by subsequent dehydration to the corresponding olefin with oxalic acid in boiling toluene.

1-Phenylcyclohexene.—Foote PhLi was condensed with cyclohexanone in Et_2O according to the procedure of Ginsburg and Pappo[5] to give 1-phenylcyclohexanol which was dehydrated with oxalic acid in boiling toluene to yield 1-phenylcyclohexene.

1-(2,3-Dimethoxyphenyl)cyclohexene.—1-(2,3-Dimethoxyphenyl)cyclohexanol was prepared according to Bergmann, *et al.*,[6] by the addition of veratrole to Foote *n*-BuLi followed by condensation with cyclohexanone. The resultant alcohol was dehydrated with oxalic acid.

Rate Measurements.—Olefin, freshly distilled mercaptoacetic acid, and a catalytic amount of Bz_2O were accurately weighed in a 10-ml reaction vessel fitted with a ground-glass stopper, mixed, and placed in a constant-temperature bath (30°). The rates of addition were followed titrimetrically. At appropriate times, aliquots were removed and dissolved in C_6H_6 (Fisher reagent grade), a few drops of pyridine were added, and the unreacted mercaptan was titrated with 0.0500 *N* I_2 in EtOH to a faint yellow color.

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Antimalarial Compounds.[1] X.[2] Biguanide and Amidinourea Derivatives of Diphenyl Sulfide, Sulfoxide, and Sulfone

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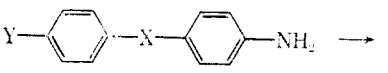
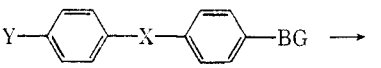
It is known that 4,4′-diaminodiphenyl sulfone (DDS) and some of its derivatives are useful in the treatment of some forms of malaria.[3] As the starting point of the presently described experiments, we obtained a number of biguanide and amidinourea derivatives of diphenyl sulfone, sulfoxide, and sulfide and their mononitro derivatives. The choice of the compounds was based upon our previous findings, that nitroguanil, the amidinourea derivative with a nitro group, was active against malaria.[4]

Chemistry.—The starting substances were commercially available DDS (I) and the intermediates, 4-amino-4′-nitrodiphenyl sulfone (II),[5,6] 4,4′-diaminodiphenyl sulfoxide (III),[5,7] and 4-amino-4′-nitrodiphenyl sulfide (IV).[5] The reactions of I–IV with cyanoguanidine leading to V–XII (Scheme I) are described in the Experimental Section.

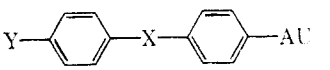
SCHEME I



I, Y = NH_2; X = SO_2
II, Y = NO_2; X = SO_2
III, Y = NH_2; X = SO
IV, Y = NO_2; X = S



V, Y = BG; X = SO_2
VI, Y = NO_2; X = SO_2
VII, Y = BG; X = SO
VIII, Y = NO_2; X = S



IX, Y = AU; X = SO_2
X, Y = NO_2; X = SO_2
XI, Y = AU; X = SO
XII, Y = NO_2; X = S

BG = $NHC(=NH)NHC(=NH)NH_2$
AU = $NHCONHC(=NH)NH_2$

The procedures reported in the literature for the syntheses of 4-nitro-4′-biguanyldiphenyl sulfone (VI)[8,9] and 4,4′-dibiguanyldiphenyl sulfone (V)[8,10] have been modified. In the search for a more convenient method of preparation of the nitrodiphenyl sulfone derivatives VI and X, the oxidation of the corresponding sulfides VIII and XII with peracetic acid was found to give satisfactory results.

Toxicity.[11]—Acute toxicity of V–XII on oral and intraperitoneal administration was tested (Table I).

TABLE I

	Toxicity, mg/kg (mice) LD_{50}			Antimalarial act. rel parasitemia mg/kg/day				
No.	*po*	ip	$LD_{0/4}$[b]	2.5	10	40	160	320
IX	2000	*a*	20				Inactive	
X	2000	800	50			75	32.5	13
VII	1760	77	50				Inactive	
XI	1500	195	112				Inactive	
VIII	1030	48	5				Inactive	
XII	900	640	112	76	101	92	0.224	0.056
V[8,9]	1400	110	20				Inactive	
VI[8,10]	1500	176	112	71	68	58	25	13

[a] Low solubility did not allow the preparation of solutions of an effective concentration. [b] The highest dose, administered on 4 consecutive days, that produced no deaths or weight loss.

Clonic convulsions were observed after administration of V, VII, and VIII. No toxic effects were shown by VI, IX–XI. Considerable differences between the LD_{50} in oral and interperitoneal administration tests of some of the compounds indicate their poor gastrointestinal absorption.

The highest dose which, administered on four consecutive days, produced no death and no decrease of body weight was also determined ($LD_{0/4}$). It ranged

(1) The financial support of this work from the World Health Organization is gratefully acknowledged.

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(11) Tests were carried out at the Institute of Drugs, Warsaw, Poland.

TABLE II

Amine No.	Amine g	Cyanoguanidine, g	HCl, ml	H_2O, ml	EtOH, ml	Reaction time, min	Product No.	Yield g	Yield %	Mp, °C	Recrystn solvent
I	22.3	17.0	20.0	50		60	V[8,9]	25.0	57.5	258–260[a]	H_2O
II	4.0	0.9	1.2		3	60	VI[8,10,b]	1.0	57.0	183–184	Dil Me_2CO
III	11.6	9.2	9.2		50	45	VII	5.8	63.0	206–207	DMSO
IV	5.0	1.7	2.0	8		20	VIII	5.0	68.5	232–235	EtOH

[a] Dihydrochloride. [b] Code number T 1214.

from 5.0 mg/kg for VIII to 112 mg/kg for VI, XI, and XII (Table I).

Antimalarial Activity.[12]—Three compounds showed antimalarial activity: VI, X, and XII. Compound XII was the most active but showed a slight toxicity at the active doses, loss of weight at 160 mg/kg, LD_{80} = 320 mg/kg; VI was less active but no signs of toxicity were detected. The therapeutic dose is probably higher than 1000 mg/kg; X was less active but more toxic than VI; the results are collected in Table I.

Experimental Section

All analytical data of the new compounds were in agreement with the calculated ones for the expected structures. Ir absorption bands were also as expected. Biguanides V–VIII (Table II) were obtained as follows. The amines I–IV were mixed with HCl, solvent, and cyanoguanidine and refluxed; the resulting hydrochlorides were recrystallized (V) or converted into the bases (VI–VIII).

Amidinoureas IX–XII were obtained from biguanides on heating in dilute HCl (Table III).

TABLE III

Biguanide No.	Biguanide g	10% HCl, ml	Reaction time, min	Product No.	Yield g	Yield %	Mp, °C	Recrystn solvent
V	2.0	8	30	IX	1.5	75	246–247[a]	H_2O
VI	1.0	4	10	X	0.6	60	172–173	Dil Me_2CO
VII	2.5	5	15	XI	1.25	50	220–221[b]	EtOH
VIII	3.0	2.5	30	XII[c]	1.0	33	221–223	Dil pyridine

[a] Dihydrochloride. [b] Dihydrochloride monohydrate. [c] Code number T 1213.

Oxidation of VIII and XII.—To 3.3 g of VIII in 10 ml of AcOH, 8.0 g of 20% AcO_2H was added during 10 min; the temperature rose to 6 0–70°; after 2 hr the solvent was evaporated *in vacuo*, the mixture was made alkaline, and the resulting product was recrystallized from dilute Me_2CO yielding 2.7 g (75%) of VI, mp 183–184°. Similarly, 3.3 g of XII in 16 ml of AcOH gave 2.3 g (65%) of X, mp 172–173°.

Toxicity.[11]—Acute toxicity on oral administration was tested with Swiss male albino mice in groups of ten animals. The compounds were administered by stomach tube in a 5% suspension of aqueous gum arabic at 0.8 mg/20 g of body weight. The LD_{50} was calculated graphically according to Litchfield and Wilcoxon by the modification of Roth. The animals were observed for 10 days. Acute toxicity on intraperitoneal administration was investigated with compounds suspended in 4% Tween 80. The doses were 0.2 ml/20 g of body weight (Table I).

Antimalarial Activity.[12]—Tests were carried out using an old laboratory strain (strain N) of *Plasmodium berghei berghei*. Mice were inoculated intravenously with *ca.* 10^7 parasitized rbc on day 1. They were dosed orally with drugs in 10% (v/v) methylcellulose on days 1–4. Blood films were taken on fifth day. The percentage of red blood cells containing parasites was counted and compared with that of untreated control mice. Five mice were used for each dose. The relative parasitemia was calculated as a percentage of the controls (Table I).

(12) Tests were carried out at the National Institute for Medical Research, London.

Acknowledgments.—We wish to express our gratitude to Dr. L. J. Bruce-Chwatt and Dr. J. Haworth of the World Health Organization for their kind interest in our research and aiding us with supplies of instruments and materials. We are greatly indebted to Dr. F. Hawking, National Institute of Medical Research, London, for offering us facilities to carry the antimalarial tests, to Mrs. T. Bolesławska for assistance in the synthetic work, and to Mr. R. O. Folwell for help with antimalarial tests.

Catalytic Hydrogenolysis of Benzylmethylamino Analogs of Methadone and α-Methadol

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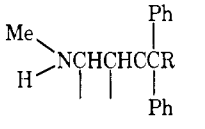
The great majority of analgetics with morphine-like effects are tertiary amines.[1,2] Among the few examples of active secondary amines that have been reported are the N-methylamino analogs of methadol and acetylmethadol,[3] normorphine,[2] and certain 6,-14-endoethenotetrahydrothebaines.[4] Interest in analgetics with secondary amino functions has been aroused as a result of a hypothesis implicating such bases as intermediates in the mediation of analgesia.[2,5]

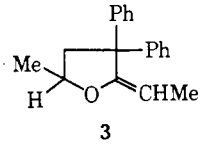
3-Methylamino-1,1-diphenylpropylamines (**1**) (R is an oxygenated function) have proved difficult to synthesize from corresponding N-dimethylamino analogs. Thus, treatment of methadone (**2a**) and α-methadol (**2b**) with BrCN yields the cyclic products **3** and **4**, respectively, rather than the N-cyanomethyl derivatives, potentially capable of hydrolysis to the



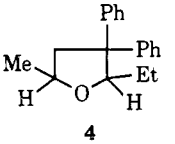
1

$Me_2NCHMeCH_2CPh_2R$

2a, R = COEt
b, R = CHOHEt
c, R = CH(OCOMe)Et



3



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