portions to 88 ml. (1.0 mole) of vigorously stirred phosphorus trichloride contained in a 250 ml. neck flask equipped with mechanical stirrer and a reflux condenser. Moisture was excluded by means of a drying tube attached to the top of the condenser. The oxide was all added during a 10 min. period, but did not appear to react although it went into solution. No phosphorous acid layer appeared. Next day the solution was heated under reflux for 1 hr., cooled, filtered to remove a viscous yellow oil, and distilled to remove the excess phosphorus trichloride. The residual viscous oil solidified on cooling to a glass which was unreactive toward water, ethanol, or piperidine, and which did not therefore contain the desired bis(2,3,5,6-tetramethylphenyl)phosphinous chloride.

WILMINGTON 98, DEL.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PITTSBURGH]

Phosphonic Acids and Esters. III.[1] Formation of 3-(2,5-Diphenylfuryl)phosphonic Acid in the Reaction of Dibenzoylethylene and Phosphorus Trichloride[2]

CLAIBOURNE E. GRIFFIN AND JOHN T. BROWN

Received May 31, 1960

The reaction of dibenzoylethylene and phosphorus trichloride in the presence of acetic anhydride is shown to lead to the formation of 3-(2,5-diphenylfuryl)phosphonic acid (VI) and not the product reported in the literature, 1,2-dibenzoylethylphosphonic acid (II). The structure of VI is confirmed by an examination of absorption spectra, independent synthesis, thermal dephosphonylation to 2,5-diphenylfuran, and a typical Diels-Alder reaction sequence leading to a terphenylphosphonic acid, which was independently synthesized.

Phosphonic acids in which the phosphono grouping is directly attached to a heterocyclic system have received little attention previously; heterocyclic phosphonic acids (I) incorporating the thiophene,[3] pyrazoline,[4] acridine,[5] tetrahydrofuran,[6] quinoline,[7] dihydrocoumarin,[8] pyridine,[9] and triazine[10] ring systems have been reported. In only this limited number of cases have heterocycles and their derivatives proved amenable to the introduction of the phosphono grouping by conventional procedures. An interest in the spectra of phosphonates[11] directed our attention toward an alternate synthetic mode of greater potential applicability. The variety of methods available for the synthesis of acyclic phosphonic acids suggested that ring closure of suitably substituted acids by methods common in heterocyclic chemistry might be a feasible route to I.

A particularly promising class of compounds appeared to be the phosphonic acids incorporating a 1,4-diketone structure, e.g. 1,2-dibenzoylethylphosphonic acid (II). Ring closures of 1,4-diketones are well established routes to furans, pyrroles, thiophenes, and pyridazines; application of known cyclization procedures to compound II should lead to phosphonic acids incorporating these heterocyclic systems.

Conant demonstrated that the addition of phosphorus trichloride to a variety of α,β-unsaturated ketones led to the formation of β-ketophosphonic acids by 1,4-addition.[12] In an extension of this work, Drake and Marvel reported that the addition of phosphorus trichloride to dibenzoylethylene (III) in the presence of acetic anhydride led to the formation of a cyclic adduct (IV) which was readily hydrolyzed to II.[13] The adduct was not isolated or further characterized but treatment with tetradecanol-1 led to the formation of 1-chlorotetradecane and a product formulated as V.

This experiment, employing techniques unavailable to the original investigators, led to different results in our hands; no change was made in the

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(3) H. Sachs, *Ber.*, 25, 1514 (1892).

(4) A. Michaelis and R. Pasternak, *Ber.*, 32, 2398 (1899).

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(7) A. Burger, J. B. Clements, N. D. Dawson, and R. B. Henderson, *J. Org. Chem.*, 20, 1383 (1955).

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(10) H. Schroeder, *J. Am. Chem. Soc.*, 81, 5658 (1959). The assignment of a phosphonate structure in this study appears questionable.

(11) Examination of the ultraviolet absorption spectra of a number of substituted phenylphosphonic acids has led to the postulation of only a very weak resonance interaction between the phosphono group and the benzene ring, *cf.* L. D. Freedman and G. O. Doak, *J. Am. Chem. Soc.*, 77, 6221 (1955) and previous references. A more favorable environment for such resonance interaction is anticipated in certain of the heterocyclic phosphonic acids because of the greater electron donating ability of heterocyclic systems, notably pyrrole and thiophene, *cf.* A. R. Katritsky, *Quart. Revs. (London)*, 13, 353 (1959).

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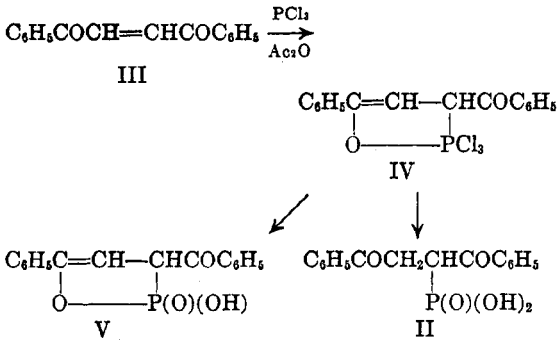
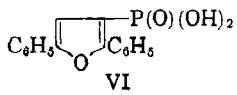


reaction conditions employed by Drake and Marvel. A mixture of III, phosphorus trichloride, and acetic anhydride was held at 33–38° for three hours, dissolved in chloroform, and hydrolyzed with the calculated amount of water to yield a crystalline product. Recrystallization from methanol gave a material (VI) of m.p. 196–197°.[14] Elemental analyses and the neutralization equivalent of VI were compatible with an empirical formula of $C_{16}H_{13}O_4P$ (structure II requires $C_{16}H_{15}O_5P$). Further evidence for the non-identity of VI and II, the reported product of the reaction, was provided by an examination of the absorption spectrum of VI. Structure II would be expected to show absorption closely akin to that of dibenzoylethane: λ_{max} 244 mμ (ε 26,500), 318 mμ (ε 600) and benzoyl absorption in the infrared, 1667 cm.$^{-1}$ [15] Compound VI is transparent in the 1600–1800 cm.$^{-1}$ region of the infrared and shows the following absorption in the ultraviolet: λ_{max} 225 mμ (ε 30,200), 318 mμ (ε 36,400).

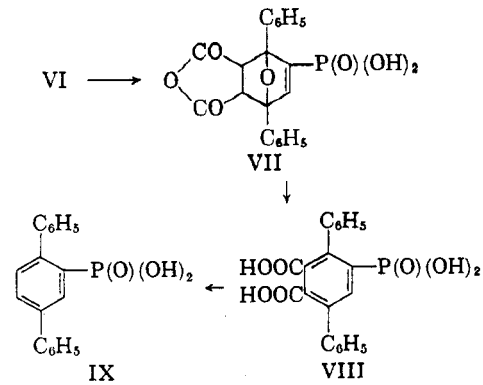
Two structures may be proposed for VI. The empirical formula is identical with that of compound V isolated by Drake and Marvel and the observed melting point of VI is in accord with that reported for V. However, the neutralization equivalent obtained and the lack of typical benzoyl absorption in both the ultraviolet and infrared eliminated structure V, as well as II, as a formulation for VI. Analytical and spectrophotometric data are consistent with the formulation of VI as 3-(2,5-diphenylfuryl)phosphonic acid. The ultraviolet spectrum of VI is very similar to that



reported for 2,5-diphenyl furan: λ_{max} 226 mμ (ε 16,200), 324 mμ (ε 29,200).[16] The hyperchromic shift observed for VI relative to the parent furan is consistent with the effect observed in the spectra of a number of arylphosphonic acids[11] and indicative of a weak resonance interaction between the phosphono group and the furan ring. A very weak hypsochromic shift is observed; this may arise by interference of the phosphono group with the planarity of the 1,4-diphenyl butadiene system, the dominant chromophore of the molecule. *Ortho* phosphono groupings in the biphenylphosphonic acids cause a similar disruption of planarity leading to a comparable effect on absorption spectra.[17] Further, the infrared spectrum of VI is almost identical with that of 2,5-diphenylfuran; the only significant differences lie in the presence of bands typical of phosphonic acid structures, *e.g.*, phosphoryl absorption at 1227 cm.$^{-1}$ and very broad bands at 2690 and 2260 cm.$^{-1}$ The latter pair of bands has recently been shown to be characteristic of the phosphonic acids.[18]

Further evidence in support of the furan structure for VI was provided by an alternate synthesis and by chemical studies. Reaction of III with diethyl phosphonate in the presence of dibenzoyl peroxide gave a red oil which could neither be crystallized nor distilled. The infrared spectrum of this oil showed negligible contamination by the reactants and was consistent with that of the expected product, the diethyl ester of II. Hydrolysis of this oil with concentrated hydrochloric acid led to the formation of VI, both ester hydrolysis and acid catalyzed dehydrative cyclization occurring. The formation of furans from 1,4-diketones under such conditions is well known. Reaction of III with dimethyl phosphonate under similar conditions led to an oil which was readily hydrolyzed to VI. The infrared spectrum of this oil was consistent with that of the expected product, the dimethyl ester of II.

Compound VI gave a typical Diels-Alder reaction in refluxing toluene with maleic anhydride. The adduct (VII) was aromatized by heating with hydrobromic acid in glacial acetic acid[19] and hydrolyzed in basic medium to give the tetra-



(14) Drake and Marvel report the recrystallization of II from ethyl acetate to give a product melting at 183–185°, while V melts at 197–198°.

(15) L. P. Kuhn, R. E. Lutz, and C. R. Bauer, *J. Am. Chem. Soc.*, 72, 5058 (1950).

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basic acid (VIII); decarboxylation of VIII gave 2,5-diphenylphenylphosphonic acid (IX). The terphenylphosphonic acid (IX) was identical in all respects with a sample prepared by an alternate unquivocal route: reaction of the diazonium fluoroborate derived from 2,5-diphenylaniline[20] with phosphorus trichloride by the general procedure of Doak and Freedman.[21]

Freedman, Doak, and Petit recently reported the thermal dephosphonylation of a variety of arylphosphonic acids[22]; decomposition occurs at 240° to yield the arene and inorganic phosphate. When compound VI was heated at 240° for three hours, decomposition occurred with the formation of 2,5-diphenylfuran (38%) and a residue of inorganic phosphate. Thus it appears that thermal dephosphonylation is capable of extension to highly stabilized heterocyclic systems. Similar treatment of IX led to the formation of *p*-terphenyl in 71% yield.

While these studies were in progress, a sample of VI which had been exposed to moisture for a period of six weeks was examined and found to melt at 184–186°; Drake and Marvel report II to melt at 183–185°. This material gave the analytical values expected for a monohydrate of VI and its infrared spectrum was essentially identical with that of VI. Drying at 150° for six hours over phosphorus pentoxide gave anhydrous VI; the monohydrate could also be formed by refluxing VI in aqueous hydrochloric acid or by recrystallization of VI from wet solvent. Thus it appears that the material to which Drake and Marvel assigned structure V is the isomeric 3-(2,5-diphenylfuryl)phosphonic acid (VI) and the material assigned structure II is the isomeric monohydrate of VI. Primary evidence for these structural assignments is based upon techniques unavailable to the original investigators.

The establishment of structures for the final products of this reaction casts some doubt upon the assignment of structure IV to the initial adduct. In a repetition of the addition reaction, the adduct was examined. After completion of the three-hour reaction period, unchanged phosphorus trichloride and acetic anhydride were removed under reduced pressure to yield a highly reactive dark oil; the extreme sensitivity to moisture of this oil complicated further investigation. Attempted distillation at reduced pressure gave only decomposition with the formation of an intractable tar; no phosphorus trichloride was observed in the distillate, indicating that the reaction was not reversible under these conditions. Attempted purification of the oil by column chromatography led to hydrolysis and the isolation of VI as the only characterizable product. The extreme complexity of the infrared spectrum of the adduct indicates a possible mixture of materials, although only a negligible amount of III remains unchanged. Significant absorption occurred in the carbonyl region (1764 and 1704 cm.$^{-1}$) and in the phosphoryl region (1274 cm.$^{-1}$). The higher frequency carbonyl band may be attributed to a vinyl acetate type grouping; the acetyl assignment is further strengthened by the appearance of C-methyl absorption at 1441 cm.$^{-1}$ Thus the incorporation of acetyl in the adduct is indicated. Conant[12] has observed that the presence of an acetylating agent is necessary for conjugate addition of phosphorus trichloride to unsaturated ketones; in the absence of acetic acid or anhydride, the addition reaction appears to be reversible. The lower frequency carbonyl band is in the benzoyl region while the phosphoryl frequency is typical of phosphonic dihalides.[23] Because the extreme sensitivity of the oil renders purification difficult, the parallel reaction of benzalacetophenone and phosphorus trichloride is under investigation. Preliminary studies indicate this adduct to be more stable and it is hoped that these studies will allow the determination of adduct structure and reaction course.

EXPERIMENTAL[24]

3-(2,5-Diphenylfuryl)phosphonic acid (VI). *Method A. By reaction of dibenzoylethylene* (III) *and phosphorus trichloride.* A mixture of 23.6 g. (0.10 mole) of III, 13.7 g. (0.10 mole) of phosphorus trichloride and 10.2 g. (0.10 mole) of acetic anhydride was held at 33–38° for 3 hr. Careful cooling was necessary as the reaction was vigorously exothermic. The volatile material was removed under reduced pressure (60 mm.) at 70°; the residual viscous oil was dissolved in chloroform and 15 g. of water was added dropwise. A yellow-green solid separated which could not be recrystallized from ethyl acetate, but was readily recrystallized from methyl alcohol to give, after drying *in vacuo* over phosphorus pentoxide, 23.4 g. (78%) of VI, m.p. 196–197°, λ_{max} 225 mμ (ε 30,200), 318 mμ (ε 36,400). The infrared spectrum of the product was almost identical with that of 2,5-diphenylfuran (common bands at 1582, 1054, 1026, 930, 908, 760, 755, and 687 cm.$^{-1}$), showed characteristic phosphonic acid absorptions at 2690, 2260, and 1227 cm.$^{-1}$ and was essentially transparent in the 1600–1800 cm.$^{-1}$ region.

Anal. Calcd. for $C_{16}H_{13}O_4P$: C, 64.00; H, 4.33; P, 10.32; neut. equiv., 150.1. Calcd. for $C_{16}H_{15}O_5P$ (II): C, 60.38; H, 4.75; P, 9.73; neut. equiv., 159.1. Found: C, 63.99; H, 4.36; P, 10.15; neut. equiv., 151.2, 148.1.

In one experiment, the product was isolated by basic extraction of the chloroform suspension and reacidification. No effect was observed on either yield or product composition when the amount of water employed for hydrolysis was decreased to a minimum of 3.6 g. (0.20 mole); hydrolysis was incomplete when lesser amounts were employed.

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(24) Melting points are uncorrected. Analyses in part by Geller Microanalytical Laboratories, Bardonia, N. Y. Ultraviolet and infrared spectra were recorded by Cary model 14 and Perkin-Elmer model 21 spectrophotometers. The spectrophotometers were provided by generous grants from the National Institutes of Health and the National Science Foundation.

Method B. By reaction of diethyl phosphonate and III. A mixture of 23.6 g. (0.10 mole) of III, 55.2 g. (0.40 mole) of diethyl phosphonate, and 1.0 g. of dibenzoyl peroxide was held at 90–95° for 24 hr. Upon completion of reaction, unchanged diethyl phosphonate (17.8 g.) was removed by distillation under reduced pressure; the residual red oil resisted all attempts at crystallization and decomposed on attempted distillation at 10^{-3} mm. The infrared spectrum showed bands characteristic of benzoyl (1664 cm.$^{-1}$), phosphoryl (1289 cm.$^{-1}$), and P—O-ethyl (1158 cm.$^{-1}$) groupings as expected for the diethyl ester of II; negligible contamination was indicated by comparison with the infrared spectra of the starting materials. The oil was refluxed with constant boiling hydrochloric acid for 24 hr.; the semisolid product was collected by filtration, washed thoroughly with ether, dissolved in dilute aqueous sodium hydroxide, decolorized with activated carbon, and filtered. Acidification of the filtrate gave colorless crystals which were recrystallized from methanol to give, after drying over phosphorus pentoxide, 17.0 g. (56.7%) of VI, which was identical in all respects (mixture melting point, infrared and ultraviolet absorption spectra) with the product obtained by method A.

Similar results were obtained when dimethyl phosphonate was treated with III under identical conditions; hydrolysis gave VI in 51.2% yield.

Dibenzoylethylene–phosphorus trichloride adduct. Phosphorus trichloride, acetic anhydride, and III were allowed to react as in method A. Upon completion of the reaction, the volatile material was removed under reduced pressure (1 mm.) at 70° to give a viscous red oil. Attempted distillation at 10^{-3} mm. gave decomposition with the formation of an intractable tar; the distillate contained trace amounts of acetic acid, but no phosphorus trichloride was observed (infrared spectrum). Attempted crystallization from anhydrous nonhydroxylic solvents and chromatographic separation on alumina led to hydrolysis with the isolation of VI as the only characterizable product; any exposure to moisture led to the formation of VI. The infrared spectrum (film) was extremely complex with clearly defined bands at the following frequencies: 1764, 1704, 1587, 1497, 1441, 1366, 1353, 1274, 1196, 1012, 962, 923, 796, 760, and 686 cm.$^{-1}$ Comparison of adduct and starting material spectra indicated negligible contamination of the adduct by either III or acetic anhydride. Chlorine and carbon-hydrogen analyses and molecular weight determinations gave nonreproducible values due to hydrolysis during manipulation.

2,5-Diphenylphenylphosphonic acid (IX). *Method A. Diels-Alder sequence from* VI. A suspension of 18.0 g. (0.06 mole) of VI and 9.8 g. (0.10 mole) of maleic anhydride in 150 ml. of toluene was refluxed for 8 hr.; the suspension was filtered to give a crystalline mixture of the adduct (VII) and the furylphosphonic acid (VI). The mixture was washed thoroughly with ether, dissolved in methanol, and chromatographed on a 60-cm. column of adsorption alumina (Fisher A-540); the column was eluted successively with benzene, ether, chloroform, acetone, and methanol. The combined methanol fractions were evaporated to yield 6.7 g. of VI (identified by mixture melting point with an authentic sample). The chloroform fractions were collected and reduced in volume to yield a crystalline material; recrystallization from a mixture of methanol and ethyl acetate gave 7.9 g. (33.1%) of the adduct (VII), m.p. 132–134°.

Anal. Calcd. for $C_{20}H_{15}O_7P$: C, 60.31; H, 3.80; P, 7.78. Found: C, 60.52; H, 3.75; P, 8.01.

A mixture of 7.8 g. (0.20 mole) of the adduct (VII), 10 ml. of 40% hydrobromic acid, and 100 ml. of glacial acetic acid was refluxed for 6 hr.; the reaction mixture was poured over ice, filtered, and washed thoroughly with ice cold ethyl acetate. The solid product was dissolved in excess 10% aqueous sodium hydroxide and held at 60–65° for 3 hr.; upon cooling, the reaction mixture was acidified with sulfuric acid. The crystalline product was removed by filtration and recrystallized from dimethylformamide to give 5.4 g. (70%) of 3,4-dicarboxy-2,5-diphenylphenylphosphonic acid (VIII), m.p. 190–191°.

Anal. Calcd. for $C_{20}H_{15}O_7P$: C, 60.31; H, 3.80; P, 7.78; neut. equiv., 97.1. Found: C, 60.48; H, 3.61; P, 7.97; neut. equiv., 96.3, 95.8.

Decarboxylation of VIII was achieved by the general method of McDonald and Campbell.[25] A solution of 4.0 g. (0.01 mole) of acid VIII in excess aqueous sodium carbonate was treated with a solution of 20.0 g. of potassium ferricyanide in 50 ml. of water. The solution was heated on the steam bath for 1 hr. and allowed to stand overnight at room temperature. After filtration, the solution was acidified with hydrochloric acid; the product was filtered, washed with water, and recrystallized from methanol to give 2.3 g. (74.1%) of 2,5-diphenylphenylphosphonic acid (IX), m.p. 237–238°.

Anal. Calcd. for $C_{18}H_{15}O_3P$: C, 69.67; H, 4.87; P, 9.98; neut. equiv., 155.1. Found: C, 69.95; H, 5.08; P, 10.11; neut. equiv., 154.7, 154.9.

Method B. Diazonium fluoroborate method. 2,5-Diphenylaniline was prepared according to the procedure of Basford[26] in 35% over-all yield from 4-cyclohexyldiphenyl.[26] The amine was converted to the corresponding diazonium fluoroborate and phosphonylated by the general procedure of Doak and Freedman.[21] Ethyl acetate was used as reaction medium and cuprous chloride as the catalyst. During steam distillation of the reaction mixture, the phosphonic acid crystallized in the distilling flask. The crude acid was removed by filtration and then washed thoroughly with water, acetone, and ether; recrystallization from methanol gave IX (17%), which was identical (mixture melting point and infrared spectra) with the acid obtained by method A.

Thermal dephosphonylations. 3-(2,5-Diphenylfuryl)phosphonic acid (3.0 g., 0.01 mole) was heated at 240° in a nitrogen atmosphere for 3 hr.; upon cooling to 95°, the melt was poured into water. The solidified product was filtered, washed with water, and recrystallized from ethanol to give 0.84 g. of 2,5-diphenylfuran (38%), m.p. 88–89° (reported[27] m.p. 89.5–90°). A mixture melting point of this material with an authentic sample was not depressed.

2,5-Diphenylphenylphosphonic acid (IX) was dephosphonylated in the same manner to yield *p*-terphenyl (71%). The product was identified by lack of mixture melting point depression and identity of infrared spectra with that of an authentic sample.

3-(2,5-Diphenylfuryl)phosphonic acid monohydrate. A sample of the acid (VI) which had been exposed to moisture for 6 weeks was found to melt at 184–186°; the reported melting point of II is 183–185°.[13] The infrared spectrum of this material was essentially identical with that of VI; analytical values were those expected for a monohydrate of VI.

Anal. Calcd. for $C_{16}H_{13}O_4P \cdot H_2O$: C, 60.38; H, 4.75; neut. equiv., 159.1. Found: C, 60.24; H, 4.57; neut. equiv., 159.4, 158.7.

The monohydrate was converted readily to VI by heating at 150° (1 mm.) over phosphorus pentoxide. Formation of the monohydrate could also be accomplished by refluxing VI in aqueous hydrochloric acid, recrystallization from aqueous methanol, or by allowing VI to stand over water in a closed system for 6 days.

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PITTSBURGH 13, PA.

[CONTRIBUTION NO. 30 FROM THE L. G. RYAN RESEARCH LABORATORIES OF MONSANTO CANADA LIMITED AND THE RESEARCH LABORATORIES OF AYERST, MCKENNA AND HARRISON LIMITED]

Bacteriostats. IV.[1] ω-Amino Acid Amide Derivatives

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A number of *N,N'*-disubstituted ω-amino acid amides have been prepared for evaluation as bacteriostats. The preparations and bacteriostatic properties of the compounds are described.

N,N'-Disubstituted glycineamides have been prepared for evaluation as tuberculostats[4] and tri- and tetrasubstituted glycineamides have been patented as pharmacological agents.[5] Some of the products described by Bersch and Döpp,[4] especially *N,N'*-di(4-ethoxyphenyl)- and *N,N'*-di(4-butoxyphenyl)glycineamides showed high activity *in vitro* against *M. tuberculosis*. Thus it was considered to be of interest to determine the general bacteriostatic effectiveness of *N,N'*-disubstituted ω-amino acid amides, $RNH(CH_2)_nCONHR'$. The substituents were varied to include both aryl and aralkyl groups which are known to increase bacteriostatic activity in other structures.[6]

A variety of methods are available for the preparation of *N,N'*-disubstituted amino acid amides. The most general procedure consists of treating an ω-haloacyl chloride with an amine to yield the *N*-substituted ω-haloacid amide, which is then heated with an amine to yield the desired product.[5] Symmetrically substituted products may be prepared in a single step by refluxing the amine and the haloacyl chloride in toluene in the presence of sodium carbonate. The symmetrically substituted glycineamides also may be obtained by refluxing an amine with glyoxal sodium bisulfite.[7,8] However, the most convenient process for a large scale laboratory preparation of symmetrically substituted glycineamides is the condensation of an amine with ethyl chloroacetate at 125–140°.[9] Symmetrically substituted 3-aminopropionamides are readily prepared in one step by heating an amine with acrylic acid.[10]

Bacteriostatic activities. It may be seen from the results in Table I that chain length is of secondary importance in determining bacteriostatic effectiveness. For values of *n* of 1, 2, and 5 the most effective substituent on either nitrogen atom was the 3,4-dichlorophenyl group. The most active single compound was *N,N'*-di(3,4-dichlorophenyl)-3-aminopropionamide and the homologous glycineamide and 6-aminocaproamide were slightly less effective. When the functional groups were separated by a longer polymethylene chain, as in the undecanoamide derivatives ($n = 10$), the 3,4-dichlorobenzyl group was considerably more effective than the 3,4-dichlorophenyl group when substituted on the amino nitrogen. This result is in accord with other observations made on compounds in which the bacteriostatic activity is largely due to an isolated basic functional group.

N,N'-Di(3,4-dichlorophenyl)glycineamide hydrochloride has a low acute toxicity for mice (>1.2 g./kg.). However, its bacteriostatic potency was considerably reduced in the presence of serum. The minimal inhibitory concentration for *Strept. faecalis*, for example, fell from 1:1,280,000 to 1:160,000 in the presence of serum. *N,N'*-Di(3,4-dichlorophenyl)-3-aminopropionamide showed a similar deactivation by serum.

EXPERIMENTAL[11]

Amines. 3-Phenylpropylamine was prepared by the modified phthalimide synthesis[12] from 3-phenylpropyl bromide.

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