from ethanol).

Anal. Calcd for $C_{17}H_{18}O_5S$: S, 9.56. Found: S, 9.52.

2-Aminomethyl-2-methyl-1,4-benzodioxan.—The above tosylate was heated in an autoclave with excess NH_3 in ethanol (1:1) at 150° for 7 days. The mixture was evaporated to dryness, and the residue was triturated with ethereal HCl to give the hydrochloride (49%), mp 210–216°.

Anal. Calcd for $C_{10}H_{13}NO_2 \cdot HCl$: Cl, 16.45. Found: Cl, 16.52.

2-Guanidinomethyl-2-methyl-1,4-benzodioxan Tosylate [7, R = NHC(=NH)NH$_2$].—The above amine hydrochloride was basified and the isolated amine was treated with 1-amidino-3,5-dimethylpyrazole sulfate according to general procedure B.[1] The crude products from several runs were combined and converted to the tosylate salt, mp 182.5–184.5° (from water and then 1-butanol).

Anal. Calcd for $C_{11}H_{15}N_3O_2 \cdot C_7H_8O_3S$: C, 54.95; H, 5.89; N, 10.68. Found: C, 54.85; H, 5.55; N, 10.52.

Ethyl spiro(1,4-benzodioxan-2,1′-cyclopropane)-2′-carboxylate (8a and 9a) was prepared from 2-methylene-1,4-benzodioxan and ethyl diazoacetate by method A of ref 3a. The mixture of esters (59%) formed was collected over the boiling range 120–180° (0.01–0.07 mm).

Spiro(1,4-benzodioxan-2,1′-cyclopropane)-2′-carboxylic Acids (8b and 9b).—The above ester mixture (40 g) was stirred under reflux with NaOH (40 g in 60 ml of water) for 2 hr. The cooled reaction mixture was acidified, and the precipitated acids were filtered. Recrystallization from 2.5 l. of water gave the *anti* acid (17.1 g, 48%), mp 158–162°.

Anal. Calcd for $C_{11}H_{10}O_4$: C, 64.07; H, 4.89. Found: C, 63.50; H, 4.80.

Concentration of the mother liquor from the above crystallization to 500 ml resulted in a crop of the *syn* acid (7.2 g, 20%), mp 110–113°.

Anal. Found: C, 64.80; H, 4.76.

The corresponding *anti* and *syn* methyl esters required for nmr spectroscopy were prepared from the acids with ethereal diazomethane; they were not characterized other than by spectroscopy. The methyl ester of **8b** showed an AB quartet (center δ 4.05, J = 11 cps) for the geminal dioxane ring protons, a sharp singlet for CO_2CH_3 (δ 3.47), and a well-resolved ABC pattern for the cyclopropyl protons (Table II). The methyl ester of **9b** showed a singlet (δ 4.37) for the dioxane ring protons, a sharp singlet for CO_2CH_3 (δ 3.61), and a deceptively simple[18] ABC[15] pattern for the cyclopropyl protons. The acids **8b** and **9b** gave similar but less well resolved spectra. The cyclopropyl regions in the spectra of the methyl esters were analyzed with the aid of a computer (Table II).

Table II

Compd	Coupling constants, cps			Chemical shifts, ppm		
				δ_A	δ_B	δ_C
Methyl ester of series **8b**	J_{AB} = 6.84	J_{AC} = 9.39	J_{BC} (*gem*) = −6.74[a]	1.92	1.88	1.24
Methyl ester of series **9b**	$\frac{1}{2}(J_{AB} + J_{AC})$ = 8.3 (deceptively simple case)			2.01	1.25	1.25

[a] For example, see K. B. Wiberg and B. J. Nist [*J. Am. Chem. Soc.*, **85**, 2788 (1963)], who report negative geminal coupling constants in cyclopropane derivatives ranging from −4.3 to −8.4 cps.

In the **8b** *syn* series, the protons of the dioxane ring appear as an AB quartet, that is, with different chemical shifts. This is in agreement with the assignment of the carbomethoxy group to the side of the cyclopropane ring closest to these protons. Alternatively, in the *anti* series **9b**, the protons of the dioxane ring appear as a singlet, and this is in accord with the substituent

(14) M. Karplus, *J. Chem. Phys.*, **33**, 316 (1960).

(15) Nomenclature of J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High-Resolution Nuclear Magnetic Resonance", McGraw-Hill Book Co., Inc., New York, N. Y., 1959.

(16) J. Mills, M. M. Boren, W. E. Bunting, W. N. Camon, Q. F. Soper, and M. J. Martell, Abstracts, 132nd National Meeting of the American Chemical Society, New York, N. Y., Sept 1957, p 7-O.

(17) C. D. Hurd and H. E. Winberg, *J. Am. Chem. Soc.*, **73**, 917 (1951).

(18) R. J. Abraham and H. J. Bernstein, *Can. J. Chem.*, **39**, 216 (1961).

being on the side of the cyclopropane ring remote from these protons.

anti-**2'-Aminospiro(1,4-benzodioxan-2,1'-cyclopropane) (9c).**—The *anti* acid above was converted *via* the mixed carboxylic–carbonic anhydride procedure[3a] to the azide, which on pyrolysis gave the isocyanate. Alkaline hydrolysis[3a] of the isocyanate gave the amine (45%), isolated as the hydrochloride, mp 211–213° (from 2-propanol).

Anal. Calcd for $C_{10}H_{11}NO_2 \cdot HCl$: C, 56.20; H, 5.62; Cl, 16.60. Found: C, 56.27; H, 5.67; Cl, 16.45.

N,N'-Bis[2'-*syn*-spiro(1,4-benzodioxan-2,1'-cyclopropyl)]-urea.—The *syn* acid was converted *via* the mixed carboxylic–carbonic anhydride procedure[3a] to the azide. This was pyrolyzed to give the crude isocyanate, which was hydrolyzed with alkali.[3a] When cold, the reaction mixture was filtered. From the filtrate, the amine hydrochloride (6%) was isolated by extraction with dilute HCl. The solid filtered from the reaction was recrystallized from ethanol to give the urea (53%): mp 213–216°; ν_{max} 3370, 1645 cm^{-1}.

Anal. Calcd for $C_{21}H_{20}N_2O_5$: N, 7.37. Found: N, 7.40.

syn-**2'-Aminospiro(1,4-benzodioxan-2,1'-cyclopropane) (8c).**

A.—The N,N'-disubstituted urea above was treated with 2 equiv of phthalic anhydride according to Manske.[10] After trituration with aqueous $NaHCO_3$, the product was recrystallized from ethanol to give *syn*-**2'-N-phthalimidospiro(1,4-benzodioxan-2,1'-cyclopropane)** (69%): mp 164–167°; ν_{max} 1790, 1745, 1730 cm^{-1}.

A suspension of this derivative in ethanol was treated under reflux with an equimolar quantity of hydrazine for 15 min. The hot reaction mixture was acidified with HCl and, when cold, it was filtered. The filtrate was basified and extracted with ether, and the ether extract was treated with gaseous HCl to precipitate the amine hydrochloride (79%), mp 220–222°.

B.—Alternatively, the crude isocyanate obtained on pyrolysis of the azide derived from the *syn* acid was hydrolyzed with concentrated HCl[3] to give in one step the amine hydrochloride (62% from the acid), mp 220–222°.

Anal. Calcd for $C_{10}H_{11}NO_2 \cdot HCl$: C, 56.20; H, 5.66; Cl, 16.60. Found: C, 56.35; H, 5.61; Cl, 16.44.

anti-**2'-Guanidinospiro(1,4-benzodioxan-2,1'-cyclopropane) Sulfate (2b).**—The free *anti* amine, isolated from the hydrochloride, mp 211–213°, was heated at 90° for 5 hr with 1-amidino-3,5-dimethylpyrazole sulfate[1] (1 equiv) in water. The product (13%) was obtained by filtration from the cooled reaction mixture and subsequent recrystallization from water. It had mp 288–290°.

Anal. Calcd for $C_{11}H_{13}N_3O_2 \cdot 0.5H_2SO_4$: C, 49.25; H, 5.26; N, 15.67. Found: C, 49.52; H, 5.59; N, 15.58.

syn-**2'-Guanidinospiro(1,4-benzodioxan-2,1'-cyclopropane) Tosylate (2a).**—The *syn* amine hydrochloride (mp 220–222°) was converted to the tosylate salt by treatment of an aqueous solution of the hydrochloride with 1 equiv of *p*-toluenesulfonic acid. The tosylate salt was refluxed in 95% ethanol with cyanamide (10 equiv) for 16 hr. The mixture was concentrated under vacuum and treated with ether. The precipitated material was recrystallized from water to give the product (80%), mp 175–177°.

Anal. Calcd for $C_{11}H_{13}N_3O_2 \cdot C_7H_8O_3S$: C, 55.23; H, 5.37; N, 10.73. Found: C, 55.09; H, 5.07; N, 10.51.

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as-Triazines. I. 5-Sulfanilamido Derivatives and Intermediates[1]

W. E. Taft[2] and R. G. Shepherd

Organic Chemical Research Section, Lederle Laboratories Division, American Cyanamid Company, Pearl River, New York 10965

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A series of *as*-triazines bearing 6-alkyl (or hydrogen) and 3- and/or 5-chloro, -methoxy, -methylthio, -oxo, or -thioxo groups has been prepared. The 5 position has been established as more reactive than the 3 toward nucleophilic substitution with sulfanilamide anion. The 5-sulfanilamido-*as*-triazines have good solubility but have little or no oral antibacterial activity against infections in mice.

Until the present study, exploration of the sulfanilamido-*as*-triazine series was extremely limited, only two examples of this series having been recorded.[3,4] These were 3-sulfanilamido-*as*-triazines bearing benzo[3] or phenyl[4] substituents in the 5 and 6 positions. Simpler sulfanilamido-*as*-triazines appeared accessible through 3-amino-,[5] 3-amino-5-methyl-,[6] and 3-amino-5,6-dimethyl-*as*-triazines.[5] However, attempts to couple these amines with *p*-nitro- or *p*-acetylaminobenzenesulfonyl chloride gave complex mixtures which yielded none of the desired products. Although 3-amino-5,6-diphenyl- and 3-aminobenzo-*as*-triazines have been used successfully in such reactions, the alkyl analogs are unstable to these conditions and yield water-soluble products, presumably as a result of ring cleavage.

A possible alternative route appeared to be the reaction of a methoxy- or methylthio-*as*-triazine with sodium sulfanilamide, a route which had been employed in the *s*-triazine series.[7] Furthermore, a displacement reaction had been effected with ammonia on 6-methyl-*as*-triazine-3,5-dithione.[8] During the course of our work, examples of methylthio displacements from *as*-triazines by hydrazine[9] and by ammonia were reported.[10] A suitable intermediate for such a reaction appeared to be 5,6-dimethyl-3-methylthio-*as*-triazine, accessible through the corresponding 3-thione. Repetition of

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(2) To whom correspondence should be addressed at Acadian Instruments, P. O. Box 342, Don Mills, Ontario, Canada.

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