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XXXVIII.—*Additive Compounds of Antipyrylaminodiacetic Acid and its Salts with Neutral Salts.*

By Robert George Fargher and Harold King.

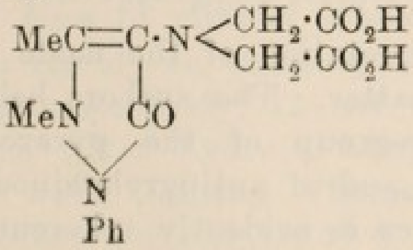
The capacity of the weakly basic substance antipyrine to form additive compounds with very varied organic substances, generally containing oxygen, and with metallic salts of organic and inorganic acids, has often come to light in attempts to explain its incompatibility in pharmacy and to modify or supplement its action in therapeutics.

Apart from two compounds with calcium chloride,

$$(C_{11}H_{12}ON_2)_3,CaCl_2,12H_2O$$

and $(C_{11}H_{12}ON_2)_3,2CaCl_2,9H_2O$, described by Pfeiffer and Wittka (*Ber.*, 1915, **48**, 1289), no complexes are known with the haloids of the alkali or alkaline earth metals.

A simple derivative of antipyrine, antipyryl-4-aminodiacetic acid (D.R.-P. 144393),

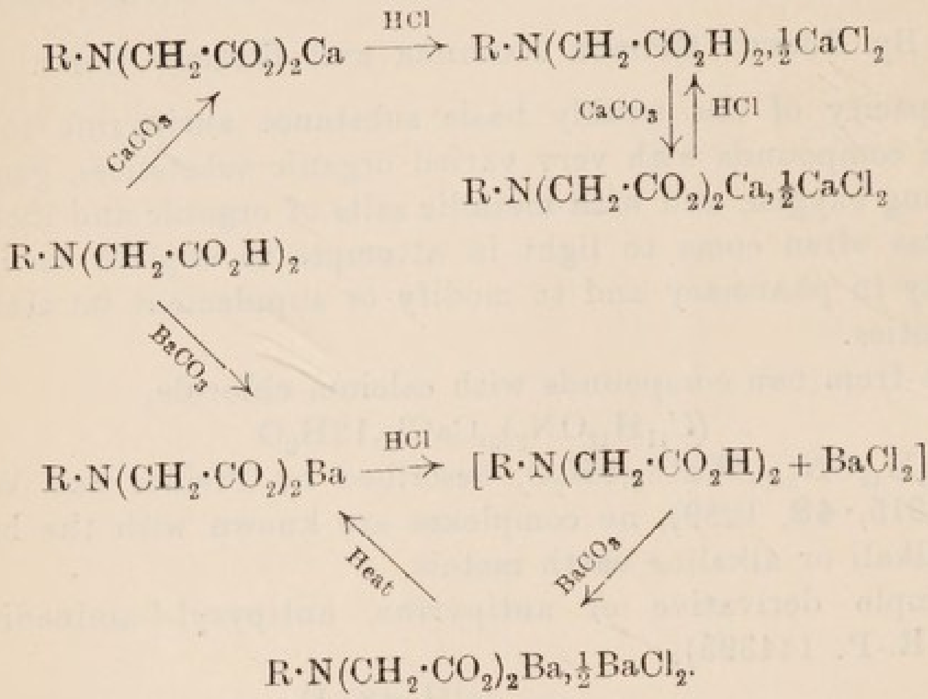


has been found by the authors to furnish an unusually interesting series of simply molecular, additive compounds with the haloids of the alkali and alkaline earth metals. Though the salts of this acid are dismissed in the original specification with the statement that the barium salt was obtained only as a hard, dry mass, the authors have found that the calcium, strontium, and barium salts are well-defined, crystalline substances containing various proportions of water of crystallisation, and have isolated, but with greater difficulty, crystalline sodium and potassium salts.

Additive compounds of two molecules of the acid with one of calcium chloride, calcium bromide, or strontium chloride, and of one molecule of the acid with one of sodium, lithium, or potassium chloride, have been prepared, but the analogous compounds from magnesium or barium chloride were not obtained.

The combining power is, moreover, retained by the calcium, strontium, barium, and magnesium salts of the acid, two molecules of the salt uniting with one of the corresponding metallic chloride.

The mode of preparation of these complexes is sufficiently indicated in the experimental portion of the paper. Attention may, however, be drawn to the ease with which their formation and isolation can be realised experimentally. The following diagram shows the behaviour of the calcium and barium salts, where R represents the antipyryl group:



A satisfactory interpretation of the mode of attachment is a much more difficult matter. The authors believe that it is conditioned by the keto-group of the pyrazolone nucleus. The capacity of antipyrine and of antipyrylaminodiacetic acid and its salts to form complexes is evidently inherent in the pyrazolone nucleus, and, adopting the usual single-ring structure for this nucleus rather than the Michaelis bridged structure, the two seats of residual affinity are the tervalent methylated nitrogen atom and the oxygen of the carbonyl group. The calcium and lithium haloids are known to form complex ammines with ammonia, but only in the dry state. With bivalent oxygen compounds, however, the additive products with the alkali and alkaline earth metal haloids are very numerous, many of them crystallising from aqueous solution. Of these, the most thoroughly investigated (by Pfeiffer and his co-workers; also King and Palmer, *Biochem. J.*, 1920, **14**, 574) are the addition products of neutral salts with glycine and such simple derivatives of glycine as glycylglycine, sarcosine, betaine, and alanine. Pfeiffer and Wittka (*loc. cit.*) consider the neutral salt to be attached to the carbonyl group of the cyclic form of these substances, no other representation being possible for betaine. On this basis, the glycine–calcium chloride complex is represented thus, $(\overline{\mathrm{NH_3\cdot CH_2\cdot CO\cdot O}})_2 \ . \ . \ . \ \mathrm{CaCl_2}$. In agreement with this, they observed that diketopiperazine united additively with two molecules of lithium chloride or bromide.

Moreover, the deep blue colour of copper glycine is usually interpreted by the cyclic structure

$$CH_2{<}\begin{matrix}CO_2\\NH_2\end{matrix}{>}Cu{<}\begin{matrix}CO_2\\NH_2\end{matrix}{>}CH_2$$

and it retains this structure, as shown by the colour, when it combines with a molecule of calcium chloride. The copper salt of antipyrylaminodiacetic acid, however, is pale blue, pointing to absence of affinity in the tertiary-bound nitrogen atoms.

There can, therefore, be little doubt that the molecular complexes of what are substantially the same series of neutral salts with antipyrylaminodiacetic acid have their origin in the residual affinity of the carbonyl group.

Experimental.

Salts of Antipyrylaminodiacetic Acid.

The *calcium* salt is prepared by boiling the concentrated solution of the calcium chloride compound of the free acid (*vide infra*) with excess of calcium carbonate and filtering while still hot, when it quickly sets to a mass of minute prisms sparingly soluble in cold water, but more readily on warming. It forms at least two hydrates, containing, respectively, 12 and 6 molecules of water of crystallisation, the lower hydrate being obtained by rapid crystallisation from warm solution (Found in *dodecahydrate*, Ca = 6·9; loss in a vacuum over H_2SO_4 = 37·4. $C_{15}H_{15}O_5N_3Ca,12H_2O$ requires Ca = 7·0; H_2O = 37·7 per cent. Found in *hexahydrate*, Ca = 8·7; loss in a vacuum over H_2SO_4 = 23·2; Ca in dried salt = 10·9, 11·0. $C_{15}H_{15}O_5N_3Ca,6H_2O$ requires Ca = 8·6; H_2O = 23·2 per cent. $C_{15}H_{15}O_5N_3Ca$ requires Ca = 11·2 per cent.).

The *barium* salt is obtained by heating a concentrated aqueous solution of the barium chloride addition compound (*vide infra*). It separates rapidly on stirring in minute, flattened prisms containing one and a-half molecules of water of crystallisation. The ammonium salt, obtained from the calcium salt by addition of excess of ammonium oxalate in boiling solution, yields the same product. It is, however, very difficult to remove the last traces of calcium oxalate, which are held in solution with great persistency. The barium salt is soluble in cold water, and separates on heating the solution on the water-bath in well-formed, rectangular plates. It thus shows the properties of the barium glycerylphosphates, but crystallises much more handsomely (Found, for different preparations: H_2O = 5·2, 5·7; Ba in anhydrous salt = 30·2, 29·7.

$$C_{15}H_{15}O_5N_3Ba,1\tfrac{1}{2}H_2O$$

requires H_2O = 5·6. $C_{15}H_{15}O_5N_3Ba$ requires Ba = 30·2 per cent.).

The *strontium* salt was prepared from the calcium salt *via* the ammonium salt. It crystallised, like the calcium salt, in clusters of needles containing either 9 or 6 molecules of water of crystallisation (Found for *nonahydrate*: Sr = 15·4, 15·5.

$$C_{15}H_{15}O_5N_3Sr,9H_2O$$

requires Sr = 15·45 per cent. Found for *hexahydrate*: H_2O = 21·5; Sr in anhydrous salt = 21·4. $C_{15}H_{15}O_5N_3Sr,6H_2O$ requires H_2O = 21·1. $C_{15}H_{15}O_5N_3Sr$ requires Sr = 21·6 per cent.).

The *sodium* and *potassium* salts were also obtained crystalline. They are much more readily soluble in water than the salts already described, but separate in well-defined prisms from very concentrated solutions. The *copper* salt forms a pale blue, crystalline powder, somewhat sparingly soluble in cold water.

Additive Compounds of Antipyrylaminodiacetic Acid with Neutral Salts.

With Calcium Chloride.—To a solution of 4·73 grams of chloroacetic acid in 12·5 c.c. of water were added 8 grams of calcium carbonate and 5·1 grams of 4-aminoantipyrine. The mixture was heated to boiling for two hours, a further 1·2 grams of chloroacetic acid and 2·6 grams of calcium carbonate added, and the heating continued for a further two hours. After filtration, the solution was concentrated somewhat and acidified with hydrochloric acid (Congo paper), when, on keeping, it set to a mass of crystals, which were purified by recrystallisation from water. The compound forms well-defined, rhombic prisms, which, on heating, effervesce at 165° (corr.). It dissolves readily in water or alcohol, but sparingly, if at all, in benzene, chloroform, ether, or light petroleum. Addition of sodium chloride to the concentrated aqueous solution causes deposition of the free acid as an oil. It usually contains 8 molecules of water of crystallisation, but two other hydrates have been obtained containing 5 and 4 molecules of water respectively. The pentahydrate only loses 3 molecules of water at 60° in a vacuum. The tetrahydrate separates in large, hard crystals (Found, in *octahydrate*: Cl = 8·0, 8·1; N = 9·5, 9·6; Ca = 4·4. M.W. by titration with baryta = 891·3. Loss in a vacuum over H_2SO_4 = 15·43. $(C_{15}H_{17}O_5N_3)_2,CaCl_2,8H_2O$ requires Cl = 7·9; Ca = 4·5; N = 9·4; H_2O = 16·13 per cent. M.W. = 893·6).

(Found, in *pentahydrate*, loss in a vacuum over H_2SO_4 = 10·5; loss at 60° in a vacuum = 6·2; Cl = 8·4. M.W. by titration = 846·6. $(C_{15}H_{17}O_5N_3)_2,CaCl_2,5H_2O$ requires H_2O = 10·7; Cl = 8·4; loss of $3H_2O$ = 6·4 per cent. M.W. = 839·6.)

(Found, in *tetrahydrate*, M.W. by titration=818·0; loss in a vacuum=8·9. Calc.: H_2O=8·8 per cent. M.W.=821·5.)

With Calcium Bromide.—This complex was prepared by faintly acidifying (Congo paper) a concentrated solution or a suspension of the calcium salt, when it crystallised readily in well-defined prisms containing 11 molecules of water of crystallisation (Found: M.W. by titration=1037. Calc.: M.W.=1036·6).

A second hydrate was obtained crystallising in tufts of soft, silky needles. It contained 6½ molecules of water of crystallisation (Found: M.W. by titration=956; Br=16·8; H_2O=12·4; Ca=4·3. $(C_{15}H_{17}O_5N_3)_2,CaBr_2,6\frac{1}{2}H_2O$ requires Br=16·7; H_2O=12·3; Ca=4·2 per cent. M.W.=955·5).

With calcium iodide, the product was not homogeneous, the calcium:iodine ratio being approximately 1:1·5, and the proportion of iodine decreasing on recrystallisation. The ratio was not altered appreciably by the addition of various proportions of calcium iodide to the solution before rendering neutral or faintly acid to Congo paper.

With Strontium Chloride.—The addition product of the acid and strontium chloride is decomposed by water, with liberation of the free acid as an oil. The pure crystalline complex is obtained in the form of small needles by keeping a concentrated solution of strontium antipyrylaminodiacetate to which concentrated hydrochloric acid has been added until there is incipient formation of an oil, at 0°, for some hours. It contains 2½ molecules of water of crystallisation (Found: M.W. by titration=840; H_2O=5·7; Cl=8·4. $(C_{15}H_{17}O_5N_3)_2,SrCl_2,2\frac{1}{2}H_2O$ requires H_2O=5·3; Cl=8·4 per cent. M.W.=842).

With Sodium Chloride.—The double compound with sodium chloride is obtained by acidification of the concentrated solution of the sodium salt with hydrochloric acid. It forms a felted mass of minute, prismatic needles readily soluble in water or in alcohol and containing 3 molecules of water of crystallisation (Found: Cl=8·2; N=9·9; Na=5·2. $C_{15}H_{17}O_5N_3,NaCl,3H_2O$ requires Cl=8·2; N=9·7; Na=5·3 per cent.).

With Potassium Chloride.—This is prepared in a manner similar to that described above. It separates in clusters of small, needle-shaped prisms containing $3H_2O$ (Found: Cl=7·8; N=9·5; K=8·6. $C_{15}H_{17}O_5N_3,KCl,3H_2O$ requires Cl=7·9; N=9·4; K=8·7 per cent.).

With Lithium Chloride.—This derivative crystallises in minute, rhombic prisms containing $3H_2O$ (Found: Cl=8·4.

$$C_{15}H_{17}O_5N_3,LiCl,3H_2O$$

requires Cl=8·5 per cent.).

Additive Compounds of the Salts of Antipyrylaminodiacetic Acid with Neutral Salts.

The *calcium chloride* compound of the calcium salt remains in the residual liquor from the preparation of the calcium salt from the calcium chloride compound of the acid. It forms minute, hair-like needles, which contain 12 molecules of water of crystallisation. Unlike the barium chloride compound of the barium salt, it does not dissociate in solution with separation of the calcium salt on heating or on seeding with the salt (Found: Ca=11·4; Cl=6·7. $(C_{15}H_{15}O_5N_3Ca)_2,CaCl_2,12H_2O$ requires Ca=11·5; Cl=6·8 per cent.).

The *barium chloride* compound of the barium salt was prepared by the interaction of aminoantipyrine and chloroacetic acid in presence of barium carbonate, and separated before acidification as a mass of minute, silky needles containing 12 molecules of water of crystallisation. It dissociated on heating in aqueous solution, with formation of the free barium salt (Found: Ba=30·9; Cl=5·4; H_2O=16·5. $(C_{15}H_{15}O_5N_3Ba)_2,BaCl_2,12H_2O$ requires Ba=30·9; Cl=5·4; H_2O=16·2 per cent.).

The *magnesium chloride* compound of the magnesium salt was prepared in the same manner, using magnesia in place of barium carbonate. It dissolved fairly readily in water, from which it separated in diamond-shaped plates containing 11 molecules of water of crystallisation (Found: Mg=7·4, H_2O=20·3. $(C_{15}H_{15}O_5N_3Mg)_2,MgCl_2,11H_2O$ requires Mg=7·5; H_2O=20·3 per cent. Found, in dried material: Cl=9·1. Calc.: Cl=9·1 per cent.).

The *strontium chloride* compound of the strontium salt was prepared by crystallising the salt in presence of a considerable excess of strontium chloride. When one, two, or three molecular proportions of the chloride were present, only the strontium salt separated. It crystallised in well-defined, flattened prisms containing $11H_2O$ (Found: Sr=22·7; Cl=6·3; H_2O=17·4.

$$(C_{15}H_{15}O_5N_3Sr)_2,SrCl_2,11H_2O$$

requires Sr=22·6; Cl=6·1; H_2O=17·0 per cent.).

Antipyrylaminodiacetic Acid and its Ethyl Ester.

Antipyrylaminodiacetic acid could not be obtained crystalline, in spite of many attempts. It forms a colourless, viscid syrup readily soluble in water or in alcohol. The *ethyl* ester, prepared by esterification with alcoholic hydrogen chloride or hydrogen sulphate, was obtained after removal of most of the alcohol, addition of water, basification with sodium carbonate, saturation with sodium chloride, and extraction with ether, as a pale yellow oil, which did not crystallise after remaining for several months over paraffin wax in a desiccator. On distillation at 10 mm. pressure, it decomposed completely. Before analysis, it was left for a considerable time in a partial vacuum over potassium hydroxide, calcium chloride, and paraffin wax (Found: C=61·2; H=7·0; N=10·9. $C_{19}H_{25}O_5N_3$ requires C=60·8; H=6·7; N=11·2 per cent.).

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