

Cyanoethylation of some dimethyl- and trimethylphenols

J. R. MERCHANT. F.A.Sc., MEERA S. KAMATH AND SUNEEL Y. DIKE

Organic Chemistry Department, Institute of Science, Bombay 400032

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ABSTRACT

Cyanoethylation of some dimethyl- and trimethylphenols in acidic and basic media has been investigated. The cyanoethyl derivatives obtained were hydrolysed to the corresponding acids which on cyclisation with PPA afforded either dihydrocoumarin or chromanone whose structures were assigned on the basis of chemical and spectral evidence.

1. INTRODUCTION

In a previous communication we have reported our findings on the cyanoethylation of the methyl- and ethyl ethers of phenols.¹ We wish to report in this paper some interesting observations on the cyanoethylation of dimethyl- and trimethylphenols in acidic and basic media.

It has been reported in literature that phenols on reaction with acrylonitrile in the presence of alkali afforded phenoxypropionitriles.² However, in acid medium phenols undergo nuclear cyanoethylation whereas dihydric phenols like resorcinol yield directly dihydrocoumarins.³ No work has been reported so far on the cyanoethylation of dimethyl- and trimethylphenols under different conditions. This study is important since in these cases the methyl groups also have a directing influence on the course of the reaction.

Two dimethylphenols, *viz.*, 2, 3- and 2, 5- were chosen for the study in acidic medium, since in the case of other dimethylphenols no unusual reactions were likely to occur. Amongst the trimethylphenols, the cyanoethylation of 2, 3, 5-trimethylphenol only was studied under acidic

conditions whereas under basic conditions the reaction of 2, 3, 5-, 2, 4, 5-, 2, 4, 6- and 3, 4, 5-trimethylphenols was investigated.

Cyanoethylation of 2, 5-dimethylphenol was carried out using five moles of acrylonitrile per mole of the phenol using sym. tetrachloroethane as the solvent. Dry HCl gas was passed continuously through the mixture kept at 0–10° for 1.5 hr and later at 95–100° for another 1.5 hr. After the usual workup two compounds were isolated of which one was found to be alkali soluble (I *a*) and the other alkali insoluble in larger amounts (II *a*).

The alkali soluble component (I *a*) on hydrolysis yielded the propionic acid (I *b*), the cyclisation of which with polyphosphoric acid gave hydroxyindanone (III), the structure was confirmed by the preparation of a 2, 4-DNP derivative.

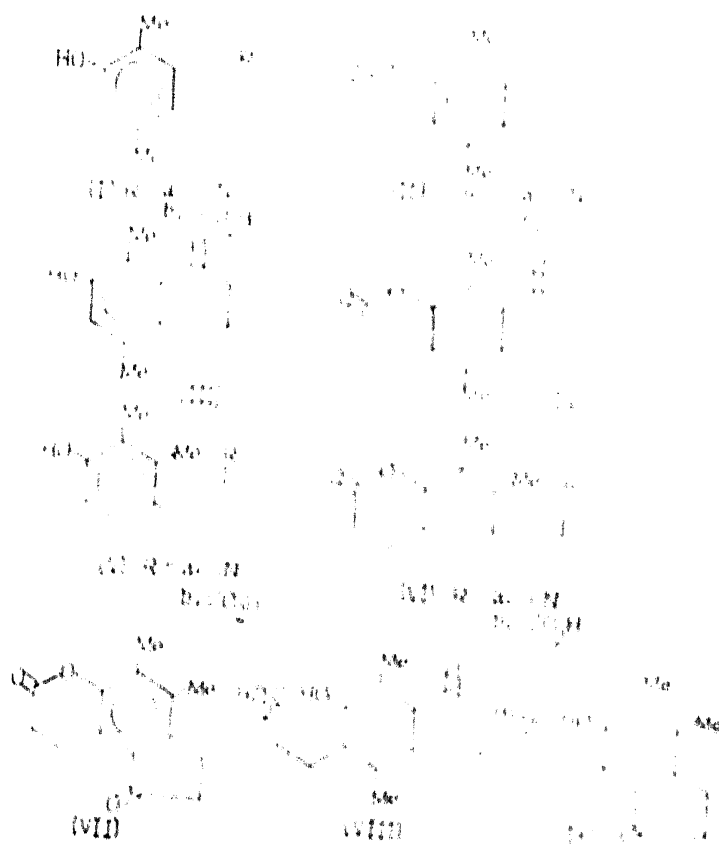
The alkali insoluble component (II *a*) was found to be 3, 4-dihydro-5, 8-dimethyl-6-propionitrile-benzopyran-2-one. On hydrolysis of the latter with conc. HCl the corresponding propionic acid derivative was isolated, which cyclised with PPA to yield cyclopenta (g)-1, 2H-benzopyran-3, 4-dihydro-5, 9-dimethyl-2, 8-dione. The nmr spectrum of the latter was in full agreement with the structure (IV). It gave a crystalline 2, 4-DNP and its ir spectrum also confirmed its structure, showing two carbonyl bands at 1760 (C = O coumarin) and 1680 (C = O cyclopentenone) cm^{-1} .

Cyanoethylation of 2, 3-dimethylphenol under the same conditions in acidic medium afforded after the usual work up, two compounds one of which was alkali soluble (V *a*) and the other insoluble (VI *a*).

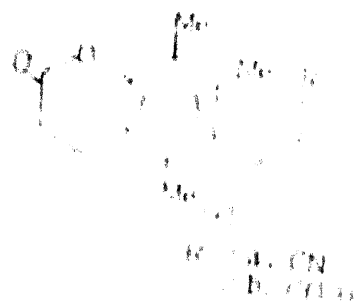
The alkali soluble component (V *a*), yield (50 mg), on hydrolysis yielded the propionic acid (V *b*), which was not worked up further.

The alkali insoluble component was found to be 2H, -1-benzopyran-3, 4-dihydro-7-, 8-dimethyl-6-propionitrile-2-one which on hydrolysis with conc. HCl gave the propionic acid (VI *b*) which was cyclised with PPA to yield the cyclopenta (f)-1, 2H-benzopyran-3, 4-dihydro-5, 6-dimethyl-3, 9-dione (VI *I*). It gave 2, 4-DNP derivative and its ir spectrum further confirmed its structure.

In order to further ascertain the structures of (IV), (VII), they were refluxed with aqueous sodium hydroxide (10%) when the dihydrobenzopyran ring was ruptured to yield 4, 7-dimethyl-5-carboxyethyl-6-hydroxy-indan-1-one (VIII) and 4, 5-dimethyl-7-carboxyethyl-6-hydroxy-indan-1-one (IX) respectively. Both gave correct elemental analysis and molecular weights (Ms) and formed crystalline 2, 4-DNP derivatives.

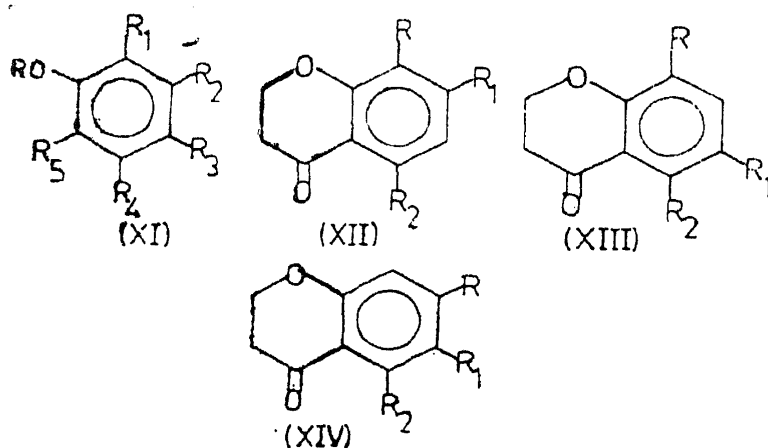


Cyanoethylation of 2, 3, 5-trimethylphenol under similar acidic conditions afforded only a single compound (X *a*) in 40% yield. Its i.r. spectrum was in agreement with the structure (X *a*). The latter on hydrolysis gave the propionic acid (X *b*) in 60% yield.



Cyanoethylation of 2, 3, 5-trimethylphenol in the presence of sodium hydroxide solution (10%) gave in fairly good yield, (XI *a*)¹ which on hydrolysis with conc. HCl yielded the propionic acid (XI *b*)². It cyclized with PPA to yield the 4H-1-benzopyran-2, 3-dihydro-5, 7, 8-trimethyl-4-one (XII),³ m.p. 42–43°.

2, 4, 5-, 2, 4, 6- and 3, 4, 5-trimethylphenols were cyanoethylated in basic media to yield (XI *c*), (XI *e*) and (XI *g*) which on hydrolysis with conc. HCl gave the propionic acids (XI *d*), (XI *f*) and (XI *h*) respectively.



Cyclisation of the acids (XI *d*) and (XI *h*) as before gave the corresponding 4H-1-benzopyran-2, 3-dihydro-4-one derivatives (XIII) and (XIV) respectively. The propionic acid (XI *f*) could not be cyclised because no position was available for the cyclisation to take place.

An interesting observation was made during the process of acid hydrolysis of (XI *a*), (XI *c*), (XI *e*) and (XI *g*), with conc. HCl. Within ten minutes of the commencement of refluxing, needles accumulated in the condenser, which were identified to be those of original trimethylphenols resulting due to dealkylation. At the same time, the corresponding propionic acids were also isolated from the solution.

As a point of interest (XII) and (XIII) were converted to the corresponding chromenes (b.p. 228–30°/ 2–2.5 mm) and (b.p. 275–80°/4–4.5 mm) respectively by heating the chromanols (m.p. 135–137°) and (m.p. 100–102°) respectively with oxalic acid. The chromanols were obtained by the LiAlH₄ reduction of chromanones (XII) and (XIII) respectively.

TABLE 1

XI	R	R ₁	R ₂	R ₃	R ₄	R ₅
<i>a</i>	OCH ₂ CH ₂ CN	CH ₃	CH ₃	H	CH ₃	H
<i>b</i>	OCH ₂ CH ₂ COOH	CH ₃	CH ₃	H	CH ₃	H
<i>c</i>	OCH ₂ CH ₂ CN	CH ₃	H	CH ₃	CH ₃	H
<i>d</i>	OCH ₂ CH ₂ COOH	CH ₃	H	CH ₃	CH ₃	H
<i>e</i>	OCH ₂ CH ₂ CN	CH ₃	H	CH	H	CH ₃
<i>f</i>	OCH ₂ CH ₂ COOH	CH ₃	H	CH ₃	H	CH ₃
<i>g</i>	OCH ₂ CH ₂ CN	H	CH ₃	CH ₃	CH ₃	H
<i>h</i>	OCH ₂ CH ₂ COOH	H	CH ₃	CH ₃	CH ₃	H

2. EXPERIMENTAL

Cyanoethylation of 2, 5-dimethylphenol in acid medium

Finely powdered anhydrous aluminium chloride (6 g) was added slowly to a cold solution of 2, 5-dimethylphenol (5 g) and acrylonitrile (15 ml) in a dry system containing tetrachloroethane (35 ml). Dry hydrogen chloride was passed through the resulting mixture maintained at 10–15° for 1.5 hr. The homogeneous mixture was then heated on a water-bath at 90–95° for 2.5 hr more with the continuous passage of dry hydrogen chloride. The dark red material was decomposed with ice and extracted with ether. The ether layer was washed thoroughly with sodium hydroxide solution (10%), water and dried. Removal of the solvent left behind a pinkish-red liquid which was vacuum distilled to remove tetrachloroethane. The residual mass solidified into a pale yellow mass (II *a*); yield (40%). It crystallised from benzene as colourless needles, m.p. 118–120° (Found: C, 73.7; H, 6.8; N, 6.3; C₁₄H₁₅O₂N requires: C, 73.4; H, 6.5; N, 6.1 %).

The sodium hydroxide solution (10%) washings were collected and acidified. It was extracted with chloroform, washed with water and dried. Removal of the solvent left behind a pink oil, which distilled at 222–224°/3–3.5 mm (I *a*). The latter solidified on cooling, yield 250 mg. It crystallised from petrol-ether (40–60°) as white needles, m.p. 58–60° (Found C, 74.9; H, 7.1; N, 8.6; C₁₁H₁₃ON requires: C, 75.4; H, 7.4; N, 8.9%).

IR (Nujol): 3350 (broad, OH), 2250 (C ≡ N), 1620, 1600 (aromatic) cm⁻¹.

NMR (CDCl₃): δ 2.2 [6H, *s*, 2 (CH₃)]; 2.6 (2H, *t*, CH₂-CN), 2.8 (2H, *t*, benzylic CH₂); 5.7 (1H, *s*, OH), 6.6 (1H, *s*, ar.); 6.9 (1H, *s*, ar.).

Hydrolysis of (I a) and (II a):

The cyanoethyl derivative (I *a*) or (II *a*) was heated under reflux with conc. hydrochloric acid (10 ml, for 100 mg of solid) for 1 hr. On cooling a solid separated, which was collected and dissolved in a minimum amount of sodium bicarbonate solution. The bicarbonate solution on acidification gave (I *b*) or (II *b*) respectively.

I *b*: It crystallised from benzene-petrol-ether (40–60°) as silky white needles, m.p. 101–103°. Yield 45%. (Found: C, 68.1; H, 6.9; C₁₁H₁₄O₃ requires: C, 68.05; H, 7.2%).

II *b*: It crystallised from benzene-petrol-ether (40–60°), as white silky needles, m.p. 156–158°. Yield 50% (Found: C, 67.2; H, 7.0; C₁₄H₁₁O₄ requires: C, 67.7; H, 6.5%),

IR (CH_2Cl_2): 3300 ~ 2500 (broad COOH), 1770 (C = O coumarin).
Mass: m/e (248).

Cyclisation of I b:

The acid (*I b*) was added to a mixture of phosphorus pentoxide (10 g for 300 mg of acid) and phosphoric acid (4 ml) preheated at 100° for 30 min. The heating was continued for 2 hr more with occasional shaking. The reaction was decomposed with water, extracted with chloroform, and washed thoroughly with aqueous sodium bicarbonate. Then, washed with water and later with sodium hydroxide solution (10%). The alkali washings were collected and acidified with conc. hydrochloric acid. It was again extracted with chloroform, washed with water and dried. Removal of the solvent left behind a thick yellow oil (*III*). Yield 10%. It gave a bright red 2, 4-DNP as granules, m.p. above 300°. (Found: N, 16.1; $\text{C}_{17}\text{H}_{16}\text{O}_5\text{N}_4$ requires N, 15.7%).

Cyclisation of II b:

The cyclisation of (*II b*) was carried out in the same way as in the case of (*I b*). The chloroform extract, as in the previous case was washed only with sodium bicarbonate solution and water. Removal of the solvent left behind a pale yellow solid (*IV*), which crystallised from benzene-petrol-ether (40–60°), as yellow granules, m.p. 209–11°. Yield 70%. (Found: C, 72.6; H, 6.4% $\text{C}_{14}\text{H}_{14}\text{O}_3$ requires: C, 73.0; H, 6.1%).

IR (Nujol): 1760 (C = O coumarin) 1680 (C = O cyclopentenone), 1600 (aromatic) cm^{-1} .

Mass: m/e (230).

NMR (CDCl_3): δ 2.3 (3H, s, CH_3); 2.5 (3H, s, CH_3); 2.6 ~ 3.2 (8H, 4(CH_2)).

It gave a 2, 4-DNP as bright orange flakes, m.p. above 315°. (Found: N, 14.0; $\text{C}_{20}\text{H}_{18}\text{O}_6\text{N}_4$ requires: N, 13.7%).

Cyanoethylation of 2, 3-dimethylphenol in acid medium:

The above cyanoethylation of 2, 3-dimethylphenol was carried out as described before and the reaction was worked up as usual. From this reaction also two products (*V a*) alkali soluble and (*VI a*) alkali insoluble were isolated.

The alkali soluble component (*V a*) was obtained in very poor yield (50 mg) as brown thick oil, which was directly subjected to hydrolysis by

refluxing it with conc. hydrochloric acid (10 ml for 1 hr). It was extracted with chloroform, washed with water and then with sodium bicarbonate solution. The bicarbonate washings were collected and acidified with conc. hydrochloric acid. It was extracted with chloroform, washed well with water and dried over anhydrous sodium sulphate. Removal of the solvent left behind a brown thick oil (V b). Yield (10 mg). B.P. 280-3 mm. (Found: C, 68.3; H, 6.9; $C_{11}H_{14}O_3$ requires: C, 68.1; H, 7.2%). The amount of the acid was very small and so its cyclization with PPA was not attempted.

The alkali insoluble component (VI a), yield (3.8 g) was crystallised from benzene-petrol-ether (40:60) as pale yellow cubes, m.p. 105-107° (Found: C, 73.8; H, 7.0; N, 6.3. $C_{14}H_{16}O_2N$ requires: C, 73.4; H, 6.5; N, 6.1%).

Hydrolysis of (VI a):

The cyanoethyl derivative (VI a) was heated under reflux with conc. hydrochloric acid (10 ml for 100 mg of solid) for 1 hr. The reaction was worked up as usual. It afforded the propionic acid (VI b), which crystallised from benzene-petrol-ether (40:60) as white needles, m.p. 14-14.5°. Yield 60%. (Found: C, 67.8; H, 6.4. $C_{13}H_{16}O_2$ requires: C, 67.7; H, 6.5%).

Cyclisation of VI b:

The propionic acid (VI b) was added to a mixture of phosphorus pentoxide (10 g. for 300 mg. of acid) and phosphonic acid (4 ml) preheated at 100° for 30 min. The heating was continued for 2 hr more with occasional shaking. On working up of the reaction as usual gave yellow solid (VII), which crystallised from benzene as yellow needles, m.p. 198-197°. Yield 30%. (Found: C, 72.9; H, 6.0. $C_{14}H_{14}O_3$ requires: C, 73.0; H, 6.1%).

IR ($CHCl_3$): 1760 ($C=O$ coumarin); 1680 ($C=O$ cyclopentenone) cm^{-1} . It gave 2, 4-DNP as orange needles, m.p. above 280°. (Found: N, 13.2. $C_{20}H_{18}O_6N_1$ requires: N, 13.7%).

Action of aqueous sodium hydroxide (10%) on (IV) and (VII)

The cyclopentabenzopyrans (IV) or (VII), (100 mg) were refluxed with sodium hydroxide solution (10%, 20 ml) for 30 min on a wire gauze. It was filtered, acidified with dilute acetic acid and cooled, when yellow granules separated out to yield (VIII) or (IX) respectively. The solid was collected and washed six to seven times with water to remove traces of acetic acid.

VIII: It crystallised from benzene as yellow needles, m.p. 200-201°. Yield 40%. (Found: C, 68.1; H, 6.8. $C_{14}H_{16}O_4$ requires: C, 67.7; H, 6.5%).

It gave 2, 4-DNP as orange needles, m.p. above 300° (Found: N, 13.2; $C_{20}H_{20}O_7N_4$ requires: N, 13.1%).

X: It crystallised from benzene as yellow needles, m.p. 183–185°. Yield 50%. (Found: C, 68.1, H, 6.4. $C_{14}H_{16}O_4$ requires: C, 67.7; H, 6.5%).

It gave 2, 4-DNP as orange needles, m.p. 299–300°. (Found: N, 13.3; $C_{20}H_{20}O_7N_4$ requires: N, 13.1%).

Cyanoethylation of 2, 3, 5-trimethylphenol in the acid medium

Under similar conditions of cyanoethylation as in the previous case of dimethylphenols, 2, 3, 5-trimethylphenol (5.3 g) gave (X a) (3.4 g), crystallised from benzene-petrol-ether (40–60°) as yellow granules, m.p. 145–147°. (Found: C, 73.9; H, 6.9; N, 5.3; $C_{18}H_{21}ON$ requires: C, 74.1; H, 7.0; N, 5.8%).

IR (CH_2Cl_2), 1760 (C = O coumarin).

mass: m/e (243).

NMR ($CDCl_3$): δ 2.25 (3H, s, CH_3), 2.3 (6H, s, 2 (CH_3)), 2.4 ~ 3.3. (8H, 4 (CH_2)).

Hydrolysis of X a:

Hydrolysis as before gave (X b) as white needles, m.p. 200–202°. Yield 60%. It crystallised from benzene-petrol-ether (40–60°) (Found: C, 68.5; H, 6.9; $C_{15}H_{18}O_4$ requires: C, 68.7; H, 6.9 %).

Cyanoethylation of Trimethylphenol in the Presence of Sodium Hydroxide Solution (10%).

A mixture of trimethylphenol (0.01 mol.) dioxane (3.0 ml), acrylonitrile (1.5 ml) and aqueous sodium hydroxide solution (1.5 ml., 10%) was heated under reflux for 20 hr. It was then extracted with chloroform, washed with sodium hydroxide solution (10%), water and dried. Removal of the solvent left behind the cyanoethylated derivative (XI).

XI a: Crystallised from benzene-petrol-ether (40–60°) as yellow needles m.p. 89–92°. Yield 30% (Found: C, 76.3; H, 8.1; N, 7.2; $C_{12}H_{15}ON$ requires: C, 76.2; H, 7.9; N, 7.4%).

XI b: Crystallised from benzene-petrolether (40–60°) as colourless needles, m.p. 123–25°. Yield: 35% (Found: C, 75.9; H, 7.5; N, 7.7; $C_{12}H_{15}ON$ requires: C, 76.2; H, 7.9; N, 7.4%).

XI *c*: Crystallised from benzene-petrol-ether (40–60°) as colourless needles, m.p. 64–67°. Yield: 35% (Found: C, 76.5; H, 8.2; N, 7.1. $C_{12}H_{15}ON$ requires: C, 76.2; H, 7.9; N, 7.4%).

XI *g*: Crystallised from ethylacetate-petrol-ether (40–60°) as yellow needles, m.p. 105–107°. Yield 28%. (Found: C, 76.5; H, 8.0; N, 7.4; $C_{12}H_{15}ON$ requires: C, 76.2; H, 7.9; N, 7.4%).

Hydrolysis of XI (a), (c), (e), (g):

The cyanoethylated derivative was heated with conc. hydrochloric acid (10 ml), for 100 mg of solid for 1 hr. Within ten minutes of the commencement of refluxing needle shaped crystals accumulated in the condenser. They were found to be those of the original trimethylphenol. The solution was cooled when a solid separated out, which was collected and dissolved in sodium bicarbonate solution. On acidification with conc. hydrochloric acid the propionic acid derivative separated.

XI *b*: Crystallised from benzene-petrol-ether (40–60°) as pink needles, m.p. 128–130°. Yield 25% (Found: C, 68.8; H, 7.7. $C_{12}H_{16}O_3$ requires: C, 69.2; H, 7.7%).

XI *d*: Crystallised from benzene-petrol-ether (40–60°) as colourless granules, m.p. 131–133°. Yield 20%. (Found: C, 69.0; H, 7.6; $C_{16}H_{16}O_3$ requires: C, 69.2; H, 7.7%).

XI *f*: Colourless thick oil, b.p. 195–198°/2–2.5 mm. Yield 25%. (Found: C, 69.0; H, 7.6; $C_{12}H_{16}O_3$ requires: C, 69.2; H, 7.7%).

XI *h*: Crystallised from benzene-petrol-ether (40–60°) as colourless needles, m.p. 134–136°. Yield 28% (Found: C, 69.0; H, 7.6; $C_{12}H_{16}O_3$ requires: C, 69.2; H, 7.7%).

Cyclisation of XI (b), (d), (f):

The propionic acid derivative was added to a mixture of phosphorus pentoxide (10.0 g for 300 mg of solid) and phosphoric acid (4.0 ml) preheated at 100° for 30 min and later³ continued for 2 hr more with occasional shaking. The reaction was worked up as before when the requisite, 4H-2, 3-dihydrobenzopyran-4-one derivative was afforded.

XII: Crystallised from methanol as colourless needles, m.p. 42–43°. Yield 25%. (Found: C, 76.0; H, 7.1. $C_{12}H_{14}O_2$ requires: C, 75.8; H, 7.4%).

It gave 2, 4-DNP derivative as red prisms, m.p. above 320° (Found: N, 15.5. $C_{18}H_{18}O_5N_4$ requires N, 15.1%).

XIII: Crystallised from ethylacetate-petrol-ether (40–60°) as yellow needles, m.p. 72–74°. Yield 20%. (Found: C, 75.6; H, 7.8. $C_{12}H_{14}O_2$ requires: C, 75.8; H, 7.4%).

IR (CH_2Cl_2): 1700 (C = O); 1585, 1480, 890 (aromatic) cm^{-1} .

It gave 2, 4-DNP derivative as red prisms, m.p. 233–234° (Found: N, 14.7. $C_{18}H_{18}O_5N_4$ requires: N, 15.1%).

XIV: Crystallised from benzene-petrol-ether (40–60°) as yellow needles, m.p. 47–48°. Yield 30% (Found: C, 76.2; H, 7.7; $C_{12}H_{14}O_2$ requires: C, 75.8; H, 7.4%).

IR (CH_2Cl_2): 1700 (C = O); 1610, 1565, 1480, 860 (aromatic) cm^{-1} .

It gave 2, 4-DNP as red prisms above 320° (Found: N, 15.4; $C_{18}H_{18}O_5N_4$ requires: N, 15.1%).

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