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Reaction of Polymethylbenzyl Cyanides with Fuming Nitric Acid. A New Route to Polysubstituted 3-Isochromanone Synthesis[1)]

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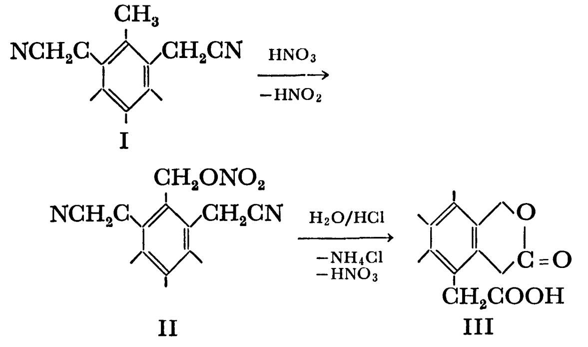
Synopsis. Treatment of pentamethylbenzyl cyanide and bis(cyanomethyl)tetramethylbenzenes with fuming nitric acid in dichloromethane led to the regiospecific nitrooxylation of the methyl group adjacent to the cyanomethyl group, giving the corresponding benzyl nitrates in good yields. On acid hydrolysis, these nitrates were readily converted into 3-isochromanone derivatives.

Action of cold fuming nitric acid upon polymethylbenzenes leads to the formation of benzyl nitrates.[2)] High regiospecificity for the side-chain attack offers a potential as a new entry into various types of benzylic compound. As part of our study concerned with this type of reaction, we report here a convenient preparation of certain polysubstituted 3-isochromanones (3,4-dihydro-1*H*-2-benzopyran-3-ones), useful intermediates for 3(2*H*)-isoquinolinone synthesis. Previously reported routes to 3-isochromanones involve the haloalkylation of phenylacetic acids,[3)] the Baeyer-Villiger reaction of 2-indanones,[4)] or the lactonization of *o*-acylphenylacetic acid derivatives.[5)]

4,6-Bis(cyanomethyl)-1,2,3,5-tetramethylbenzene (I), readily obtained by chloromethylation of isodurene and subsequent treatment of the bis-chloride with sodium cyanide, underwent reaction with fuming nitric acid in dichloromethane at 0—5 °C, giving a high yield of a crystalline product, mp 172—173 °C with decomposition, which had a formula $C_{14}H_{15}N_3O_3$ and showed strong infrared bands due to CH_2ONO_2 group at 1645, 1624, 1286, and 870 cm^{-1}. The unaltered presence of cyano group was shown by the peak at 2245 cm^{-1}. The proton NMR spectrum of the product exhibited absorptions at δ 2.33 (s, 3H), 2.40 (s, 6H), 3.82 (s, 4H), and 5.65 (s, 2H). Loss of the lower-field methyl peak of I indicated that the methyl group flanked with cyanomethyl groups on both sides had been converted into a nitrooxymethyl group. These data are only compatible with the formulation of the product as 5-nitrooxymethyl-4,6-bis(cyanomethyl)-1,2,3-trimethylbenzene (II).

When an ethanolic solution of II was heated with dilute hydrochloric acid under gentle reflux, there were obtained white prisms with the composition $C_{14}H_{16}O_2$, mp 187—189 °C. This compound showed the infrared bands at 3200—2600 (OH), 1738, 1706 (C=O), 1220 (O–CO), 1010 (C–O), and 927 cm^{-1} (OH), and proton NMR peaks at δ 2.23 (s, 6H), 2.27 (s, 3H), 3.70 (s, 2H), 3.75 (s, 2H), and 5.34 (s, 2H). With aqueous alkali it went into solution and was again precipitated on acidification. From its mode of reaction and spectral data, therefore, the product was formulated as 6,7,8-trimethyl-3-isochromanone-5-acetic acid (III).



A similar treatment of 3,6-bis(cyanomethyl)-1,2,4,5-tetramethylbenzene gave 5-nitrooxymethyl-3,6-bis(cyanomethyl)-1,2,4-trimethylbenzene, which was then converted into 5,7,8-trimethyl-3-isochromanone-6-acetic acid. Pentamethylbenzyl cyanide offered an easy access to 5,6,7,8-tetramethyl-3-isochromanone over 2-cyanomethyl-3,4,5,6-tetramethylbenzyl nitrate. In every case side-chain nitrooxylation took place on the methyl group adjacent to the cyanomethyl group. 4,6-Bis(cyanomethyl)-5-ethyl-1,2,3-trimethylbenzene could, potentially, afford a substance analogous to III. However, treatment of this cyanide with nitric acid followed by acid hydrolysis resulted in the formation of intractable gummy substance.

Like existing methods of preparation, our route to 3-isochromanone synthesis is also subject to limited application. It appears to be applicable only to some fully substituted benzyl cyanides carrying two methyl groups in *para* relationship. However, easy access to starting materials, satisfactory yield, and ease of manipulation would make this procedure still useful for some 3-isochromanone synthesis.

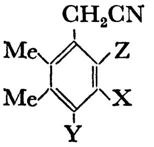
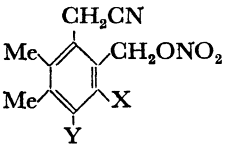
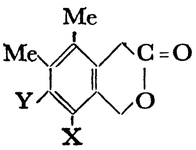
Experimental

Melting points are uncorrected. Proton NMR spectra were recorded at 60 MHz using deuteriochloroform as a solvent and TMS as an internal standard. IR spectra were obtained in Nujol with a Jasco 402G spectrophotometer. Satisfactory analyses were obtained for all new compounds.

Polymethylbenzyl cyanides were prepared from the corresponding chlorides by treatment with sodium cyanide in aqueous acetonitrile. Physical properties of benzyl cyanides, benzyl nitrates, and 3-isochromanones obtained in context with the present work are listed in Table 1. No attempt has been made to optimize the conditions.

Procedure for the Nitration of Benzyl Cyanides. A solution of nitric acid (d=1.5; 6.3 g) in dichloromethane (5 ml) was added with stirring to a suspension of benzyl cyanide (0.01 mol) in the same solvent (15 ml) cooled to −5—0 °C in a salt-ice bath. After addition, the mixture was allowed to warm and maintained at room temperature for several hours. It was then worked up by pouring into water, sep-

TABLE 1. PHYSICAL PROPERTIES OF SOME POLYSUBSTITUTED BENZYL CYANIDES, BENZYL NITRATES, AND 3-ISOCHROMANONES

Compound	X	Y	Z	Mp (°C)	Proton NMR spectrum (δ)
	Me	Me	Me	113—115	2.18 (3Me), 2.26 (2Me), 3.52 (CH_2)
	CH_2CN	Me	Me	210—211	2.25 (Me), 2.34 (2Me), 2.42 (Me), 3.71 ($2CH_2$)
	CH_2CN	Me	Et	185—186	1.23 (Me), 2.27 (Me), 2.35 (2Me), 2.78 (CH_2), 3.72 ($2CH_2$)
	Me	CH_2CN	Me	269—270	2.34 (4Me), 3.73 ($2CH_2$)
	Me	Me	—	116—118	2.25 (2Me), 2.33 (2Me), 3.74 ($2CH_2$)
	CH_2CN	Me	—	177—178	2.33 (Me), 2.40 (2Me), 3.82 ($2CH_2$), 5.65 (CH_2)
	Me	CH_2CN	—	123—130	2.38 (2Me), 2.44 (Me), 3.72 (CH_2), 3.79 (CH_2), 5.62 (CH_2)
	Me	Me	—	106—108	2.22 (2Me), 2.25 (2Me), 3.68 (CH_2), 5.37 (CH_2)
	CH_2COOH	Me	—	187—189	2.23 (2Me), 2.27 (Me), 3.70 (CH_2), 3.75 (CH_2), 5.34 (CH_2)
	Me	CH_2COOH	—	220—222	2.24 (2Me), 2.28 (Me), 3.69 (CH_2), 3.82 (CH_2), 5.37 (CH_2)

arating the organic layer, and evaporating the solvent to give a nitrate as crystalline solid or somewhat pasty cake. It was recrystallized from ethanol. Yields ranged from 67 to 85%.

Procedure for the Hydrolysis of 2-Cyanomethylbenzyl Nitrates to 3-Isochromanones. Dilute hydrochloric acid (10%; 10 ml) was added to a solution of benzyl nitrate (2.5 g) in ethanol (20 ml) and the mixture was heated under gentle reflux for several hours. The yellow solution was then evaporated under reduced pressure to give a residue, which was extracted and crystallized from aqueous ethanol to give 3-isochromanone as fine needles or plates. Yields ranged from 47 to 75%.

The use of concentrated acid led to the extensive formation of an alkali-soluble resin. 3-Isochromanones are readily soluble in ethanol, sparingly soluble in hot water, and almost insoluble in light petroleum.

References

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