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Notes

Antihypertensive Activity of 1-Dimethylphosphinylmethyl-4-arylpiperazines

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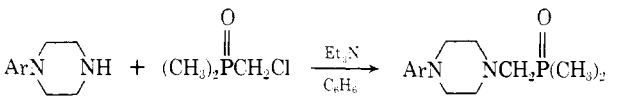
1-Alkyl-4-phenylpiperazines have been shown to possess potent antihypertensive activity.[1] Our interest in phosphorus-containing molecules with pharmacological activity[2] has prompted the preparation of a series of arylpiperazines bearing an *N*-dimethylphosphinylmethyl moiety [$-CH_2P(O)(CH_3)_2$] as potential antihypertensive agents.

The compounds were synthesized by the alkylation reaction shown below.

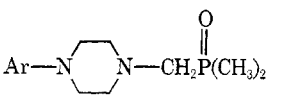


The structures and the physical and antihypertensive data for these novel 1-dimethylphosphinylmethyl-4-arylpiperazines are recorded in Table I.

Pharmacological Results. The compounds of Table I were initially screened for antihypertensive activity using spontaneous hypertensive rats (SHR) by a standard indirect tail-cuff method.[3] In a standard 3-day test, systolic blood pressure readings were made at 0 time (control) on days 1 and 3, and at 2 hr after administration of the compound on days 1 and 3. Dosing was orally at 100 mg/kg at 0 hr on days 1, 2, and 3 on groups of six animals per test. Activity was determined by comparison of the treatment blood pressure values with the 0 time (control) blood pressure readings. Comparisons were made using the paired t test method for evaluation of statistical significance.[4] A value of -15 mm or more is considered significant.

From Table I it will be seen that compounds where Ar = phenyl or substituted phenyl are active. Inserting a heteroatom in the Ar ring (2-pyridyl, compound 8) or separating the Ar group from the piperazine ring by a methylene bridge ($C_6H_5CH_2$, compound 9) abolished activity. Compounds 1, 4, and 7 showed especially marked reductions in blood pressure in the SHR screen and were there-

Table I



Compd	Ar	Yield, %[a]	Mp, °C	Recrystn solvent[b]	Formula[c]	Antihypertensive act. (Δ mm)[d] Day 1	Day 3
1	C_6H_5	79	149–151	A	$C_{13}H_{21}N_2OP$	−25	−43
2	$2\text{-}ClC_6H_4$	88	222–223 dec	B	$C_{13}H_{20}ClN_2OP \cdot HCl$	−12	−16
3	$3\text{-}ClC_6H_4$	34	108–110	C	$C_{13}H_{20}ClN_2OP$	±	±
4	$4\text{-}ClC_6H_4$	55	184–187	B	$C_{13}H_{20}ClN_2OP$	−10	−54
5	$2\text{-}CH_3C_6H_4$	77	114–117	D	$C_{14}H_{23}N_2OP$	−20	−14
6	$4\text{-}CH_3COC_6H_4$	82	170–172	A	$C_{15}H_{23}N_2O_2P$	±	±
7	$3\text{-}CF_3C_6H_4$	74	217–218 dec	E	$C_{14}H_{20}F_3N_2OP \cdot 2HCl$	−87	−66
8	$2\text{-}C_5H_4N$	61	116–120	A	$C_{12}H_{20}N_3OP$	−6	+1
9	$C_6H_5CH_2$	34	110–113	C	$C_{14}H_{23}N_2OP$	−2	+3

[a] Isolated yield of crude solid, fairly pure by melting point and tlc. [b] A = acetone, B = EtOH, C = cyclohexane, D = A + hexane, E = MeOH + Et_2O. [c] All compounds were analyzed for C, H, and N within ±0.4% of the theoretical values. [d] The experimental procedures are described in the text; ± indicates marginal or transient activity.

fore evaluated further. It should be noted that without the $-CH_2P(O)(CH_3)_2$ moiety, the starting arylpiperazines leading to **1**, **4**, and **7** when tested in the SHR model at 100 mg/kg po caused death in all animals within 5 hr, preceeded by a short period of hyperexcitability and convulsions.

A dose-response study in the SHR revealed the MED's for **1**, **4**, and **7** to be 2.5, 10, and 25 mg/kg, respectively. For comparison, guanethidine was found to have an MED of 5.0 and hydralazine of 2.5 mg/kg.

All three compounds were examined in the acute anesthetized (pentobarbital) dog and only a short transitory hypotension was observed at iv doses up to 20 mg/kg.

Thus, although these compounds were uninteresting in lowering blood pressure in acute experiments on dogs, they did show a significant hypotensive effect in spontaneous hypertensive rats.

Experimental Section

Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Microanalyses were performed by Micro-Tech Laboratories, Inc., Skokie, Ill. Spectral data (ir and nmr) of new compounds were in accord with structure.

The arylpiperazines used as starting materials were purchased from Aldrich Chemical Co., Milwaukee, Wis.

General Dimethylphosphinylmethyl Alkylation Procedure. A stirred mixture of the arylpiperazine† (0.10 mol), chloromethyldimethylphosphine oxide[5] (0.11 mol), and triethylamine (0.11 mol) as HCl acceptor in 300 ml of C_6H_6 was refluxed under N_2 for 10–24 hr. The mixture was then filtered while hot to remove precipitated $Et_3N \cdot HCl$. The filtrate was concentrated to a small volume (*ca.* 50 ml), and work-up was continued as follows.

(1) If the crystalline product separated voluminously during concentration, it was filtered, washed with C_6H_6, dried, and recrystallized from the solvent indicated in Table I (compounds **1**, **4**, and **6**).

(2) If the product was very soluble in C_6H_6, the remainder of the solvent was removed *in vacuo* to a waxy crystalline solid which was triturated with ether or hexane, filtered, dried, and recrystallized (compounds **5** and **8**). Sometimes an oil was obtained which was induced to crystallize by scratching or freezing (compounds **3** and **9**).

(3) When a residual oil could not be solidified, it was dissolved in ether or EtOH and added to a cold 5 *N* solution of ethanolic HCl. The precipitated salt was filtered, washed with ether, dried, and recrystallized (compounds **2** and **7**).

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†The arylpiperazines leading to compounds 2-4 were purchased as the mono- or dihydrochloride salts requiring an additional 1 or 2 equiv of Et_3N in the alkylation procedure in order to liberate the piperazine base *in situ*.

Antimalarials. 3. Fluorenemethanols†

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The medicinal chemistry of compounds containing the fluorene nucleus continues to be of interest. Clinical studies of tilorone [2,7-bis[2-(diethylamino)ethoxy]-9-fluorenone dihydrochloride] as a broad-spectrum antiviral agent and antitumor agent have been reviewed.[1,2] Alkylaminoalkyl esters of fluorenone-2,7-dicarboxylic acid have been reported to be potent antiviral agents and interferon inducers.[3] Quaternary nitrogen-substituted choline ester derivatives of fluorene have neuromuscular blocking activity.[4] A series of 4-(3-alkylamino-2-hydroxypropoxy)-9-fluorenones have β-adrenergic blocking and antiarrythmic activity and inhibit blood platelet aggregation.[5,6] Fluorene-2-acetic acids and analogs are potent antiinflammatory agents.[7] In the botanical field attention has been drawn to the morphactins[8,9] which are synthetic growth regulators derived from fluorene-9-carboxylic acid.

Prior to the present work 11 nonhalogenated 2-fluorenemethanols had been tested as antimalarials[10] and weak activity observed in 2 of them; it was suggested[11] that "another position for the side chain might have been more advantageous." In addition to these, 16 other derivatives of fluorene, 9-fluorenone, and 9-fluorenol (none of them an aminoalkylmethanol) were described in the Wiselogle treatise;[12] none were active.

More recently 1-, 2-, 3-, and 4-aminofluorenes and halogenated derivatives were condensed with diphenic anhydride to give 32 diphenamic acids and the related imides. Weak antimalarial activity was observed in the single case of *N*-(2-fluorenyl)diphenimide.[13]

At the time our work began it was already apparent that a nitrogen-containing ring structure was not a necessary feature for high antimalarial activity; the phenanthrenemethanols were known to be among the most active antimalarials.[14,15]

Chemistry. The synthesis routes to the compounds listed in Table I involved conversion of the carboxyl group in the appropriate fluorene- or fluorenenonecarboxylic acid to the desired di-*n*-butylaminomethylmethanol side chain by the procedure used previously.[16] The syntheses of **1**, **4**, and **7** were uncomplicated. During the synthesis of **2** $NaBH_4$ reduction of bromomethyl 9-keto-4-fluorenyl ketone gave 9-hydroxy-4-fluorenylethylene oxide, the immediate precursor of **2**. However, during the analogous synthesis of **5** the reduction of bromomethyl 2,7-dichloro-9-keto-4-fluorenyl ketone gave a mixture of oxides containing 9-keto and 9-hydroxy groups, respectively. When the 9-hydroxy oxide was separated from the mixture and characterized we attempted to convert it to **5** in the usual way but obtained impure **6**. Because of this difficulty we made **5** by the sodium borohydride reduction of the free base of **6**. The 9-keto oxide precursor of **6** was easily obtained by simply allowing the borohydride reduction of the bromomethyl ketone to proceed in the presence of air. 9-Keto-4-fluorenylethylene oxide, the precursor of **3**, was made by oxidation of the 9-hydroxy oxide by manganese dioxide.[17]

When the conventional synthesis was applied to fluorene-9-carboxylic acid we were unable to prepare the nec-

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