

425. *Some Observations on Salts of Amidines and Related Compounds.*

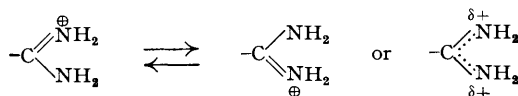
By JAMES WALKER.

Carboxylic acids are of value for the characterisation of *unsubstituted* amidines, and *vice versa*. A possible mechanism by which substances containing an unsubstituted amidino-group readily form highly crystalline salts with certain acids, especially carboxylic acids, is discussed and several extensions are mentioned.

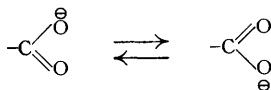
In a previous paper (Fuller, Tonkin, and Walker, *J.*, 1945, 633) it was stated that, where crystallisation of the hydrochlorides of amidines unsubstituted in the amidine group proved difficult because of excessive solubility, double decomposition with sodium benzoate afforded much less soluble benzoates. This device, using both benzoates and acetates, has been found invaluable in a number of cases (Walker, *J.*, 1947, 1684; Forrest, Fuller, and Walker, *J.*, 1948, 1501; Forrest and Walker, *ibid.*, p. 1939) for the ready isolation of highly crystalline salts of amidines, and further consideration of the factors involved appears to be warranted. Carboxylic acid salts of amidines are not new substances and a number were prepared by Pinner ("Die Imidoäther und ihre Derivate," Berlin, 1892), incidental to his researches on imino-ethers and amidines, and one may note, in passing, that the so-called iminohydrins, or *isoamides*, of Eschweiler (*Ber.*, 1897, **30**, 998; Hantzsch and Voegelen, *ibid.*, 1901, **34**, 3142) proved to be carboxylic acid salts of amidines (Rule, *J.*, 1918, **113**, 3), but no systematic application of these salts has hitherto been developed. Complementary to the author's use of salts of carboxylic acids for the characterisation of unsubstituted amidines is the use of salts of unsubstituted amidines for the characterisation of carboxylic acids. The latter is, of course, similar to the familiar application of *S*-benzylthiuronium chloride (Donleavy and Johnson, *Science*, 1923, **57**, 753; Rugeley and Johnson, *J. Amer. Chem. Soc.*,

1925, **47**, 2995; Anderson, *J. Biol. Chem.*, 1927, **74**, 548; Donleavy, *J. Amer. Chem. Soc.*, 1936, **58**, 1004; Veibel and Lillelund, *Bull. Soc. chim.*, 1938, **5**, 1153; Veibel and Ottung, *ibid.*, 1939, **6**, 1434) and of its *p*-chloro- (Dewey and Sperry, *J. Amer. Chem. Soc.*, 1939, **61**, 3251), *p*-bromo- (Dewey and Shasky, *ibid.*, 1941, **63**, 3526), and *p*-nitro-derivatives (Rupe and Zweidler, *Helv. Chim. Acta*, 1940, **23**, 1025), and also of *S*-1-naphthylmethylthiuronium chloride (Bonner, *J. Amer. Chem. Soc.*, 1948, **70**, 3508) for the characterisation of carboxylic acids, since the salt-forming amidino-group is common to amidines and isothioureas; amidines, however, are superior to isothioureas for this purpose as they are stronger bases and recovery of the carboxylic acid is cleaner when amidines are employed, there being no danger of contamination with other acidic products such as is found when thiuronium salts are used (Anderson, *loc. cit.*; Kass, Nichols, and Burr, *J. Amer. Chem. Soc.*, 1942, **64**, 1061; Veibel and Lillelund, *loc. cit.*). Beyond the fact that *S*-benzylthiuronium salts have an established use in the laboratory for the characterisation of carboxylic acids, and also of sulphonic (R. F. Chambers and Scherer, *Ind. Eng. Chem.*, 1924, **16**, 1272; E. Chambers and Watt, *J. Org. Chem.*, 1941, **6**, 376) and sulphinic acids (Hann, *J. Amer. Chem. Soc.*, 1935, **57**, 2166), it does not appear that any significance, particularly of a theoretical kind, has been attached to this property of the amidino-group of forming highly crystalline, and often sparingly soluble, salts with certain acids.

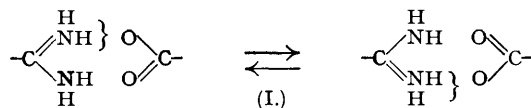
The constitution of salts of *S*-alkylisothioureas was discussed by Taylor (*J.*, 1917, **111**, 650; 1920, **117**, 4) in terms of ideas then still prevailing, and Lecher and his collaborators (*Annalen*, 1924, **438**, 154, 169; 1925, **445**, 35), who introduced the term "thiuronium," advanced the views acceptable at the present time as to the constitution of these salts, and also of those of amidines and *O*-alkylisoureas, in so far as the *kations* are concerned; these contain the resonating system



to which is ascribable the basic strength of these substances. With due acknowledgment to the earlier views of Hantzsch (*Ber.*, 1917, **50**, 1422), Lecher *et al.* (*Annalen*, 1925, **445**, 35) also presented the interpretation of the carboxylate ion acceptable at present, largely on the basis of the formal analogy between the amidinium group and the carboxylate ion, but they did not have occasion to discuss salts formed between the two. In considering now the behaviour



of the carboxylic acid salts of amidines, isothioureas, or isoureas, it is to be noted that the resonance in the *kation* is complementary to that in the anion, and it is suggested that ionic bonds are formed *simultaneously* between the two oxygen atoms sharing the negative charge in the carboxylate ion and the two nitrogen atoms sharing the positive charge in the amidinium group. Furthermore, the coplanarity of the *seven* atoms comprising the amidinium group, arising as a consequence of resonance stabilisation (cf. Mills, *J.*, 1943, 194), leads to (I) as a representation of the amidine salt of a carboxylic acid, in which the seven atoms of the amidinium group, the three atoms of the ionised carboxyl group, and the respective atoms to which these groups are linked, *i.e.*, twelve atoms altogether, are coplanar and assume a relatively rigid configuration of minimum potential energy, the implicit hydrogen bonds being short and relatively strong. Such association *in solution* into doublet ion-pairs of a relatively



rigid oriented type is considered to be the prelude to the formation of crystalline aggregates, which proceeds by hydrogen bonding between the lateral amidinium hydrogen atoms and the oxygen atoms of the carboxylate groups in neighbouring doublet ion-pairs. It is obvious that purely chemical studies cannot supply the proof of these suggestions, and *X*-ray diffraction evidence is being sought. A survey of the literature, summarised in the form of a histogram, shows that the melting points of an extensive and heterogeneous range of *S*-benzyl-

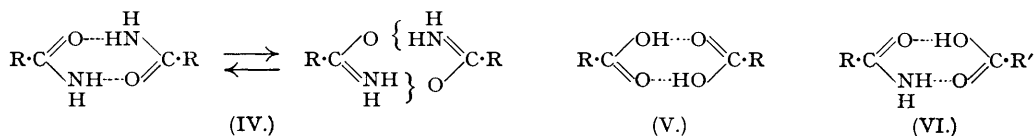
p-substituted *S*-benzyl-, and *S*-1-naphthylmethyl-thiuronium salts of carboxylic acids cover only a small range of temperature, which suggests that the forces which bind crystals of this type together are comparable in strength throughout the series and that the radicals attached to the $-S-C(NH_2)_2^{\oplus}NH_2$ and $-C(O)^{\ominus}O$ groups respectively make little or no contribution to the stability of the crystal; furthermore, it is exceptional to find such a salt of a carboxylic acid containing water of crystallisation. On the other hand, the sulphonic acid salts of the same bases show a more random distribution of melting point and occasionally contain water of crystallisation. In extension of the views developed above in advancing (I) this would be expected, since the anions of sulphonic acids are triply degenerate, while the amidinium group is doubly degenerate. The dissimilarity in the degree of degeneracy in this case allows of greater latitude on the part of the sulphonate ion in the organisation of the crystal including the hydrogen bonding involved in the incorporation of water of crystallisation. Data are lacking for a similar survey of amidine salts but the amidine salts of carboxylic acids appear to have higher melting points than those found for *S*-benzylthiuronium salts.

On the basis of (I) a reasonable interpretation can be advanced for the failure of substituted amidines to form crystalline salts with carboxylic acids with any degree of ease. Mono-substituted (*e.g.*, *N*-methyl) amidinium ions would, on resonance theory, be expected to exist in *syn*- (II) and *anti*- (III) forms, the resonance energy being a measure of the torsional rigidity of the C-N link (*cf.* Mills, *loc. cit.*). In the case of (II) the alkyl group inhibits sterically the



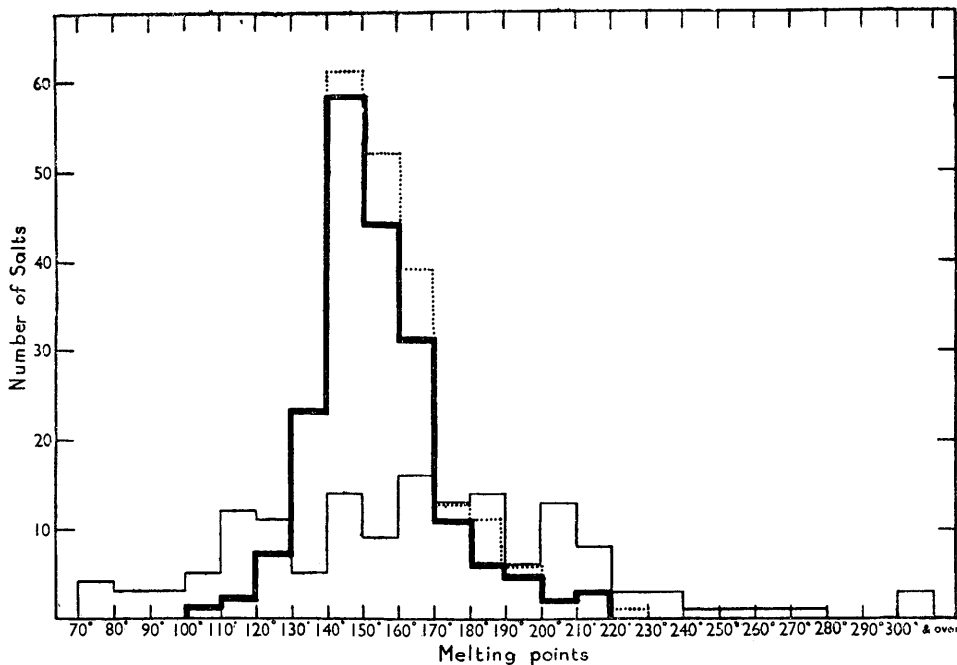
formation of a doublet ion-pair of type (I), while (III) could form a doublet ion-pair of type (I) with only *one* hydrogen atom available for hydrogen bonding, whereas *two* are required for the progressive formation of the crystal, as in diketopiperazine (Corey, *J. Amer. Chem. Soc.*, 1938, **60**, 1598); analogous considerations are applicable to the reduced association found in amides on *N*-substitution as shown by infra-red absorption spectra (Buswell, Downing, and Rodebush, *ibid.*, 1940, **62**, 2759). Incidentally, the structure (I), developed above, is formally reminiscent of the association of amides (IV) and of the well-known dimerisation of carboxylic acids (V), similar considerations being applicable to the products formed from amides and carboxylic acids (VI) (Topin, *Ann. Chim. Phys.*, 1896, **5**, 99; Titherley, *J.*, 1904, **85**, 1673; Henle, *Ber.*, 1905, **38**, 1373).

It is obvious that acids other than carboxylic acids should be capable of forming salts with the amidino-group to which analogous considerations could be applied. Particularly interesting examples are to be found in the reaction between nitrous acid and substances containing this



group; thus, benzamidine reacts with nitrous acid in the presence of excess of hydrochloric acid to give a dinitroso-derivative, "Benzenyldioxytetrazotsäure," which has acidic properties and separates from solution in the reaction in which it is produced in the form of its salt with unchanged benzamidine (Lossen, *Annalen*, 1891, **263**, 82), analogous behaviour being shown by *S*-arylisothiureas (Arndt, *Annalen*, 1913, **396**, 1) and by *S*-alkylisothiureas (Backer and Stedehouder, *Rec. Trav. chim.*, 1933, **52**, 923, 1039). In each case the acid, $R \cdot C(\ddot{N} \cdot \ddot{N} \cdot \ddot{O}) \cdot N \cdot \ddot{N} \cdot \text{OH}$ or $R \cdot C(\ddot{N} \cdot \ddot{N} \cdot \ddot{O}) \cdot \text{NH} \cdot \ddot{N} \cdot \ddot{O}$, affords a symmetrical resonating anion, $R \cdot C(\ddot{N} \cdot \ddot{N} \cdot \ddot{O}) \cdot \ddot{N} \cdot \ddot{N} \cdot \ddot{O}^{\ominus}$ or $R \cdot C(\ddot{N} \cdot \ddot{N} \cdot \ddot{O}) \cdot \ddot{N} \cdot \ddot{N} \cdot \ddot{O}$, and the crystal unit of the salts which separate from the reaction mixtures can be represented as (VII); indeed, Arndt (*loc. cit.*) succeeded in converting the *S-p*-tolylisothiourea salt of dinitroso-*S-p*-tolylisothiourea, *via* the potassium salt, into the benzamidine salt.

Any anion capable of providing suitably situated alternative positions for the negative charge and having a resonance energy, and hence a resonance frequency, similar to that of the amidinium group might be expected to undergo with the latter ionic association similar to



Distribution of *m. p.s* of S-benzyl-, S-p-chlorobenzyl-, S-p-bromobenzyl-, and S-p-nitrobenzyl-thiuronium salts of 193 carboxylic (—) and of 149 sulphonic (.....) acids.

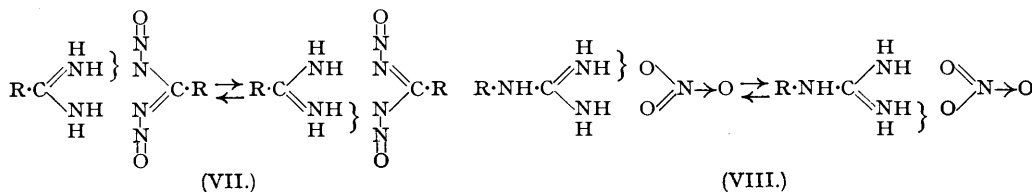
Mean *m. p.* of carboxylic acid salts, 154°, with a standard deviation of 18°; mean *m. p.* of sulphonic acid salts, 165°, with a standard deviation of 46°.

The dotted additions to the carboxylic acid columns comprise the S-1-naphthylmethylthiuronium salts of 28 carboxylic acids.

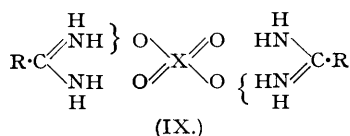
Data from: Anderson, loc. cit.; Archer et al., J. Amer. Chem. Soc., 1945, **67**, 43; Bair and Suter, *ibid.*, 1942, **64**, 1978; Baker and Carlson, *ibid.*, p. 2657; Baker et al., *ibid.*, p. 1096; Baker et al., J. Org. Chem., 1947, **12**, 186; Bergel et al., J., 1944, 415; Bonner, loc. cit.; Bordwell et al., J. Amer. Chem. Soc., 1946, **68**, 139; 1945, **67**, 827; Caldwell and Kornfeld, *ibid.*, 1942, **64**, 1695; Campaigne and Suter, *ibid.*, p. 3040; *ibid.*, 1946, **68**, 880; Chambers and Scherer, loc. cit.; Chambers and Watt, loc. cit.; Chodroff, Kapp, and Beckmann, J. Amer. Chem. Soc., 1947, **69**, 256; Christian and Jenkins, J. Amer. Pharm. Assoc., 1945, **34**, 147; Clemo and Legg, J., 1947, 539; Clemo and Turnbull, J., 1947, 124; Cocker, J., 1946, 36; Dewey and Shasky, loc. cit.; Dewey and Sperry, loc. cit.; Donleavy, loc. cit.; Emerson and Smith, J. Amer. Chem. Soc., 1940, **62**, 1869; English and Cavaglieri, *ibid.*, 1943, **65**, 1085; Fierz-David et al., *Helv. Chim. Acta*, 1946, **29**, 1718; Gaunt et al., J. Soc. Dyers Col., 1947, **63**, 48; Gripenberg, *Ann. Acad. Sci. Fennicae*, 1943, A, **59**, No. 14, 7; Hann, loc. cit.; Hann and Keenan, J. Physical Chem., 1927, **31**, 1084; Hardegger, *Helv. Chim. Acta*, 1946, **29**, 1195; Hardegger et al., *ibid.*, 1945, **28**, 628; Haynes and Jones, J., 1946, 503; Hennion and Schmidle, J. Amer. Chem. Soc., 1943, **65**, 2468; Huber et al., *ibid.*, 1945, **67**, 1148; Kass et al., loc. cit.; Kimura and Taniguti, J. Soc. Chem. Ind. Japan, 1939, **42** (Supp.), 234; Komori and Ueno, *Bull. Chem. Soc. Japan*, 1937, **12**, 433; Kratzl, *Ber.*, 1943, **76**, 895; 1944, **77**, 717; Kratzl and Däubner, *ibid.*, p. 519; Leonard and Spoerri, J. Amer. Chem. Soc., 1946, **68**, 526; Levey and Lewis, J. Biol. Chem., 1947, **168**, 213; McPhee and Klingsberg, J. Amer. Chem. Soc., 1944, **66**, 1132; McPhee and Lindstrom, *ibid.*, 1943, **65**, 2177; B.P. 567,438; U.S.P. 2,337,576; Plattner et al., *Helv. Chim. Acta*, 1946, **29**, 730; Pucher and Vickery, J. Biol. Chem., 1946, **163**, 169; Rugeley and Johnson, loc. cit.; Ruggli and Dahn, *Helv. Chim. Acta*, 1944, **27**, 867; Rupe and Frey, *ibid.*, p. 627; Rupe and Zweidler, loc. cit.; Schenkel et al., *Helv. Chim. Acta*, 1944, **27**, 1437; Schmid and Karrer, *ibid.*, 1945, **28**, 722; Seidel et al., *ibid.*, 1944, **27**, 663; Shoppee and Reichstein, *ibid.*, 1942, **25**, 1611; Smith and Rouault, J. Amer. Chem. Soc., 1943, **65**, 745; Snyder and Handrick, *ibid.*, 1944, **66**, 1860; Soper et al., *ibid.*, 1948, **70**, 2849; Stiller et al., *ibid.*, 1940, **62**, 1785; Suter et al., J. Org. Chem., 1945, **10**, 470; Suter and Bordwell, J. Amer. Chem. Soc., 1943, **65**, 507; Suter et al., *ibid.*, 1941, **63**, 1594; Suter and Milne, *ibid.*, 1943, **65**, 582; Suter and Truce, *ibid.*, 1944, **66**, 1105; Taylor, loc. cit.; Urist and Jenkins, J. Amer. Chem. Soc., 1941, **63**, 2943; Veibel, *ibid.*, 1945, **67**, 1867; Veibel and Lillelund, loc. cit.; Veibel and Ottung, loc. cit.; Vischer and Reichstein, *Helv. Chim. Acta*, 1944, **27**, 1332; v. Wacek, *Ber.*, 1944, **77**, 85; v. Wacek and Kratzl, *ibid.*, 1943, **76**, 1209; v. Wacek et al., *ibid.*, 1942, **75**, 1348; Whitmore and Landau, J. Amer. Chem. Soc., 1946, **68**, 1797; Work, J., 1947, 222.

Where the same salt has been described by more than one group of authors, the mean *m. p.* was taken, when the individual observations agreed to within a few degrees; in a few cases where the *m. p.s* of a salt, recorded by different observers, showed considerable divergence, that salt was omitted from the survey.

(I). In a similar manner, the excellence of nitrates for the isolation and characterisation of substituted guanidines, long known in the laboratory, may be interpreted by the formation



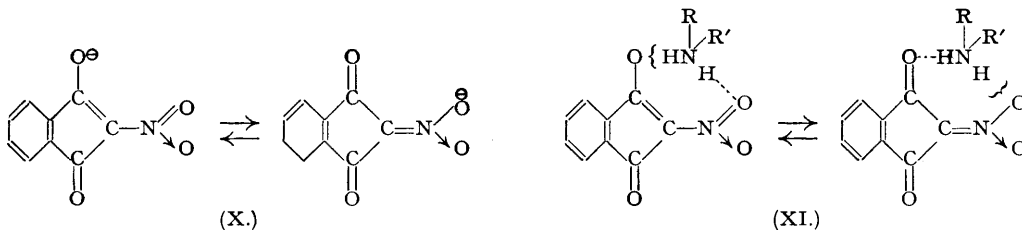
in solution of (VIII) from which the crystal is thereafter progressively built up; nitrates are also useful for the characterisation of amidines, several examples being recorded below. On the basis of (I), dibasic acids of the type H_2XO_4 should provide with amidines normal salts of the type (IX) with the atom X in a tetrahedral environment at a centre of symmetry. These are exemplified by the preparation of *benzamidinium chromate* and *tetrahydrogeranamidinium sulphate*; an attempt to prepare tetrahydrogeranamidinium hydrogen sulphate by double decomposition yielded the normal sulphate instead, and similar behaviour has been observed with *S*-benzylthiuronium hydrogen sulphate, which passed readily into the normal sulphate on recrystallisation from water (Lecher *et al.*, *Annalen*, 1925, 445, 58). Thiosulphates would be expected to show similar behaviour, and *benzamidinium thiosulphate* and *tetrahydrogeranamidinium thiosulphate* have been prepared; the former has been described by Crayen (*Ber.*, 1891, 24, 385), who obtained it in a remarkable transformation by allowing the product



from the reaction of carbon disulphide with benzamidoxime to decompose in air at 100° , recalling the formation of phenylacetamidinium thiosulphate by the action of air on an alcoholic solution of phenylacetothioamide (Bernthsen, *Annalen*, 1877, 184, 321).

The essential feature of structure (I) is that the anion and cation hold each other electrostatically and rigidly in a preferred orientation, and this behaviour may well underlie the activities of amidines, guanidines, *isothioureas*, and *isoureas* as drugs, since Fastier (*Nature*, 1944, 154, 429; *Brit. J. Pharmacol.*, 1948, 3, 198; Fastier and Smirk, *J. Pharm. Exp. Ther.*, 1947, 89, 256) has shown that these substances, besides showing close analogies in their chemical behaviour, form a single well-defined pharmacological group in addition to the well-known chemotherapeutic activity of individual compounds. In these cases the resonating acidic group forming ionic bonds with the amidino-group in the drug may be identified with functional groups in the cellular structures affected by the drugs in question. It should be borne in mind also that in nucleoproteins there is essentially a salt-like union of nucleic acid with a basic protein and that it may be with this type of linkage that chemotherapeutic agents of the amidine type exert their action.

It seems worth while to consider in this connexion, too, the property of 2-nitroindane-1 : 3-dione of readily forming rather sparingly-soluble salts with primary and secondary amines, but not with tertiary amines (Wanag, *Ber.*, 1936, 69, 1066; *J. Gen. Chem. Russia*, 1947, 17, 2080; Wanag and Lode, *Ber.*, 1937, 70, 547). As a working hypothesis the author would



suggest that the anion (X) in virtue of resonance has the power of forming rigid ion-pairs (XI) with the cations of *primary* and *secondary* amines, which have *two* hydrogen atoms

available for hydrogen bonding, and that the crystal is thereafter progressively built up from mutually oriented ion-pairs; kations of *tertiary* amines having but *one* hydrogen atom attached to nitrogen cannot form ion-pairs of type (XI). Here again, orthodox methods of organic chemistry cannot supply proof or disproof of this theory and it would be helpful to have X-ray diffraction evidence. While the discrimination of 2-nitroindane-1 : 3-dione between primary and secondary bases on the one hand and tertiary bases on the other is sharply defined, a similar trend is discernible with dilituric acid (5-nitrobarbituric acid) (Redemann and Niemann, *J. Amer. Chem. Soc.*, 1940, **62**, 590), which might be expected to show similar behaviour. The diliturates of representative primary and secondary amines are sparingly soluble salts, while those of tertiary bases are much more soluble; a few heterocyclic bases, however, afford sparingly soluble diliturates.

The experimental portion of this communication describes a number of salts of amidines and related compounds prepared and examined in the light of the considerations outlined above, separation of a crystalline solid phase on double decomposition in cold fairly concentrated aqueous solution being used as a criterion of ready crystallisation. To illustrate the effects of substitution in the amidine group on the crystallisation of salts, benzamidine hydrochloride, 2-phenyldihydroglyoxalinium chloride, and 2-phenylglyoxalinium nitrate were studied; only benzamidine hydrochloride yielded a benzoate and an acetate under the standard conditions, and neither of the other two bases afforded crystalline salts of simple carboxylic acids. 2-Phenylglyoxalinium *p*-nitrobenzoate was obtained readily in a highly crystalline condition, the nitro-group doubtless facilitating crystallisation, and it should be noted that Fargher and Pyman (*J.*, 1919, **115**, 217) record several cases of crystalline hydrogen oxalates in the glyoxaline series, where the second carboxyl group has undoubtedly a powerful influence. As a substituted analogue of S-benzylthiuronium chloride and one which would still be markedly basic, 2-benzylthiodihydroglyoxalinium chloride was prepared and found to lack entirely the capacity of the former salt to yield precipitates with aqueous solutions of the sodium salts of a number of carboxylic acids.

As it appeared probable that a branched-chain aliphatic amidine might show some activity against the tubercle bacillus (cf. Buu-Hoï, *Nature*, 1945, **156**, 392; also Newbery and Webster, *J.*, 1947, 738), tetrahydrogeranamidinium sulphate was kindly tested *in vitro* by Dr. D'Arcy Hart against *M. tuberculosis* and against *M. phlei*, but the observed activity was not of a high order.

EXPERIMENTAL.

General Method for the Preparation of Salts by Double Decomposition.—Concentrated cold aqueous solutions of base hydrochloride (or other salt) (0.001—0.01 g.-mol.) and the sodium, potassium, or ammonium salt of the carboxylic (or other) acid (1.1 equivs.) were mixed, crystallisation being induced, if necessary, by scratching. Water was added, if necessary, in sufficient amount to give a clear solution at the b. p. and, after cooling, the crystals were collected and crystallised to constant m. p., one recrystallisation usually sufficing. The solubility gradients are usually such that quite small volumes of solvent are required for recrystallisation, and yet little loss is experienced if suitable methods are used.

p-Methylsulphonylbenzamidinium acetate crystallised from 3 parts of water in stellate clusters of colourless rectangular prisms, m. p. 236—237° (efferv.) (Found: C, 46.7; H, 5.3; N, 10.8. $C_8H_{10}O_2N_2S, C_2H_4O_2$ requires C, 46.5; H, 5.4; N, 10.9%). *p*-Methylsulphonylbenzamidinium nitrate separated from 2 parts of water in stout colourless prisms, m. p. 208—209° (Found: N, 16.0. $C_8H_{10}O_2N_2S, HNO_3$ requires N, 16.1%). *p*-Sulphonamidobenzamidinium benzoate crystallised from 5 parts of water in long fine needles, m. p. 231—232° (Found: C, 52.1; H, 4.6; N, 13.1. $C_7H_9O_2N_3S, C_6H_5O_2$ requires C, 52.3; H, 4.7; N, 13.1%). *p*-Sulphonamidobenzamidinium acetate crystallised from 3 parts of water in stellate clusters of colourless rectangular prisms, m. p. 227—228° (Found: C, 41.5; H, 4.9; N, 15.9. $C_7H_9O_2N_3S, C_2H_4O_2$ requires C, 41.7; H, 5.0; N, 16.2%). *p*-Sulphonamidobenzamidinium nitrate separated from 2 parts of water in small stout prisms, m. p. 195—196° (Found: N, 19.8, 19.8. $C_7H_9O_2N_3S, HNO_3, H_2O$ requires N, 20.0%). Benzamidinium benzenesulphonate crystallised from rather more than one part of water in colourless thin plates, nearly rectangular in outline, m. p. 175—176° (Found: N, 10.1. Calc. for $C_7H_8N_2, C_6H_5O_3S$: N, 10.2%); Rouiller (*Amer. Chem. J.*, 1912, **47**, 475) records m. p. 173°, and Oxley and Short (*J.*, 1946, 147) record m. p. 175—175.5°. Benzamidinium thiosulphate separated from 2 parts of water in large, thin, transparent, hexagonal plates, m. p. 217° (decomp.) (Found: N, 16.0. Calc. for $2C_7H_8N_2, H_2S_2O_3$: N, 15.8%); Crayen (*loc. cit.*) records m. p. 222°. Benzamidinium chromate crystallised from about 8 parts of water in stout canary-yellow rhombs, m. p. 184° (decomp.) (Found: C, 46.9; H, 5.3; N, 15.6. $2C_7H_8N_2, H_2CrO_4$ requires C, 46.9; H, 5.0; N, 15.6%). S-Methylthiuronium benzoate crystallised from about 12 parts of water in colourless rectangular prisms, m. p. 184—185° (efferv.) (Found: N, 13.4. $C_2H_5N_2S, C_6H_5O_2$ requires N, 13.2%). O-Methyluronium salicylate crystallised from 0.8 part of water in fine prisms, m. p. 138—139° (Found: N, 13.3. Calc. for $C_2H_6ON_2, C_7H_6O_3$: N, 13.2%); Basterfield and Powell (*Canadian J. Res.*, 1929, **1**, 261) record m. p. 128°. Guanidinium benzoate crystallised from 1.5 parts of water in fine, colourless, obliquely-terminated crystals, attaining lengths up to 3 cm., m. p. 225—226° (Found: N, 23.0. $CH_5N_3, C_6H_5O_2$ requires N, 23.2%). 2-Phenyl-

glyoxalium p-nitrobenzoate crystallised from about 30 parts of water in fine silky needles, m. p. 166° (Found : N, 13.8. $C_9H_8N_2C_7H_5O_4N$ requires N, 13.5%); the unsubstituted benzoate was precipitated as a gum which did not crystallise in the course of several months.

Tetrahydrogeranamidine Hydrochloride.—(i) Technical citronellal (46.5 g.) was hydrogenated in methyl alcohol (200 c.c.) in the presence of 2% palladised strontium carbonate (5 g.) with hydrogen at 3 atm. pressure. Hydrogenation proceeded slowly and was complete in about 12 hours. Dihydro-citronellal (31 g.), b. p. 100—104°/26 mm., was obtained on fractionation of the product. The aldehyde (28 g.) was treated with hydroxylamine hydrochloride (13 g.) and sodium acetate crystals (25.5 g.) in aqueous alcohol (to homogeneity) in the cold for 48 hours. The resulting product, isolated by pouring into water and extraction with ether, afforded the oxime (25.4 g.), b. p. 128—134°/25 mm., which was then heated under reflux with acetic anhydride (100 c.c.) for an hour; the tetrahydrogeranonitrile (19 g.), b. p. 115°/25 mm., obtained on fractionating the product gave somewhat low values for nitrogen but it was sufficiently pure for conversion into the amidine.

(ii) A mixture of tetrahydrogeranonitrile (45.7 g.) and absolute alcohol (70 c.c.) was saturated with dry hydrogen chloride at 0° and the solution was kept for a week in the ice-chest. Solvent and excess of hydrogen chloride were removed in a vacuum and the resulting syrup was set aside in a pressure bottle with 10% alcoholic ammonia solution for several days at 37°. The solution was then filtered and evaporated to dryness. The residue was taken up in water, giving a clear solution becoming turbid on continued addition of water. The diluted solution was extracted several times with ether and the aqueous layer was then evaporated to dryness. The residue was exhaustively dried by repeated extraction with absolute alcohol and evaporation of the extract to dryness. The product (35.1 g.) then crystallised slowly. Crystallisation from dry acetone afforded small colourless leaflets of *tetrahydrogeranamidine hydrochloride*, m. p. 95—96.5° (Found : N, 13.3. $C_{10}H_{22}N_2.HCl$ requires N, 13.6%).

Tetrahydrogeranamidinium benzoate crystallised from about 70 parts of water in pearly plates, m. p. 189° (Found : N, 9.4. $C_{10}H_{22}N_2.C_7H_5O_2$ requires N, 9.6%). The *sulphate* crystallised from about 70 parts of water in plates, m. p. 291° (decomp.) (Found : C, 54.3; H, 10.3; N, 13.0. $2C_{10}H_{22}N_2.H_2SO_4$ requires C, 54.7; H, 10.5; N, 12.8%). The normal sulphate (Found : N, 13.0%) was obtained when an attempt was made to prepare the hydrogen sulphate. The *thiosulphate* crystallised from about 70 parts of water in plates, m. p. 221° (decomp.) (Found : N, 12.4. $2C_{10}H_{22}N_2.H_2S_2O_3$ requires N, 12.3%). The *nitrate* crystallised from about 40 parts of water in pearly plates, m. p. 152—153° (Found : N, 18.0. $C_{10}H_{22}N_2.HNO_3$ requires N, 18.0%).

2-Benzylthiodihydroglyoxalium Chloride.—An alcoholic solution of ethylenethiourea (5.6 g.) (Johnson and Edens, *J. Amer. Chem. Soc.*, 1942, **64**, 2706) and benzyl chloride (6.7 g.) was heated under reflux for several hours and the solvent was then distilled off. The *product* separated from a small volume of isopropyl alcohol in small stout prisms (10 g.), m. p. 145—145.5° (Found : N, 12.4. $C_{10}H_{12}N_2S.HCl$ requires N, 12.3%).

2-Phenyldihydroglyoxalium Chloride.—2-Phenyldihydroglyoxaline was obtained in good yield from benziminoethyl ether hydrochloride and ethylenediamine (cf. Austrian Patent 150,307), the base being isolated by ether extraction after the addition of excess of caustic alkali. Aspinall (*J. Org. Chem.*, 1941, **6**, 895) showed that 2-substituted iminazolines were readily hydrolysed by hot water to monoacyl-ethylenediamines, and Hill and Aspinall (*J. Amer. Chem. Soc.*, 1939, **61**, 822) prepared the hydrochlorides of the former bases by passing dry hydrogen chloride into alcoholic solutions of the bases. It should be noted, however, that the ready hydrolysis of the free bases in hot water is what would be expected in amidines and that neutralisation with mineral acid affords salts that are quite stable to water. 2-Phenyldihydroglyoxalium chloride was obtained by dissolving the free base in spirit, adding a slight excess of N-hydrochloric acid, and evaporating the solution to dryness on the water-bath. The chloride crystallised from isopropyl alcohol in short stout prisms, m. p. 234°; Hill and Aspinall (*loc. cit.*) record m. p. 244° (corr.).

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