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Aminoalkyldibenzo[*a*,*e*]cyclopropa[*c*]cycloheptene Derivatives. A Series of Potent Antidepressants

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G. D. Searle and Company, Chicago, Illinois. *Received June 11, 1973*

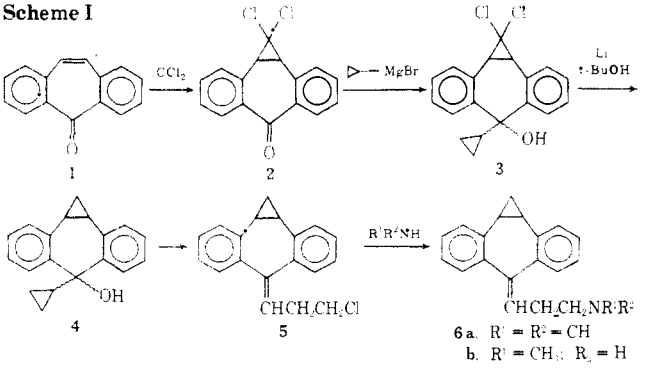
A new series of antidepressants, aminoalkyldibenzo[*a*,*e*]cyclopropa[*c*]cycloheptenes, has been synthesized and evaluated. One member of the series, **6b**, represents one of the most potent antidepressants reported to date.

The need for new antidepressants has existed since it became apparent with clinical experience that imipramine and amitryptyline lacked a quick onset of action and also possessed troublesome side effects. We felt that molecular modification in this area could lead to compounds with greater potency and minimal peripheral activity, properties that should lead to improvements over existing therapy. For example, anticholinergic activity has been related to a sedative component in known antidepressants, a limiting side effect in many instances.[1]

Most of the currently available antidepressants are based on a tricyclic nucleus in which the two aromatic rings are forced out of plane by the central connecting links. One modification which has not been reported is the fusion of a cyclopropyl ring to the dibenzocycloheptene system as in **6** to give a more rigid system. Although this was expected to change the chemical and pharmacological properties of this molecule, a surprising magnitude of difference was recognized early in the failure of this system to react similarly to the tricyclics. For example, tertiary alcohols formed from Grignard reactions on the ketone intermediates **2** and **8** were very resistant to dehydration, probably due to the ring strain existing in the tetracyclic system. Other chemical conversions similarly required forcing conditions. After this work was underway, the key cyclopropyl ketone intermediate **8** was reported,[2] although the synthetic sequence was not as useful as the sequence already discovered in our laboratory and reported here.[3]

Chemistry. The major route used to prepare the 5-aminoalkylidene compounds is outlined in Scheme I. Introduction of the cyclopropane ring was most efficiently accomplished by reaction of dichlorocarbene (generated from sodium methoxide and ethyl trichloroacetate) with dibenzo[*a*,*d*]-5*H*-cyclohepten-5-one **1** at 0–5° in benzene. Some of the other routes examined included Zn/Cu-CH_2I_2, CH_2N_2, and Et_2Zn-CH_2I_2 on either the free or protected ketones. The dichlorocarbene reaction gave the best results. The dichlorocyclopropane product **2** proved to be a key intermediate for subsequent conversions to the desired materials. It was stable to strong acid conditions and reacted smoothly with Grignard reagents to give good yields of aminoalkyl- or alkylcarbinols. No interaction of the Grignards with the cyclopropyl halogens was observed. Reaction of **2** with cyclopropylmagnesium bromide gave the cyclopropylcarbinol **3** which was dechlorinated with Li-*t*-BuOH to give a high yield of **4**. A variety of reducing reagents and conditions was tried for dechlorination [*e.g.*, $(n\text{-Bu})_3SnH$, $Zn(H^+)$, H_2/catalyst]; all were less desirable than the procedure reported here. Rearrangement of the cyclopropylcarbinol **4** in HCl-HOAc gave the chloropropylidene intermediate **5**. Under these conditions the fused cyclopropyl ring remained intact. Amination of the chloropropylidene **5** with a variety of amines gave the final products **6**.

Scheme I



6a, $R^1 = R^2 = CH_3$
b, $R^1 = CH_3$; $R^2 = H$

Alternate routes to these compounds as well as to the dichloro analogs are described in Scheme II. Preparation of the parent ketone **8** of this series was best accomplished by Li-*t*-BuOH reduction of the alcohol **7** followed by reoxidation. Ketone **8** reacted smoothly with Grignard reagents to give the alcohols **9**. A number of attempts to dehydrate **9** were unsuccessful, either leading to no reac-

† This paper is dedicated to my former professor and advisor, Dr. Alfred Burger.

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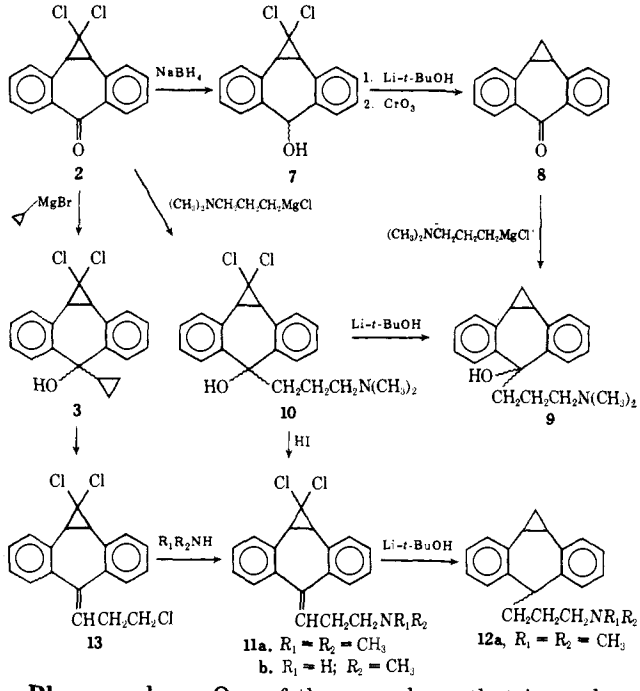
tion or decomposition. The amino alcohols **10** derived directly from the dichlorocyclopropyl ketone **2** were similarly unreactive; *e.g.*, refluxing Ac_2O gave the acetate ester and not the olefin. Dehydration to **11** was successful in refluxing HI–HOAc. No decomposition of the dichlorocyclopropyl function was observed under a wide variety of reaction conditions, thus indicating the utility of this group as a "protected" cyclopropyl function. Li-*t*-BuOH dechlorination of **11** resulted in concomitant reduction of the alkene to give the aminopropyl compounds **12.** No attempt was made to determine the syn-anti stereochemistry of the intermediates (*e.g.*, **3**, **9**, **10**) since the final products (*e.g.*, **6**) prepared from these intermediates lacked this stereochemical feature.

Scheme II



Pharmacology. One of the procedures that is used extensively for the pharmacologic evaluation of potential or new antidepressant drugs is the effect of these agents in antagonizing the actions of reserpine in mice. The reserpine model of depression has gained wide acceptance because of the similarities of the symptoms seen in reserpine-treated mice and the depression seen in man.

The method used in evaluating **6a**, **6b**, and **12a** was similar to that described by Lapin.[4] Groups of ten male HAM/ICR mice (Charles River) weighing 24–28 g were placed in separate holding cages at 8:00–8:30 A.M. Thirty minutes later the mice were admininstered either saline (control), protriptyline (reference standard), or the test compound. Three hours after this treatment each mouse was removed from the holding cage and the rectal temperature was measured to the nearest 0.1° using a Yellow Springs telethermometer. Each mouse was then injected intraperitoneally with 5.0 mg/kg of reserpine. Rectal temperatures were then recorded hourly for the next 4 hr. The decreased body temperature caused by reserpine was compared for the control group and the test compound by means of a Student's t test.

Results

Protriptyline was chosen as the reference standard because it was the most potent tricyclic tested on a milligram per kilogram basis for reversing the hypothermia in mice caused by reserpine. The results of **6a**, **6b**, and **12a** (as the phosphate salts) for both ip and ig administration are summarized in Table I.

Table I. Minimally Effective Dose (in mg/kg) of a Drug Reversing Reserpine-Induced Hypothermia in Mice

Route of admin	Protriptyline	**6b** (SC 27123)	**12a** (SC 28025)	**6a** (SC 27741)
ig	0.25	0.0005	2.0	0.5
ip	0.025	0.025	0.025	0.025

The unusually high oral activity (ig) of **6b** has been confirmed several times in this assay and in a number of additional antidepressant models. In all cases, oral activity is higher than by the intraperitoneal route. Additional studies will be necessary to determine an explanation for these effects. Based on the bioassay presented, **6b** represents one of the most potent antidepressants reported to date.

In general, the structure–activity relationships for this series appear similar to those of known antidepressant series. Small alkyl groups on the amino function give the most desirable activity with the monomethyl compound the most potent. The fusion of the cyclopropyl ring to the tricyclic system serves to "lock" the conformation of the molecule, allowing more efficient receptor fit and thus increased potency.

Experimental Section

Melting points were taken on a Thomas-Hoover apparatus and are uncorrected. The structures of all novel compounds were confirmed by nmr and ir. Where analyses are indicated by symbols of the elements, the analytical results were within ±0.4% of the theoretical values.

1,1-Dichloro-1,1a,6,10b-tetrahydrodibenzo[*a,e*]cyclopropa[*c*]cycloheptene-6-one (2). To a stirred solution at 0–5° of 60 g (0.29 mol) of dibenzo[*a,d*]-5*H*-cycloheptene-5-one in 1 l. of benzene and 200 ml of petroleum ether was added 60 g (0.1 mol) of sodium methoxide followed by the dropwise addition of 200 g (0.1 mol) of ethyl trichloroacetate over a period of 1 hr. The suspension was stirred at 0–5° for 5 hr and then allowed to come to room temperature. H_2O (200 ml) was added and the benzene layer was separated, washed with H_2O, and dried over $MgSO_4$. Evaporation of the benzene gave an oil which on crystallization from EtOH yielded 52.0 g (62%) of colorless crystals, mp 129–131°. An analytical sample had mp 131–133°. *Anal.* ($C_{16}H_{10}Cl_2O$) C, H, Cl.

6-Cyclopropyl-1,1-dichloro-1,1a,6,10b-tetrahydrodibenzo[*a,e*]cyclopropa[*c*]cycloheptene-6-ol (3). To 2.43 g of Mg (0.1 g-atom) in 25 ml of THF (distilled from $LiAlH_4$) was added dropwise 13.3 g (0.11 mol) of cyclopropyl bromide in 25 ml of THF. The reaction started spontaneously and the addition was maintained at a sufficient rate to maintain reflux. The solution was then refluxed 2 hr and cooled slightly and 18.9 g (0.065 mol) of **2** was added in 200 ml of THF. After refluxing 15 min, the reaction was poured into excess H_2O containing 20 g of NH_4Cl and extracted with ether. The ether extracts were washed with H_2O and dried over $MgSO_4$. Evaporation of the ether gave a yellow oil which was chromatographed on silica. The product was eluted with 30% petroleum ether–benzene and crystallized from EtOH to give 15.4 g (77% yield) of white crystals, mp 140–143°. *Anal.* ($C_{19}H_{16}Cl_2O$) C, H.

6-Cyclopropyl-6-hydroxy-1,1a,6,10b-tetrahydrodibenzo[*a,e*]cyclopropa[*c*]cycloheptene (4). Method A. To cyclopropylmagnesium bromide [prepared from 8 g (0.067 mol) of cyclopropyl bromide and 1.4 g of Mg (0.058 g-atom) in 50 ml of THF as before] was added 6.3 g (0.029 mol) of 1,1a,6,10b-tetrahydrodibenzo[*a,e*]cyclopropa[*c*]cyclohepten-6-one (**8**) in 100 ml of THF at a temperature just below reflux. After refluxing 1 hr, the reaction was poured into excess H_2O containing 7 g of NH_4Cl. Extraction with ether, drying over $MgSO_4$, and evaporation yielded a yellow oil. This oil was chromatographed on a 1-in. dry column using 350 g of silica gel containing 8% H_2O. The desired product was eluted with benzene in fractions 2–6 (using 50-ml fractions). Evaporation of the benzene gave a colorless oil (5.0 g, 66% yield). *Anal.* ($C_{19}H_{18}O$) C, H.

Method B. To a stirred solution, under N_2, of 8.8 g of **3** (0.027 mol) in 50 ml of THF was added 0.615 g (0.027 mol) of $LiNH_2$. After stirring 0.5 hr, 3 g of *t*-BuOH was added, followed by 2 g of

Li wire (cut in small pieces) over a period of 1 hr. After an additional 1 hr of stirring, the excess Li was decomposed by careful addition of H_2O. The resulting mixture was extracted with ether; the extracts were washed with H_2O and dried over $MgSO_4$. Evaporation of the ether gave a colorless oil (6 g, 85% yield). The nmr spectrum of this oil was identical with that of the product obtained in the previous reaction.

6-(3-Chloropropylidene)-1,1a,6,10b-tetrahydrodibenzo[a,e]cyclopropa[c]cycloheptene (5). A solution of 0.5 g (0.002 mol) of 4 in 5 ml of acetic acid containing 10 drops of concentrated HCl was stirred at room temperature and then refluxed 1 hr. On cooling, crystals appeared (0.3 g, 50% yield). Recrystallization from ethanol gave the analytical sample, mp 148–149°. *Anal.* ($C_{19}H_{17}Cl$) C, H, Cl. The mass spectrum shows mol wt 280 for this compound.

6-(3-Dimethylaminopropylidene)-1,1a,6,10b-tetrahydrodibenzo[a,e]cyclopropa[c]cycloheptene Oxalate (6a). A solution of 2.7 g (0.01 mol) of **5** in 30 ml of benzene containing 50 ml of dimethylamine was heated at 100° for 19 hr. The solvents were evaporated, water and NH_4OH were added, and the mixture was extracted with ether. The ether extracts were dried over K_2CO_3 and evaporated to give an amber oil. The oxalate, from EtOH, yielded 3.0 g (80%) of yellowish white crystals, mp 194–195°. The analytical sample had mp 195–197°. *Anal.* ($C_{23}H_{25}NO_4$) C, H, N.

6-(3-Methylaminopropylidene)-1,1a,6,10b-tetrahydrodibenzo[a,e]cyclopropa[c]cycloheptene Oxalate (6b). Under the conditions above, 1.45 g (0.005 mol) of **5** was allowed to react with 50 ml of methylamine in 30 ml of benzene to give the product, isolated as the oxalate, mp 203–205° (0.9 g, 50% yield). *Anal.* ($C_{22}H_{23}NO_4$) C, H, N.

1,1-Dichloro-1,1a,6,10b-tetrahydrodibenzo[a,e]cyclopropa[c]cyclohepten-6-ol (7). To a stirred suspension of 10.0 g (0.035 mol) of **2** in 300 ml of MeOH was added 3.0 g (0.08 mol) of $NaBH_4$. After stirring 15 min at 25°, the solution was refluxed 2 hr and poured into 1 l. of H_2O containing 25 ml of concentrated HCl. Filtration of the solid, washing with water, and air drying yielded 10.0 g (97%) of white crystals, mp 164–168°. *Anal.* ($C_{16}H_{12}Cl_2O$) C, H, Cl.

1,1a,6,10b-tetrahydrodibenzo[a,e]cyclopropa[c]cyclohepten-6-ol. To a stirred solution of 30 g (0.1 mol) of **7** in 300 ml of THF was added 2.55 g (0.11 mol) of $LiNH_2$ and the suspension was stirred for 0.5 hr. Concomitant addition of *t*-BuOH (9 g) and Li wire (12 g, cut in small pieces) was carried out. Reaction began after 6 g of *t*-BuOH and 6 g of Li wire had been added and the remaining reagents were added to make the total addition time approximately 1.5 hr. The reaction was cooled periodically to keep the temperature below reflux. After addition, the reaction was stirred 1 hr and then the excess Li was decomposed by slow and careful addition of H_2O. The mixture was diluted with H_2O and extracted with ether; the ether extracts were washed with water and dried over $MgSO_4$. Evaporation of the ether gave a solid which was recrystallized from EtOH. Two crops were obtained: 9.0 g of white crystals, mp 142–152°, and 8.7 g of amber crystals, mp 123–133° (from EtOH–H_2O) (total yield 80%). These were used in the next step without further purification.

1,1a,6,10b-Tetrahydrodibenzo[a,e]cyclopropa[c]cyclohepten-6-one (8). To a stirred solution of 8.8 g (0.04 mol) of 1,1a,6,10b-tetrahydrodibenzo[a,e]cyclopropa[c]cyclohepten-6-ol in 20 ml of acetone was added 14 ml of Jones reagent dropwise. The reaction mixture was stirred an additional 15 min, poured into H_2O, and extracted with ether. The ether extracts were washed well with H_2O, dried over $MgSO_4$, and evaporated to give light yellow crystals. Recrystallization from EtOH gave 6.4 g (75%) of white crystals, mp 79–82°. *Anal.* ($C_{10}H_{12}O$) C, H.

6-(3-Chloropropylidene)-1,1-dichloro-1,1a,6,10b-tetrahydrodibenzo[a,e]cyclopropa[c]cycloheptene (13). A solution of 14.25 g (0.043 mol) of **3** in 200 ml of acetic acid containing 25 ml of concentrated HCl was stirred at room temperature for 1 hr and then refluxed 1.5 hr. The solvents were evaporated; toluene was added and removed *in vacuo* leaving a light yellow oil. Trituration with a minimum amount of EtOH and filtration yielded 14.7 g (98%) of white crystals, mp 97.5–98.5°. *Anal.* ($C_{19}H_{15}Cl_3$) C, H, N.

6-(3-Methylaminopropylidene)-1,1-dichloro-1,1a,6,10b-tetrahydrodibenzo[a,e]cyclopropa[c]cycloheptene (11b). A solution of 3.1 g (0.01 mol) of **13** and 50 ml of methylamine in 50 ml of benzene was heated at 95° in a pressure reactor for 18 hr. The cooled solution was washed with H_2O; the benzene layer was dried over K_2CO_3 and evaporated to give a yellow oil. The oxalate was isolated and recrystallized from EtOH to give 1.9 g (44% yield) of white crystals, mp 209–215°. *Anal.* ($C_{22}H_{21}Cl_2NO_4$) C, H, N.

6-(3-Dimethylaminopropyl)-6-hydroxy-1,1a,6,10b-tetrahydrodibenzo[a,e]cyclopropa[c]cycloheptene (9). To a stirred solution of 3.76 g (0.01 mol) of **10** in 30 ml of THF under N_2 was added 0.230 g (0.01 mol) of $LiNH_2$. The suspension was stirred 0.5 hr at room temperature and 1.1 g (0.015 mol) of *t*-BuOH was added, followed by 2 g of Li wire (cut in small pieces) over a period of 1 hr. An exothermic, easily controllable, reaction resulted which subsided by the end of the addition. After an additional 1 hr, the excess Li was decomposed by careful addition of H_2O. It was then diluted with H_2O and extracted with ether and the ether extracts were dried over K_2CO_3. Evaporation of the ether gave a yellow solid which on recrystallization from EtOH yielded 1.7 g (55%) of colorless crystals, mp 130–135°. *Anal.* ($C_{21}H_{25}NO$)C, H, N.

6-(3-Dimethylaminopropyl)-1,1a,6,10b-tetrahydrodibenzo[a,e]cyclopropa[c]cycloheptene (12a). To a stirred solution of 7.3 g (0.016 mol) of **11a** in 60 ml of THF was added 0.46 g (0.02 mol) of $LiNH_2$ and the suspension was stirred 1 hr. Addition of 3 g of *t*-BuOH followed by 4.0 g of Li wire (cut in small pieces) over a period of 1 hr caused an exothermic reaction. The mixture was stirred an additional hour and decomposed by careful addition of H_2O. The mixture was diluted with H_2O and the organic layer separated. The aqueous layer was extracted with ether and the combined organic extracts were dried over K_2CO_3. Evaporation yielded a dark oil containing some EtOH-insoluble material which was separated and discarded. The remaining oil (2.5 g) was chromatographed on alumina and the peak fractions (eluted with 5% EtOAc–C_6H_6) were collected. Addition of oxalic acid in ethanol to a 0.5-g fraction (major fraction) and dilution with Et_2O gave the oxalate (0.2 g, 3%), mp 165–170°. Recrystallization from EtOH gave white crystals, mp 175–178°. This was identified as the 6-aminopropyl compound as opposed to the 6-aminopropylidene compound by comparison of the uv spectra with standard compounds. *Anal.* ($C_{23}H_{27}NO_4$) C, H, N.

1,1-Dichloro-6-(3-dimethylaminopropyl)-1,1a,6,10b-tetrahydrodibenzo[a,e]cyclopropa[c]cyclohepten-6-ol (10). To 2.43 g (0.1 g-atom) of Mg in a dry flask with stirring was added 10 ml of THF, 0.5 ml of ethyl bromide, and a crystal of iodine, followed by 15 g (0.14 mol) of freshly distilled 3-dimethylaminopropyl chloride in 20 ml of THF dropwise. To the resulting Grignard was added 10.0 g (0.034 mol) of **2** in 100 ml of THF dropwise. After addition, the solution was refluxed 2 hr and poured into 500 ml of H_2O containing 20 g of NH_4Cl. The solid was filtered, washed with H_2O, and recrystallized from EtOH to yield 7.2 g (56%) of white crystals, mp 170–171°. *Anal.* ($C_{21}H_{23}Cl_2NO$) C, H, N, Cl.

6-Acetoxy-1,1-dichloro-6-(3-dimethylaminopropyl)-1,1a,6,10b-tetrahydrodibenzo[a,e]cyclopropa[c]cycloheptene Oxalate. A solution of 1.0 g (0.003 mol) of **10** in 20 ml of Ac_2O was refluxed 4 hr. The Ac_2O was removed *in vacuo*; the residue was treated with H_2O and made basic with K_2CO_3. The resulting mixture was extracted with ether; the ether extracts were washed with H_2O, dried over K_2CO_3, and evaporated to give a light yellow oil. The oxalate salt was prepared as white crystals (1.0 g, 79%), mp 234–240°. *Anal.* ($C_{25}H_{27}Cl_2NO_6$) C, H, N.

6-Acetoxy-6-(3-dimethylaminopropyl)-1,1a,6,10b-dibenzo[a,e]cyclopropa[c]cycloheptene Oxalate. A solution of 500 mg (0.0016 mol) of **9** in 10 ml of Ac_2O was relfuxed for 3 hr. The Ac_2O was removed *in vacuo* and the residue was triturated with aqueous K_2CO_3 and ether. The ether layer was separated, dried over K_2CO_3, and evaporated to give a light amber oil. The oxalate salt (300 mg, 44% yield) had mp 147–153°. Recrystallization from EtOH gave the analytical sample, mp 150–153°. *Anal.* ($C_{25}H_{28}NO_6$) C, H, N.

6-(3-Dimethylaminopropyl)-1,1a,6,10b-tetrahydro[a,e]cyclopropa[c]cyclohepten-6-ol (9). To a stirred solution of 3-dimethylaminopropylmagnesium chloride [prepared as before from 0.243 g (0.01 g-atom) of Mg and 2 g (0.018 mol) of 3-dimethylaminopropyl chloride in 30 ml of THF] was added 1.15 g (0.005 mol) of **8** in 20 ml of THF. The green solution turned colorless after 0.5 hr of reflux. After 2 hr of reflux the reaction was poured into excess H_2O containing 5 g of NH_4Cl and extracted with ether. The ether extracts were washed with H_2O, dried over K_2CO_3, and evaporated to give white crystals. After recrystallization from EtOH–petroleum ether, 1.15 g (74% yield) of white crystals, mp 134–136°, was isolated. *Anal.* ($C_{21}H_{25}NO$) C, H, N.

6-(3-Dimethylaminopropylidene)-1,1-dichloro-1,1a,6,10b-tetrahydrodibenzo[a,e]cyclopropa[c]cycloheptene Oxalate (11a). A solution of 1.0 g (0.0027 mol) of **10** in 4 ml of 47% HI, 5 ml of HOAc, and 1 ml of concentrated HCl was refluxed 2 hr. The reaction was poured into an aqueous K_2CO_3 solution and extracted with ether; the ether extracts were washed with H_2O and dried over K_2CO_3. Evaporation of the ether gave a colorless oil which was dissolved in EtOH and treated with an ethanolic solution of

oxalic acid to give the oxalate, mp 164–168°. The analytical sample from EtOH had mp 166–176°. *Anal.* ($C_{23}H_{23}Cl_2NO_4$) C, H, N.

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Synthesis and Antimalarial Effects of 1-(3,4-Dichlorophenyl)-3-[4-[(1-ethyl-3-piperidyl)amino]-6-methyl-2-pyrimidinyl]guanidine and Related Substances†,‡

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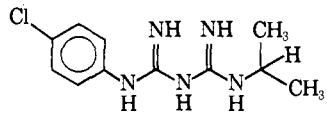
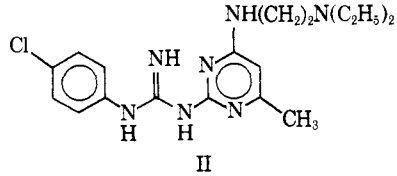
One hundred and twenty-one 1-aryl-3-[4-[[(mono- and dialkylamino)alkyl]amino]-6-methyl-2-pyrimidinyl]guanidines (VIII) were synthesized by the condensation of the requisite 1-(4-chloro-6-methyl-2-pyrimidinyl)-3-arylguanidine (VII) with the appropriate polyamine in EtOH, HOAc, or C_6H_5Cl in the presence of NaOH. The 1-(4-hydroxy-6-methyl-2-pyrimidinyl)-3-arylguanidine precursors (VI), prepared by the condensation of a substituted aniline with 2-(cyanoamino)-4-hydroxy-6-methylpyrimidine (V) or *via* an arylbiguanide (IV) and a β-keto ester, were readily converted to the chloropyrimidines VII utilizing $POCl_3$. Ninety of the new pyrimidinylguanidines possessed "curative" activity against *Plasmodium berghei* at single subcutaneous doses ranging from 20 to 640 mg/kg, and nearly all of them were less toxic for mice than the reference drug 1-(*p*-chlorophenyl)-3-[[[2-(diethylamino)ethyl]amino]-6-methyl-2-pyrimidinyl]guanidine (II). Orally, 62 compounds exhibited suppressive activity against *P. berghei* comparable with or superior to II, while 46 of them were 2 to 30 times as potent as quinine hydrochloride. Fifty-nine compounds also displayed strong suppressive activity against *P. gallinaceum* in chicks, 17 of which "cured" chicks at single subcutaneous doses of 60–320 mg/kg. One of the more promising compounds, 1-(3,4-dichlorophenyl)-3-[4-[(1-ethyl-3-piperidyl)amino]-6-methyl-2-pyrimidinyl]guanidine (**61**), possessed strong activity against cycloguanil- and DDS-resistant lines of *P. berghei* and was designated for preclinical toxicological studies and clinical trial. Structure-activity relationships are discussed.

During the evolutionary process that led to the development of chlorguanide (I),[2,3] it was discovered that various 1-phenyl-3-(4-amino-2-pyrimidinyl)guanidines possessed strong antimalarial effects against *Plasmodium gallinaceum* in chicks.[4] One of the most potent members of the



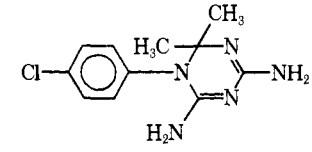
I

series, namely 1-(*p*-chlorophenyl-3-[4-[[2-(diethylamino)ethyl]amino]-6-methyl-2-pyrimidinyl]guanidine (II),[4,5] proved to be roughly equivalent to quinacrine in antimalarial potency and toxicity and was therefore selected for expanded chemotherapeutic studies and clinical trial.[6]



II

Compound II was subsequently shown to be effective against *P. cathemerium* and *P. relictum* in canaries,[6] *P. knowlesi* in rhesus monkeys,[7] and *P. falciparum*, *P. vivax*, *P. malariae*, and *P. ovale* in man.[6,8-11] However, this drug and related pyrimidinylguanidine derivatives were not pursued further with the advent of chlorguanide and its active metabolite, cycloguanil (III).



III

Curd, Davey, and Rose advanced the working hypothesis that the antimalarial activity of chlorguanide and its precursors might be associated with the linking of an aryl group and the amidine moiety $-N{=}C{-}N{=}C{-}NHR_1$ through groupings capable of prototropic change.[12] Since this structural feature is common to all the compounds that exhibited activity, whether pyrimidines of the type II or biguanides of type I, it was reasonable to postulate that the ultimate mechanism of parasiticidal action should be shared by all these compounds. It was, therefore, tacitly assumed that strains of malarial parasites that are resistant to chlorguanide (I) would also be cross-resistant to the pyrimidinylguanidine II and related substances. Subsequent studies demonstrated conclusively that this is not the case. Thus, no cross resistance was observed when II was tested against a strain of *P. gallinaceum* that was resistant (20–40-fold) to chlorguanide,[13,14] a strain of *P. berghei* that was resistant (100-fold) to sulfadiazine and cross-resistant with chlorguanide,[15] and strains of *P. knowlesi* that were resistant to chlorguanide (2400-fold)[7] and pyrimethamine (>2 × 10^6-fold).[16] Furthermore, when a normal drug-sensitive strain of *P. gallinaceum* was subjected for nearly 2.5 years to intensive treatment with II, no drug resistance was acquired.[13,14]

When confronted in 1965 with the challenge of devel-

†This is communication 35 of a series on antimalarial drugs. For paper 34, see ref 1.

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§This paper is dedicated in tribute to Professor Alfred Burger—esteemed teacher, scientist, editor, and friend.