

EXPERIMENTAL

Preparation of 2,4,6-trinitrazaheptane (III) from IV. Six and three-tenths grams (0.10 mole) of 99% nitric acid and 31.5 g. (0.15 mole) of trifluoroacetic anhydride were mixed at -10° , then allowed to warm to 10° . Two and eight-tenths grams (0.010 mole) of tris(*N*-nitro-*N*-methylamino-methyl)amine⁷ (IV), m.p. $116-117^{\circ}$, was added portionwise with stirring and cooling. The temperature was maintained at 10° . After addition was complete the temperature was raised to 20° for 5 min. The volatile materials were then removed under reduced pressure and the viscous residue treated with ether. One gram of solid, m.p. $150-160^{\circ}$, was filtered. This was recrystallized from butanone to give 0.5 g. (21% yield) of 2,4,6-trinitrazaheptane, m.p. $166-168^{\circ}$. Another recrystallization from butanone raised the melting point to $168-169^{\circ}$. The compound melts to a clear liquid with no apparent decomposition.

Anal. Calcd. for $C_4H_{10}N_6O_6$: C, 20.17; H, 4.23; N, 35.29; mol. wt. 238. Found: C, 20.26; H, 4.21; N, 35.56; mol. wt. 246 (Rast).

The infrared spectrum showed nitramino absorption at 6.40μ (broad), 6.55μ , and 7.80μ , and a strong band at 13.07μ .⁸

Preparation of 2,4,6-trinitrazaheptane (III) from II. Two and one-half grams (0.008 mole) of crude bis(*N*-nitro-*N*-methylaminomethyl)(2-propyl)amine (II) was dissolved in 20 ml. of acetic anhydride and heated to 55° . To this was added a solution of 3.4 g. (0.042 mole) of ammonium nitrate in 4.6 g. (0.073 mole) of 99% nitric acid. After 15 min. at 55° the solution was poured into 500 ml. of ice and water. One-half gram of solid, m.p. $110-120^{\circ}$, separated. This was recrystallized from chloroform to give 0.3 g. of material, m.p. $155-160^{\circ}$. Recrystallization from butanone gave 0.1 g. of material, m.p. $166-168^{\circ}$. The infrared spectrum of this material was identical with the spectrum of III prepared in the previous experiment.

Anal. Calcd. for $C_4H_{10}N_6O_6$: C, 20.17; H, 4.23; N, 35.29. Found: C, 20.43; H, 4.67; N, 36.02.

Treatment of IV with acetic anhydride and nitric acid. Three and six-tenths grams (0.013 mole) of IV was added to a solution of 8.8 ml. (0.21 mole) of 99% nitric acid and 24 ml. (0.26 mole) of acetic anhydride at 0° . After addition was complete, the solution was warmed to 30° and maintained there 25 min. The slightly yellow solution was poured into 250 ml. of ice and water. No insoluble material separated.

Treatment of tris-[N-nitro-N-(β -cyanoethyl)aminomethyl]amine (V) with trifluoroacetic anhydride and nitric acid. Six and three-tenths grams (0.10 mole) of 99% nitric acid was added to 31.5 g. (0.15 mole) of trifluoroacetic anhydride at 0° . The solution was warmed to 10° . Four grams (0.010 mole) of V was added, with stirring, to the solution. There was no noticeable temperature rise. The temperature was raised to 15° where the solid dissolved. The solution was then poured into 250 ml. of ice and water. About 2 g. of oil separated. The oil was dissolved in 25 ml. of methylene chloride and 0.025 g. of solid separated, m.p. $135-138^{\circ}$. A mixed melting point with a sample of V gave no depression; hence, the solid was starting material. The oily material, soluble in methylene chloride, was not investigated but probably was not the desired 1,9-dicyano-3,5,7-trinitrazaanonane, as this compound should be a relatively high melting, insoluble material as judged by the character of other 2,4,6-trinitrazaheptane derivatives.

Preparation of bis(N-nitro-N-Methylaminomethyl)(2-propyl)amine (II). Two grams (0.026 mole) of methyl nitramine was added to 2.1 g. (0.026 mole) of 37% formaldehyde solution. This solution was cooled to 0° and 0.77 g. (0.013 mole) of isopropylamine was added. After a few minutes an oil separated and settled to the bottom. The reaction mixture

was warmed to 25° . After 30 min. the water was evaporated under reduced pressure to leave 2.5 g. of material, m.p. $27-30^{\circ}$. The material was not characterized but was assumed to be II on the basis of the analogous preparation of bis(*N*-nitro-*N*-methylaminomethyl)methylamine.⁹

Preparation of tris[N-nitro-N-(β -cyanoethyl)aminomethyl]amine (V). Eleven and one-half grams (0.10 mole) of β -cyanoethylnitramine was dissolved in 8.33 g. of 37% aqueous formaldehyde solution and chilled to 0° . Then 2.02 g. (0.33 mole) of 28% aqueous ammonia was added to the solution. The solution was poured into a shallow dish and left uncovered at room temperature until the water had evaporated. There was 12.9 g. (97% yield) of white solid remaining, m.p. $100-120^{\circ}$. Two recrystallizations from acetonitrile gave 7 g. of V, m.p. $136-138^{\circ}$.

Anal. Calcd. for $C_{12}H_{18}N_{10}O_6$: C, 36.18; H, 4.55; N, 35.17; mol. wt. 398. Found: C, 36.03; H, 4.51; N, 35.11, 35.30; mol. wt. 354 (cryoscopic method using ethylene carbonate).

The low value for the experimentally determined molecular weight may be due to partial dissociation of the compound. After V was kept in a closed bottle for any length of time, the odor of formaldehyde was evident when the bottle was opened. Also the melting point always dropped when the material was stored for several months.

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Orientation in the Nitration of 2',5'-Dimethoxyacetophenone¹

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Received December 4, 1959

The nitration of 2',5'-dimethoxyacetophenone has been studied under a variety of conditions and found to lead to the formation of a mixture of the 4'- and 6'-nitro isomers, with the 6'-nitro isomer accounting for approximately 50 to 80% of the product, depending on the conditions. Extensive substitution in the 6' position has previously been reported for several compounds of similar structure;⁴ this behavior has been considered to be anomalous.^{4a,b} The high proportion of substitution in the 6' position is consistent with the predicted relative stabilities of the transition states. Only in the case of substitution in this position is the tran-

(1) Research supported in part by National Science Foundation grant G 7358.

(2) This paper is based partly on a thesis submitted by C. R. Hamel in partial fulfillment of the requirements for the degree of Master of Science at Clarkson College of Technology, January 1959.

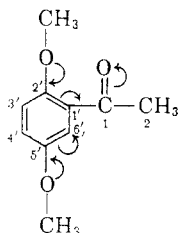
(3) Participant, National Science Foundation Research Participation Program for High School Science Teachers, Clarkson College of Technology, June-August, 1959.

(4) (a) G. S. Hammond, F. J. Modic, and R. M. Hedges, *J. Am. Chem. Soc.*, **75**, 1388 (1953); (b) K. A. Kobe and T. B. Hudson, *Ind. Eng. Chem.*, **42**, 356 (1950); (c) L. Rubenstein, *J. Chem. Soc.*, 127, 1998 (1925).

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sition state stabilized by conjugation of the 2'-methoxy group with the carbonyl side chain.



The relative stabilities of the transition states for substitution in the 3' and 4' positions are not obvious from a consideration of their resonance structures, although it appears reasonable that electrons should be released more readily to the 4' position by the 5'-methoxy group than to the 3' position by the 2'-methoxy group, since the latter is conjugated with the carbonyl side chain.⁵ Considerably more of the 4'-nitro isomer was obtained with a mixture of nitric acid and sulfuric acid than with nitric acid alone. If the attacking reagents in the two media are nitronium ion and nitric acidium ion respectively,⁶ the difference in isomer distribution can be attributed to higher activation energies and resultant greater selectivity in the case of the latter. An alternative explanation suggested on the basis of results with compounds of somewhat analogous structure involves the effect of the degree of solvation of the nitronium ion on transition state stabilities.^{4a} That the carbonyl group plays the determining role in substitution in the 6' position was demonstrated by the exclusive formation of the 4'-nitro compound on the nitration of 1-ethyl-2,5-dimethoxybenzene.⁷

EXPERIMENTAL⁸

Nitration of 2',5'-dimethoxyacetophenone. Run A. To 40 ml. of concd. nitric acid (sp. gr. 1.42) at -20° was added with stirring 8.0 g. of 2',5'-dimethoxyacetophenone⁹ over a period of 4 hr. The mixture was stirred for an additional 2.5 hr. at -20° , then poured into 500 ml. of ice water. The product was isolated by filtration, washed free of acid and dried. The yield was 9.7 g. (97% assuming mononitration) of a yellow powder.

Run B. The procedure was the same as in *Run A* except that the addition and aging periods were shortened to 90 and 15 min. respectively. The yield was 8.4 g. (84%) of a yellow powder exclusive of a small amount of gummy material adhering to the stirrer.

(5) For a discussion of an analogous situation see G. W. Wheland, *Resonance in Organic Chemistry*, John Wiley and Sons, Inc., New York, N. Y., 1955, pp. 505-507.

(6) E. S. Halberstadt, E. D. Hughes, and C. K. Ingold, *J. Chem. Soc.*, 2441 (1950).

(7) This finding is consistent with the results reported for 2,5-dimethoxytoluene by H. Erdtmann, *Proc. Roy. Soc. (London)*, **A 143**, 177 (1934) and H. Gilman, J. Swiss, H. Willis, and F. Yoeman, *J. Am. Chem. Soc.*, **66**, 798 (1944).

(8) Microanalyses by Geller Laboratories, Bardonia, N. Y.

(9) L. D. Abbott and J. D. Smith, *J. Biol. Chem.*, **179**, 365 (1949).

Run C. The procedure was the same as in *Run B* except that the nitrating medium consisted of a mixture of 40 ml. of nitric acid and 20 ml. of concd. sulfuric acid (sp. gr. 1.84). The yield was 8.6 g. (86%) of a yellow powder exclusive of a small amount of gummy material adhering to the stirrer.

Run D. To a solution of 8.65 g. of 2',5'-dimethoxyacetophenone in 30 ml. of glacial acetic acid was added with stirring a mixture of 6.1 ml. of concd. nitric acid and 18.3 ml. of glacial acetic acid over a 5-hr. period. The temperature was kept close to the freezing point of the mixture (5° to 12°) throughout the addition. The mixture was maintained at 5° for 22 hr., then quenched with 200 ml. of ice water. The resulting suspension was stirred for several hours to break up lumps, then chilled and the product isolated by filtration, washed, and dried. No attempt was made to isolate additional product from the filtrate. The yield was 8.4 g. (78%) of an orange-yellow powder.

In addition to the above runs, a number of nitrations were attempted which resulted in the formation of intractable dark gums or tars, presumably because of oxidation. In these experiments 2',5'-dimethoxyacetophenone was added dropwise to concd. nitric acid at 5° , and to 4:1, 2:1, and 1:1 mixtures (by volume) of concd. sulfuric acid and concd. nitric acid at -20° .

Determination of isomer distribution. Activated alumina (Merck reagent aluminum oxide, suitable for chromatographic adsorption) was partially deactivated by slurrying with methanol and air-drying overnight. The alumina was charged in benzene to a bed depth of 90 mm. in a 110×10 mm. column. A solution of 0.2000 g. of nitration product in 3 ml. of benzene was fed to the top of the column and development effected with benzene at a rate of approximately 35 ml. per hr. Two well-resolved yellow bands were eluted separately and analyzed spectrophotometrically (Beckman DU) after appropriate dilutions with ethanol. A small, immobile red band containing less than 2% of the charge was also obtained. The more mobile yellow band represented 2',5'-dimethoxy-4'-nitroacetophenone, the less mobile yellow band 2',5'-dimethoxy-6'-nitroacetophenone (3',6'-dimethoxy-2'-nitroacetophenone). The analytical peaks employed for the determination of the two compounds were 365μ and 335μ respectively. Samples of the pure isomers obtained by fractional crystallization of the nitration product from methanol were used as standards. A third yellow band, less mobile than the 6'-nitro isomer and representing an extremely small amount of material was observed in analyzing the product from *Run D*. The material balances based on the spectrophotometric analyses of the eluates and the weights charged to the column ranged from 95 to 105%. In the analysis of the product from *Run A*, the column eluates were not assayed spectrophotometrically but evaporated to dryness to yield the individual isomers in a high state of purity. The material balance in this case was 102%. The results of the isomer distribution determinations were as follows:

Run	Medium	Temp.	% 4'	% 6'
A	HNO ₃	-20°	21	79
B	HNO ₃	-20°	23, 23	77, 77
C	HNO ₃ -H ₂ SO ₄	-20°	51, 47	49, 53
D	HNO ₃ -HOAc	5 to 12°	34	66

*1-Ethyl-2,5-dimethoxybenzene.*¹⁰ Mossy zinc (140 g.) was amalgamated by a standard procedure¹¹ and the amalgam refluxed with 263 ml. of concd. hydrochloric acid and 175 ml. of water while 35 g. of 2',5'-dimethoxyacetophenone was added over a 1-hr. period. Reflux was continued for 22 hr., during which time 97 ml. of additional concd. hydrochloric

(10) G. R. Ramage and C. V. Stead, *J. Chem. Soc.*, 3602 (1953).

(11) E. L. Martin, *Org. Reactions*, **I**, 163 (1942).

acid was added in 10-ml. increments. The oily upper layer was then separated, dried with calcium chloride and fractionated under reduced pressure. The main fraction, b.p. 65–67.5°/5 mm., consisted of 15.7 g. (49%) of a pale yellow liquid. Refractionation gave a colorless analytical sample, b.p. 68–70°/7 mm., n_D^{25} 1.5148, f.p. –4 to –6.5°.

Anal. Calcd. for $C_{10}H_{14}O_2$: C, 72.3; H, 8.5. Found: C, 72.6; H, 8.4.

1-Ethyl-2,5-dimethoxy-4-nitrobenzene. 1-Ethyl-2,5-dimethoxybenzene (8.0 g.) was nitrated by the procedure used in *Run D* for 2',5'-dimethoxyacetophenone with the exception that the mixture was quenched immediately after completion of the acid addition. The reaction was considerably more vigorous than in the case of 2',5'-dimethoxyacetophenone. The yield was 9.2 g. (92%) of yellow needles, m.p. 79–80°. Recrystallization from either methanol or benzene-petroleum ether did not raise the melting point.

Anal. Calcd. for $C_{10}H_{13}O_4N$: N, 6.6. Found: N, 6.7.

Attempts at nitration with concd. nitric acid at –18° and –35° resulted in the formation of dark tars.

Determination of structure of the nitro compounds. The structure of 1-ethyl-2,5-dimethoxy-4-nitrobenzene was established by its oxidation to 2,5-dimethoxy-4-nitrobenzoic acid followed by demethylation of the latter to 2,5-dihydroxy-4-nitrobenzoic acid, a known compound.¹² The structure of 2',5'-dimethoxy-4'-nitroacetophenone was determined by its conversion to 2,5-dimethoxy-4-nitrobenzoic acid; that of 2',5'-dimethoxy-6'-nitroacetophenone by its conversion to 2,5-dimethoxy-6-nitrobenzoic acid, a compound also obtained from 2-bromo-2',5'-dimethoxy-6'-nitroacetophenone.¹³ The position of the nitro group in the latter compound has been established by its conversion to 4,4',7,7'-tetramethoxyindigotin by treatment with ammonium sulfide.¹³

1-Ethyl-2,5-dimethoxy-4-nitrobenzene (3.0 g.) was refluxed for 6 hr. with a solution of 9.0 g. of potassium permanganate and 34.5 ml. of 5% sodium hydroxide in 500 ml. of water. Following removal of manganese dioxide by filtration, the solution was extracted with ether, then acidified to pH 1 with 10% sulfuric acid. The material thus precipitated was recrystallized from hot water, yielding orange-red crystals of 2,5-dimethoxy-4-nitrobenzoic acid, m.p. 192–193° dec.

Anal. Calcd. for $C_9H_9O_6N$: N, 6.2; neut. equiv., 227. Found: N, 6.3; neut. equiv., 231.

A mixture of 0.23 g. of 2,5-dimethoxy-4-nitrobenzoic acid, 0.20 ml. of glacial acetic acid and 1.49 ml. of 49% hydrobromic acid was heated at 125–160° for 18 hr. The acetic acid was then removed under reduced pressure and the residue extracted with ether. The solid obtained on evaporation of the ether was recrystallized from hot water, yielding orange-red needles of 2,5-dihydroxy-4-nitrobenzoic acid, m.p. 244–245 dec. (no depression on mixing with an authentic sample prepared by an independent, unambiguous procedure^{12,14}; identical ultraviolet and visible absorption spectra with maxima at 278 m μ and 425 m μ in benzene; deep violet color with alkali¹²).

2',5'-Dimethoxy-4'-nitroacetophenone was isolated as yellow needles, m.p. 122–123°, from the fractional crystallization of the crude nitration product from *Run A*.

Anal. Calcd. for $C_{10}H_{11}O_5N$: C, 53.3; H, 4.9; N, 6.2. Found: C, 53.4; H, 5.1; N, 6.2.

Treatment of this material with hypohalite yielded 2,5-dimethoxy-4-nitrobenzoic acid, m.p. 192–193° dec. (no depression on mixing with a sample of the product obtained from the oxidation of 1-ethyl-2,5-dimethoxybenzene; identi-

cal ultraviolet absorption spectra with maxima at 277 m μ and 360 m μ in benzene).

2',5'-Dimethoxy-6'-nitroacetophenone was also isolated from the fractional crystallization as pale yellow needles, m.p. 72–73°.

Anal. Calcd. for $C_{10}H_{11}O_5N$: C, 53.3; H, 4.9; N, 6.2. Found: C, 53.0; H, 4.9; N, 6.3.

Treatment of this material with hypohalite yielded 2,5-dimethoxy-6-nitrobenzoic acid, m.p. 192–193° dec. (no depression on mixing with a sample prepared from 2-bromo-2',5'-dimethoxy-6'-nitroacetophenone by the haloform reaction¹⁵; identical ultraviolet absorption spectra with maxima at 325 m μ in benzene; large depression in melting point on mixing with a sample of 2,5-dimethoxy-4-nitrobenzoic acid).

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Chalcones. IV. Synthesis of Chloro- and Nitrochalcones

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Received February 2, 1960

Syntheses of some methylchalcones have been reported.^{1b,2} The present communication records the synthesis of isomeric chloro- and nitro-substituted chalcones obtained by the Claisen-Schmidt condensation of resacetophenone, resacetophenone dimethyl ether, and *o*-hydroxyacetophenone with isomeric chlorobenzaldehydes and of resacetophenone and *o*-hydroxyacetophenone with *m*-nitrobenzaldehyde.

Condensation of *o*-chlorobenzaldehyde with resacetophenone, taken in stoichiometric proportion, at room temperature for eight days, gave the 2',4'-dihydroxy-2-chlorochalcone in a good yield (58.7%) and without the formation of any resinous products. The same condensation could also be effected by heating at 60° for three hours, and subsequently leaving the reaction mixture at room temperature for twenty-two hours to give the above chalcone in 55% yield.

In the synthesis of 2',4'-dihydroxy-3-chlorochalcone the yield was found to increase from 18–33% by using four times the stoichiometric amount of *m*-chlorobenzaldehyde. But a considerable amount of *m*-chlorobenzoic acid was formed in this condensation.

It is interesting to find that the isomeric 2',4'-dihydroxy-4-chlorochalcone is pyrochromatic—becomes orange on heating and yellow on cooling.

Condensation of isomeric chlorobenzaldehydes with resacetophenone, under similar experimental conditions, gave significant differences in the yields

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(14) The authors are grateful to Smith & Nephew Research, Ltd., Hunsdon, England for this sample.

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