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Synthesis of Monoaryl- and Diarylphosphorus Analogs of Methadone

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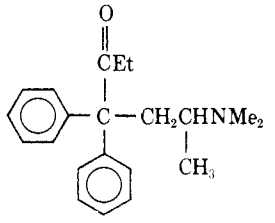
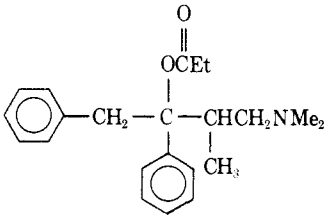
Fourteen monoarylphosphorus analogs of methadone belonging to three structural types (**4**, **5**, and **6**) were synthesized by reacting various chloroalkylamines with the appropriate phosphorus compounds. The phosphorus compounds were selected to vary the steric, electronic, and solubility properties of the final products. Ten diarylphosphorus analogs of methadone of two structural types (**7** and **8**) were synthesized in a similar manner. The success of the alkylation reaction for both series was markedly affected by the solvent system utilized. Pharmacological screening by the hot-plate and acetic acid writhing methods revealed moderate analgetic activity in some of the compounds apparently related to the lipophilicity of the molecule.

The research of Bockmuhl, Erhart, and Schaumann which produced methadone (**1**) has stimulated other researchers[1] to explore the relationship of chemical structure to pharmacological activity of various arylpropylamines. The introduction of propoxyphene (**2**) as an analgetic with low addiction liability was the result of such a systematic exploration of arylpropylamines. Recently the use of methadone (**1**) as a morphine substitute in the treatment of narcotic addiction has stimulated further interest in the exploration of arylpropylamines as analgetics.



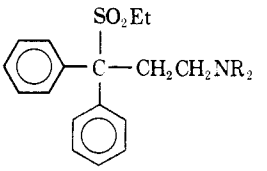
1



2

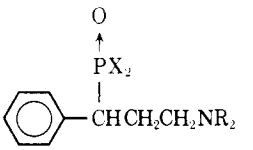
The general feature of the analgetic receptor proposed by Beckett and Casy,[2] an aromatic group with the proper orientation and distance from a basic nitrogen, encompasses the structure of most active analgetics. Methadone and meperidine both contain a polar side chain emanating from the carbon attached to the aromatic group. The function of the polar side chain remains a matter of conjecture although changes in this group can markedly affect the activity of the compound. The existance of an optimum in the chain length of the alkyl group attached to the polar side chain[3] implies a parabolic relationship between analgetic activity and solubility of the type proposed by Hansch[4] for many other types of medicinal agents. Others have explored the relationship between lipophilicity and analgetic activity.[5]

Other groups may be substituted for polar groups containing carbon. Previously, Slenk, Suter, and Archer[6] had synthesized a series of sulfones **3** related to methadone and found reasonable analgetic activity. Consequently,

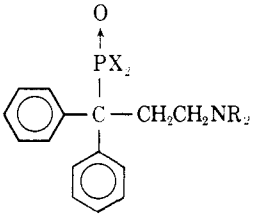


3

the authors synthesized and evaluated some phosphorus analogs of methadone of the types shown by **4**, **5**, and **6** (monarylphosphorus analogs of methadone) and **7** and **8** (diarylphosphorus analogs of methadone), each series utilizing a different phosphorus-containing group in place of



4, X = C_6H_5; NR_2 = dialkylamino
5, X = OEt; NR_2 = dialkylamino
6, X = Et; NR_2 = dialkylamino



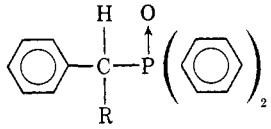
7, X = C_6H_5; NR_2 = dialkylamino
8, X = OEt; NR_2 = dialkylamino

† This paper is dedicated to my former major professor, Dr. Alfred Burger, to whom medicinal chemistry owes much.

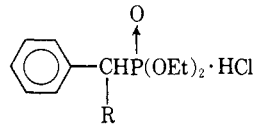
‡ Taken in part from the dissertation presented by M. S., July 1970, to the Graduate School of N. D. S. U. in partial fulfillment of the requirements for the Doctor of Philosophy Degree.

§ Taken in part from the dissertation presented by V. S. R., August 1971, to the Graduate School of N. D. S. U. in partial fulfillment of the requirements for the Master of Science Degree.

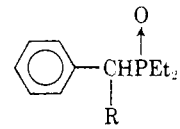
Table I. Physical Constants of Monoarylphosphorus Analogs of Methadone



A



B



C

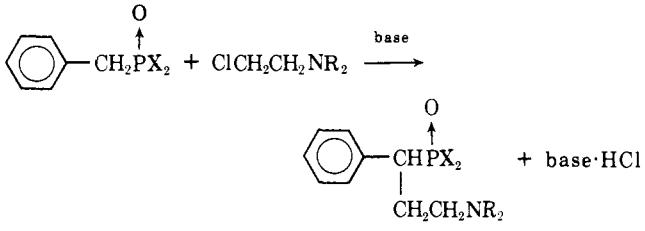
Compd no.	R	Crystn solvent	Mp, °C[a]	Yield, %	Empirical[b] formula
	1-(1-Phenyl-3-dialkylaminoalkyl)diphenylphosphine Oxides (A)				
4a	$CH_2CH_2N(Me)_2$	EtOH–H_2O	183–184	66	$C_{23}H_{26}NOP$
4b	$CH_2CH_2N(Et)_2$	EtOH–H_2O	148–150	59	$C_{25}H_{30}NOP$
4c	CH_2CH_2-c-NC_4H_8	EtOH–H_2O	201–202	83	$C_{25}H_{28}NOP$
4d	CH_2CH_2-c-NC_5H_{10}	Methylcyclohexane	187–189	66	$C_{26}H_{30}NOP$
4e	CH_2CH_2-c-$N(CH_2CH_2)_2O$	EtOH–H_2O	213–214	78	$C_{25}H_{28}NO_2P$
4f	$CHCH_3CH_2N(Me)_2$	EtOH–H_2O	202–205	48	$C_{24}H_{28}NOP$
4g	$CH_2CH_2CH_2N(Me)_2$	EtOH–H_2O	179–181	76	$C_{24}H_{28}NOP$
	Diethyl 1-(1-Phenyl-3-dialkylaminoalkyl)phosphonate Hydrochlorides (B)				
5a	$CH_2CH_2N(Me)_2 \cdot HCl$	*i*-PrOH–$(i\text{-Pr})_2O$	130–131	36	$C_{15}H_{26}NO_3P \cdot HCl$
5b	$CH_2CH_2N(Et)_2 \cdot HCl$	*i*-PrOH–$(i\text{-Pr})_2O$	120–121	30	$C_{17}H_{30}NO_2P \cdot HCl$
5c	CH_2CH_2-c-$NC_5H_{10} \cdot HCl$	*i*-PrOH–$(i\text{-Pr})_2O$	156–157	38	$C_{18}H_{30}NO_3P \cdot HCl$
5d	CH_2CH_2-c-$N(CH_2CH_2)_2O \cdot HCl$	*i*-PrOH–$(i\text{-Pr})_2O$	163–164	23	$C_{17}H_{28}NO_4P \cdot HCl$
	1-(1-Phenyl-3-dialkylaminoalkyl)diethylphosphine Oxide (C)				
6a	$CH_2CH_2NMe_2 \cdot HCl$	$CHCl_3$–EtOAc	165–166	46	$C_{15}H_{26}NOP \cdot HCl$
6b	CH_2CH_2-c-$NC_5H_{10} \cdot HCl$	*i*-PrOH–$(i\text{-Pr})_2O$	218–219	49	$C_{18}H_{30}NOP \cdot HCl$
6c	CH_2CH_2-c-$N(CH_2CH_2)_2O \cdot HCl$	*i*-PrOH–$(i\text{-Pr})_2O$	216–218	47	$C_{17}H_{28}NO_2P \cdot HCl$

[a] All melting points are uncorrected. [b] All compounds were analyzed for C, H, and N.

the propionyl group of methadone (**1**). The substituents on the phosphorus atom were varied to provide a spectrum of solubility, electronic, and steric properties in the series for increased probability of obtaining analgetic activity.

Since the monoarylphosphorus analogs of methadone (**4**, **5**, and **6**) met the requirements of the analgetic receptor and the necessary intermediates were readily available, the synthesis shown in Scheme I was undertaken. The alkylation of benzyldiphenylphosphine oxide with the appropriate chloroalkylamines to produce 1-(1-phenyl-3-dialkylaminoalkyl)diphenylphosphine oxides (**4**) proceeded smoothly in refluxing toluene with sodium hydride as the base. The properties of these compounds are described in Table I. The second series of phosphorus analogs of methadone, diethyl 1-(1-phenyl-3-dialkylaminoalkyl)phosphonates (**5**), were more difficult to prepare. Reaction of diethyl benzylphosphonate with the appropriate chloroalkylamine in the presence of sodium methylsulfinylmethide in dimethyl sulfoxide produced the desired compounds (Table I). The final structural variation in the series of monoarylphosphorus analogs of methadone (**6**) contained a diethylphosphoryl group and was synthesized by reacting benzyldiethylphosphine oxide with the appropriate chloroalkylamine. Several solvent systems were required; the dimethylamino analog was synthesized in toluene with sodium hydride as the base and the piperidino and morpholino analogs were prepared using sodium methylsulfinylmethide in dimethyl sulfoxide.

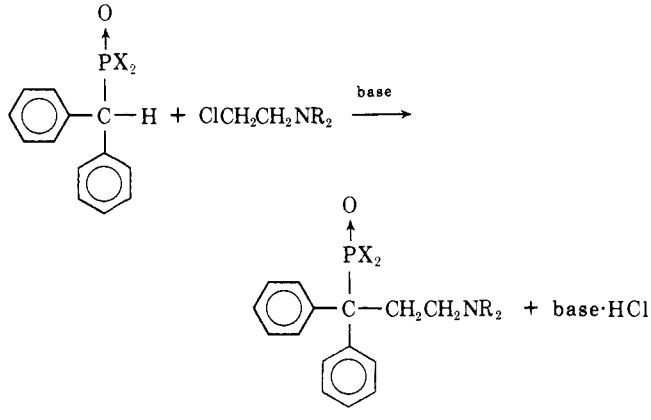
Scheme I



X = OC_2H_5, C_2H_5, or C_6H_5
NR_2 = dialkylamino or cycloalkylamino

The synthesis of the diarylphosphorus analogs of methadone (**7** and **8**) was carried out according to the method shown in Scheme II. The extra phenyl group adjacent to the phosphoryl group of the starting material will stabilize

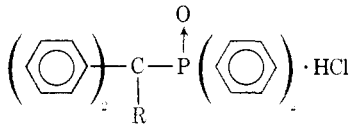
Scheme II



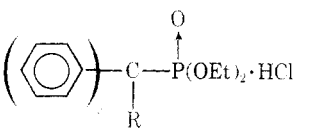
X = OC_2H_5 or C_6H_5
NR_2 = dialkylamino or cycloalkylamino

the negative charge produced by attack of base on the parent compound, but the steric hindrance caused by the extra phenyl group will cause the carbanion to be less reactive toward chloroalkylamines. The first series of diarylphosphorus analogs of methadone, the 1-(1,1-diphenyl-3-dialkylaminoalkyl)diphenylphosphine oxides (**7**), was prepared. The synthesis of these compounds failed in refluxing toluene, but when the higher boiling solvent xylene was used good yields of the products were obtained. The physical properties of these compounds (**7**) are described in Table II. The synthesis of the second series of diarylphosphorus analogs of methadone, diethyl 1-(1,1-diphenyl-3-dialkylaminoalkyl)phosphonates (**8**), required the use of two solvent systems. The dimethylamino derivative **8a** was synthesized using sodium hydride in xylene and the diethylamino (**8b**) and the piperidino (**8c**) derivatives

Table II. Physical Constants of Diarylphosphorus Analogs of Methadone



D

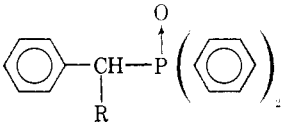


E

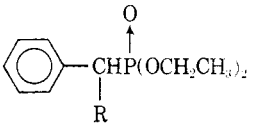
Compd no.	R	Crystn solvent	Mp, °C[a]	Yield, %	Empirical[b] formula
	1-(1,1-Diphenyl-3-dialkylaminoalkyl)diphenylphosphine Oxide Hydrochlorides (D)				
7a	$CH_2CH_2N(Me)_2 \cdot HCl$	*i*-PrOH–(*i*-Pr)$_2$O	194–196 dec	54	$C_{29}H_{30}NOP \cdot HCl$
7b	$CH_2CH_2N(Et)_2 \cdot HCl$	*i*-PrOH–(*i*-Pr)$_2$O	153–154 dec	52	$C_{31}H_{34}NOP \cdot HCl$
7c	CH_2CH_2-c-$NC_4H_8 \cdot HCl$	*i*-PrOH–(*i*-Pr)$_2$O	236–238 dec	58	$C_{31}H_{32}NOP \cdot HCl$
7d	CH_2CH_2-c-$NC_5H_{10} \cdot HCl$	*i*-PrOH–(*i*-Pr)$_2$O	172–175 dec	52	$C_{32}H_{34}NOP \cdot HCl$
7e	CH_2CH_2-c-$N(CH_2CH_2)O \cdot HCl$	*i*-PrOH–(*i*-Pr)$_2$O	218–220	57	$C_{31}H_{32}NO_2P \cdot HCl$
7f	$CHCH_3CH_2N(Me)_2 \cdot HCl$	*i*-PrOH–(*i*-Pr)$_2$O	186–188	39	$C_{30}H_{32}NOP \cdot HCl$
7g	$CH_2CH_2CH_2N(Me)_2 \cdot HCl$	*i*-PrOH–(*i*-Pr$_2$)O	238–240	57	$C_{30}H_{32}NOP \cdot HCl$
	Diethyl 1-(1,1-Diphenyl-3-dialkylaminoalkyl)phosphonate Hydrochlorides (E)				
8a	$CH_2CH_2N(Me)_2 \cdot HCl$	*i*-PrOH–(*i*-Pr)$_2$O	154–155	38	$C_{21}H_{30}NO_3P \cdot HCl$
8b	$CH_2CH_2N(Et)_2 \cdot HCl$	*i*-PrOH–(*i*-Pr)$_2$O	154–155 dec	37	$C_{23}H_{34}NO_3P \cdot HCl$
8c	CH_2CH_2-c-$NC_5H_{10} \cdot HCl$	*i*-PrOH–(*i*-Pr)$_2$O	162–164 dec	34	$C_{24}H_{34}NO_3P \cdot HCl$

[a,b] See footnotes, Table I.

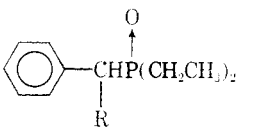
Table III. Pharmacological Properties of Monoarylphosphorus Analogs of Methadone



F



G



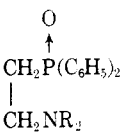
H

Compd no.	R	LD_{50},[a] mg/kg (95% confidence limits)	Hot-plate ED_{50},[b] mg/kg (95% confidence limits)	Acetic acid ED_{50},[c] mg/kg (95% confidence limits)
	Morphine	495.3 (482.0–508.9)	1.32 (1.06–1.50)	1.30 (1.07–1.60)
	1-(1-Phenyldialkylaminoalkyl)diphenylphosphine Oxides (F)			
4a	$CH_2CH_2N(CH_3)_2$	228.4 (226.7–230.4)	85.1 (81.1–89.3)	84.4 (75.1–94.8)
4b	$CH_2CH_2N(CH_2CH_3)_2$	174.2 (169.6–178.8)	6.2 (5.0–7.6)	6.8 (5.1–9.2)
4c	CH_2CH_2-c-NC_4H_8	167.1 (165.7–168.5)	47.9 (44.4–51.7)	55.1 (46.9–64.8)
4d	CH_2CH_2-c-NC_5H_{10}	84.8 (81.0–88.9)	24.7 (20.9–29.2)	21.2 (18.4–24.4)
4e	CH_2CH_2-c-$N(CH_2CH_2)_2O$	151.3 (146.8–156.0)	10.1 (8.7–11.7)	7.0 (4.9–10.0)
4f	$CHCH_3CH_2N(CH_3)$	148.4 (145.8–151.1)	19.7 (16.3–23.7)	18.9 (15.0–23.9)
	Diethyl 1-(1-Phenyl-3-dialkylaminoalkyl)phosphonate Hydrochlorides (G)			
5a	$CH_2CH_2N(CH_3)_2 \cdot HCl$	596.9 (594.4–598.3)	248.7 (240.5–257.2)	260.3 (249.9–270.9)
5b	$CH_2CH_2N(CH_2CH_3)_2 \cdot HCl$	391.7 (387.5–395.9)	144.2 (140.5–147.9)	141.3 (134.4–148.4)
5c	CH_2CH_2-c-$NC_5H_{10} \cdot HCl$	332.3 (329.1–335.4)	105.0 (100.5–109.8)	102.4 (100.0–105.4)
5d	CH_2CH_2-c-$N(CH_2CH_2)_2O \cdot HCl$	507.9 (500.8–515.2)	104.4 (99.6–109.4)	105.6 (100.0–111.4)
	(1-Phenyl-3-piperidinopropyl)diethylphosphine Oxide Hydrochloride (H)			
6b	CH_2CH_2-c-$NC_5H_{10} \cdot HCl$	500–700[d]	191 (184–198)	196 (183–210)

[a] Determined by the method of Litchfield and Wilcoxon.[11] [b] Determined by the method of Eddy and Leimbach.[12] [c] Determined by the method of Koster, Anderson, and DeBeer.[13] [d] Insufficient material for a complete LD_{50} determination. These doses gave 0–100% mortality, respectively, and the LD_{50} should be within this range.

were prepared using potassium *tert*-butoxide in benzene. The diethylphosphine oxide analogs were not prepared in this series because of difficulties experienced in synthesizing large amounts of diphenylmethyldiethylphosphine oxide which serves as the starting material for the series.

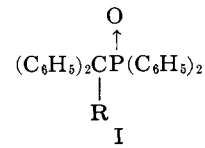
Structure–Activity Relationships. Examination of Table III reveals several trends in the structure–activity relationships of the monoarylphosphorus analogs of methadone. The greater lipophilic character of the diphenylphosphoryl group (series **4**) compared to the diethoxyphosphoryl group (series **5**) possibly represents a more optimum solubility and offers a reasonable explanation for the differences in activity. The possible binding of the additional phenyl groups on the phosphorus group of series **4** cannot be unequivocally excluded. However, a very similar series of diphenylphosphine oxides (**9**) was previously synthesized by Burger and Shelver[7] and tested for analgetic action. No activity was found in these compounds



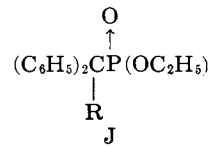
9

and although the dialkylaminoalkyl side chain of the present series (**4**, **5**, or **6**) contains one more carbon atom than **9**, it seems reasonable the phosphorus phenyl groups on either **9** or **4**, **5**, or **6** are not interacting with the analgetic receptor site. A comparison of **5c** with **6b** indicates the diethoxyphosphoryl group to be more active than the diethylphosphoryl group. Although a major difference between these groups is electronic and the result indicates electronic differences may play a role in determining the activity of compounds as analgetics; the groups also differ in solubility characteristics which might also explain the pharmacological differences. The nitrogen substituent ex-

Table IV. Pharmacological Properties of Diarylphosphorus Analogs of Methadone



I



J

Compd no.	R	LD_{50}[a] (95% confidence limits)	Hot-plate ED_{50}[b] (95% confidence limits)	Acetic acid ED_{50}[c] (95% confidence limits)
	1-(1,1-Diphenyl-3-dialkylaminoalkyl)diphenylphosphine Oxide Hydrochlorides (I)			
7a	$CH_2CH_2N(CH_3)_2$	74.9 (72.8–77.0)	10.2 (8.5–12.1)	11.8 (10.0–13.8)
7b	$CH_2CH_2N(C_2H_5)_2$	76.1 (73.9–78.3)	15.2 (13.0–17.8)	15.6 (13.0–18.6)
7c	CH_2CH_2-c-NC_4H_8	65.7 (63.7–67.7)	13.3 (11.6–15.2)	11.7 (9.0–15.1)
7d	CH_2CH_2-c-NC_5H_{10}	69.3 (66.7–72.1)	11.2 (10.0–12.6)	9.3 (7.3–11.9)
7e	CH_2CH_2-c-$N(CH_2CH_2)_2O$	141.7 (139.2–144.2)	17.2 (14.5–20.6)	25.8 (20.2–32.9)
7f	$CHCH_3CH_2N(CH_3)_2$	43.9 (42.3–45.6)	14.6 (12.5–17.0)	13.8 (10.7–16.2)
7g	$CH_2CH_2CH_2N(CH_3)_2$	70.7 (68.7–72.8)	22.1 (17.6–27.9)	19.0 (13.5–26.8)
	Diethyl 1-(1,1-Diphenyl-3-dialkylaminopropyl)phosphonate (J)			
8c	CH_2CH_2-c-NC_5H_{10}	50–75[d]	11.1 (8.8–13.9)	11.7 (10.0–13.8)

[a–d] See footnotes, Table III.

erts an effect on the analgetic activity of series **4** and maximum activity is found in the diethylamino and the morpholino derivatives. Series **5** shows maximum activity in the piperidino and morpholino derivatives. The morpholino compound seems to show less toxicity than the piperidino compound in all of the series in which these compounds were compared. In general, the toxicity of the monoarylphosphorus analogs was highest in those compounds of reasonable activity.

The results of the pharmacological testing of the diarylphosphorus analogs of methadone are found in Table IV. In most cases the diaryl compounds are considerably more active as analgetics than the corresponding monoaryl compounds. The additional lipophilicity of the diaryl analogs might provide a more optimum transport or a stronger lipophilic receptor binding. Alternatively, the increased activity might be due to increased specific binding with the analgetic receptor site either directly or indirectly through conformational modification. The effect of the substituent on the phosphorus group is difficult to evaluate since only one compound of the second series was tested. From the available data the pharmacological activity of the diarylphosphorus compounds is less sensitive to variation of the phosphorus substituent than the monoarylphosphorus analogs. Compounds with near optimum log *P* values are located in a relatively flat portion of the log activity–log *P* curve. In such molecules structural changes which effect only log *P* will produce small changes in activity assuming the change in log *P* is small relative to the curvature of the log activity–log *P* plot. If the primary role of the additional phenyl group in the diarylphosphorus analogs of methadone is to provide the optimum log *P* value, perhaps the small changes in activity produced by changes in the phosphorus component might be understandable. Interestingly, the effect of the substituents on the nitrogen is also minimal in series **7**. Lengthening or branching of the alkyl chain connecting the dialkylamino group and the carbon bearing the aromatic and phosphorus groups seems to have little effect on the analgetic activity. These observations also support the previous conclusions concerning the importance of the lipophilic balance in this series. Unfortunately, toxicity is the highest in compounds with good analgetic activity.

Experimental Section

Melting points were taken with a Thomas-Hoover apparatus and are uncorrected. Infrared spectra were determined on a Perkin-Elmer 337 spectrometer using potassium bromide pellets. Nmr spectra were run on a Varian A-60 spectrometer using $CDCl_3$ as a solvent and TMS as a reference. All elemental analyses were determined by the Alfred Bernhard Microanalytical Laboratory, Germany, using vanadium pentoxide as a catalyst in the oxidative determination of carbon and hydrogen. All samples were dried for 24 hr before shipment and the hygroscopic series (**5**, **6**, and **8**) were routinely dried by the analyst immediately prior to analysis.

2-Chloralkylamines were purchased in the form of their hydrochlorides. Prior to use in the alkylating reactions the salt was dissolved in water; the aqueous solution was made basic and extracted with toluene. The toluene extracts were rigorously dried prior to use. (Care must be used in the handling of these compounds because of their vesicant properties.)

1-(1-Phenyl-3-dialkylaminoalkyl)diphenylphosphine Oxides (4). To a solution of 0.027 mol of benzyldiphenylphosphine oxide in 150 ml of dry toluene was added 0.054 mol of sodium hydride. The mixture was refluxed for 4 hr (an orange color appears after 30 min). The dried solution of the appropriate chloralkylamine was added dropwise over a 1-hr period and the mixture refluxed for an additional 12 hr. The reaction mixture was poured onto a mixture of ice and 5 ml of 40% sodium hydroxide, and the solid which precipitated was collected. Some additional compound was obtained by extraction. The physical properties of the compounds prepared by this method are found in Table I.

Diethyl 1-(1-Phenyl-3-dialkylaminopropyl)phosphonate (5). Sodium methylsulfinylmethide was generated as previously reported[8] by heating a suspension of 0.033 mol of sodium hydride in 100 ml of dry DMSO between 65 and 70°. After the evolution of hydrogen ceased and the solution had cooled to room temperature, 0.026 mol of diethyl benzylphosphonate was slowly added to the solution. A dried toluene extract of the appropriate chloroalkylamine was added to the reaction mixture over a 1-hr period. After the mixture had stirred for 12 hr it was poured into ice and extracted with benzene. The residual material was converted to the hydrochloride. The properties of the compounds prepared by this method are reported in Table I.

1-(1-Phenyl-3-dialkylaminopropyl)diethylphosphine Oxides (6). The preceeding procedure was used to synthesize the diethylphosphine oxides except benzyldiethylphosphine oxide (prepared by the method used by Hays[8]) was utilized as the starting phosphorus compound. The hydrochlorides of the diethylphosphine oxides prepared by this method were extremely hydroscopic and often had to be dried in benzene using a Dean-Stark trap to remove the water. The physical properties of these compounds are listed in Table I.

1-(1,1-Diphenyl-3-dialkylaminopropyl)diphenylphosphine Oxide (7). A suspension of 0.0135 mol of benzyldiaryldiphenylphosphine oxide (prepared by the method of Downie and Morris[9]) and 0.033 mol of sodium hydride was refluxed in 150 ml of xylene for 4 hr. A toluene extract containing the appropriate chloroalkylamine was added to the refluxing mixture over a period of 1–2 hr. After refluxing for 12 hr the reaction mixture was poured onto ice and extracted with ether. Upon extracting the combined ether layers with 5% hydrochloric acid, a precipitate formed which was collected. The products prepared by this method were recrystallized from appropriate solvents and their properties are described in Table II.

Diethyl 1-(1,1-Diphenyl-3-dialkylaminopropyl)phosphonate (8). Two methods were used to synthesize these compounds. The first method was identical with the procedure used to prepare 7 described previously. The hydrochloride did not precipitate and had to be isolated in a conventional acid–base extraction and the hydrochloride was prepared by passing hydrogen chloride gas through an ether solution of the basic material isolated from the reaction. In the second procedure a solution of 0.02 mol of diethyl benzyldiarylphosphonate (prepared by the method of Smith and Burger[10]) and 0.03 mol of potassium *tert*-butoxide in dry benzene was stirred at room temperature for 15 min. The dried toluene extract of the chloroalkylamine was added and the solution refluxed overnight. The reaction mixture was worked up in the conventional manner and the compounds prepared by this method are described in Table II.

Pharmacology. The LD_{50} determination was conducted utilizing a minimum of five 25–30 g male Swiss–Webster strain mice in each of at least five groups. The drugs were administered in a phosphate buffer (Sorensen pH 4.7) or in distilled water. Animals of each dosage level were given the drug intraperitoneally and placed in observation cages for 24 hr. Death was observed to occur within 15 min after administration of the drug or the animal survived. The recorded data were analyzed by a probit method developed by Litchfield and Wilcoxon[11] and adapted for use in a computer by W. H. S. The results of the toxicity experiments are given in Tables III and IV.

The ED_{50} for the hot-plate method was determined using essentially the method of Eddy and Leimbach.[12] The hot plate used was a metal cup immersed in a constant temperature water bath maintained at 55°. The mouse was placed on the hot plate and a stop watch started. The time needed for the mouse to react to the heat was recorded. The end point occurred when the mouse licked a front foot or attempted to alternately hold its hind feet in the air. The reaction time was determined at 5, 10, 20, 30, 45, and 60 min after the animal received the drug. The area of the reaction time–time after drug curve was determined by means of a computer program utilizing the reaction times recorded. The average for 100 control animals was 401.9 sec-min with a standard deviation of 41.2 sec-min. For the drug testing, the animals were tested for consistency of their reaction and if these times were consistent, the drug was administered intraperitoneally. After 15 min the reaction times of the mouse were determined at the specified periods and the area of the curve was computed. An animal was judged to show analgesia if the area of his reaction time curve exceeded that of the control by more than two standard deviations. Ten animals were used at each dosage level and five dosage levels were used for each drug. The ED_{50} was calculated by the same computer program used for the LD_{50} experiments. The results for the hot-plate ED_{50} experiments are found in Tables III and IV.

The acetic acid writhing ED_{50} study utilized the technique developed by Koster.[13] The drug was administered subcutaneously to five groups of ten mice for each drug. After 15 min the animals were challenged with a dose of 60 mg/kg of 0.6% acetic acid administered intraperitoneally. The animals were observed for 30 min. Animals showing obvious writhing were recorded as not showing analgesia and those which showed no writhing were recorded as showing analgesia. The per cent of animals showing analgesia was recorded and these data were used for the calculation of the ED_{50} using the previously described computer program. The results of the acetic acid writhing test are found in Tables III and IV.

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Stereochemical Studies on Medicinal Agents. 16.[1] Conformational Studies of Methadone and Isomethadone Utilizing Circular Dichroism and Proton Magnetic Resonance

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The solution conformations of methadone (1), isomethadone (2), and their respective HCl and MeI salts have been investigated using CD and nmr. The fact that the sign of the Cotton effect of 1 undergoes solvent-induced inversion in CH_3OH (compared to hexane and $CHCl_3$) while 2 or salts of 1 and 2 show no such change suggests that 1 exhibits a high degree of conformational mobility compared to 2. When dissolved in CD_3OD, only 1 was found to undergo a rapid intramolecularly catalyzed proton exchange, thus suggesting the presence of a significant population of conformers 1a and 1c. Conformational analysis based on the C-5,6 vicinal coupling constants indicated approximately a 1:1:2 ratio of the three possible staggered conformations of 1 in $CDCl_3$. A perturbation of this distribution occurred in CD_3OD. This behavior was not observed in the case of 2 and its derivatives, and this is consistent with a much higher degree of conformational homogeneity in 2. In the case of 2, nmr analysis together with other data suggests that 2b is the predominant rotamer. It is proposed that the higher enantiomeric (−/+) analgetic potency ratio of 2 relative to 1 may in part be related to their difference in conformational flexibility. On this basis it is suggested that 2 might possess more selective action than 1 and might be worthy of investigation as a suitable alternative to 1 in the maintenance of addicts.

The conformations of the narcotic analgetics, methadone (**1**)[2,3] and isomethadone (**2**),[3] have been the subjects of considerable stereochemical investigation,[4-10] as these positional isomers differ from many other types of narcotic analgetics in their formal degree of conformational flexibility. As early as 1954, Beckett and Casy[4] suggested that these compounds possessed a preferred conformation which was postulated to fit a hypothetical receptor site.

† This paper is dedicated to Professor Alfred Burger in recognition of his many accomplishments in the field of medicinal chemistry.