Preparation and Schistosomicidal Activity of Some 4-Hydroxymethyl-3-chloroanilines

D. ROSI, T. R. LEWIS, R. LORENZ, H. FREELE, D. A. BERBERIAN, AND S. ARCHER

Sterling-Winthrop Research Institute, Rensselaer, New York

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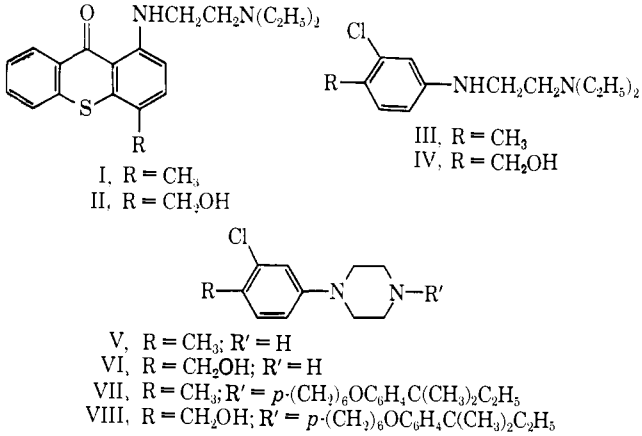
N-(3-Chloro-4-hydroxymethylphenyl)-N′,N′-diethylethylenediamine (IV) and N-(3-chloro-4-hydroxymethylphenyl)piperazine (VI) were prepared by chemical and microbiological methods. They were found to be more active schistosomicidal agents than the corresponding 4-methyl derivatives (III and V). The *p*-pentylphenoxyhexyl analog of VI was prepared chemically and found to be more active than the 4-methyl derivative (VII). Both were far weaker than the structurally simpler compounds, IV and VI.

The discovery by Kikuth and Gönnert[1] that lucanthone (I) was an orally effective schistosomicidal agent led to a great deal of structural modification of the parent nucleus in an attempt to develop better agents.[2] One of the simplest modifications which was active was a mirasan (III)[3] in which the diethylaminoethylamino side chain and the *p*-methyl group are retained but the other features of the molecule are represented by a chlorine atom. This drug was quite active in mice, but apparently was ineffective in monkeys and man.[2] The related piperazine (V) is also an active schistosomicidal drug in mice but it is believed to be ineffective in higher species.[2] The latest entry in this class is the piperazine VII.[4] The substance was reported to be an effective schistosomicidal agent in *Schistosoma mansoni* infected mice. It was claimed to be active in monkeys also.



I, R = CH_3
II, R = CH_2OH

III, R = CH_3
IV, R = CH_2OH

V, R = CH_3; R′ = H
VI, R = CH_2OH; R′ = H
VII, R = CH_3; R′ = *p*-$(CH_2)_6OC_6H_4C(CH_3)_2C_2H_5$
VIII, R = CH_2OH; R′ = *p*-$(CH_2)_6OC_6H_4C(CH_3)_2C_2H_5$

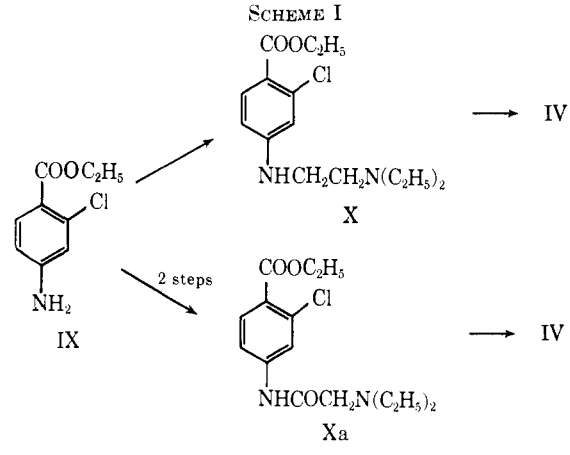
Recently it has been demonstrated that a microbial transformation product of lucanthone, the 4-hydroxymethyl derivative (II), is also a metabolite of I and is indeed the therapeutically active form of lucanthone.[5] It was also found that the biological activity of the related thiochromones and xanthen-9-ones is greatly enhanced when the 4-methyl group was replaced by the 4-hydroxymethyl group. It was thought that in this group of compounds metabolic hydroxylation of the 4-methyl was a necessary prelude for schistosomicidal action.

In our laboratory it was found that III and V were quite active in mice but markedly less so in hamsters. Rosi, *et al.*,[6] found that mouse liver microsomes efficiently hydroxylated III to IV, and V to VI but that hamster liver microsomes carried out this conversion very ineffectively if at all. It was also demonstrated that after oral administration of III to mice a substantial amount of IV was detected in the urine, while in a similar experiment with hamsters no IV could be seen on thin layer chromatograms. It was concluded that as in the case of lucanthone, III and V were being metabolically converted by the animal host to therapeutically active agents.

In the present paper we describe the microbiological and chemical synthesis of the aniline derivatives IV, VI, and VIII and discuss their schistosomicidal activity in mice and hamsters.

The benzyl alcohol (IV) was prepared according to Scheme I. Catalytic reduction of ethyl 2-chloro-4-

SCHEME I



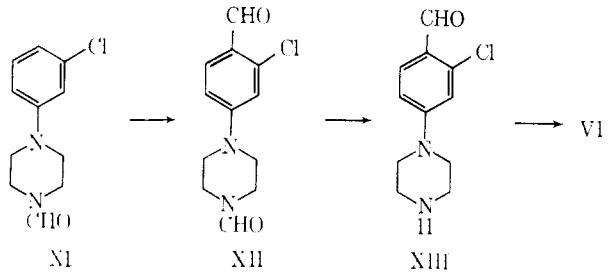
nitrobenzoate gave a mixture of IX and ethyl *p*-aminobenzoate. The Raney nickel–hydrazine method[7] gave much better results. Alkylation of the ester IX with diethylaminoethyl chloride afforded X in very poor yield. Reduction ($LiAlH_4$) to IV completed the synthesis. Some hydrogenolysis apparently took place since the presence of III could be detected on tlc. A somewhat better synthesis from the amino ester IX consisted of chloroacetylation of the amine to furnish the N-chloroacetyl derivative which in turn was treated with diethylamine to give the amino amide

(1) W. Kikuth and R. Gönnert, *Ann. Trop. Med. Parasitol.*, **42**, 259 (1949).
(2) R. Gönnert, *Bull. World Health Organ.*, **25**, 702 (1961).
(3) H. Mauss, H. Kolling, and R. Gönnert, *Med. Chem., Abhandl. Med. Chem. Forschungsstaetten I. G. Farbenind.*, **5**, 185 (1956).
(4) A. O. Geiszler, P. M. Bauman, A. Alter, P. M. Bauman, A. O. Geiszler, and G. F. Otto, Reports given at the Annual Meeting of the American Society of Tropical Medicine and Hygiene, New York, N. Y., Nov 7, 1964.
(5) D. Rosi, G. Peruzzotti, E. W. Dennis, D. A. Berberian, H. Freele, B. F. Tullar, and S. Archer, *J. Med. Chem.*, **10**, 867 (1967).
(6) D. Rosi, A. J. Merola, and S. Archer, *Life Sci.*, in press.
(7) D. Balcom and A. Furst, *J. Am. Chem. Soc.*, **75**, 4334 (1953).

(Xa) which upon reduction with $LiAlH_4$–$AlCl_3$ gave IV. In view of the excellence of the microbiological method which was developed simultaneously (*vide infra*), no further attempts were made to improve the chemical synthesis.

The synthesis of N-(3-chloro-4-hydroxymethylphenyl)piperazine (VI) is shown in Scheme II. *m*-Chlorophenylpiperazine was formylated to give the amide (XI) which was subjected to the Vilsmeier–Haack reaction.[8] The aldehyde XII was then hydrolyzed to XIII. $NaBH_4$ reduction furnished VI in 49% over-all yield, based on 1-(*m*-chlorophenyl)piperazine.

SCHEME II



The same approach was used to synthesize VIII. 1-(*m*-Chlorophenyl)piperazine was condensed with 6-(*p*-*t*-pentylphenoxy)hexyl bromide and the resulting product was formylated as above. Reduction ($NaBH_4$) gave VIII.

The diamine III was used as a substrate in microbiological oxidations. In preliminary runs it was found that a number of microorganisms converted this substance to more polar metabolites. The most efficient conversion was realized with *Aspergillus sclerotiorum*, the same organism which was used for the lucanthone–hycanthone oxidation.[5] In addition to IV another polar spot was visualized on the thin layer chromatogram. In view of the fact that it gave a positive response with the DNP reagent and disappeared when the reaction mixture was pretreated with $NaBH_4$ before tlc analysis, it was concluded that we were dealing with the 4-carboxaldehyde corresponding to IV. Under optimum conditions it was possible to convert 161 g of substrate III to 106 g of the alcohol (IV) on a 10-l. scale. *A. sclerotiorum* was also the organism of choice for converting V to VI. The over-all yield compared favorably with the chemical method in this case also.

Biological Activity.—Our previous experience with lucanthone (I) and some of its congeners[5] led us to believe that the simpler analogs such as III and V were also being converted *in vivo* to the schistosomicidally active drugs IV and VI, respectively. In fact we carried out a metabolic study with III before the comparative schistosomicidal bioassay was run.[6] On the basis of relative amounts of IV excreted in the urine of mice and hamsters we were able to predict correctly that III would be more active in the former species. It is clear from Table I that the hydroxymethyl derivatives IV and VI are more active in the hamster and in the mouse than the corresponding 4-methyl analogs III and V.

Since VII is an analog of V it was considered that it, too, was being subjected to *in vivo* hydroxylation to VIII. The Abbott workers reported that VII was active in mice at doses of 12.5 mg/kg ip.[4] In our laboratory the oral ED_{50} of VII was found to be 93 mg/kg in mice and >400 mg/kg in hamsters. The corresponding hydroxymethyl analog VIII was more active than VII in both rodent species. However, the newer piperazines are considerably less active than the simpler drugs shown in Table I.

TABLE I

SCHISTOSOMICIDAL ACTIVITY OF THE ANILINE DERIVATIVES

Compd	ED_{50},[a] mg/kg	
	Mouse	Hamster
III	13.0 ± 2.7	45 ± 17.0
IV	15.0 ± 2.8	9.0 ± 2.4
V	7.5 ± 2.0	84 ± 2.9
VI	1.7 ± 0.23	3.75 ± 0.47
VII	93 ± 21	>400
VIII	36 ± 6.8	225 ± 91

[a] The ED_{50} is the dose (milligrams per kilogram) which, when given once a day for 5 days to rodents infected 46 days earlier, reduces the adult worm count by 50%.

Experimental Section[9]

Ethyl 2-Chloro-4-aminobenzoate (IX).—A solution of 49.5 g of ethyl 2-chloro-4-nitrobenzoate[10] and 40 ml of 100% hydrazine hydrate in 1 l. of alcohol was warmed slightly and a small amount of Raney Ni was added. The mixture was refluxed for 0.5 hr and allowed to stand at room temperature for 2 hr. The catalyst was removed by filtration and the filtrate was evaporated to dryness. The white residue was crystallized from 150 ml of absolute ethanol to give 33.7 g of the ester, mp 105.5–107°.[11] The mother liquors yielded a second crop, 5.2 g, mp 103–106°.

N-(3-Chloro-4-hydroxymethylphenyl)-N′,N′-diethylethylenediamine (IV).—The amino ester IX (26 g) and chloroethyldiethylamine (52 g) were heated in a sealed tube for 15 min at 180–200°. The mixture was poured into water and decanted from an insoluble gummy solid. The aqueous phase was adjusted to pH 6.0 and extracted with ether. The ether was evaporated, the residue was dissolved in 100 ml of absolute alcohol, and 4.5 g of picric acid was added. After about 3 min at the boil, the mixture was cooled and filtered. The crude picrate (8.0 g) was crystallized from ethanol and filtered; 7.0 g, mp 149.5–150.5°.

Anal. Calcd for $C_{15}H_{23}ClN_2O_2 \cdot C_6H_3N_3O_7$: N, 13.27; Cl, 6.72. Found: N, 13.30; Cl, 6.98.

The base was liberated from the picrate and distilled to furnish a fraction, bp 190–194° (0.5 mm), 2.5 g.

A solution of the ester in 35 ml of dry ether was added to a slurry of 350 mg of $LiAlH_4$ in 65 ml of ether. The whole was refluxed gently for 30 min and worked up in the usual way. Examination of the crude mixture by tlc indicated that some hydrogenolysis had occurred to furnish III. The mixture was chromatographed on a column of silica gel using ether–triethylamine as the developing solvent. The separation was monitored by tlc. The fractions containing only the desired alcohol were combined and evaporated to dryness. The crude alcohol (1.0 g) melted at 61.5–65.0° and showed a new peak at 2.75 (OH) and no 5.85-μ peak ($COOC_2H_5$) in the infrared spectrum. After crystallization from hexane–benzene, crystals (870 mg) were obtained which melted at 65.5–67.0°.

Anal. Calcd for $C_{13}H_{21}ClN_2O$: N, 10.71; Cl, 13.81. Found: N, 10.84; Cl, 13.36.

Ethyl 4-(ω-Chloroacetamido)-2-chlorobenzoate.—A solution of 68 g (0.6 mole) of chloroacetyl chloride in 210 ml of $(ClCH_2)_2$ was added slowly to a refluxing solution of 115 g (0.58 mole) of ethyl 4-amino-2-chlorobenzoate in 350 ml of $(ClCH_2)_2$. After

(8) See M. R. deMaheas, *Bull. Soc. Chim. France*, 1989 (1962), for a review of this reaction.

(9) Analyses were carried out under the supervision of Mr. K. D. Fleischer. Spectra were run under the supervision of Dr. R. K. Kullnig, who assisted in the interpretation of the nmr spectra, which were run on the Varian A-60 instrument.

(10) J. Büchi, R. Lieberherr, and M. Flury, *Helv. Chim. Acta*, **34**, 2076 (1951).

(11) M. Rubin, H. C. Marks, H. Wishinsky, and A. Lanzilotti, *J. Am. Chem. Soc.*, **68**, 623 (1946).

all the acid chloride was added the solution was refluxed for 1.5 hr, cooled, and diluted with 1 l. of pentane. The solution was placed in the refrigerator overnight and filtered, and the crystals were collected, washed with pentane, and dried; 135 g (83%), mp 119–122°.

Anal. Calcd for $C_{11}H_{11}Cl_2NO_3$: N, 5.07; Cl, 25.68. Found: N, 5.16; Cl, 25.95.

Ethyl 2-Chloro-4-(ω-diethylaminoacetamido)benzoate.—A solution of 133 g (0.481 mole) of the above ester and 106 g (1.44 moles) of diethylamine in 1 l. of benzene was refluxed for 4 hr. The whole was reduced to half-volume and washed with water. The organic layer was extracted with dilute HCl. The acid extracts were washed with ether, made basic, and extracted with ether again. The second ether extract was dried and concentrated. The residue was dissolved in isopropyl alcohol and treated with 1 equiv of concentrated HCl. The solution was treated with ether to the point of turbidity and set aside and cooled. The crystals of the hydrochloride which separated were filtered off and dried; 144 g (86%), mp 150–151°.

Anal. Calcd for $C_{13}H_{21}ClN_2O_3 \cdot HCl$: Cl, 20.30. Found: Cl, 20.09.

N-(3-Chloro-4-hydroxymethylphenyl)-N′,N′-diethylethylenediamine (IV) from Xa.—A solution of 23.4 g (0.177 mole) of $AlCl_3$ in 300 ml of tetrahydrofuran (THF) was prepared by cautious addition of the salt to the solvent. The solution was added in one portion to a suspension of 52 g (1.37 moles) of $LiAlH_4$ in 2.0 l. of THF at −12°. The free base from 117 g (0.374 mole) of the ester (Xa) in 200 ml of THF was added over a 45-min period to the $LiAlH_4$–$AlCl_3$ solution with stirring while the temperature of the latter was kept between −8 and −12°. The mixture was stirred for 6 hr at −6 to −12° and then hydrolyzed by the careful addition of 165 ml of 35% aqueous NaOH. The resulting emulsion was broken with 20 g of powdered KOH. The mixture was filtered and the filter cake was washed with THF. The filtrate was concentrated to dryness *in vacuo* leaving a residue which weighed 84 g. It was dissolved in 75 ml of warm benzene and the solution was diluted with 100 ml of pentane. On standing 44.5 g (46%) of IV separated, mp 64–67°. Upon recrystallization from benzene–pentane with the aid of charcoal, pure white IV was obtained which melted at 66–68°.

1-(*p*-*t*-Pentylphenoxyhexyl)-4-(*m*-chlorophenyl)piperazine.—A solution of 81.5 g of 6-(*p*-*t*-pentylphenoxy)hexyl bromide,[12] 49 g of *m*-chlorophenylpiperazine, 50.5 g of triethylamine, and 500 ml of toluene was heated under reflux for 6 hr. The mixture was left overnight and then filtered to remove the triethylamine hydrobromide. The residue was concentrated to a small volume and put on a 200-g silica gel column and eluted with 2% isopropylamine–ether. This operation removed some color. The eluate was evaporated to dryness and converted to the hydrochloride in ether with alcoholic HCl. There was obtained a total of 71 g of the hydrochloride, mp 116–119°. A sample was recrystallized from ethanol–ether for analysis, mp 119–121.5°.

Anal. Calcd for $C_{27}H_{40}ClN_2O \cdot HCl$: N, 5.85. Found: N, 5.83.

2-Chloro-4-[4-(*p*-*t*-pentylphenoxy)hexyl-1-piperazinyl]benzyl Alcohol (VIII).—To a solution of 29 g of $POCl_3$ in 44 g of dimethylformamide (DMF) there was added a solution of 50 g (0.104 mole) of 1-(*p*-*t*-pentylphenoxyhexyl)-4-(*m*-chlorophenyl)piperazine hydrochloride in 150 ml of DMF over a period of 15 min with the temperature held at 15°. After the addition was complete, the mixture was heated at 120–130° for 35 min and then poured onto 1 kg of ice. The solid was filtered, washed with water and dilute NH_3, and then taken up in ether. The extracts were washed (H_2O, 5% NaOH, saturated NaCl). The ether layer was dried ($MgSO_4$) and concentrated to leave a viscous oil, 48 g. This was dissolved in 600 ml of methanol, and 8.0 g of $NaBH_4$ was added in 2.0-g portions over a period of 1.5 hr. The methanol was removed and the residue was crystallized from about 1 l. of hexane. A semisolid (39 g) separated and was chromatographed on 100 g of silica gel using 2% isopropylamine and ether as the eluting solvent. The crystallizing fractions were combined and recrystallized from boiling hexane to furnish 20 g of pure VIII, mp 73–74°.

Anal. Calcd for $C_{28}H_{41}ClN_2O_2$: N, 5.92. Found: N, 6.02.

2-Chloro-4-(1-piperazinyl)benzaldehyde Hydrochloride (XIII).—A solution of 78.6 g (0.40 mole) of 1-(*m*-chlorophenyl)piperazine, 22.2 g (0.48 mole) of formic acid, and 100-ml of benzene was refluxed using a Dean–Stark apparatus to collect water. In 2 hr 9 ml of water was collected. The solution was concentrated and the residue was distilled. The fraction, bp 153–164° (0.1 mm), was collected as the product, 86.0 g (96.5%). This crude material was used in the next step.

$POCl_3$ (20.3 g, 0.15 mole) was added dropwise with stirring to 75 ml of DMF as the temperature rose to 40°. It was stirred at this temperature for 0.5 hr, cooled, and then added with efficient stirring to a solution of 22.5 g (0.1 mole) of 1-(*m*-chlorophenyl)-4-formylpiperazine (XI) in 50 ml of DMF which was being heated on the steam bath. After the addition was complete the reaction mixture was stirred at 95° for 1 hr. About 60 ml of DMF was removed *in vacuo* and the residue was poured onto a slurry of ice and water. The cold solution was made alkaline with 35% NaOH and the extracted ($CHCl_3$). The combined extracts were washed with water and then concentrated. The dark residue was heated for 0.5 hr with 100 ml of 2.5 *N* HCl on the steam bath. After cooling overnight the crystalline precipitate was collected on a filter and washed with isopropyl alcohol. The yield of hydrochloride was 14.2 g (55%), mp 247° dec.

Anal. Calcd for $C_{11}H_{13}ClN_2O \cdot HCl$: N, 10.73; Cl, 27.15. Found: N, 10.80; Cl, 27.35.

2-Chloro-4-(1-piperazinyl)benzyl Alcohol (VI).—A slurry of 28.5 g (0.109 mole) of the hydrochloride XIII in 200 ml of methanol was treated with 9.0 ml of 35% NaOH solution and cooled to 0°. To this mixture there was added a solution of 4.5 g of $NaBH_4$ in 40 ml of water. The methanol was removed *in vacuo;* care was taken not to overheat the reaction mixture. The residue was treated with 50 ml of 1% NaOH solution and the mixture was extracted ($CHCl_3$). The combined extracts were decolorized with charcoal and dried (Drierite). After evaporation, there remained 23.2 g (95%) of the desired piperazine (VI), mp 118–120° (uncor), identical in all respects with material prepared by the microbiological route.

Microbiological Oxidation of 1-(3-Chloro-4-methylphenyl)-piperazine Hydrochloride.—The stock culture of *Aspergillus sclerotiorum* was grown initially at 26° for 10–14 days on slants in a nutrient medium consisting of Difco maltose (40 g/l.), Difco proteose peptone No. 3 (10 g/l.), and Bacto agar (15 g/l.). These slants were used to prepare seed for the fermentations in the following way. Sterile distilled water (10 ml) was added to the slant and the spores and some vegetation growth were shaken loose with a sterile hooked needle to form a uniform suspension. This was added to a 2-l. flask containing 700 ml of a sterile soy–dextrose medium of the following composition: 15 g of soybean meal, 20 g of dextrose, 5 g of yeast, 5 g of salt, 5 g of K_2HPO_4, and enough tap water to make the final volume 1 l. The pH was adjusted to 6.5 with HCl just prior to sterilization at 121° for 15 min. These cotton-plugged flasks were placed on a rotary shaker (2.5-cm throw at 240 rpm) and incubated for about 3 days at 26°.

Ten liters of a soy–dextrose medium of the following composition was used for the fermentation itself: 1 kg of cerelose, 150 g of soybean meal, 50 g of yeast, 50 g of salt, 2.5 g of $MgSO_4 \cdot 7H_2O$, 13.8 g of $NaH_2PO_4 \cdot H_2O$, 301 g of $Na_2HPO_4 \cdot 12H_2O$, and tap water to make the final volume 10 l. The solution with pH 7.3 was sterilized as above. One seed flask was added to the above solution which was stirred in a fermenter kept in a water bath at 28°. After 24 hr the addition of V was begun. About 10 g/day was added in two portions over a period of 5 days. The total amount of substrate consumed was 53 g. Four such fermentations were carried out simultaneously so that 212 g of 1-(3-chloro-4-methylphenyl)piperazine hydrochloride (0.86 mole) was used as a substrate. To each fermentation vessel there was added 130 ml of 10 *N* NaOH to stop further growth of the organism. Each vessel was extracted with two 20-l. portions of CH_2Cl_2, and the extracts were partially concentrated *in vacuo*. The residues from four such extractions were combined and then evaporated to furnish a crystalline residue weighing 150 g. This was recrystallized from 800 ml of ethyl acetate after an insoluble fraction (4.5 g, mp 180°) was filtered off. On cooling the warm solution, 120 g of cream-colored crystals of VI deposited, melting at 122° (cor). A second slightly less pure crop weighing 23.5 g was collected on concentration of the mother liquors. The total yield of combined crops was 143.5 g or 73% of the theoretical.

Anal. Calcd for $C_{11}H_{15}ClN_2O$: N, 12.36; Cl, 15.64. Found: N, 12.43; Cl, 15.44.

The uv spectrum showed the following $\lambda_{max}^{95\% \text{ EtOH}}$ 211 mμ (ε 24,300), 256 (13,900), 291 sh (1800). The nmr spectrum (20%

(12) A. Alter, Belgian Patent 628,766 (Aug 22, 1963); *Chem. Abstr.*, **60**, 8044e (1964).

$CDCl_3$ 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 (R_f, 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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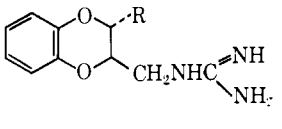
Syntheses are described of 2-methyl- and *trans*-3-methyl-2-guanidinomethyl-1,4-benzodioxan and of *syn*- and *anti*-2'-guanidinospiro(1,4-benzodioxan-2,1'-cyclopropanes) (**2a** and **b**). The stereochemistry of the compounds was determined by nmr spectroscopy, and their adrenergic neurone blocking 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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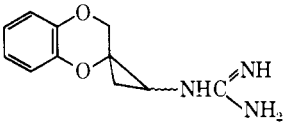
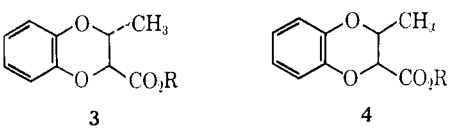


2a *syn*
b *anti*

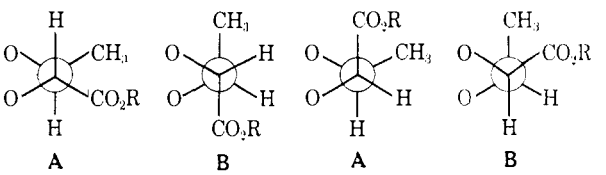
ring were described, the only reference to a substituent in the dioxane ring was to the 3-methyl derivative which was prepared and tested as a mixture of *cis* and *trans* isomers.

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

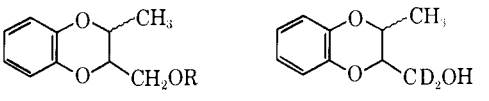


3 **4**



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