PART I

Formation of malonmono arylamides on partial hydrolysis of cyanacet arylamides using (a) polyphosphoric acid (b) 75 % sulphuric acid ; and preparation of malonmono arylacids.

PART I

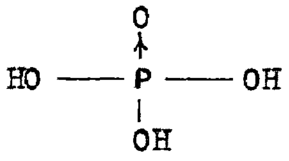
Theoretical

Snyder and Werber (J. Amer. Chem. Soc., 1950, 72, 2962) reported for the first time the application of polyphosphoric acid as a reagent in organic chemistry. In recent years polyphosphoric acid (PPA) has achieved prominence in synthetic organic chemistry as is seen from the review made by Frank D. Popp and William E. McEwen (Chem. Rev., 1958, 58, 321). Polyphosphoric acid is a mixture of phosphorus pentoxide and syrupy phosphoric acid. It is used as a condensing agent as well as a general acid catalyst ; and in the present investigation it is described as a hydrolytic agent and as a condensing agent.

Bell R.N. (Ind. Eng. Chem., 1948, 40, 1464), while determining the composition of strong phosphoric acids, found four acids between $H_2O.P_2O_5$ and $3H_2O.P_2O_5$ and an unidentified acid, all of which occoured as mixtures down to $3H_2O.P_2O_5$. He showed that at all phosphorus pentoxide levels, orthophosphoric acid, pyrophosphoric acid between 72 and 85 % P_2O_5 and a highly polymerized meta-phosphoric acid above 83 % P_2O_5 were present.

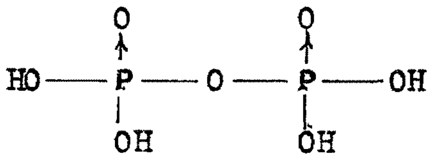
The unidentified acid, occouring at a slightly lower phosphorus pentoxide contents than the highly polymerized meta acid, is believed to be a lower polymer of meta-phosphoric acid. No difference in composition was found between strong phosphoric acids prepared by heat and those prepared by the addition of phosphorus pentoxide.

The structures of some of the individual phosphoric acids found in polyphosphoric acid are shown by Thilo and Sauer (J. Prakt. Chem., 1957, 4 , 4, 324) as follows :



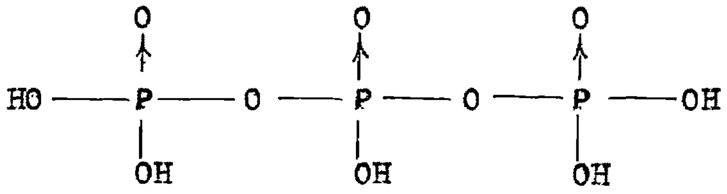
$$\mathrm{HO-\overset{\overset{\displaystyle O}{\uparrow}}{\underset{\underset{\displaystyle OH}{|}}{P}}-OH}$$

Orthophosphoric acid



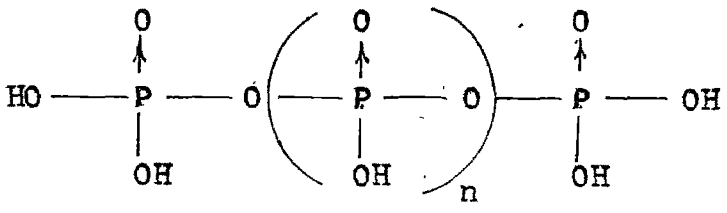
$$\mathrm{HO-\overset{\overset{\displaystyle O}{\uparrow}}{\underset{\underset{\displaystyle OH}{|}}{P}}-O-\overset{\overset{\displaystyle O}{\uparrow}}{\underset{\underset{\displaystyle OH}{|}}{P}}-OH}$$

Pyrophosphoric acid



$$\mathrm{HO-\overset{\overset{\displaystyle O}{\uparrow}}{\underset{\underset{\displaystyle OH}{|}}{P}}-O-\overset{\overset{\displaystyle O}{\uparrow}}{\underset{\underset{\displaystyle OH}{|}}{P}}-O-\overset{\overset{\displaystyle O}{\uparrow}}{\underset{\underset{\displaystyle OH}{|}}{P}}-OH}$$

Tripolyphosphoric acid



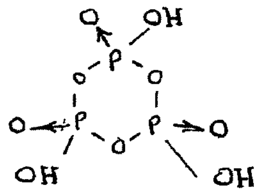
$$\mathrm{HO-\overset{\overset{\displaystyle O}{\uparrow}}{\underset{\underset{\displaystyle OH}{|}}{P}}-O\left(-\overset{\overset{\displaystyle O}{\uparrow}}{\underset{\underset{\displaystyle OH}{|}}{P}}-O\right)_{n}-\overset{\overset{\displaystyle O}{\uparrow}}{\underset{\underset{\displaystyle OH}{|}}{P}}-OH}$$

n = 2, Tetrapolyphosphoric acid

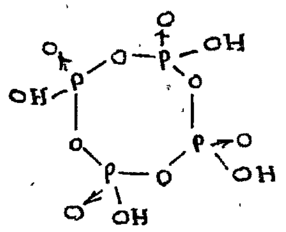
n = 3, Pentapolyphosphoric acid

The contents of the commercial phosphoric acid, by filter paper chromatographic method, were found to be orthophosphoric acid, pyrophosphoric acid and linear polyphosphoric acids, having a theoretical P_2O_5 content of 81-85 %. Although commercial polyphosphoric acid

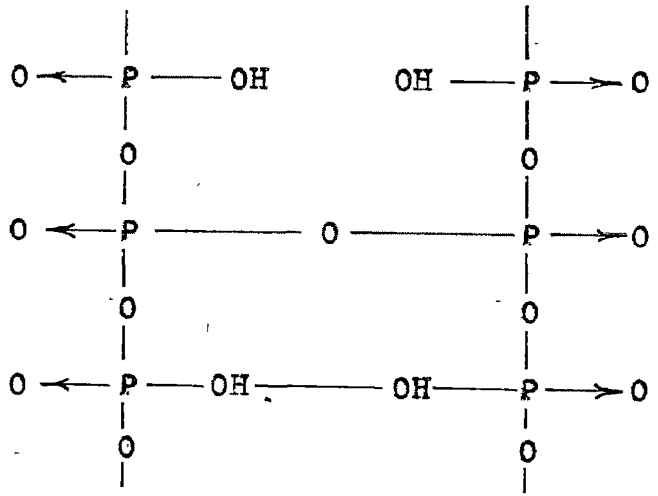
(82-84 % P_2O_5) does not contain any detectable quantity of cyclic phosphoric acids, small amount of these acids have been found in mixtures having a theoretical P_2O_5 content greater than 85 %. Polyphosphoric acid, having content of 90 % P_2O_5, contained three percent trimetaphosphoric acid and also a trace of tetrametaphosphoric acid. It has been shown that condensed polyphosphoric acids, having P_2O_5 content greater than 85 %, contained some cross-linked (branched) polyphosphoric acids. Since, the evidence for the presence of the cyclic acids appears only when cross-linked polyphosphoric acids are also present, there is some possibility that the cyclic acids, arise only upon hydrolysis of the cross-linked acids. Although this problem has not been resolved, the cyclic and cross-linked structures are as follows :



Trimetaphosphoric acid



Tetrametaphosphoric acid



A cross-linked polyphosphoric acid

Polyphosphoric acid is a clear, colourless, extremely viscous, hygroscopic liquid, having a specific gravity of 2.060 at 20°C, when theoretical content of P_2O_5 equals 83 % and it is conveniently fluid at 60°C. Another point of interest with regard to condensed polyphosphoric acid is that, for any given content of phosphorus pentoxide, the same ratio of component acid results, no matter what the method of preparation of the acid, provided that a homogenous melt is obtained during the preparation. The versatility and general utility of polyphosphoric acid arise from the fact that it is a mild reagent even though a strong dehydrating agent. Generally, it does not bring about charring of organic compounds, and it does not undergo a violent reaction with hydroxylic compounds. It does not bring about the phosphonation of aromatic compounds. For these reasons it is a better reagent than the other reagents such as sulphuric acid, hydrogen fluoride, phosphoric anhydride or aluminium chloride (Kennard K.C., Org. Chem. Bull., Eastman Kodak Co., No. 1, 1957, 29).

Various workers have prepared and used different concentrations of polyphosphoric acid to bring about the reactions. Fritz Uhlig (Angew. Chem., 1954, 66, 435 ; Chem. Abst., 1955, 49, 10159) prepared polyphosphoric acid by slowly adding 150-210 g. P_2O_5 with stirring and cooling to 100 ml. phosphoric acid (d. 1.709) and subsequently heating in a boiling water-bath for several hours. This mixture contained 80-84 % P_2O_5 content and was found to be highly active polyphosphoric acid. Hauser and Murray

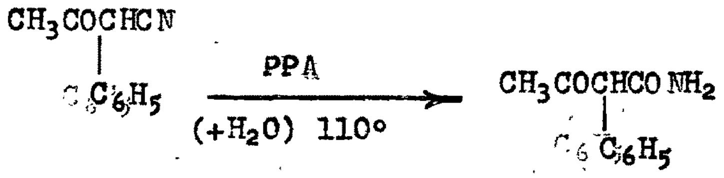
(J. Amer. Chem. Soc., 1955, 77, 2851) used commercial polyphosphoric acid (15 g.) to cyclise crotonates (3.0 g.) into their quinoline derivatives. Stephenson (Miss) (J. Chem. Soc., 1956, 2557) prepared polyphosphoric acid by adding phosphorus pentoxide (63.0 g.) in phosphoric acid (36.0 ml.) at 105°C till the mixture became clear and this amount was used for the 0.01 mole of the reactant. Sukh Dev (J. Ind. Chem. Soc., 1955, 32, 255) prepared this reagent by dissolving phosphorus pentoxide (140 g.) with syrupy ortho phosphoric acid (60 ml. ; 85 %) in a flask, which was immediately stirred with a glass rod till homogenous ; the heat of the reaction sufficed for the almost complete dissolution of the anhydride, and in case of any particles remained undissolved, the flask was heated on a steam-bath at 60°C till clear, and this quantity was applied to cyclise 0.20 mole of the reactant. Further, Krishna Rao and Sukh Dev. (J. Ind. Chem. Soc., 1957, 34, 255) prepared this reagent from P_2O_5 (270 g.) and syrupy phosphoric acid (d. 1.75 ; 116 ml.).

Moreover, Fritz Uhlig (loc.cit.) observed that for determining optimum operating conditions, the amount of organic substance was mixed with 10-30 times the amount of polyphosphoric acid. If the mixture darkens immediately, ice-cooling is required ; if the colour changes showly, room-temperature is preferable ; if any little colour change occours, heating is necessary.

Polyphosphoric acid as a hydrolysing agent :

In the hydrolysis of nitriles to acids, the use of 100 % phosphoric acid has been known for some long time (G. Berger and S.C.J. Oliver, Rec. trav. chim., 1927, 46, 600). The effectiveness of polyphosphoric acid in the Beckmann rearrangement (E.C.Horning, V.L.Stromberg and H.A.Lloyd, J. Amer. Chem. Soc., 1952, 74, 5153) indicated the rather exceptional stability of amides in polyphosphoric acid reagent. Again Snyder and Elston (J. Amer. Chem. Soc., 1954, 76, 3039) found polyphosphoric acid to be effective in the reactions of carboxylic acids with weakly basic amines to yield the corresponding amides, i.e., acetic acid and 2,4-dinitroaniline gave 92 % yield of 2,4-dinitroacetanilide. Further, these authors also observed that the simple aromatic and aliphatic nitriles were hydrolysed to the corresponding amides in high yields by reaction with polyphosphoric acid for approximately one hour at 110°C. Benzonitrile for example, was converted to benzamide in a 96 % yield. Ethyl malonate was isolated in 65 % yield from the hydrolysis of ethyl cyanoacetate. But, this method was not found to be suitable for the hydrolysis of sterically hindered nitriles. Thus, 2,4,6-triisopropylbenzonitrile and 1-hydroxy-2-cyano-3-methylnaphthalene were inert even at 160°C, while at this temperature, cyanomesitylene underwent both hydrolysis and decarboxylation to give mesitylene.

Hauser and Murray (loc.cit.) prepared 4-hydroxyquinoline from anil, which was obtained from aniline and β-ketonitrile ; and they observed that polyphosphoric acid was effective in order to bring about both the steps, viz., partial hydrolysis and cyclisation in a single process to form a quinoline derivative. Thus, α-acetyl α-tolunitrile I (β-ketonitrile) with polyphosphoric acid at 110°C is partially hydrolysed to β-ketoamide (II) which at 140°C undergoes cyclisation to give a 4-hydroxyquinoline derivative. The partial hydrolysis is expressed as :



$$\underset{\textstyle C_6H_5}{CH_3COCHCN} \xrightarrow[(+H_2O)\ 110°]{PPA} \underset{\textstyle C_6H_5}{CH_3COCHCONH_2}$$

I II

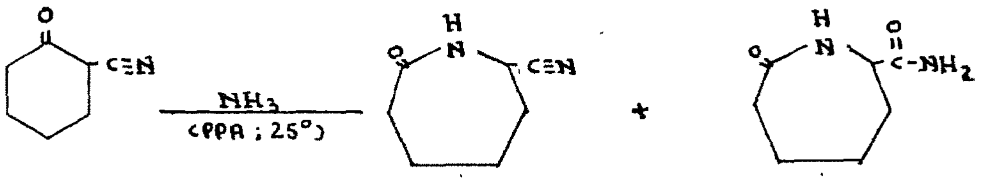
Again, Hauser and Eby (J. Amer. Chem. Soc., 1957, 79, 725) hydrolysed some β-ketonitriles into their corresponding β-ketoamides by the method of Hauser and Hoffenberg (J. Org. Chem., 1955, 20, 1448 ; 1482) with boron fluoride in aqueous acetic acid as well as by the method of Snyder and Elston (loc.cit.) with polyphosphoric acid, and the conclusion was drawn that both the boron fluoride and polyphosphoric acid methods generally gave good yield of β-ketoamides. Also these methods were considered superior to other known methods, one of which involved the ammonolysis of the respective β-ketoesters (J.T.Abrams and F.S.Kipping, J. Chem. Soc., 1934, 1988). Moreover, most other β-ketoesters that would be required for the preparation of β-ketoamides, which are not readily available, have been obtained from β-ketonitriles as under :

$$CH_3CN \xrightarrow[(2)RCOOCH_3]{(1)\ NaNH_2} RCOCH_2CN \xrightarrow[(\ +H_2O\ )]{BF_3\text{-}HAc \text{ or } PPA} RCOCH_2CONH_2$$

(R = $-C_6H_5$ or $-\ Cl{\cdot}C_6H_4\text{-}m$).

The boron fluoride method involved the rapid saturation of a mixture of the β-ketonitrile and aqueous acetic acid with the reagent, under which condition the temperature rose spontaneously to 120-140°C. The reaction was complete within a short time of about 10-20 minutes. The phosphoric acid method consisted generally in heating the β-ketonitriles with the reagent at the steam-bath temperature for 30 minutes. It should be pointed out that the reaction of β-ketonitriles with boron trifluoride in aqueous acetic acid produced a boron difluoride complex of the β-ketoamides from which the β-ketoamides were subsequently liberated by means of hot sodium acetate solution.

Robert Conley (J. Org. Chem., 1958, 23, 1330) described the method for effecting the Schmidt transformation of ketones employing polyphosphoric acid both as the solvent and the catalyst. For example 2-cyanocyclohexanone (I), on rearrangement and ring expansion, gave two products of 7-membered ring, viz., 7-cyano-2-keto-hexamethylenimine (II) and 7-carboxamido-2-ketohexamethylenimine(III) as under:



(I) (II) (III).

The above amido-lactam (III) was also found to be formed from product (II) by hydration of the cyano group using polyphosphoric acid at 60°C. It was also found that the cyano-lactam (II) could be quantitatively converted to the amido-lactam (III).

Sulphuric acid and other hydrolytic agents :

The hydrolysis of nitriles to carboxylic acids is usually effected by refluxing with concentrated solutions of sulphuric acid or sodium hydroxide. Kaszuba (J. Amer. Chem. Soc., 1945, 67, 1227) carried out the hydrolysis of acrylo-nitrile to acrylic acid with ice-cold mixture of concentrated sulphuric acid and ice. Goldberg, Ordas and Carsch (J. Amer. Chem. Soc., 1947, 69, 260) hydrolysed 9-cyanophenanthrene in ethylene glycol monoethyl ether with potassium hydroxide and obtained phenanthroic acid . Similarly, valeric acid (King, J. Chem. Soc., 1935, 982) and isocaproic acid (Noyer, J. Amer. Chem. Soc., 1901, 23, 393) have been obtained from their respective nitriles by the alkali hydrolysis in good yields.

Cocker and Lapworth (J. Chem. Soc., 1931, 1391) observed that α-amino nitriles, however, revert too readily to cyanide, ammonia or amine in presence of alkalies and cannot, therefore, satisfactorily be converted into the amino acids except by means of acid reagents. While the free α-amino-nitriles as a class are among the most unstable nitriles known and readily lose or exchange their cyanogen group (as -CN-cyanidion), their salts are much stable with mineral acids, and show no tendency to behave in this manner even at 125°C provided that a sufficient concentration of mineral acid is maintained in the system. The hydrolysis of amino-nitriles to amino-acids is carried out with 40 % sulphuric acid by slow addition with constant agitation, and then heated for 3 hours at 125°C. After cooling, it was diluted with water and the acid was obtained on treatment with barium carbonate.

Turner (J. Amer. Chem. Soc., 1946, 68, 1607) carried out the acid hydrolysis of dimethylaminoacetonitrile which was cooled first at -15°C, and was mixed with equally cold concentrated sulphuric acid. The reaction mixture was kept for eighty-five hours at room temperature, and then poured upon ice and made alkaline with concentrated ammonium hydroxide, gave the desired acid. Buck et al.(J. Amer. Chem. Soc., 1930, 52, 5202) hydrolysed p-dimethylaminobenzaldehyde cyanohydrin by dissolving in sulphuric acid (sp.gr. 1.84) below 15°C, and after about fifteen minutes, the reaction mixture was poured over crushed ice and obtained the amide on careful neutralisation with ammonia.

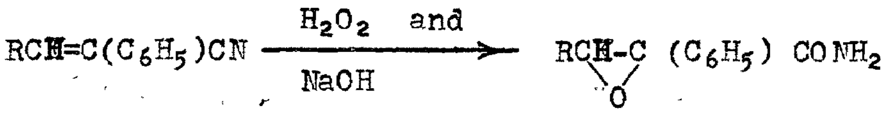
Tiemann and Stephan (Ber., 1882, 15, 2035) converted several arylamino nitriles into the corresponding amides by treatment with concentrated sulphuric acid, and isolating the product by pouring the reaction mixture on ice and neutralising it with ammonia. Cook and Cox (J. Chem. Soc., 1949, 2334) applied the acid hydrolysis with methylaminoacetonitrile, where no product of hydrolysis was obtained, but when sulphuric acid solution was poured into well-cooled 95 % ethanol solution of the above compound N-methylglycineamide hydrogen sulphate was obtained in quantitative yield, and this salt, on neutralisation with sodium methoxide in methanol, gave 90 % yield of

N-methylglycineamide. Thus, this process proved to be satisfactory in the hydrolysis of α-isopropylamino-n-, α-methylaminoiso-, and α-isopropylaminoisovaleronitrile.

Sperber, Papa and Schwenk (J. Amer. Chem. Soc., 1948, <u>70</u>, 3091) carried out the conversion of tributylacetonitrile to tributylacetamide on a steam-bath for twelve hours using 80 % sulphuric acid. Tributylacetamide was not further hydrolysed to tributylacetic acid by different concentrations of sulphuric acid or by various other hydrolytic agents, viz., nitrous anhydride, concentrated hydrochloric acid, phosphoric acid, a mixture of acetic and sulphuric acids, and aqueous alkali etc. But alkylnitriles in organic solvents in the presence of a gaseous hydrogen chloride gave a good yield of trialkylacetic acids.

Wenner (J. Org. Chem., 1950, <u>15</u>, 548) carried out the acid hydrolysis of arylacetonitriles by rapid stirring with aqueous concentrated hydrochloric acid at moderate temperature without using the organic solvent, and thus free arylacetic acids or their amides were prepared in high yields. Benzyl cyanide when treated with concentrated hydrochloric acid with rapid stirring gave phenylacetamide. The reaction can be carried out even at 10°C, but the strength of hydrochloric acid should be of 30 % to effect the conversion of the nitrile into the amide. Further hydrolysis of an amide to acid proceeds slowly, but the speed of hydrolysis increases considerably when the amide is heated with more dilute acid. So amides are formed from nitriles upto about 60°C, which remain undissolved, and at higher temperature, the corresponding acids result. Several polynuclear arylacetonitriles were hydrolysed in the same way without difficulty. Moreover, the alkoxy-substituted nitriles yield the corresponding amides, if the reaction temperature does not exceed 50-60°C ; but at higher temperature the hydrochloric acid will lead to cleavage of the alkoxy groups.

West (J. Amer. Chem. Soc., 1920, 42, 1662) used hydrogen peroxide, which reacted with aliphatic and aromatic nitriles in alkaline solution at 50°C to give amides in 50-95 % yield. This reaction is exothermic and is followed by the evolution of oxygen. The hydrogen peroxide was used in concentrations varying from 3 % to 30 %, but in the case of o-substituted benzonitriles, which were difficult to hydrolyse, required the higher concentration of the reagent. Wiley and Morgan Jr. (J. Org. Chem., 1950, 15, 800) partially hydrolysed adiponitrile and sebaconitrile with alkaline 3 % hydrogen peroxide and obtained ω -cyano-valeramide and ω -cyanopelargonamide. They also tried other methods including alkaline and acid hydrolysis, but the yields of amides were low or in some case no amide was formed at all. Murray and Cloke (J. Amer. Chem. Soc., 1934, 56, 2749) prepared glycidamides by hydrogen peroxide from certain olefinic nitriles. Thus,



$$RCH{=}C(C_6H_5)CN \xrightarrow[NaOH]{H_2O_2 \text{ and}} \underset{\diagdown O \diagup}{RCH{-}C}\,(C_6H_5)\,CONH_2$$

It has been observed in the present investigation that both polyphosphoric acid and 75 % sulphuric acid have been found to serve as efficient hydrolytic agents which bring about hydrolysis of nitriles, although the former is chiefly used as a condensing agent to effect cyclisation (discussed in P.II) ; but the latter is found to be a better hydrolytic agent in adding a molecule of water into the nitrile group of cyanacet arylamides, giving the corresponding malon mono arylamides.

The present work was undertaken with a view to obtain suitable intermediates, viz., malon mono arylamides, and malon aryl acids, required for the proposed synthesis of 2,4-dihydroxyquinolines. The malon mono arylamides (substituted amides of malonic acid) are, thus, separately prepared in good yields, on partial hydrolysis of cyanacet arylamides (substituted amides of cyanacetic acid) with polyphosphoric acid and with 75 % sulphuric acid. Again, malon mono arylamides, thus obtained, when further treated with polyphosphoric acid, simultaneously underwent further hydrolysis and cyclisation giving 2,4-quinolinediols.

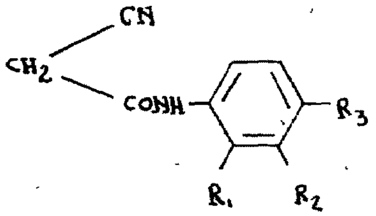
It may be noted that cyanacet arylamides have been partially hydrolysed into malon mono arylamides with polyphosphoric acid, which, at the same time in a single step operation, was found to be ineffective to cyclise the former amides into quinolinediols. Moreover, the use of 75 % sulphuric acid was found to be quite effective in good yields to partially hydrolyse these very nitriles, giving the corresponding malon mono arylamides, which were not consequently cyclised into quinolinediols, using concentrated sulphuric acid or a mixture of acetic anhydride and concentrated sulphuric acid. Moreover, these malon mono amides on further hydrolysis gave malon aryl acids in very poor yields.

Cyanacetanilide (Compt. rend., 1895, <u>121</u>, 189) cyanacet-p-toluidide (Compt. rend., 1889, <u>108</u>, 1116), cyanacetbenzylamide (Guareschi, Chem. Centr., 1892, 1,382) have been known, but no reliable details of the methods employed in their preparation could be found. Therefore, in the preparation of substituted amides of cyanacetic acid Whiteley's method (J. Chem. Soc., 1903, 83, 24) was followed.

Cyanacet arylamides

Requisite amounts of ethyl cyanacetate and pure arylamine were mixed in a round-botton flask which was heated with an air condenser at 160-170°C. for six hours. The contents of the flask, when hot were then poured into a mortar, where the whole mass solidified. The solid was broken and triturated with a mixture of equal volumes of benzene and light petroleum. It was then filtered and the process was repeated until the reddish colour of the solid disappeared, and then it was crystallised from acetic acid.

The following cyanacet arylamides (I) have, thus, been prepared:-



(I).

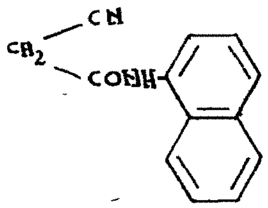
(1) Cyanacetanilide : ($I, R_1=R_2=R_3=H$)
(2) Cyanacet-o-toluidide : ($I, R_2=R_3=H$; $R_1=CH_3$)
(3) Cyanacet-m-toluidide : ($I, R_1=R_3=H$; $R_2=CH_3$)
(4) Cyanacet-p-toluidide : ($I, R_1=R_2=H$; $R_3=CH_3$)
(5) Cyanacet-p-chloroanilide : ($I, R_1=R_2=H$; $R_3=Cl$)

(6) Cyanacet-o-anisidide : ($I, R_2=R_3=H$; $R_1=OCH_3$)

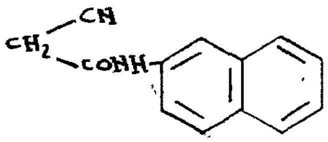
(7) Cyanacet benzylamide : ($C_6H_5CH_2NH.COCH_2CN$)

(8) Cyanacet-1:3:4-xylidide : ($I, R_1=H$; $R_2=R_3=CH_3$)

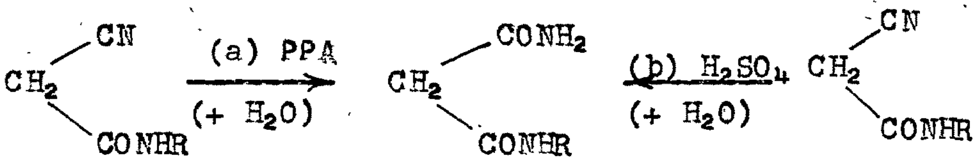
(9) Cyanacet-α-naphthylamide :



(10)Cyanacet-β-naphthylamide :



The above mentioned cyanacet arylamides (I) have been partially hydrolysed using (a) polyphosphoric acid (PPA) and (b) 75 % sulphuric acid, when the corresponding malon mono arylamides (II) have been obtained in each case. The course of reaction in each is expressed as follows:-



(I) (II) (I)

where, R is phenyl, tolyl,xylyl,naphthyl, etc.groups.

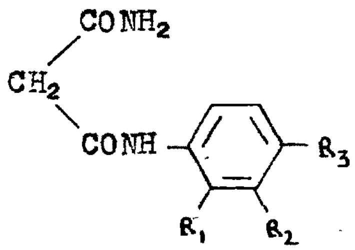
(<u>Methods of preparation</u>)

<u>Malon mono arylamides</u> :

(a) <u>Polyphosphoric acid</u> : Cyanacet arylamide (I ; 0.01 M) was dissolved in a clear solution of polyphosphoric acid, obtained by dissolving phosphorus pentoxide (10.0 g.) in phosphoric acid (6.0 ml. ; d.1.75) and heated for 2 hours at 110°C. The reaction mixture, on pouring into water, gave a white product, which was filtered and crystallised from aqueous alcohol. It was found to be malon mono arylamide.

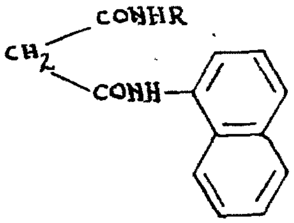
(b) <u>75 % sulphuric acid</u> : Cyanacet arylamide (I ; 0.01 M) was dissolved in 10.0 ml. of ice-cold 75 % sulphuric acid and the reaction mixture was kept over-night at room temperature. It was then poured into ice-cold water giving a white product, which was crystallised as above and identified as malon mono arylamide (Mehta and Patel, Curr.Sci., 1959, <u>28</u>, 200 ; J. Sci. industr. Res., 1961, <u>20B</u>, 457).

Accordingly the following malon mono arylamides (II) have been prepared :

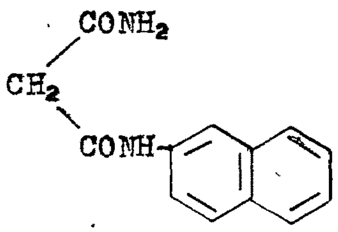


(II)

(1) Malon monoanilide : (II,R_1=R_2=R_3=H)
(2) Malon mono-o-toluidide : (II,R_2=R_3=H ; R_1=CH_3)
(3) Malon mono-m-toluidide : (II,R_1=R_3=H ; R_2=CH_3)
(4) Malon mono-p-toluidide : (II,R_1=R_2=H ; R_3=CH_3)
*(5) Malon mono-p-chloroanilide : (II,R_1=R_2=H ; R_3=Cl)
*(6) Malon mono-o-anisidide : (II,R_2=R_3=H ; R_1=OCH_3)
*(7) Malon mono-benzylamide : ($C_6H_5CH_2NHCOCH_2CONH_2$)
(8) Malon mono-1:3:4-xylidide : (II,R_1=H ; R_2=R_3=CH_3)
(9) Malon mono-α-naphthylamide :



(10) Malon mono-β-naphthylamide :



Compounds marked with asterisks (*) are reported for the first time.

The identity of malon mono arylamides, prepared by each of the above methods (a) and (b) was established by analysis as well as by comparing their respective melting points and mixed melting points with those of the authentic samples, which are prepared by hydrolysing malon diarylamides by means of liquor ammonia (0.88 d.) according to Whiteley's method (loc.cit.) and Backes, West and Whiteley, (J. Chem. Soc., 1921, 119, 359) as modified by Naik et al.(Naik, Desai and Parekh, J. Ind. Chem. Soc., 1930, 7, 137 ; Naik and Patel, ibid.,1932, 9, 185). The yields obtained in both the above methods were almost quantitative, but the products obtained by the use of 75 % sulphuric acid were cleaner and this method was found to be relatively simple. Both sulphuric acid and polyphosphoric acid are found to be the most efficient hydrolysing agents, which are employed,here,in divising these simpler methods for the preparation of malon mono arylamides, when compared with the above method of Whiteley et al. (loc.cit.). Further, half a molecule of water of crystallisation is found to be present only in malon monoanilide (1) and in malon mono-p-toluidide (4). This was determined by treating the hydrate of an amide over toluene vapours under vacuum in Abden Helden apparatus, on the basis of the difference in weight before and after the heating of that particular amide-hydrate.

In order to obtain malon arylacids, some of the above mentioned malon mono arylamides have further been attempted to hydrolysed using 10 % alcoholic potassium hydroxide. It has also been observed that these malon mono arylamides on acid or alkali hydrolysis in hot gave a mixture mainly of malonic acid and a very small amount of malon arylacids. The yields of malon arylacids are thus found to be very poor and this method for complete hydrolysis of malon mono arylamides is not at all suitable for the preparation of malon arylacids with 10 % alcoholic potassium hydroxide in hot or in cold.

However the malon arylacids, viz., malon anilic acid, malon-m-toluidic acid, malon-p-toluidic acid and malon 1:3:4-xylidic acid, have been obtained on complete hydrolysis of malon monoanilide, malon mono-m-toluidide, malon mono-p-toluidide and malon mono-1:3:4-xylidide respectively using 10 % alcoholic potassium hydroxide in cold as under:

Malon mono arylamide (0.01 M) was treated with 15 ml. of alcoholic potassium hydroxide (10 %) and the reaction mixture was kept at room temperature for 24 hours. It was then neutralised with hydrochloric acid, extracted with ether and the product malon arylacid, obtained in very poor yield, was crystallised from water or from aqueous alcohol. In this way the above mentioned malon arylacids have not been obtained by complete hydrolysis of the corresponding malon mono arylamides. These malon arylacids have been identified by comparing the melting points and mixed melting points with the corresponding authentic samples. Another method was, therefore, explored in order to prepare the proposed malon arylacids, which are used as suitable intermediates for the synthesis of quinolinediols.

Malon aryl acids

It is interesting to note that the malon mono arylamides on further treatment with polyphosphoric acid underwent cyclisation giving 2,4-dihydroxyquinolines ; whereas concentrated sulphuric acid or a mixture of acetic anhydride and concentrated sulphuric acid as a cyclising agent was found to be ineffective with these amides. Moreover, quinolinediols obtained from malon mono arylamides are found to be in poor yields ; whereas those prepared from malon aryl acids are in good yields. Hence, the malon aryl acids, which may serve as better intermediates than the malon mono arylamides, have been prepared with a view to synthesise 2,4-dihydroxyquinolines, which also serve as useful intermediates in the preparation of a series of antimalerials.

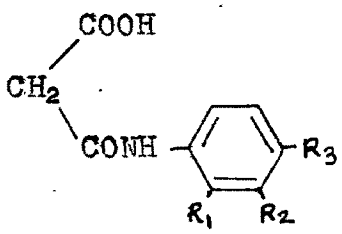
A number of malon arylacids have thus been prepared by the method of Chattaway and Olmsted (J. Chem. Soc., 1910, 97, 938) as modified by Ahluwalia et al. (loc.cit.) as under:

Method of Preparation :

A mixture of pure arylamine (0.1 M) and ethyl malonate (0.175 M) was gently refluxed for fo~~u~~rty minutes in a flask attached to an air condenser of such a length that the alcohol formed was allowed to escape, while the malonic ester flowed back into the flask. The product was then mixed with twice the bulk of ethyl alcohol and allowed to cool, when malon dianilide-$PhNHCOCH_2CONHPh$- precipitated, which was filtered out. The filtrate was poured into excess of water and on shaking ethyl malon anilate-$PhNHCOCH_2COOC_2H_5$- separated as an oil, which slowly solidified. The mixture of amine and ester was thus converted into malon dianilide and ethyl malon anilate (amate).

In order to prepare malon arylacid, a solution of 8.0 g. sodium carbonate in 70.0 ml. water was added to the above oily filtrate (amate) and steam was blown through the mixture for about an hour until the ester at first separated as an oil had completely disappeared. The cooled liquid gave a slight turbidity of a trace of malon dianilide which was filtered and clear filtrate is obtained on concentration of alcohol by gentle heating. On adding hydrochloric acid in slight excess to the above filtrate malon arylacid precipitated which was crystallised from very dilute alcohol or water (Mehta and Patel, J. Sci. Industr. Res., 1960, 19B, 436-38).

The following malon arylacids have thus been prepared by the above method from different arylamines and ethyl malonate :



(III)

(1) Malon-anilic acid : $(III, R_1=R_2=R_3=H)$

*(2) Malon-o-toluidic acid : $(III, R_2=R_3=H \; ; \; R_1=CH_3)$

(3) Malon-m-toluidic acid : $(III, R_1=R_3=H \; ; \; R_2=CH_3)$

(4) Malon-p-toluidic acid : $(III, R_1=R_2=H \; ; \; R_3=CH_3)$

*(5) Malon-m-chloroanilic acid : $(III, R_1=R_3=H \; ; \; R_2=Cl)$

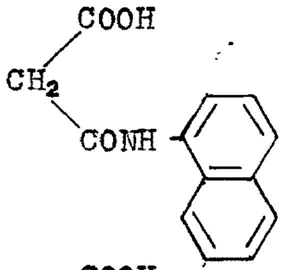
*(6) Malon-p-chloroanilic acid : $(III, R_1=R_2=H \; ; \; R_3=Cl)$

*(7) Malon-o-anisidic acid : $(III, R_2=R_3=H \; ; \; R_1=OCH_3)$

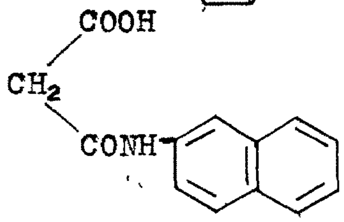
*(8) Malon-p-anisidic acid : $(III, R_1=R_2=H \; ; \; R_3=OCH_3)$

(9) Malon-1:3:4-xylidic acid : $(III, R_1=H \; ; \; R_2=R_3=CH_3)$

*(10) Malon-α-naphthylanilic acid :



*(11) Malon-β-naphthylanilic acid :



Malon arylacids marked with asterisks (*) are reported for the first time.

Thus both polyphosphoric acid and 75 % sulphuric acid are found to be very efficient hydrolytic agents, involving simpler methods to effectively bring about the partial hydrolysis of cyanacetarylamides, forming the corresponding malon mono arylamides ; whereas malon arylacids and malon mono arylamides with polyphosphoric acid as the cyclising agent have respectively undergone cyclisation giving 2:4-dihydroxyquinolines (Part II).

EXPERIMENTAL

Malon mono arylamides :

Malon monoanilide :

(a) Cyanacet anilide (1.6 g. ; 0.01 M) was dissolved in a clear solution of polyphosphoric acid, prepared by dissolving phosphorus pentoxide (10.0 g.) in phosphoric acid (6.0 ml. ; d. 1.75), and heated in an oil bath at 110°C for 2 hr. with a calcium chloride guard tube. The reaction mixture, on pouring into water, gave white product, which was filtered and crystallised from aqueous alcohol ; m.p. 133°C. Yield : 1.45 g.

(b) Cyanacetanilide (1.6 g. ; 0.01 M) was dissolved in ice-cold 75 % sulphuric acid (10.0 ml.) and the reaction mixture was kept over-night at room temperature. A clear white product was obtained when the mixture was poured into 25 ml. of cold water. It was then filtered and crystallised from aqueous alcohol ; m.p.133°C. Yield 1.5 g.

The identity of malon mono anilide, prepared by each of the above methods, was established by comparing its ~~respective~~ melting point and mixed melting point with that of the authentic sample as well as by the analysis.

Analysis :

4.360 mg. of the substance gave 0.575 ml. of nitrogen at 29°C and 761 mm. pressure.

Found : N = 14.93 %.

$C_9H_{10}O_2N_2.1/2H_2O$ requires : N = 14.97 %.

In the same way the following other cyanacet arylamides have been partially hydrolysed by the separate application of the above methods (a) and (b), giving in each case the corresponding malon mono arylamides, which are identified as usual by their respective melting points, mixed melting points and by analysis.

Malon-mono-o-toluidide :

Cyanacet-o-toluidide (1.92 g.) was separately treated as before both by polyphosphoric acid as well as by 75 % sulphuric acid. The crude product, obtained in each case, was crystallised from aqueous alcohol, m.p. 162°C. Yield 1.8 g.

Analysis :

9.30 mg. of the substance gave 1.202 ml. of nitrogen at 33°C and 754 mm. pressure.

Found : N = 14.30 %.

$C_{10}H_{12}O_2N_2$ requires : N = 14.58 %.

Malon-mono-m-toluidide :

Cyanacet-m-toluidide (1.92 g.) was treated as before and the malon-mono-m-toluidide, obtained by each method, was crystallised from aqueous alcohol, m.p. 164°C. Yield, 1.75 g.

Analysis :

9.34 mg. of the substance gave 1.186 ml. of nitrogen at 29°C and 758 mm. pressure.

Found : N = 14.32 %.

$C_{10}H_{12}O_2N_2$ requires : N = 14.58 %.

Malon-mono-p-toluidide :

Cyanacet-p-toluidide (1.92 g.) was separately treated as before and malon-mono-p-toluidide obtained in each case was crystallised from aqueous alcohol, m.p.144°C. Yield, 1.80 g.

Analysis :

4.772 mg. of the substance gave 0.565 ml. of nitrogen at 28°C and 761 mm. pressure.

Found : N = 13.64 %.

$C_{10}H_{12}O_2N_2.1/2H_2O$ requires : N = 13.93 %.

Malon-mono-p-chloroanilide :

Cyanacet-p-chloroanilide (2.12 g.) was treated as before by both the methods and malon-mono-p-chloroanilide thus,obtained in each was crystallised from aqueous alcohol, m.p. 145°C. Yield, 2.0 g.

Analysis :

8.98 mg. of the substance gave 1.08 ml. of nitrogen at 32°C and 758 mm. pressure.

Found : N = 13.43 %.

$C_9H_9O_2N_2Cl$ requires : N = 13.17 %.

Malon-mono-o-anisidide :

Cyanacet-o-anisidide (1.96 g.) was separately treated as before and malon-mono-o-anisidide was crystallised as usual in each case, m.p. 164°C. Yield, 1.80 g.

Analysis :

11.34 mg. of the substance gave 1.325 ml. of nitrogen at 28°C and 757 mm. pressure.

Found : N = 13.20 %.

$C_{10}H_{12}O_3N_2$ requires : N = 13.46 %.

Malon-mono-benzylamide :

Cyanacet-benzylamide (1.92 g.) was treated as before by both the methods and the malon-mono-benzylamide thus obtained in each was crystallised as above, m.p. 120°C. Yield, 1.7 g.

Analysis :

4.960 mg. of the substance gave 0.666 ml. of nitrogen at 29°C and 760 mm. pressure.

Found : N = 14.88 %.

$C_{10}H_{12}O_2N_2$ requires : N = 14.58 %.

Malon-mono-1:3:4-xylidide :

Cyanacet-1:3:4-xylidide (2.06 g.) was separately treated as before and in each case the malon-mono-1:3:4-xylidide was crystallised as above, m.p. 165°C. Yield, 1.85 g.

Analysis :

11.38 mg. of the substance gave 1.420 ml. of nitrogen at 34°C and 758 mm. pressure.

Found : N = 13.84 %.

$C_{11}H_{14}O_2N_2$ requires : N = 13.60 %.

Malon-mono-α-naphthylamide :

Cyanacet-α-naphthylamide (2.28 g.) was treated as before by both the methods and in each case malon-mono-α-naphthylamide was crystallised as above, m.p. 145°C. Yield, 2.0 g.

Analysis :

10.40 mg. of the substance gave 1.18 ml. of nitrogen at 35°C and 758 mm. pressure.

Found : N = 12.54 %.

$C_{13}H_{12}O_2N_2$ requires : N = 12.27 %.

Malon-mono-β-naphthylamide :

Cyanacet-β-naphthylamide (2.28 g.) was separately treated as before and in each case the malon-mono-β-naphthylamide was crystallised as above, m.p. 188°C. Yield, 1.90 g.

Analysis :

9.98 mg. of the substance gave 1.108 ml. of nitrogen at 32°C and 758 mm. pressure.

Found : N = 12.40 %.

$C_{13}H_{12}O_2N_2$ requires : N = 12.27 %.

Malon arylacids :

Malon-anilic acid :

A mixture of aniline (9.3 g.) and ethyl malonate (28.0 g.) was heated to gentle boiling for fo~~u~~rty minutes in a flask attached to an air-condenser. The product was then treated with warm ethyl alcohol (100 ml.) when malon dianilide ($NHPhCOCH_2CONHPh$) crystallised out on cooling and the reaction mixture was then filtered. To the filtrate an aqueous solution of sodium carbonate in excess was added, and steam was blown through it for about an hour, till the oily layer that separated had disappeared. A small amount of the dianilide, that appeared on cooling, was filtered out. The filtrate,on acidification with hydrochloric acid, gave a white product, which was filtered and crystallised from water, m.p. 136°C. Yield, 6.5 g.

Malon-mono-anilide (0.01 M) dissolved in 15 ml. alcoholic potassium hydroxide (10 %) in cold and the reaction mixture was kept at room temperature for 24 hrs. It was then neutralised with hydrochloric acid extracted with ether and crystallised from aqueous alcohol, m.p. 136°C, in very poor yield. Mixed m.p. with malon anilic acid, described above, was not depressed.

Malon-o-toluidic acid :

A mixture of o-toluidine (10.7 g.) and ethyl malonate (28.0 g.) was treated as above and the malon-o-toluidic acid, thus, obtained was crystallised from water, m.p. 144°C. Yield, 7.3 g.

Analysis :

4.14 mg. of the substance gave 9.494 mg. of carbon dioxide and 2.154 mg. of water.

6.70 mg. of the same substance gave 0.426 ml. of nitrogen at 28°C and 761 mm. pressure.

Found : C = 62.58 % ; H = 5.821 % ; N = 7.22 %.
$C_{10}H_{11}O_3N$ requires : C = 62.16 % ; H = 5.74 % ; N = 7.25 %.

Malon-m-toluidic acid :

A mixture of m-toluidine (10.7 g.) and ethyl malonate (28.0 g.) was treated as above and malon-m-toluidic acid, thus obtained was crystallised from water, m.p. 105-106°C. Yield, 6.9 g.

Malon mono-m-toluidide (0.01 M) was dissolved in 15 ml. alcoholic potassium hydroxide (10 %) in cold and the reaction mixture was kept at room temperature for 24 hrs. It was then neutralised with hydrochloric acid, extracted with ether and crystallised from alcohol, m.p. 105°C in very poor yield. Mixed m.p. with malon-m-toluidic acid, described above, was not depressed.

Malon-p-toluidic acid :

A mixture of p-toluidine (10.7 g.) and ethyl malonate (28.0 g.) was treated as above and malon-p-toluidic acid thus obtained, was crystallised from water, m.p. 156°C. Yield 7.8 g.

Malon-mono-p-toluidide (0.01 M) dissolved in 15 ml. alcoholic potassium hydroxide (10 %) in cold and the reaction mixture was kept at room temperature for 24 hrs. It was then neutralised with hydrochloric acid, extracted with ether and crystallised from alcohol m.p. 156°C in very poor yield. Mixed m.p. with malon-p-toluidic acid, described above, was not depressed.

Malon-m-chloroanilic acid :

A mixture of freshly distilled m-chloroaniline (12.7 g.) and ethyl malonate (28.0 g.) was treated as above and the malon-m-chloroanilic acid was crystallised from water, m.p. 131°C. Yield, 9.8 g.

Analysis :

6.18 mg. of the substance gave 0.337 ml. of nitrogen at 30°C and 761 mm. pressure.

Found : N = 6.15 %.

$C_9H_8O_3NCl$ requires : N = 6.55 %.

Malon-p-chloroanilic acid :

A mixture of p-chloroaniline (12.7 g.) and ethyl malonate (28.0 g.) was treated as above and the said acid was crystallised from water. m.p. 145°C. Yield, 8.4 g.

Analysis :

4.09 mg. of the substance gave 7.530 mg. of carbon dioxide and 1.412 mg. of water.

6.06 mg. of the same substance gave 0.327 ml. of nitrogen at 30°C and 761 mm. pressure.

Found : C = 50.22 % ; H = 3.86 % ; N = 6.08 %.

$C_9H_8O_3NCl$ requires : C = 50.58 % ; H = 3.74 % ; N = 6.55 %.

Malon-o-anisidic acid :

A mixture of o-anisidine (12.3 g.) and ethyl malonate (28.0 g.) was treated as above, the said acid was crystallised from water, m.p. 148°C. Yield, 7.9 g.

Analysis :

6.82 mg. of the substance gave 0.381 ml. of nitrogen at 30°C and 761 mm. pressure.

Found : N = 6.30 %.

$C_{10}H_{11}O_4N$ requires : N = 6.70 %.

Malon-p-anisidic acid :

A mixture of p-anisidine (12.3 g.) and ethyl malonate (28.0 g.) was treated as above and the said acid was crystallised from water, m.p. 157°C. Yield, 7.6 g.

Analysis :

6.06 mg. of the substance gave 0.352 ml. of nitrogen at 29°C and 761 mm. pressure.

Found : N = 6.57 %.

$C_{10}H_{11}O_4N$ requires : N = 6.70 %.

Malon-1:3:4-xylidic acid :

A mixture of freshly distilled 1:3:4-xylidine (12.0 g.) and ethyl malonate (28.0 g.) was treated as above and the said acid was crystallised from water. m.p.156°C. Yield, 7.3 g.

Malon mono-1:3:4-xylidide (0.01 M) was dissolved in 15 ml. alcoholic potassium hydroxide (10 %) in cold and the reaction mixture was kept at room temperature for 24 hrs. It was then neutralised with hydrochloric acid extracted with ether and crystallised from alcohol, m.p. 156°C, in very poor yield. Mixed m.p. with malon-1:3:4-xylidic acid, described above, was not depressed.

Malon-α-naphthylanilic acid :

A mixture of α-naphthylamine (14.3 g.) and ethyl malonate (28.0 g.) was treated as above and the said acid was crystallised from water, m.p. 155°C. Yield, 10.6 g.

Analysis :

5.90 mg. of the substance gave 0.307 ml. of nitrogen at 30°C and 760 mm. pressure.

Found : N = 5.86 %.

$C_{13}H_{11}O_3N$ requires : N = 6.11 %.

Malon-β-naphthylanilic acid

A mixture of β-naphthylamine (14.3 g.) and ethyl malonate (28.0 g.) was treated as above and malon-β-naphthylanilic acid thus obtained was crystallised from water, m.p. 176°C. Yield, 9.5 g.

Analysis :

4.93 mg. of the substance gave 12.318 mg.of carbon dioxide and 2.246 mg. of water.

6.70 mg. of the same substance gave 0.352 ml. of nitrogen at 28°C and 760 mm. pressure.

Found : C = 68.21 % ; H = 5.10 % ; N = 5.96 %.

$C_{13}H_{11}O_3N$ requires : C = 68.11 % ; H = 4.84 % ; N = 6.11 %.

Table 1

Malonmono arylamides

S.No.	Malon mono arylamides	Molecular formula	M.P.°C	Yield %	Nitrogen Found %	Nitrogen Reqd. %
1.	Malon mono-phenylamide	$C_9H_{10}O_2N_2.1/2\ H_2O$	133	93.7	14.93	14.97
2.	Malon mono-o-toluidide	$C_{10}H_{12}O_2N_2$	162	93.7	14.30	14.58
3.	Malon mono-m-toluidide	$C_{10}H_{12}O_2N_2$	164	91.0	14.32	14.58
4.	Malon mono-p-toluidide	$C_{10}H_{12}O_2N_2.1/2\ H_2O$	144	89.5	13.64	13.93
5.	Malon mono-p-chloroanilide	$C_9H_9O_2N_2Cl$	145	94.0	13.43	13.17
6.	Malon mono-o-anisidide	$C_{10}H_{12}O_3N_2$	164	91.0	13.20	13.46
7.	Malon mono-benzylamide	$C_{10}H_{12}O_2N_2$	120	90.0	14.88	14.58
8.	Malon mono-1:3:4-xylidide	$C_{11}H_{14}O_2N_2$	165	92.0	13.84	13.60
9.	Malon mono-α-naphthylamide	$C_{13}H_{12}O_2N_2$	145	98.0	12.54	12.27
10.	Malon mono-β-naphthylamide	$C_{13}H_{12}O_2N_2$	188	96.0	12.40	12.27

Table 2

Malon arylacids

S.No.	Compound	Molecular formula	M.P. °C	Yield %	Nitrogen		Carbon		Hydrogen	
					Found %	Reqd. %	Found %	Reqd. %	Found %	Reqd. %
1.	Malon-anilic acid	$C_9H_9O_3N$	136	70.0	-	-	-	-	-	-
2.	Malon-o-toluidic acid	$C_{10}H_{11}O_3N$	144	72.8	7.22	7.25	62.58	62.16	5.82	5.74
3.	Malon-m-toluidic acid	$C_{10}H_{11}O_3N$	106	64.5	-	-	-	-	-	-
4.	Malon-p-toluidic acid	$C_{10}H_{11}O_3N$	156	74.8	-	-	-	-	-	-
5.	Malon-m-chloroanilic acid	$C_9H_8O_3NCl$	131	77.0	6.15	6.55	-	-	-	-
6.	Malon-p-chloroanilic acid	$C_9H_8O_3NCl$	145	66.1	6.08	6.55	50.22	50.58	3.86	3.74
7.	Malon-o-anisidic acid	$C_{10}H_{11}O_4N$	148	64.2	6.30	6.70	-	-	-	-
8.	Malon-p-anisidic acid	$C_{10}H_{11}O_4N$	157	61.8	6.57	6.70	-	-	-	-
9.	Malon-1:3:4-xylidic acid	$C_{11}H_{13}O_3N$	156	60.8	-	-	-	-	-	-
10.	Malon-α-naphthylanilic acid	$C_{13}H_{11}O_3N$	155	74.1	5.86	6.11	-	-	-	-
11.	Malon-β-naphthylanilic acid	$C_{13}H_{11}O_3N$	176	66.4	5.96	6.11	68.21	68.11	5.10	4.84