# The Nitration of Acylpentamethylbenzenes and 1,3-Diacyltetramethylbenzenes Bearing, as the Acyl Components, Pivaloyl, Trichloroacetyl, and Tribromoacetyl Groups. Exclusive Attack on the Methyl Group at the Most Crowded Site[1]

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When treated with concentrated nitric acid in dichloromethane at room temperature, the title compounds undergo an exclusive attack on the methyl group at the most crowded site, giving 6-acyl-2,3,4,5-tetramethylbenzyl nitrates, and 2,6-diacyl-3,4,5-trimethylbenzyl nitrates and/or (2,6-diacyl-3,4,5-trimethylphenyl)nitromethanes respectively, as the major products. While the predominant mode of the side-chain substitution reactions is nitrooxylation for acylpentamethylbenzenes and 1,3-dipivaloyl-2,4,5,6-tetramethylbenzene, it shifts to nitration for 1,3-bis(trihalogenoacetyl)-2,4,5,6-tetramethylbenzenes. Nitrodeacylation is seen to some extent for pivaloylbenzenes, but not for trihalogenoacetylbenzenes. The exclusive attack on the methyl group at the most hindered position can be explained by a sequence involving the attachment of a nitronium ion at the site *meta* to the acyl group, followed by a proton release from the resulting arenium ion to form a nitromethylenecyclohexadiene intermediate, which is then transformed into the benzylic compounds *via* a benzyl cation/nitrite anion pair.

When treated with nitric acid at a low temperature, polyalkylated aromatic compounds often suffer the side-chain substitution to give benzylic compounds in addition to the normal nuclear substitution products. The side-chain reaction is characterized by a peculiar orientation and high regiospecificity in the products, which stand in marked contrast to the ordinary side-chain substitution occurring through a homolytic mechanism. The puzzling features of this reaction have been a subject of numerous recent studies,[2] but its mechanism still remains a matter of controversy and speculation. Recently, we have made a systematic investigation of the nitration of hexamethylbenzene and presented the first quantitative data of the product distribution; these data favor the $S_N1'$ mechanism, in which the side-chain substitution products are formed from the methylenecyclohexadiene intermediate through the intervention of an ion-pair.[3] To obtain further information about the character of the reaction, especially the steric effect of the substituent group on the course of the side-chain substitution, a series of acylpentamethylbenzenes and 1,3-diacyl-2,4,5,6-tetramethylbenzenes bearing bulky acyl groups, such as pivaloyl, trichloroacetyl, and tribromoacetyl groups, have been prepared, and their reactions with concentrated nitric acid have been investigated.

## Experimental

All the melting points were determined on a hot-stage apparatus and are uncorrected. The infrared spectra were run as Nujol mulls on a Hitachi 215 spectrophotometer, and only prominent peaks were recorded. The $^1$H-NMR spectra were measured in chloroform-*d* with a Varian T-60 apparatus and a JEOL MH-100 apparatus, using TMS as the internal standard, unless otherwise stated. The mass spectra were obtained on a Hitachi RMS-4 mass spectrometer, with an ionizing current of 70 eV.

*Materials.* *1,3-Dipivaloyl-2,4,5,6-tetramethylbenzene (**7b**)* was prepared from 1,3-dipropanoylbenzene (**6**) by repeated treatment with potassium *t*-butoxide and methyl iodide.[4]

*Pentamethylpivalophenone (**3b**).* Into a mixture of pivaloyl chloride (3.4 g, 28.2 mmol), aluminium chloride (6.5 g, 48.7 mmol), and carbon disulfide (20 ml), pentamethylbenzene (**1**; 5.0 g, 33.7 mmol) in carbon disulfide (15 ml) was stirred under ice-salt-bath cooling during the course of 0.3 h. After the addition, the brown viscous mixture was stirred for a further 0.7 h at room temperature and then decomposed with dilute hydrochloric acid. The organic layer was separated, the carbon disulfide was removed, and the residual solid product was collected by filtration and subjected to chromatography over silica gel, using hexane as a solvent. The unchanged hydrocarbon and then the ketone **3b** were eluted, and the latter was recrystallized from ethanol. White needles, mp 129—130 °C. Yield, 2.8 g (42% based on the pivaloyl chloride used).

*1,3-Bis(tribromoacetyl)-2,4,5,6-tetramethylbenzene (**7d**).*[5] Bromine (8.0 g, 50 mmol) was stirred into a solution of sodium hydroxide (8.0 g, 200 mmol) in water (70 ml). The temperature was kept below 10 °C during the addition. To the resulting solution, 1,3-diacetyl-2,4,5,6-tetramethylbenzene (**5**; 1.1 g, 5 mmol) dissolved in benzene (15 ml) was added; the mixture was then heated with vigorous stirring at 60 °C, while the progress of the reaction was monitored by means of $^1$H-NMR. After 40 h, a further amount of aqueous sodium hypobromite (50 mmol) was added; heating was then continued for an additional 20 h. The organic layer was then separated, washed thoroughly with aqueous sodium hydrogensulfite and then water, and dried over magnesium sulfate. The solvent was removed, and the residue was recrystallized from benzene to give **7d** as colorless prisms; mp 195—197 °C. Yield, 2.28 g (65%).

*1,3-Bis(trichloroacetyl)-2,4,5,6-tetramethylbenzene (**7c**)* was similarly prepared by treating **5** with a large excess of aqueous sodium hypochlorite at 60 °C. It was recrystallized from benzene to give white needles; mp 138—139 °C. Yield, 37%.

*Procedures for Nitration of Acylpentamethylbenzenes and 1,3-Diacyl-2,4,5,6-tetramethylbenzenes.* Some typical examples are shown below for the nitration of α,α,α-trichloropentamethylacetophenone (**3c**) and 1,3-bis(trichloroacetyl)-2,4,5,6-tetramethylbenzene (**7c**).

*i)*: Nitric acid ($d$=1.5; 0.63 g, 10 mmol) in dichloromethane (2 ml) was added to a vigorously stirred suspension of **3c** (0.50 g, 1.7 mmol) in dichloromethane (4 ml). The

mixture was stirred at room temperature for 1.5 h and then diluted with water. The organic layer was separated, and the aqueous layer was extracted with dichloromethane. The combined organic solutions were washed thoroughly with water, dried over magnesium sulfate, and evaporated to leave a solid residue, which was recrystallized several times from hexane to give **4c** as white crystals; mp 106—109 °C. Yield 0.27 g (45%).

*ii)*: A suspension of 1,3-bis(trichloroacetyl)-2,4,5,6-tetramethylbenzene (**7c**; 1.0 g, 2.35 mmol) in dichloromethane (5 ml) was cooled to −10—0 °C, after which fuming nitric acid ($d$=1.5; 1.48 g, 23.5 mmol) was stirred in over a period of 5 min. The resulting brown mixture was stirred at room temperature for 3 h and then diluted with water. The organic layer was separated and worked up as usual to give a light brown, pasty solid, which was then passed through a short silica-gel column to obtaine the unchanged substrate (0.67 g) and a product mixture (0.151 g). The latter was then chromatographed on a thin-layer silica-gel plate, using hexane as the eluant. Two main bands were scraped off from the glass plate and extracted with ether; *1,3-bis(trichloroacetyl)-2-nitrooxymethyl-4,5,6-trimethylbenzene* (**9c**; 22 mg, 6%) was obtained from the fast moving band, and *1,3-bis(trichloroacetyl)-2-nitromethyl-5,4,6-trimethylbenzene* (**8c**; 39 mg, 11%), from the slow moving band.

In an alternative way, the product mixture was dissolved in a minimum amount of pentane, after which the solution was kept in a refrigerator for several days. Compounds **8c** and **9c** crystallized out as prisms and needles, respectively and were partially separated by hand-picking.

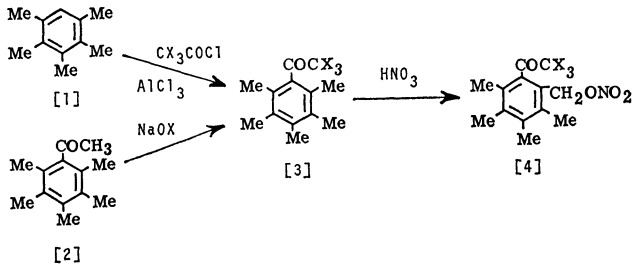
## Results and Discussion

Acylbenzenes undergo nitration mainly at the position *meta* to the acyl group, as would be expected from the deactivating effect of the acyl group. Some examples of an acyl group being replaced by a nitro group are also well known.[6] However, the literature so far contains no report on the nitration of fully methylated acylbenzenes and diacylbenzenes.

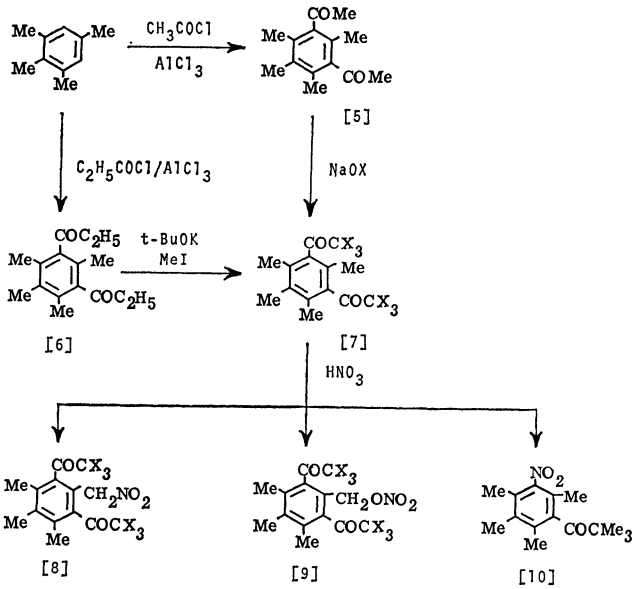
Pentamethylacetophenone (**2**) reacted slowly with concentrated nitric acid in dichloromethane at −5—0 °C to give a four-component mixture, from which the major product was isolated and identified as 6-nitrooxymethyl-2,3,4,5-tetramethylacetophenone (**4a**). On similar treatment, 1,3-diacetyl-2,4,5,6-tetramethylbenzene (**5**) gave a complex mixture of products, one component of which was isolated by TLC and identified as 5-nitro-2,3,4,6-tetramethylacetophenone (**14**). The general pattern of the reaction was similar to those found in the nitrations of pentamethylbenzoic acid[7] and pentamethylbenzamide.[8] The nitrating agent seems to attack the acetyl group partially, making the products more complicated and difficult to separate.

Based on the results obtained from these preliminary experiments, we turned to the nitration of the title hindered mono- and diketones in order to see if the replacement of the acetyl group by a bulky acyl group, such as the pivaloyl and trihalogenoacetyl groups, may produce any effect on the course of the reaction or the product distribution. Pentamethylpivalophenone (**3b**) was obtained by the Friedel-Crafts acylation of pentamethylbenzene (**1**) with pivaloyl chloride. 1,3-Dipivaloyl-2,4,5,6-tetramethylbenzene (**7b**) could not be obtained by the similar acylation of 1,2,3,5-tetramethylbenzene; after several unsuccessful attempts, it was, however, prepared by the exhaustive methylation of 1,3-dipropanoyl-2,4,5,6-tetramethylbenzene (**6**) with potassium *t*-butoxide and methyl iodide. α,α,α-Trihalogenopentamethylacetophenones (**3c** and **3d**) and 1,3-bis(trihalogenoacetyl)-2,4,5,6-tetramethylbenzenes (**7c** and **7d**) were obtained following the routes outlined in Schemes 1 and 2. The halogenation with sodium hypohalite of the **2** and **5** ketones proceeded quite slowly, and the repeated treatment of partially halogenated ketones with a fresh batch of aqueous sodium hypohalite was necessary to obtain **7c** and **7d** in acceptable yields. All of these mono- and diketones are well-crystallized solids and are poorly soluble in ordinary non-polar solvents.

The treatment of acylpentamethylbenzenes **3b**—**3d** with an excess of nitric acid ($d$=1.5) in dichloromethane at room temperature, followed by the chromatography of the product over silica gel, gave the corresponding 6-nitrooxymethyl-2,3,4,5-tetramethylacylbenzenes **4b**—**4d** in 40—60% yields. The characteristic appearance of benzylic protons as a pair of doublets at δ 5.0—5.3 and 5.4—5.5 ppm indicated the presence of a nitrooxymethyl group adjacent to the bulky acyl group. Thus, irrespective of any difference in bulkiness or electron-withdrawing ability, the propensity of the acyl group to direct an entering group on the adjacent alkyl side-chain

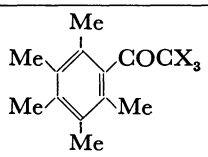
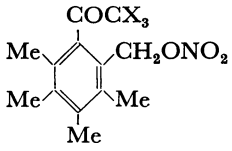
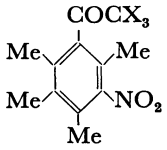
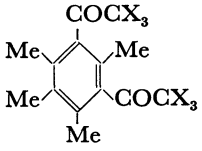
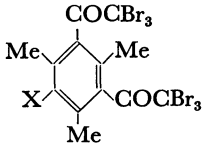


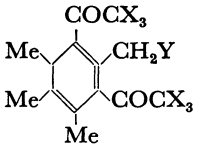

Scheme 1.




Scheme 2.

Table 1. Physical and spectral data for some polysubstituted acylbenzenes and 1,3-diacylbenzenes

| Compound | Mp/°C | IR spectra $\nu_{max}/cm^{-1}$ | $^1$H-NMR spectra $\delta$/ppm | Found (%) | Calcd (%) |
|---|---|---|---|---|---|
|  | | | | | |
| [2] X=H | 83—85 | 1700, 1300, 1170 | 2.07 (s, 2Me), 2.13 (s, 3Me)*<br>2.30 (s, MeCO) | — | —[9] |
| [3b] X=Me | 129—130 | 1690, 1100, 910 | 1.17 (s, $Me_3CCO$), 2.02 (s, 2Me),*<br>2.15 (s, 2Me), 2.19 (s, Me) | C 82.6<br>H 10.6 | 82.7<br>10.4 |
| [3c] X=Cl | 91—92 | 1735, 1095, 840, 785 | 2.17—2.33 (br. s, 5Me)* | C 52.9<br>H 5.2 | 53.2<br>5.2 |
| [3d] X=Br | 131—133 | 1725, 1090, 910, 795, 740 | 2.20, 2.23, 2.28 (incompletely*<br>resolved, 5Me) | C 36.5<br>H 3.5 | 36.6<br>3.5 |
|  | | | | | |
| [4a] X=H | 100—101 | 1690, 1615, 1275, 860 | 2.13 (s, Me), 2.23 (s, 2Me),*<br>2.27 (s, Me), 2.40 (s, MeCO),<br>5.32 (s, $CH_2$) | C 61.9<br>H 6.9<br>N 5.5 | 62.1<br>6.8<br>5.6 |
| [4b] X=Me | 100—101 | 1690, 1630, 1270, 840 | 1.16 (s, $Me_3CCO$), 2.08 (s, Me),*<br>2.23 (br. s, 3Me), 5.03 (d, $CH_2$;<br>$J$=11Hz), 5.37 (d, $CH_2$; $J$=11 Hz) | C 65.5<br>H 7.9<br>N 4.5 | 65.5<br>7.9<br>4.8 |
| [4c] X=Cl | 106—109 | 1730, 1620, 1270, 1095, 855,<br>800 | 2.20—2.42 (br. s,4Me), 5.25*<br>(d, $CH_2$; $J$=11.5 Hz), 5.38 (d,<br>$CH_2$; $J$=11.5 Hz) | C 44.1<br>H 4.0<br>N 3.9 | 44.0<br>4.0<br>4.0 |
| [4d] X=Br | 115—117 | 1715, 1630, 1275, 850 | 2.29, 2.33 (incompletely resolved,*<br>4Me), 5.35 (d, $CH_2$; $J$=12 Hz),<br>5.48 (d, $CH_2$; $J$=12 Hz) | C 32.0<br>H 2.9<br>N 2.7 | 32.0<br>2.9<br>2.9 |
|  | | | | | |
| [14] X=H | 106—108 | 1690, 1525, 1255, 1155, 840 | 2.05 (s, Me), 2.15 (s, 2Me),*<br>2.18 (s, Me), 2.38 (s, MeCO) | C 65.2<br>H 7.0<br>N 6.3 | 65.1<br>6.8<br>6.3 |
| [10] X=Me | 104—105 | 1680, 1525, 1090, 920, 850 | 1.25 (s, $Me_3CCO$), 2.08 (s, Me),*<br>2.15 (s, Me), 2.20 (s, 2Me) | C 68.2<br>H 8.2<br>N 5.2 | 68.4<br>8.0<br>5.3 |
|  | | | | | |
| [5] X=H | 126—128 | 1695, 1350, 1200 | 1.98 (s, Me), 2.12(br. s, 3Me),*<br>2.35 (s, MeCO) | — | —[9] |
| [7b] X=Me | 166—168 | 1690, 1300, 1100, 930, 910 | 1.21 (s, $Me_3CCO$), 1.24 (s, $Me_3CCO$),<br>2.00 (s, Me), 2.13 (br, s, 3Me) | C 79.7<br>H 10.2 | 79.4<br>10.0 |
| [7c] X=Cl | 138—139 | 1730, 1110, 965, 850, 770 | 2.23 (s, Me), 2.32 (s, 3Me) | C 39.5<br>H 2.8 | 39.6[5]<br>2.9 |
| [7d] X=Br | 195—197 | 1720, 1100, 950, 780, 730 | 2.23 (s, Me), 2.40 (s, 2Me),<br>2.47 (s, Me) | C 24.6<br>H 1.8 | 24.3[5]<br>1.8 |
|  | | | | | |
| [15] X=H | 162—165 | 1730, 1240, 970, 795 | 2.48 (s, 2Me), 2.52 (s, Me),<br>7.10 (s, $H_{arom}$) | C 23.3<br>H 1.5 | 23.0<br>1.5 |

| Compound | Mp/°C | IR spectra $\nu_{max}/cm^{-1}$ | $^1$H-NMR spectra $\delta$/ppm | Found (%) | Calcd (%) |
|---|---|---|---|---|---|
| [16] X=$NO_2$ | 215—217 | 1715, 1525, 1240, 790, 760 | 2.40 (s, 2Me), 2.53 (s, Me) | C 22.0<br>H 1.3<br>N 2.0 | 21.6<br>1.3<br>1.9 |
|  | | | | | |
| [9b] X=Me, Y=$ONO_2$ | 143—145 | 1685, 1635, 1280, 845 | 1.22 (s, $Me_3CCO$), 1.25 (s, $Me_3CCO$), 2.17 (s, 2Me), 2.21 (s, Me), 5.00 (d, $CH_2$; $J$=11 Hz), 5.06 (s, $CH_2$), 5.15 (d, $CH_2$; $J$=11 Hz) | C 66.4<br>H 8.3<br>N 3.5 | 66.1<br>8.0<br>3.9 |
| [9c] X=Cl, Y=$ONO_2$ | 93—95 | 1735, 1625, 1270, 840 | 2.30 (s, Me), 2.37 (s, 2Me), 5.24 (d, $CH_2$; $J$=12 Hz), 5.31 (s, $CH_2$), 5.43 (d, $CH_2$; $J$=12 Hz) | C 34.5<br>H 2.2<br>N 2.4 | 34.6<br>2.2<br>2.8 |
| [9d] X=Br, Y=$ONO_2$ | 163—165 | 1730, 1615, 1270, 855 | 2.33 (s, Me), 2.45 (s, 2Me), 5.37 (d, $CH_2$; $J$=12 Hz), 5.47 (s, $CH_2$), 5.68 (d, $CH_2$; $J$=12 Hz) | C 22.4<br>H 1.5<br>N 1.5 | 22.3<br>1.4<br>1.8 |
| [8b] X=Me, Y=$NO_2$ | 177—178 | 1690, 1560, 1300, 1090, 940 | 1.23 (s, $Me_3CCO$), 1.27 (s, $Me_3CCO$), 2.00 (s, Me), 2.12 (s, 2Me), 5.13 (br. s, $CH_2$) | C 69.2<br>H 8.5<br>N 4.0 | 69.1<br>8.4<br>4.0 |
| [8c] X=Cl, Y=$NO_2$ | 217—220 | 1740, 1565, 1310,1110, 970, 805, 780 | 2.33 (s, Me), 2.38 (s, 2Me), 5.38 (d, $CH_2$; $J$=18 Hz), 5.42 (s, $CH_2$), 5.51 (d, $CH_2$; $J$=18 Hz) | C 35.9<br>H 2.4<br>N 2.9 | 35.8<br>2.4<br>3.0 |
| [8d] X=Br, Y=$NO_2$ | 199—202 | 1730, 1565, 1310, 1095, 960, 775, 730 | 2.33 (s, Me), 2.45 (s, 2Me), 5.43 (d, $CH_2$; $J$=17 Hz), 5.64 (s, $CH_2$), 5.86 (d, $CH_2$; $J$=17 Hz) | C 23.2<br>H 1.5<br>N 1.7 | 22.8<br>1.5<br>1.9 |

* Determined in carbon tetrachloride.

was maintained through the whole series of four acylpentamethylbenzenes **3a**—**3d**. Nitrodeacylation was observed to some extent with pivalophenone, **7b**, but not at all with α,α,α-trihalogenoacetophenones, **7c** and **7d**. By similar treatment, 1,3-dipivaloyl-2,4,5,6-tetramethylbenzene (**7b**) gave 2,6-dipivaloyl-3,4,5-trimethylbenzyl nitrate (**9b**) as a side product (10—20%), in addition to the expected nitrodeacylation product, 5-nitro-2,3,4,6-tetramethylpivalophenone (**10**). Only the methyl group, flanked on both sides by bulky pivaloyl groups, suffered side-chain nitrooxylation. Those results, together with those obtained from the nitration of acylpentamethylbenzenes, **3b**—**3d**, present a striking contrast to the ordinary aromatic substitutions, which are quite sensitive to the bulkiness of the substituent groups.

The action of nitric acid upon the diacyl compounds, **7c**—**7d**, afforded a mixture of (2,6-diacyl-3,4,5-trimethylphenyl)nitromethanes, **8c**—**8d**, and 2,6-diacyl-3,4,5-trimethylbenzyl nitrates, **9c**—**9d**; the yields, as estimated from the $^1$H-NMR peak integration, were 40—45 % and 20—25%, respectively, based on the unrecovered starting materials. With these halogeno-ketones, no nitrodeacylation was observed. The methyl group between two bulky acyl groups was exclusively attacked again. In these cases, however, the major mode of the side-chain reaction changed from nitrooxylation to nitration. Such a marked change produced by a slight modification of the substituent groups was unexpected, and we can find no parallel previously in the reported literature.

At room temperature the benzylic protons of the nitrates, **9b**—**9d** and nitromethanes, **8c**—**8d**, appear as a peak cluster consisting of one double doublet signal and one singlet signal in the $^1$H-NMR spectrum (Table 1). In the high-temperature spectrum, however, this peak cluster converges into a new single peak which occurs at the average position of the corresponding peaks in the low-temperature spectrum, indicating that these nitrates and nitromethanes exist in a pair of stable conformations resulting from the *cis*/*trans* isomerism due to restricted rotation about carbonyl groups. A variable-

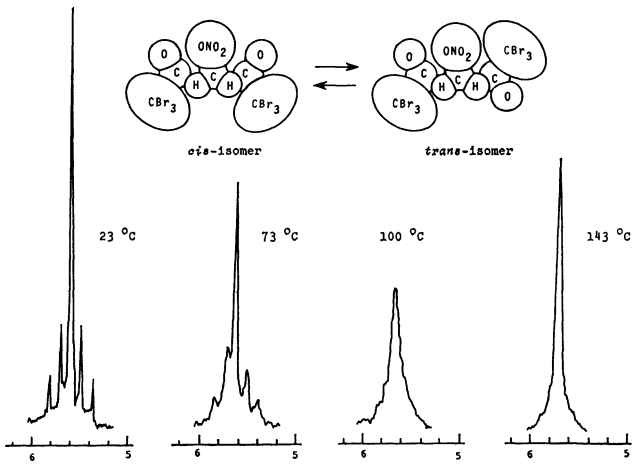
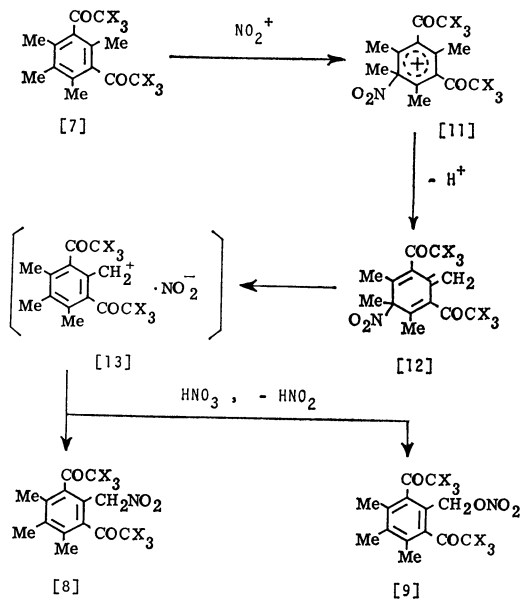



Fig. 1. Selected variable temperature $^1$H-NMR signals (100 MHz) for benzylic protons of *cis*/*trans* isomers of 2,6-bis(tribromoacetyl)-3,4,5-trimethylbenzyl nitrate (**9d**) in *o*-dichlorobenzene.



Scheme 3.

temperature $^1$H-NMR spectrum of the **9d** nitrate is shown in Fig. 1. Clearly, at room temperature and below **9d** exists in the form of *cis*/*trans* isomers, the ratio of which is estimated to be 2.6 from the peak-area integration. The details of this interesting isomerism will be described elsewhere.

An examination of the CPK molecular models of the **7b**—**7d** ketones indicates the difficulty of a direct attack by a solvated electrophile on a methyl group flanked on both sides by bulky acyl groups. Thus, the nitration and nitrooxylation occurring exclusively on the methyl group at the most crowded site can be explained by the indirect sequence depicted in Scheme 3: an *ipso* attack of a nitronium ion on the most reactive ring site of **7** to form the arenium ion (**11**) is followed by a proton release from the activated methyl group *para* to the site of attack to give the triene (**12**), which is then transformed into the benzylic compounds, **8** and **9** *via* the assumed ion-pair (**13**).[3]

The authors wish to thank Dr. Tetsuo Ohtsuki of Kyoto University for measuring the variable-temperature $^1$H-NMR spectra of hindered ketones described herein.

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