SOME DERIVATIVES OF HYDROXYPHENYLGLYCINE.(1) I.

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Alkyl and Aryl Derivatives of Hydroxyphenylglycine Nitrile.

1. p-Hydroxyanilidoacetonitrile (p-Hydroxyphenylglycine nitrile),

Bucherer and Gtolée(2) synthesized some derivatives of p-hydroxyphenylglycine nitrile from potassium cyanide, p-aminophenol hydrochloride and acetone or benzaldehyde, and p-hydroxyphenylglycine nitrile has recently been synthesized by Galatis(3) by the condensation of p-aminophenol with formaldehyde and potassium cyanide in presence of sodium sulphite.

p-Hydroxyanilidoacetonitrile was obtained applying the principle used for the synthesis of anthranilidoacetonitrile by E. Kohner(4) from p-aminophenol, formaldehyde and potassium cyanide with 89–95% yield of the theory.

Twenty one gr. of finely powdered p-aminophenol was mixed with 50c.c. of glacial acetic acid to form a homogeneous paste, cooled with ice-water and then 20 gr. of finely powdered potassium cyanide and 20 c.c. of formaline

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(1) This paper was read before the annual meeting of the Chemical Society of Japan, April 6th 1924 and at the monthly meeting, May 1st. 1925 and published in the *Osaka Kōgyōshikensho Hōkoku* (in Japanese), 5 (1924), No. 7, and will be published in the same publication, 7, (1926).

(2) *Ber.*, 39 (1906), 986.

(3) *Helvetica Chim. Acta*, 4 (1921), 574.

(4) *J. prakt. Chem.*, (2), 63 (1901), 392 ; also refer D.R.P. 117924; Friedländer, " Fortschritte der Teerfarben-fabrikation," VI (1900–1902), 572.

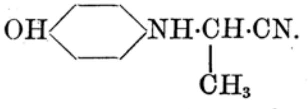
(Japanese Pharmacopœia) were added alternately in a portion of 2–3 gr. After all were added, the mixture was warmed at 70–80° for half an hour on a water bath and left to stand over night. On adding some water the nitrile was deposited, which was collected after cooling at 0°. The yield was 20 gr. The nitrile that remained in the mother liquor was extracted with ether, and after evaporating off the solvent there remained crystals weighing 5.5 gr. Total yield was 89% of the theory.

The condensation of p-aminophenol with formaline and potassium cyanide was carried out in aqueous solution ; 30 gr. of p-aminophenol hydrochloride was dissolved in 140 c.c. of water, and to a mixture of 17 c.c. of formaline (Japanese Pharmacopœia), 75 gr. of 20% aqueous potassium cyanide solution was added drop by drop with constant agitation and cooling it with ice-cold water during the reaction, thereby a voluminous greyish white precipitate was deposited. It was then warmed up to 60–70° and after all of the precipitate was dissolved the solution was cooled, and p-hydroxyphenylglycine nitrile was deposited as large transparent platy crystals. The yield was 29.1 gr. which corresponds to 95% of the theory. It melts at 103–104° (uncorr.) while Galatis described 100° as its melting point.

It gives a transient fuchsin-red coloration described by Galatis and also the same coloration with silver nitrate producing white precipitate, with ammoniacal silver nitrate a yellow color which changes to yellowish brown colloidal solution then greyish black precipitate, yellowish red coloration followed by effervescence with concentrated nitric acid, red coloration with Millon's reagent without warming, and orange coloration with potassium ferricyanide. On analysis, it gave the following results :

0.1619 gr. subst. gave 0.3859 gr. CO_2 and 0.0841 gr. H_2O. 0.0567 gr. subst. gave 8.85 c.c. N_2 (11.5°, 762 mm.). (Found : $C=65.01$; $H=5.77$; $N=18.86$. $C_8H_8ON_2$ requires $C=64.87$; $H=5.41$; $N=18.92\%$).

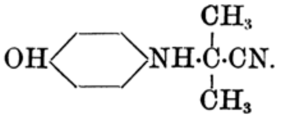
2. p-Hydroxyanilidomethylacetonitrile,



It was prepared from 10.8 gr. of p-aminophenol, 10 gr. of potassium cyanide, and 10 c.c. of 50% acetaldehyde in a manner described for the preparation of p-hydroxyanilidoacetonitrile. The yield of the crude nitrile was 7.6 gr. It was recrystallised from ether-ligroin solution in fine white microscopic leaflets which melt at 111–112° (uncorr.).

0.1220 gr. subst. gave 0.2985 gr. CO_2 and 0.0687 gr. H_2O. 0.1025 gr. subst. gave 14.85 c.c. N_2 (10°, 759.3 mm.). (Found : $C=66.73$; $H=6.23$; $N=17.54$. $C_9H_{10}ON_2$ requires $C=66.67$; $H=6.17$; $N=17.28\%$).

3. p-Hydroxyanilidodimethylacetonitrile,

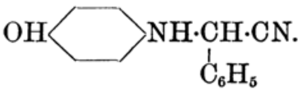


$OH\cdot C_6H_4\cdot NH\cdot C(CH_3)_2\cdot CN.$

This substance was obtained from 5.4 gr. of p-aminophenol, 5 gr. of potassium cyanide and 5 c.c. of acetone in 12 c.c. of glacial acetic acid. The yield was 7.4 gr. The purified substance is fine snow-white leaflets and melts at 140–142° while Bucherer and others described 137° as its melting point.

0.1246 gr. subst. gave 0.3104 gr. CO_2 and 0.0764 gr. H_2O. 0.1044 gr. subst. gave 13.9 c.c. N_2 (10°, 763.7 mm.). (Found: $C=67.94$; $H=6.81$; $N=16.25$. $C_{12}H_{12}ON_2$ requires $C=68.18$; $H=6.82$; $N=15.91\%$).

4. p-Hydroxyanilidophenylacetonitrile,

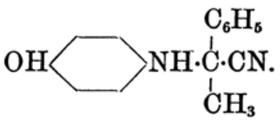


$OH\cdot C_6H_4\cdot NH\cdot CH(C_6H_5)\cdot CN.$

From 5.4 gr. of p-aminophenol, 3.5 gr. of potassium cyanide dissolving in 20 c.c. of water and 5 gr. of benzaldehyde in 50% acetic acid solution, 9.5 gr. of crude nitrile was prepared which recrystallized from luke warm benzene. The pure nitrile was yellow colored small needle-shaped crystals melting at 122–124° (uncorr.), while Bucherer and others described 113–114° as its melting point.

0.1034 gr. subst. gave 0.2839 gr. CO_2 and 0.0512 gr. H_2O. 0.1498 gr. subst. gave 16.0 c.c. N_2 (12.5°, 761 mm.). (Found: $C=74.88$; $H=5.50$; $N=12.85$. $C_{14}H_{12}ON_2$ requires $C=75.00$; $H=5.36$; $N=12.50\%$).

5. p-Hydroxyanilidophenylmethylacetonitrile,



$OH\cdot C_6H_4\cdot NH\cdot C(C_6H_5)(CH_3)\cdot CN.$

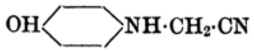
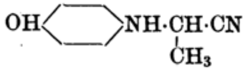
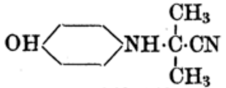
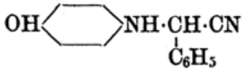
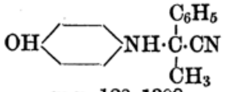
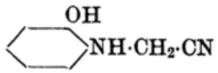
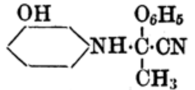
Twelve c.c. of glacial acetic acid, 5.4 gr. of p-aminophenol, 5 gr. of potassium cyanide and 10 gr. of acetophenone were treated in a similar manner as described in previous cases and 11.4 gr. of crude nitrile was obtained. It was purified from dilute alcoholic solution and melts at 128–130° (uncorr.).

0.1196 gr. subst. gave 0.3306 gr. CO_2 and 0.0674 gr. H_2O. 0.1044 gr. subst. gave 10.5 c.c. N_2 (11.5°, 757.7 mm.). (Found: $C=75.39$; $H=6.26$; $N=12.08$. $C_{15}H_{14}ON_2$ requires $C=75.62$; $H=5.88$; $N=11.76\%$).

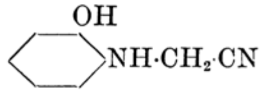
Alkyl or aryl derivatives of p-hydroxyanilidoacetonitrile described above, are soluble in both acid and alkali solutions (but aryl derivatives are insoluble in acid) and also in acetone, alcohol, ether, acetic ester, glacial acetic acid, chloroform and benzene, as I noticed in the case of p-hydroxyanilidoacetonitrile.

Other chemical behaviors of these substances towards ferric chloride, silver nitrate, Millon's reagent etc. are like those of the mother substance as will be seen in Table 1.

TABLE 1.

Substance.	Ferric chloride.	Silver nitrate.	Ammoniacal silver nitrate.	Conc. nitric acid.	Millon's reagent.	Potassium ferricyanide.
 m.p. 103–104°	fuchsin-red.	fuchsin-red producing white ppt.	yellow color → yellowish brown colloidal → greyish black ppt.	yellowish red.	red.	orange.
 m.p. 111–112°	brownish red.	pink → reddish violet producing white ppt.	brownish yellow colloidal → greyish ppt.	red.	yellow.	
 m.p. 140–142°	violet → chocolate color.	cobalt blue producing white ppt.	pale brownish grey colloidal → brownish grey ppt.	yellowish red.	yellow.	reddish brown.
 m.p. 122–124°	yellow.	yellow → brownish yellow ppt.	reddish orange colloidal.	reddish yellow.	yellow → colorless → brownish red.	
 m.p. 128–130°	bluish violet.	bluish violet producing white ppt.	greyish colloidal → brown → chocolate color.	yellowish red.	reddish orange.	
 m.p. 74–75°	yellowish red.	pale dirty red producing silver mirror accompanied with dirty brown ppt.	yellow → yellowish green → greyish black ppt.	red.	yellowish red.	reddish orange.
 m.p. 135–137°	brownish yellow.			yellowish brown.	red.	

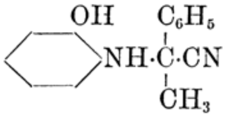
6. o-Hydroxyanilidoacetonitrile
(o-Hydroxyphenylglycine nitrile),



o-Aminophenol reacts, in the same manner as p-isomer, in presence of glacial acetic acid with formaline and potassium cyanide producing o-hydroxyanilidoacetonitrile. 14.5 Gr. of the crude nitrile was actually obtained from 14.7 gr. of aminophenol. For the purification of the nitrile, the crude product was dissolved in ether, and to the ethereal solution ligroin was added until permanent turbidity began to occur, and the solution was left to evaporate slowly in vacuo or recrystallised from luke warm benzene. It melts at 74–75° (uncorr.), and is very easily soluble in ether, alcohol, acetone, acetic ester and glacial acetic acid, less so in chloroform, benzene and water but insoluble in ligroin. It is more easily saponifiable than the corresponding para compound ; when treated with warm water or dilute caustic alkalies, the evolution of ammonia is recognized. The color reactions of the nitrile are shown in Table 1.

0.1171 gr. subst. gave 0.2781 gr. CO_2 and 0.0608 gr. H_2O. 0.1058 gr. subst. gave 16.6 c.c. N_2 (8°, 766.4 mm.). (Found : $C=64.77$; $H=5.81$; $N=19.29$. C_8H_8ON requires $C=64.87$; $H=5.41$; $N=18.92\%$).

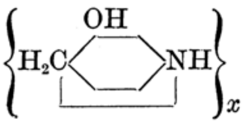
7. m-Hydroxyanilidophenylmethylacetonitrile,



This substance was obtained from 5.4 gr. of m-aminophenol, 12 c.c. of glacial acetic acid, 5 gr. of potassium cyanide and 9 c.c. of acetophenone in the manner described for the preparation of other nitriles. The yield was 5 gr. It was purified from ether-ligroin solution in fine white crystalline powder which melts at 135–137° (uncorr.). It is easily soluble in ether, alcohol, acetic ester and acetone, soluble in glacial acetic acid, less soluble in benzene and chloroform but insoluble in ligroin and water. The colour reactions of the nitrile are mentioned in Table 1.

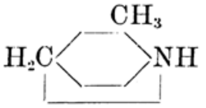
0.1093 gr. subst. gave 0.3047 gr. CO_2 and 0.0602 gr. H_2O. 0.1041 gr. subst. gave 10.2 c.c. N_2 (7.5°, 767.6 mm.). (Found : $C=75.61$; $H=6.04$; $N=12.02$. $C_{15}H_{14}ON_2$ requires $C=75.62$; $H=5.88$; $N=11.76\%$).

8. Anhydro-p-amino-o-hydroxybenzylalcohol,



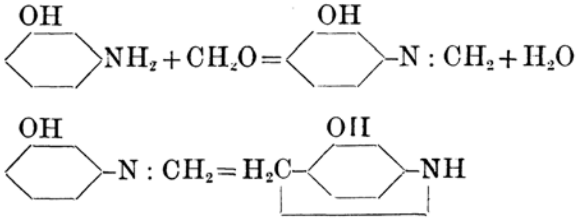
When 5.4 gr. of m-aminophenol was treated with 5 c.c. of formaline (Japanese Pharmacopœia) and 25 c.c. of 14% potassium cyanide solution in the manner described for the preparation of p-hydroxyanilidoacetonitrile, 6.3 gr. of a pale yellow amorphous powder was deposited which, after investiga-

tion of its insoluble nature in organic solvents and hydrochloric acid and melting point (does not melt under 300°), was regarded to be anhydro-p-amino-o-hydroxybenzylalcohol.

Moreover, the analytical results of the dried substance, and also the fact that anhydro-p-aminobenzylalcohol  and anhydro-p-amino-m-toluylalcohol  were synthesized from aniline and formaline, and o-toluidine and formaline, respectively,[1] give cause to presume it to be anhydro-p-amino-o-hydroxybenzylalcohol.

0.1340 gr. subst. gave 0.3430 gr. CO_2 and 0.0747 gr. H_2O 0.1159 gr. subst. gave 11.25 c.c. N_2 (8.5°, 761 mm.). (Found: C=69.28; H=6.19; N=11.84. C_7H_7ON requires C=69.39; H=5.82; N=11.57%).

As to the formation of this substance, methylene-p-aminophenol would be formed as an intermediate reaction product from m-aminophenol and formaline, which soon converts to anhydrobenzylalcohol derivatives by the intermolecular rearrangement, before hydrocyanic acid enters into the condensation with the former hypothetical compound, as may be represented by the following scheme:



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[1] D.R.P., 95184; Friedländer, "Fortschritte der Teerfarben-fabrikation," IV (1894-1897), 52; *Ber.*, 33 (1900), 252.