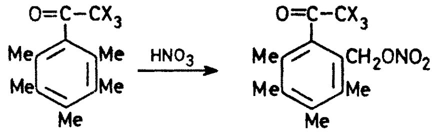
Nitration of Fully Methylated Acylbenzenes and 1,3-Diacylbenzenes bearing Bulky Acyl Groups. Side-chain Attack Occurring Exclusively on the Methyl Group at the Most Hindered Site

By HITOMI SUZUKI,* MITSUYUKI HASHIHAMA, TADASHI MISHINA, and TERUKIYO HANAFUSA
(*Department of Chemistry, Faculty of Science, Hiroshima University, Higashi-sendamachi, Hiroshima* 730, *Japan*)

Summary On treatment with concentrated nitric acid, the title compounds undergo attack on the side-chain which occurs exclusively on the methyl group at the most hindered site, giving 6-acyl-2,3,4,5-tetramethylbenzyl nitrate, and 2,6-diacyl-3,4,5-trimethylphenylnitromethane and/or 2,6-diacyl-3,4,5-trimethylbenzyl nitrate as the respective major side-chain substitution products.

ON treatment with nitric acid at room temperature, polyalkylbenzenes and their derivatives often undergo substitution on the alkyl side-chain, giving benzylic compounds in addition to normal ring substitution products.[1] The side-chain reaction is characterized by unusual orientation and high regiospecificity in the products, and the type of product markedly depends on the reagent employed; benzyl nitrate is the main product from the reaction with nitric acid, while the formation of phenylnitromethane is favoured in the reaction with acetyl nitrate. Despite recent numerous studies, the mechanism of side-chain substitution still remains a subject of controversy and speculation.[2]

We report here the side-chain substitution of highly crowded polymethyl-acyl- and -diacyl-benzenes (I) and (III), which involves exclusive attack on the methyl group at the most hindered site. We also report the first example in which a small modification of the substituent group can produce a marked change in the side-chain reaction, *i.e.*, a change from side-chain nitro-oxylation to side-chain nitration.



(I) (II)

a; X = Me
b; X = Cl
c; X = Br

Treatment of the pentamethylacylbenzenes (Ia), (Ib), and (Ic) with an excess of nitric acid ($d = 1{\cdot}5$ g cm^{-3}) in dichloromethane at room temperature, followed by chromatography on silica gel, gave the tetramethylacylbenzyl nitrates (IIa), (IIb), and (IIc), respectively, in *ca.* 40—60% isolated yields.† The characteristic appearance of benzylic protons as a pair of doublets at δ 5·0—5·3 and δ 5·4—5·5 indicated the presence of a nitro-oxymethyl group adjacent to the bulky acyl group. Similar treatment of the tetramethyldiacylbenzene (IIIa)[3] gave the trimethyldiacylbenzyl nitrate (Va) as a side product (10—20%) in addition to the expected nitro-compound (VI). In every case, the methyl group at the most hindered ring position underwent preferential nitro-oxylation. These results present a striking contrast to normal aromatic substitutions which are sensitive to the steric effect of bulky substituent groups.

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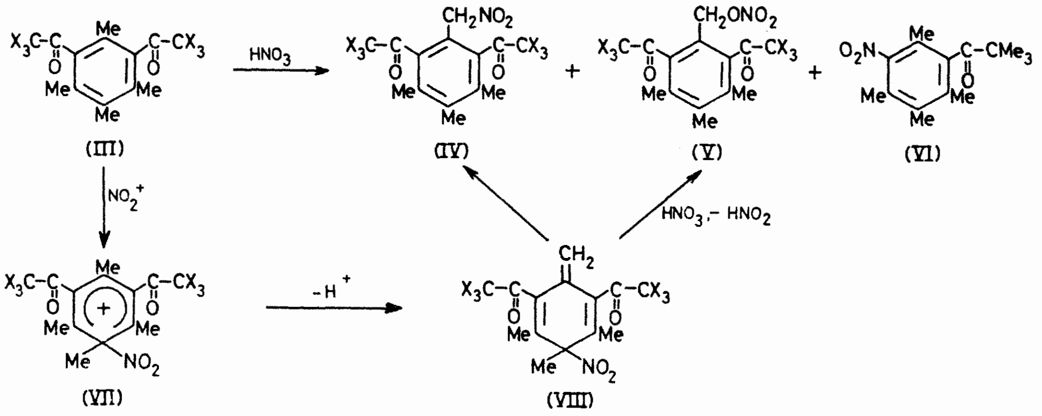
† All new compounds reported herein were characterized by their analytical and spectral data.

The action of nitric acid upon the diacyl compounds (IIIb) and (IIIc) afforded a mixture of the trimethyldiacylphenylnitromethanes (IVb) and (IVc), *ca.* 40—45% yields,‡ and the trimethyldiacylbenzyl nitrates (Vb) and (Vc), *ca.* 20—25% yields,‡ respectively. Nitrodeacylation was not observed. The methyl group flanked on both sides by bulky trihalogenoacetyl groups was again attacked exclusively. In these cases, however, the main mode of the side-chain reaction changed from nitro-oxylation to nitration. Such an effect of substituents was quite unexpected and we can find no parallel in the literature.



a; X = Me
b; X = Cl
c; X = Br

SCHEME

The exclusive attack on the methyl group at the most crowded position can be explained by a sequence involving the *ipso* attack of a nitronium ion on the most reactive ring site forming the arenium ion (VII), which releases a proton from the activated methyl group *para* to the site of attack to give the triene (VIII), which will then be transformed into the benzylic compounds (IV) and (V) (Scheme).

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‡ Isolated yields are based on unrecovered starting materials. The product mixture was separated by silica gel chromatography and further purified by t.l.c.

[1] For a review of non-conventional nitration, see H. Suzuki, *Synthesis*, 1977, 217; R. B. Moodie and K. Schofield, *Accounts Chem. Res.*, 1976, **9**, 287; S. R. Hartshorn, *Chem. Soc. Rev.*, 1974, **3**, 167.

[2] H. Suzuki, H. Yoneda, and T. Hanafusa, *Bull. Chem. Soc. Japan*, 1975, **48**, 2116; H. Cerfontain, A. Koeberg-Telder, C. Ris, and C. Schenk, *J.C.S. Perkin II*, 1975, 966; A. Fischer and J. N. Ramsay, *Canad. J. Chem.*, 1974, **52**, 3960; J. K. Kochi, *Tetrahedron Letters*, 1974, 4305; E. Baciocchi, A. Ciana, G. Illuminati, and C. Pasini, *J. Amer. Chem. Soc.*, 1965, **87**, 3953.

[3] H. Suzuki, Y. Aomori, T. Mishina, and T. Hanafusa, *Bull. Chem. Soc. Japan*, 1978, **51**, 3393.