as Quevauviller[7] has pointed out, must exist between the lipophilic and hydrophilic portion of the molecule for it to exhibit potent local anesthetic activity. Hydrophilicity in the case of G–K, might be dominating and lead to decreased activity. Interestingly, these compounds were more soluble at pH 7.4 than A–F[8] which supports this postulation.

(ii) In the acyl-substituted portion the compds having one CH_2 group were more potent than those having two CH_2 groups (A, B, G, and H); but the duration of activity of the latter class of compounds was definitely greater. Obviously, the rate of hydrolysis of these two classes of compounds might be governing their duration of action.

A marked decrease in the initial activity was observed after keeping the aqueous solutions of these compounds for 8 hr at room temperature. Hence, it became of interest to study their uv absorption pattern in distd H_2O. Initially the uv spectra of all these compounds in EtOH or H_2O exhibited a strong band between 255 and 260 mμ and a wide band around 310 mμ. Although the gross features of their uv spectra in aqueous solution after 8 hr remained unchanged, the band around 255–260 mμ now appeared as only an inflection while the broad band around 310 mμ disappeared. The uv spectral data of their aqueous solution, initially as well as after 8 hr, are presented in Table V. They suggest instability in aq solution and support our postulate that the rate of hydrolysis probably governs the duration of activity. However, the possibility of the sensitivity of these compounds toward enzymatic hydrolysis *in vivo* cannot be overruled. Finally, keeping in mind relative potency and toxicity, most of these compounds might offer a wide spectrum of useful local anesthetic activity.

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(8) All these compounds (A–F) were also investigated for their CNS depressant activity. Their solubilities at pH 7.4 were also determined spectrophotometrically because Green[a] has shown that CNS depressat activity of phenothiazines is associated with their low solubility at pH 7.4. The details of this work including some interesting account of structure activity relationship in phenothiazine series has been communicated.[b] (a) A. L. Green, *J. Pharm. Pharmacol.*, **19**, 10 (1967); (b) H. L. Sharma, S. P. Banerjee, V. N. Sharma, and R. L. Mital, *Ann. Soc. Sci. Bruxelles, Ser. 2*, **84**, 55 (1970).

Preparation and Antimalarial Activity of Compounds Related to Dypnone Guanylhydrazone[1]

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Received July 16, 1970

Early in the current Walter Reed *Plasmodium berghei* screening program, dypnone guanylhydrazone (**1**) was demonstrated to have interesting activity.[2,3] We wish to report the preparation and testing of a series of compounds designed to probe several of the structural parameters of this lead.

An early variant, the *p,p'*-dichloro compound **7**, showed a striking increase in activity and a decrease in toxicity (Table I). That the chlorodypnone residue alone was not responsible for the activity was shown by the results with the parent ketone and some simple ketone derivatives (**2–6**).

The fact that a high level of activity remained in the desmethyl (chalcone) analog **9** led us to prepare a small series in which the ketonic portion of the molecule was varied. Vinylogs and tris-*p*-chlorophenyl compounds (**10–13**) showed decreased activity. Table II presents a short series of aldehyde guanylhydrazones. The hydrocarbon nuclei used for this series are associated with quite good antimalarial action when other side chains are incorporated. Only marginal effect was noted for **14–16**, however. The results with these series suggest that peak activity resides in the more compact dypnone–chalcone type guanylhydrazones. It should be pointed out that the activity and toxicity of a large series of highly active, substituted benzophenone guanylhydrazones reported by DoAmaral, *et al.*, were strongly influenced by minor variations in ring substitution patterns.[4,5] The most active benzophenone compounds were variously substituted with Br, Cl, F, I, and CF_3 or OCF_3. The work of DoAmaral and French[5,6] also indicates that alkyl substitution of the aminoguanidine moiety is inimical to activity.

An attempt was made to prolong the activity of **7** by the use of the "repository" pamoate salt **8**. The decreased activity of **8**, however, roughly corresponded to the decreased proportion of active drug in the salt when tested in the standard mouse screen.

The guanylhydrazone derivatives were prepared by the same method used to prepare the parent dypnone derivative **1**.[7] It should be noted that aminoguanidine bicarbonate is the only aminoguanidine salt, of several available, that successfully derivatized these ketones in our hands. Other procedures, for the preparation of benzophenone guanylhydrazones, have since been reported.[4]

The 4,4'-dichloro analog **2** was prepared by $POCl_3$-catalyzed self-condensation of 4-chloroacetophenone.[8] The carbonyl derivatives **3–6** were prepared by standard procedures.

The base-catalyzed condensation of 4-chlorobenzaldehyde and 4-chloroacetophenone by a published procedure[9] gave 4,4'-dichlorochalcone,[10] the precursor to **9**.

The tris(*p*-chlorophenyl) ketone **11** was obtained from the reaction of the ylid derived from *p*-chlorophenacyl

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(1) This work was supported by the U. S. Army Medical Research and Development Command under Contract No. DA-49-193-MD-2750. This is Contribution No. 834 from the Army Research Program on Malaria.

(2) This information was provided through the courtesy of Dr. R. E. Strube of the Walter Reed Army Institute of Research.

(3) Biological investigation performed by Dr. Leo Rane of the University of Miami, Miami, Fla. by a published procedure: T. S. Osdene, P. B. Russell, and L. Rane, *J. Med. Chem.*, **10**, 431 (1967).

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TABLE I
COMPOUNDS TESTED AS ANTIMALARIAL AGENTS

No.	Structure[a]	Yield, %	Mp, °C	Formula	Analyses	Antimalarial activity[b,c] 40	80	160	320	640
1	PhC(CH3)=CHCPh(NNHC(NH)NH2)·HCl				d	3.7	4.3	5.9²/₅	8.9³/₅	9.4³/₅
						3.0	4.6	8.2	11.0	16.4
2	ArC(CH3)=CHCOAr	24	75–80		e	0.1		0.1		0.5
3	ArC(CH3)=CHCAr(NOH)	61	109–116	$C_{16}H_{13}Cl_2NO$	C, H, N	0.4		0.4		0.6
4	ArC(CH3)=CHCAr(NNHCONH2)	40	178–180	$C_{17}H_{15}Cl_2N_3O$	C, H, N	0.0		0.0		0.2
5	ArC(CH3)=CHCAr(NNHCSNH2)	39	184–185	$C_{17}H_{15}Cl_2N_3S$	C, H, N	0.0		0.2		0.2
6	ArC(CH3)=CHCAr(NNHCOCH3)	55	167–168	$C_{18}H_{16}Cl_2N_2O$	C, H, N	0.1		0.5		0.5
7	ArC(CH3)=CHCAr(NNHC(=NH)NH2)·HCl	59 (71)[f]	235–238	$C_{17}H_{16}Cl_2N_4$·HCl	C, H, N	4.5	14.9²/₅C	19.4³/₅C	23.9⁴/₅C	⁵/₅C[g]
8	ArC(CH3)=CHCAr(NNHC(=NH)NH2)·Pamoate	96	240–245 dec	$C_{17}H_{16}Cl_2N_4 \cdot C_{23}H_{16}O_6$	C, H, N	0.5	0.5	4.3	24.2²/₅	19.9⁴/₅C
9	ArCH=CHCAr(NNHC(=NH)NH2)·HCl	14	148–155	$C_{16}H_{14}Cl_2N_4$·HCl	C, H, N	6.2	9.6	12.3³/₅C	⁵/₅C	⁵/₅C
10	Ar2C=CHCAr(NNHC(=NH)NH2)·HCl·H2O	43	165–170[h]	$C_{22}H_{17}Cl_3N_4$·HCl·H_2O	C, H, N	0.1		0.9		16.7⁴/₅C
11	Ar2C=CHCH=CHCOAr(NNHC(=NH)NH2)	50	128–130	$C_{23}H_{15}Cl_3O$	C, H	0.0		0.2		0.2
12	(Ar)2C=CHCH=CHCAr(NNHC(=NH)NH2)·HCl	31	257–259[i]	$C_{24}H_{19}Cl_3N_4$·HCl	C, H, N	0.3		0.3		0.7
13	ArC(CH3)=CHCH=CHCAr(NNHC(=NH)NH2)·HCl	46 (55)[f]	203–213	$C_{19}H_{18}Cl_2N_4$·HCl	C, H, N	0.4		1.0		3.2

[a] Ar = 4-chlorophenyl. [b] Dosage given in mg/kg. Numbers give the extension in survival time in days over untreated mice in the standard mouse *P. berghei* assay. See ref 3 for procedure. Fractions indicate toxic deaths over no. of treated mice in the test group. A "C" following a fraction indicates the fraction of treated mice that are cured. [c] Increase in survival time ≤1 day at 20 mg/kg dosage. [d] Reference 2. [e] Reference 8. [f] Yield of guanylhydrazone and (adjusted yield based on unrecovered starting material). [g] This compd showed only marginal activity when tested against *P. cynomogli* in the monkey (ref 2). [h] Some reactions gave an unhydrated product, mp 210–220°. The hydrated solid retains H_2O tenaciously. [i] An isomer, mp 197–202°, was also isolated; combined yield shown. *Anal.* C, H, N.

triphenylphosphonium bromide with 3,3-bis(*p*-chlorophenyl)acrolein.[11]

Vilsmeier formylation of α-methyl-*p*-chlorostyrene gave aldehyde **17**, *p*-$ClC_6H_4C(CH_3)$=CHCHO, which was condensed with the previously mentioned ylid to give the ketone precursor to **13**.

The reaction of MeMgBr with 4,4′-dichlorobenzophenone, followed by dehydration, gave 1,1-bis(4-chlorophenyl)ethylene.[12] This compound was acylated with 4-chlorobenzoyl chloride to yield the ketonic precursor of **10**.

Experimental Section[13]

4-Chlorobenzoyltriphenylphosphonium Methylide.[14]—A mixture of 2.6 g (10 mmoles) of Ph_3P and 2.3 g (10 mmoles) of 4-chlorophenacyl bromide in xylene was boiled for 1 hr and cooled. The precipitated 4-chlorophenacyltriphenylphosphonium bromide (4.15 g, 85%) was collected, washed with Et_2O, and stirred for 24 hr with excess 10% aq Na_2CO_3. During this time, although soln did not occur, the salt was converted into the methylide. The crude product was collected, washed with H_2O, dried, and recrystd from xylene to give 1.95 g (47%) of product.

TABLE II
ALDEHYDE GUANYLHYDRAZONES
ArCH=NNHC(NH)NH_2

No.	Ar	Yield, %	Mp, °C	Formula[a]
14	9-Anthryl·HCl	92	202–210	$C_{16}H_{14}N_4$·HCl
15	1-Pyrenyl·HCl·H_2O	81	257–260	$C_{18}H_{14}N_4$·HCl·H_2O
16	9-Phenanthryl·HCl	86	274–279	$C_{16}H_{14}N_4$·HCl

[a] All compds were analyzed for C, H, N.

1,5,5-Tris(4-chlorophenyl)penta-2,4-dien-1-one (11).—A soln of 4.1 g (10 mmoles) of 4-chlorobenzoyltriphenylphosphonium methylide and 2.7 g (10 mmoles) of 3,3-bis(4-chlorophenyl)-acrolein[11] in THF was refluxed under N_2 for 3 days. The solvent was removed *in vacuo* and the dark, yellow-brown residue was dissolved in $CHCl_3$. The $CHCl_3$ soln was poured through a short column of silica gel and the yellow product in the eluate was recrystd from Et_2O–petroleum ether; yield, 2.0 g (50%). The analytical sample, mp 128–130°, was obtained by preparative tlc and recrystd from petroleum ether (bp 30–60°).

1,5,5-Tris(4-chlorophenyl)penta-2,4-dien-1-one Guanylhydrazone·HCl (12, General Method).—To a mixture of 1.25 ml of concd HCl (0.014 mole) and 16 ml of H_2O was added slowly 1.36 g (10 mmoles) of aminoguanidine·HCO_3. When CO_2 evoln was complete, 4.3 g (10 mmoles) of 1,5,5-tris(4-chlorophenyl)penta-2,4-dien-1-one was added in 75 ml of EtOH. The inhomogeneous mixture was refluxed overnight. The resulting soln was concd and the residue was triturated with Et_2O. The insol residue (1.36 g, mp 235–241°) was recrystd once from EtOH–H_2O to give the analytical sample, mp 257–259°.

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An isomer with a lower melting point pptd from the Et_2O filtrate (283 mg, mp 197–202°). *Anal.* both isomers ($C_{24}H_{19}Cl_3N_4 \cdot HCl$), C,H,N.

3-(4-Chlorophenyl)crotonaldehyde.—This experiment follows the general procedure of Schmidle and Barnett.[15] $POCl_3$ (7.7 g, 0.050 mole) was added dropwise to 14.6 g (0.020 mole) of ice-cooled DMF at a rate that did not permit the temp of the mixture to rise above 20°. To this was added 7.6 g (0.05 mole) of α-methyl-*p*-chlorostyrene (freshly distilled). The temp of the mixture was raised slowly to 80°. After 1 hr at 80°, the mixture was cooled and 30 g of NaOAc, in a minimum amount of H_2O was added. Stirring was contd for 15 min and the mixture was reheated to 80° for 15 min. After chilling, the crude product was extd from the dark reaction mixture with Et_2O. Purification was effected by chromatography over silica gel, using $CHCl_3$ elution. The yield of yellow, oily product was 2.0 g (22%). It was not characterized beyond a favorable ir spectrum.

1,5-Bis(4-chlorophenyl)hexa-2,4-dien-1-one.—A mixture of 2.0 g (11 mmoles) of 3-(4-chlorophenyl)crotonaldehyde and 4.6 g (11 mmoles) of 4-chlorobenzoyltriphenylphosphonium methylide in dioxane was refluxed under N_2 for 12 hr. The solvent was removed *in vacuo* and the residue, in $CHCl_3$ soln, was chromatographed over silica gel. A dark orange, oily substance, probably another geometrical isomer (ir spectrum), preceded the yellow, cryst product from the column; yield, 0.5 g (14%). An anal. sample, mp 110–113°, was obtained by prep tlc and subsequently recrystd from petroleum ether. *Anal.* ($C_{18}H_{14}Cl_2O$) C, H.

1,1,3-Tris(4-chlorophenyl)-1-propen-3-one.—This procedure is a modification of the general method of Bergmann, *et al.*[16] A soln of 17 g (0.0683 mole) of 1,1-bis(chlorophenyl)ethylene and 13.1 g (0.0751 mole) of 4-chlorobenzoyl chloride was heated to 240°. At this temp HCl was evolved. The acid was swept from the flask by a slow stream of N_2 gas and monitored by bubbling through a NaOH soln (phenolphthalein). After about 18 hr, acid evolution had ceased. The resulting black, solid reaction mixture was extd with EtOH several times and the extracts were filtered. The solvent was removed from the combined filtrate and the residue was chromatographed on silica gel. Elution with CCl_4 yielded starting materials and by-products. Elution with $CHCl_3$ then gave 5.15 g of moderately pure product, which was recrystd several times with EtOH to yield 2.0 g of pure product, mp 135–140°. *Anal.* ($C_{21}H_{13}Cl_3O$) C, H.

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Antispasmodic Agents. 1. Syntheses and Pharmacological Activity of Aminoalkyl 3-Substituted Phenylacetates

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Received May 19, 1970

The pronounced pharmacological activities of atropine, scopolamine, and other aminoalkyl phenylacetate esters have stimulated the preparation and evaluation of numerous analogs of such compounds for their antispasmodic properties. Although molecular modifications of atropine and scopolamine have been prepared in the hope of improving pharmacological properties of the drugs, most of them are toxic and have side effects such as mydriasis, thirst, and flushing of cheeks. Since few studies[1,2] on the syntheses of aminoalkyl phenylacetates with substituents in the benzene ring have been reported, we synthesized 48 analogs with substituents such as OH, AcO, and MeO at the 3 position in order to examine the effects of substitution in the benzene ring for antispasmodic activities *in vitro*.

The 3-substituted phenylacetic acids were prepared by alkaline hydrolysis of the substituted phenylacetonitriles. Among these acids, VIII[3] and XIII,[4] respectively, were identical with authentic samples. The nitriles were prepared in good yield by the benzyne reaction[5a,b] between 2-chloroanisole (II) and the required nitrile in the presence of $NaNH_2$ in liquid NH_3. α-*sec*-Butyl-3-hydroxyphenylacetic acid(XV) was synthesized by the condensation of 3-methoxyphenylacetonitrile (VII) with *sec*-BuBr in the presence of $NaNH_2$, followed by hydrolysis with methanolic KOH. On the usual work-up of VII with acid or alkali, only starting material was recovered. O-Methylation of XV with Me_2SO_4 afforded XII. These 3-substituted phenylacetic acids were converted into the corresponding aminoalkyl esters as follows; (A) condensation of carboxylic acids with aminoalkyl halide with the use of NaOEt; (B) condensation of acid chlorides (XVI) with aminoalkylcarbinol; and (C) condensation of haloalkyl ester (XVII), prepared from XVI, with secondary amines. Compounds **47** and **48** were acetylated with Ac_2O to give the corresponding *O*-acetates. The 3-OH compounds were converted into the 3-OCH_3 derivatives by CH_2N_2.

Pharmacology.—Table I gives the results of screening for antispasmodic and anticholinergic activities. The compounds were tested by the Magnus guinea pig ileum screen.[6] Although all the compounds were inferior to atropine sulfate in anticholinergic activity, almost half of them showed a stronger antispasmodic effect than papaverine hydrochloride. Among them, three compounds, **7**, **13**, and **30** were 10 times more effective than papaverine · HCl.

Experimental Section[7]

3-Methoxyphenylacetonitriles. General Procedure.—To a stirred solution of $NaNH_2$ (prepared from 3 moles of Na in 1.5 l. of liq NH_3 with $FeCl_3$) was added carefully 1.7–1.8 moles of nitrile within 5–10 min, and 0.8 mole of 2-chloroanisole was then added rapidly. After the mixture had been stirred for another 1.5 hr, excess $NaNH_2$ was decompd by addn of 100–120 g of NH_4Cl. The resultant mixture was poured into H_2O and extracted (PhH). The extract was evapd to give a brown oil, which was dissolved *in vacuo* to afford the corresponding phenylacetonitrile. Yields and physical constants of the compds prepared are shown in Table II.

α-*sec*-Butyl-3-methoxyphenylacetonitrile (VII).—A stirred mixture of 17 g of 3-methoxyphenylacetonitrile (III) and 5.4 g of

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