REACTION OF NITRILES

IV. Cyanoethylation of Some Amino and Hydroxy Aldehydes and Ketones.

BY J. R. MERCHANT, F.A.SC. AND J. R. PATELL

(Institute of Science, Bombay-32)

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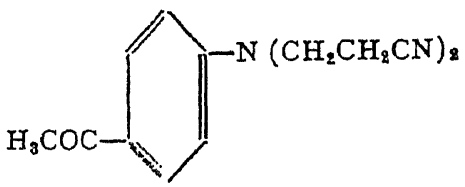
ABSTRACT

Cyanoethylation of *p*-aminoacetophenone in presence of cuprous chloride has been investigated. Cyanoethylation of hydroxyacetophenones and hydroxybenzaldehydes has also been studied. The products obtained have been hydrolysed to the corresponding acids. The acids on cyclisation have yielded the corresponding ketones.

INTRODUCTION

IN an earlier communication[1] it was reported that cyanoethylation of *p*-aminoacetophenone in presence of aqueous Triton B afforded the compound I. However, when cuprous chloride is used as a catalyst in the presence of acetic acid a different compound is formed which on the basis of analytical and I. R. spectral data (NH band) is assigned the structure II (*a*).



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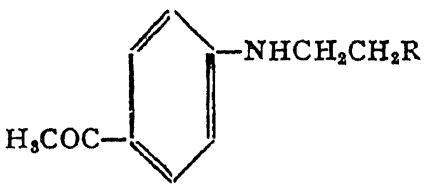
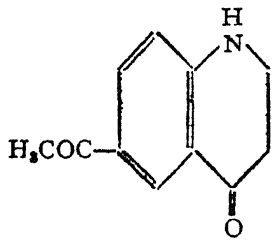


II (*a*) R=CN
(*b*) R=COOH

Hydrolysis of II (*a*) with aqueous alkali afforded an acid whose I. R. spectrum agreed with its structure as II (*b*).

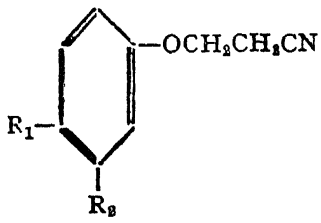
The cyclisation of II *b* was attempted with different reagents, *e.g.*, $POCl_3$, P_2O_5 when only tarry matter was isolated. However, with PPA, cyclisation readily occurred to yield the piperidone III. The latter was soluble in dilute HCl gave a crystalline 2, 4 DNP and its alcoholic solution showed a strong greenish fluorescence in U.V. light.



III

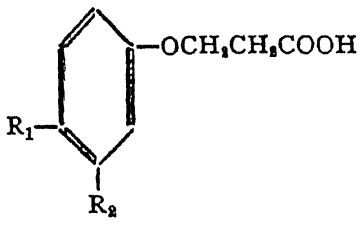
To study the reactivity of the hydroxyl group, the cyanoethylation of other hydroxyacetophenones and hydroxybenzaldehydes was also investigated.

Cyanoethylation of *p*-hydroxyacetophenone and *p*-hydroxybenzaldehyde in presence of Triton B (40% aqueous solution) or aqueous alkali (10–50% solution) afforded compounds IV *a* and IV *b* respectively. Both, on hydrolysis with concentrated HCl, afforded the corresponding acids V *a* and V *b*. Treatment with 90% H_2SO_4 led to partial hydrolysis yielding the amides VI *a* and VI *b*.

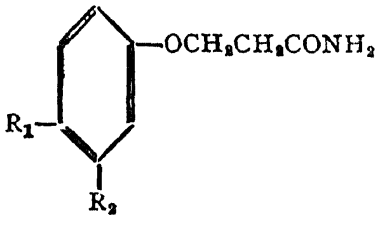


IV

(*a*) R_1=$COCH_3$; R_2=H
(*c*) R_1=H; R =$COCH_3$



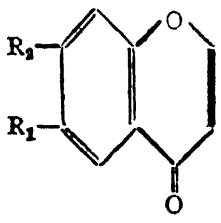
V



VI

(*b*) R_1=CHO; R=H
(*d*) R_1=H; R=CHO

Cyclisation of the acid V *a* with PPA afforded the corresponding chromanone VII *a* which formed a crystalline 2, 4 DNP derivative. However, the cyclisation of V *b* under similar conditions failed to yield the desired compound and only a black tarry mass was isolated.



VII (*a*) R_1=$COCH_3$; R_2=H
(*b*) R_1=H; R_2=$COCH_3$

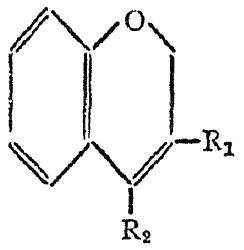
Similarly, the cyanoethylation of *m*-hydroxyacetophenone and *m*-hydroxybenzaldehyde gave IV *c* and IV *d* which on hydrolysis afforded the acids

V *c* and V *d*. Partial hydrolysis under similar conditions yielded the amides VI *c* and VI *d*. Cyclisation of V *c* with PPA led to the chromanone which was assigned the structure VII *b* on the basis of structural models.

Whereas cyanoethylation of *p*-aminoacetophenone gave different products when Triton B or cuprous chloride was used as catalyst, the cyanoethylation of hydroxyacetophenones and hydroxybenzaldehydes afforded the same product when cuprous chloride was used as a catalyst instead of Triton B.

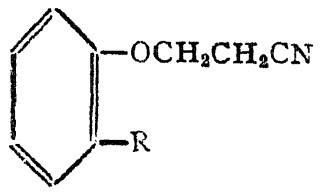
Hydrolysis of the compounds IV *a–d* with 1% aqueous potassium hydroxide solution led to the removal of the cyanoethyl group with the formation of *p*-hydroxyacetophenone, *p*-hydroxybenzaldehyde, *m*-hydroxyacetophenone and *m*-hydroxybenzaldehyde respectively which were confirmed by mixed m.p. with the pure samples.

o-Hydroxyacetophenone under similar conditions of cyanoethylation gave mostly a compound which analysed for $C_{11}H_9NO$ and has been assigned the structure VIII *a*. It's I.R. spectra shows aryl ether bands, a CN band but no CO band. This is in agreement with the observation that VIII *a* fails to yield a 2, 4-dinitrophenylhydrazone.



VIII

(*a*) R_1=CN; R_2=CH_3
(*b*) R_1=COOH; R_2=CH_3
(*c*) R_1=CN; R_2=H
(*d*) R_1=COOH; R_2=H



IX

(*a*) R=$COCH_3$
(*b*) R=CHO

Along with VIII *a* a small amount of IX *a* (insoluble in alkali) was also formed and isolated as its 2, 4-dinitrophenylhydrazone.

Hydrolysis of VIII *a* with concentrated HCl afforded an acid whose I.R. spectra shows the presence of a COOH group, aryl ether bands but no ketonic band and has been assigned the structure VIII *b*.

Cyanoethylation of salicylaldehyde in presence of Triton B has been earlier reported.[2] However, it is observed by us that invariably only VIII *c*

is formed and rarely any amount of IX *b* could be isolated from the reaction mixture. Hydrolysis of VIII *c* gave the corresponding acid VIII *d*.

Experimental

Cyanoethylation of p-*aminoacetophenone in presence of cuprous chloride to give II a.*—*p*-Aminoacetophenone (2·4 g.), acrylonitrile (3·0 ml.), acetic acid (3·0 ml.) and cuprous chloride (0·200 g.) was refluxed for 15–20 hr. The solution was cooled and excess of ammonia solution was added and then extracted with chloroform and the solvent layer washed with water. Removal of the solvent gave a sticky solid which was crystallised from methanol in long needles m.p. 136–38°. Yield 1·2 g. (found C, 70·0; H, 6·2; N, 15·0; $C_{11}H_{12}N_2O$ requires C, 70·2; H, 6·4; N, 14·9%).

I.R. 3334 (NH), 2248 (CN), 1644 (C = O), 1594, 1537, 1497 (aromatic nucleus), 835 (*p*-disubstituted benzene)/cm.

Hydrolysis of II a.—A mixture of II *a* (500 mg.) and KOH (500 mg.) in water (25 ml.) was refluxed for 15 hr. The solution was cooled and acidified till a turbidity was obtained. The solid which separated was filtered, washed with water and dissolved in minimum quantity of sodium bicarbonate solution. Acidification of the bicarbonate solution with minimum amount of HCl gave a solid (320 mg.) which was crystallised from dilute alcohol in long clusters of needles m.p. 148–50° (Found C, 63·5; H, 6·5; N, 7·0; $C_{11}H_{13}NO_3$ requires C, 63·8; H, 6·3; N, 6·8%).

I.R. 3296 (NH), 2674 (COOH), 1711 (C = O of COOH), 1651 (C = O), 1595, 1530 (aromatic nucleus), 832 (*p*-disubstituted benzene)/cm.

Cyclisation of II b to III.—The acid II *b* (300 mg.) was added to a mixture of P_2O_5 (10·0 g.) and phosphoric acid (4·0 ml.) preheated to 100° (30 mins.). After 2 hr. at 100° water was added to the mass and extracted thoroughly with chloroform. The solvent layer was washed with aqueous alkali and then water. Removal of the solvent gave a sticky solid. It was sublimed at 180–85°/0·5 mm. Yield 80 mg. It was crystallised from ethyl acetate in orange plate clusters m.p. 185–86° (Found C, 69·6; H, 5·7; N, 7·5; $C_{11}H_{11}NO_2$ requires C, 69·8; H, 5·9; N, 7·4%).

U.V. (In Methanol); $\lambda_{max.}$ (log ϵ) 245 mμ (4·27), 310 mμ (4·33), 375 mμ (3·61).

I.R. 3320 (NH), 1650, 1620 (C = O)/cm.

The compound III gave a 2, 4-dinitrophenylhydrazone m.p. 284–85° *d* (Found N, 22·8; $C_{23}H_{19}N_9O_8$ requires N, 23·0%).

Cyanoethylation of p-*hydroxyacetophenone in presence of Triton* B *to give IV a.*—A mixture of *p*-hydroxyacetophenone (2·0 g.), acrylonitrile (2·0 ml.) and 40% aqueous Triton B (1·0 ml.) was heated on a steam-bath for 20 hr. The reaction mixture was extracted with chloroform. The solvent layer was washed thoroughly with 10% aqueous sodium hydroxide solution, water and then dried. Removal of the solvent gave a solid (520 mg.) which was crystallised from methanol in colourless plates m.p. 85–87° (Found C, 70·1; H, 5·8; N, 7·1; $C_{11}H_{11}NO_2$ requires C, 69·8; H, 5·9; N, 7·4%).

The alkaline solution was acidified to give 500 mg. of *p*-hydroxyacetophenone.

The 2, 4-dinitrophenylhydrazone of IV *a* was crystallised from acetic acid in small needles m.p. 210–11° (Found N, 18·7; $C_{17}H_{15}N_5O_5$ requires N, 19·0%).

The same compound IV *a* is obtained when cuprous chloride or aqueous NaOH are used as catalyst for cyanoethylation of *p*-hydroxyacetophenone.

Hydrolysis of IV a.—A mixture of IV *a* (100 mg.) and 90% H_2SO_4 (10·0 ml.) was shaken at room temperature for 40 hr. It was then diluted with water. On leaving overnight a crystalline solid separated. The solid was filtered and dissolved in $NaHCO_3$ solution and filtered. The filtrate on acidification gave a solid (50 mg.). It was crystallised from benzene as stout needles m.p. 134–35°[3] (Found: C, 58·4; H, 6·2; $C_{11}H_{12}O_4 \cdot H_2O$ requires C, 58·4; H, 6·2%).

I.R. 3492, 3380 (OH water of crystallisation), 2522 (COOH), 1738 (C = O of COOH), 1642 (C = O), 1603, 1575, 1512 (aromatic nucleus), 837 (*p*-disubstituted benzene)/cm.

The same compound V *a* is obtained when IV *a* is refluxed with HCl for 1 hr.

The 2, 4-dinitrophenylhydrazone of V *a* crystallised from acetic acid in small red plates m.p. 229–30° (Found: N, 14·8; $C_{17}H_{15}N_4O_7$ requires N, 14·4%).

Partial hydrolysis of IV a to VI a.—The compound IV *a* (0·100 g.) and H_2SO_4 (2·0 ml. of 90% solution) was shaken for 3 hr. It was then diluted with water and extracted with chloroform. The solid obtained (25 mg.) on evaporation of the solvent was washed with benzene and crystallised from

acetone: petrol ether (40–60°) m.p. 161–62° (Found: C, 63·7; H, 6·6; N, 6·5; $C_{11}H_{13}NO_3$ requires C, 63·8; H, 6·3; N, 6·8%).

Cyclisation of V a to VII a.—The cyclisation of V *a* (300 mg.) was carried out as before. The solid (100 mg.) obtained on removal of chloroform was sublimed at 140–45°/0·5 mm. to give long needles (50 mg.) m.p. 115–18°. It was crystallised from ethyl acetate: petrol ether (40–60°) in needle clusters m.p. 116–18° (Found C, 69·9; H, 5·6; $C_{11}H_{10}O_3$ requires C, 69·5; H, 5·3%).

U.V. (In Methanol): $\lambda_{max.}$ (log ϵ) 240 mμ (4·40), 270 mμ (4·25), 320 mμ (3·49).

I.R. 1683, 1660 split (C = O), 1595 (C = O)/cm.

It gave a 2, 4-dinitrophenylhydrazone m.p. 289–90° (Found N, 20·4; $C_{22}H_{18}N_8O_9$ requires N, 20·4 %).

Cyanoethylation of m-*hydroxyacetophenone to give* IV *c.*—*m*-Hydroxyacetophenone was cyanoethylated under similar conditions to yield 300 mg. of IV *c* (from 1·0 g. of ketone). It was crystallised from ethyl acetate: petrol ether (40–60°), m.p. 61–62° (Found C, 70·0; H, 6·0; N, 7·4; $C_{11}H_{11}NO_2$ requires C, 69·8; H, 5·9; N, 7·4%).

Its 2, 4-dinitrophenylhydrazone crystallised from acetic acid as orange clusters of needles m.p. 180–81° (Found: N, 18·8; $C_{17}H_{15}N_5O_5$ requires N, 19·0%).

Hydrolysis of IV c.—The above compound IV *c* (200 mg.) was refluxed with conc. HCl (10·0 ml.) for 1 hr. The solution was cooled and the solid which separated was filtered and dissolved in minimum amount of $NaHCO_3$ solution. Acidification of the bicarbonate solution gave V *c* (120 mg.) crystallised from benzene: petrol ether (40–60°) as needles m.p. 116–17°. (Found C, 63·2; H, 6·1; $C_{11}H_{12}O_4$ requires C, 63·5; H, 5·8%).

The 2, 4-dinitrophenylhydrazone of V *c* crystallised from alcohol as plates m.p. 139–40° (Found N, 14·2; $C_{17}H_{16}N_4O_7$ requires N, 14·4%).

Partial hydrolysis of IV c to VI c.—The compound IV *c* (100 mg.) under similar conditions gave (60 mg.) of VI *c* crystallised from acetone: petrol ether (40–60°) m.p. 126–27° (Found C, 63·6; H, 6·5; N, 6·4; $C_{11}H_{13}NO_3$ requires C, 63·8; H, 6·3; N, 6·8%).

Cyclisation of V c to VII b.—Cyclisation of the acid V *c* (300 mg.) was carried out as before. The chloroform extract was concentrated to a small volume, petrol ether (40–60°) was added and left overnight when a crystalline

solid separated. It was crystallised from ethyl acetate: petrol ether (40–60°) in plates m.p. 110–12° (Found: C, 69·7; H, 5·5; $C_{11}H_{10}O_3$ requires C, 69·5; H, 5·3%).

Cyanoethylation of o-*hydroxyacetophenone to give VIII a and IX a.*—Thirty grams of the ketone was refluxed with 65 ml. of acrylonitrile and 5 ml. Triton B for 18–20 hr. The reaction mixture was extracted with chloroform and washed thoroughly with dilute sodium hydroxide solution and then with water. Removal of the solvent gave an oil which solidified on cooling. Dropwise addition of water to a methanolic solution of the solid gave VIII *a* (3·4 g.). It was crystallised from methanol: water as thin plates m.p. 59–61° (Found C, 76·9; H, 5·4; N, 8·0; $C_{1.}H_9NO$ requires C, 77·2; H, 5·3; N, 8·2%).

U.V. (In Methanol): $\lambda_{max.}$ (log ϵ) 219 mμ (4·00), 269 mμ (3·24). I.R. 2248 (CN), 1600, 1587, 1500 (aromatic nucleus), 1250, 1175 (aryl ether), 760 (*o*-disubstituted benzene)/cm.

The methanolic mother liquor was evaporated to give an oil. The 2, 4-dinitrophenylhydrazone of the fraction distilling at 160–80°/2 mm. was crystallised from acetic acid as needle clusters m.p. 210–11° (Found N, 19·2; $C_{17}H_{15}N_5O_5$ requires N, 18·9%).

Hydrolysis of VIII a.—The above compound VIII *a* (200 mg.) was hydrolysed as above to yield 70 mg. of the acid VIII *b*. It was crystallised from petrol ether (40–60°) m.p. 94–95° (Found C, 69·7; H, 5·4; $C_{11}H_{10}O_3$ requires C, 69·5; H, 5·3%).

U.V. (In Methanol): $\lambda_{max.}$ (log ϵ) 220 mμ (3·98), 271 mμ (3·31). I.R. 2640 (COOH), 1712 (C = O of COOH), 1595, 1585, 1499 (aromatic nucleus) 1240, 1180 (aryl ether) 764, (*o*-disubstituted benzene)/cm.

Cyanoethylation of p-*hydroxybenzaldehyde to give IV b.*—Under similar conditions of cyanoethylation, *p*-hydroxybenzaldehyde (10·0 g.) gave IV *b* (2·1 g.) crystallised from benzene: petrol ether (40–60°) as needles m.p. 58–60° (Found C, 68·3; H, 5·3; N, 7·7; $C_{10}H_9NO_2$ requires C, 68·6; H, 5·1; N, 8·0%).

Recovered yield of *p*-hydroxybenzaldehyde 4·5 g.

The 2, 4-dinitrophenylhydrazone of IV *b* crystallised from acetic acid as orange clusters of needles m.p. 225–26° (Found N, 19·6; $C_{16}H_{13}N_5O_5$ requires N, 19·7%).

Hydrolysis of IV b.—Hundred mg. of IV *b* on hydrolysis as above gave 50 mg. of V *b*. It was crystallised from benzene as clusters of needles m.p. 127–28°[4] (Found C, 62·2; H, 5·4; $C_{10}H_{10}O_4$ requires C, 61·9; H, 5·2%).

The 2, 4-dinitrophenylhydrazone of V *b* crystallised from dioxan as small granules m.p. 260–61° (Found N, 15·2; $C_{16}H_{14}N_4O_7$ requires N, 15·0%).

Partial hydrolysis of IV b to VI b.—On shaking IV *b* (100 mg.) with sulphuric acid as above 50 mg. of VI *b* separated out on dilution of the acid solution. It was crystallised from ethyl acetate as thin plates m.p. 169–70° (Found C, 62·1; H, 5·9; N, 7·0; $C_{10}H_{11}NO_3$ requires C, 62·2; H, 5·7; N, 7·3%).

Cyanoethylation of m-*hydroxybenzaldehyde to give IV d.*—Ten grams of *m*-hydroxybenzaldehyde on cyanoethylation as above gave 4·1 g. of an oil. The 2, 4-dinitrophenylhydrazone of the oil crystallised from acetic acid m.p. 234–35° (Found C, 53·9; H, 3·8; N, 19·4; $C_{16}H_{13}N_5O_5$ requires C, 54·0; H, 3·7; N, 19·7%).

Hydrolysis of IV d.—Refluxing IV *d* (340 mg.) with HCl under similar conditions gave V *d* (240 mg.) crystallised from benzene: petrol ether (40–60°) as needles m.p. 99–101° (Found C, 61·8; H, 5·4; $C_{10}H_{10}O_4$ requires C, 61·9; H, 5·2%).

It's 2, 4-dinitrophenylhydrazone crystallised from acetic acid as orange red clusters of needles m.p. 217–18° (Found: N, 15·1; $C_{16}H_{14}N_4O_7$, requires N, 15·0%).

Partial hydrolysis of IV d to VI d.—The above oil IV *d* (500 mg.) under similar conditions gave VI *d* (100 mg.). It was crystallised from ethyl acetate: petrol ether (40–60°) as clusters of needles m.p. 98–99° (Found C, 62·5; H, 5·9; N 7·5; $C_{10}H_{11}NO_3$ requires C, 62·2; H, 5·7; N, 7·3%).

Cyanoethylation of salicylaldehyde.—Twenty grams of salicylaldehyde was cyanoethylated as reported[2] to give 2·0 g. of an oil.

Fraction I consisting of VIII *c* distilled at 90–110°/1·5 mm. to give an oil (850 mg.) which solidified on cooling. It was crystallised from methanol: water as thin plates m.p. 49–50° (Reported[2] m.p. 48–49°) (Found C, 76·4; H, 4·8; N, 9·0; $C_{10}H_7NO$ requires C, 76·4; H, 4·5; N, 8·9%).

Fraction II consisting of IX *b* distilled at 120–35° to give an oil (440 mg.) which did not solidify as reported. Its 2, 4-dinitrophenylhydrazone crystal-

lised from acetic acid as plates m.p. 227–28° (Found: C, 54·4; H, 3·4; N, 19·5; $C_{16}H_{13}N_5O_5$ requires C, 54·0; H, 3·7; N, 19·7%).

Hydrolysis of VIII c.—The compound VIII *c* (120 mg.) was hydrolysed as before to give VIII *d* (40 mg.) crystallised from benzene as plates m.p. 185–86° (Found C, 68·0; H, 4·7; $C_{10}H_8O_3$ requires C, 68·2; H, 4·6%).

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REFERENCES

1. Merchant, J. R. and Kaushik, H. C. — *J. Bom. Univ.*, 1963–64, **32**, 27.

2. Byrant Bachmann, G. and Levine, H. A. — *J. Am. Chem. Soc.*, 1948, **70**, 599.

3. Zawadowska, Irena .. *Acta Polon. Pharm.*, 1963, **20** (1), 25;
.. *C.A.*, 1964, **61**, 8225.

4. Gresham, T. L. *et al.* .. *J. Am. Chem. Soc.*, 1949, **71**, 661.