Nitrations of acetanilides by reagents of NO₂X type¹

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The distribution of products in the nitration of a series of eight substituted acetanilides has been studied using differing nitrating agents.

With mixed nitric and sulfuric acids, attack *para* to the acetamido group is favored, while with acetyl nitrate or nitronium tetrafluoroborate, predominant *ortho* substitution occurs. It is suggested that *ortho* substitution results from $S_N 2$ displacement by a pair of substituent electrons (on nitrogen or carbonyl oxygen) on the species NO₂X (X = BF₄ or OAc), leading to formation of the most readily accessible σ complex, while the *para* substitution favored in mixed acids results from substitution in the conjugate acid of acetanilide.

Nitroacetanilides follow an unusual path with acetyl nitrate, yielding the corresponding dinitrobenzene in addition to the expected dinitroacetanilides.

Nuclear magnetic resonance spectroscopy efficiently demonstrates the structures of the reaction products, and reveals the preferred intramolecularly hydrogen-bonded conformation of *ortho*-nitroacet-anilides.

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Introduction

Much discussion has centered around aromatic nitrations by preformed nitronium salts as compared with more conventional reagents, since apparent changes in substrate selectivity occur without any great variation in positional selectivity (1–3). A recent report by Ridd (4) indicates that the unusually low substrate selectivities noted for the nitronium-salt nitrations probably reflect diffusion-controlled reaction rates. On the other hand, there are several examples where positional selectivity is highly sensitive to the nature of the substituting agent; little information is available regarding substrate selectivities in these reactions. Thus, nitration of biphenyl by nitric acid - acetic anhydride, by nitrogen pentoxide in acetonitrile, or by nitronium tetrafluoroborate in sulfolane, gives ortho:para ratios exceeding 1, while nitric acid – sulfuric acid gives a ratio of ca. 0.6 (5, 6). Nitration of anisole by nitric acid – acetic anhydride or by nitronium tetrafluoroborate in sulfolane gives ortho:para ratios close to 2, while with nitric acid - sulfuric acid, the ratio is 0.5(7, 8).

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These results have been rationalized by Taylor (6), who proposes direct interaction of p- or π -electrons of the aromatic substrate, effecting a nucleophilic displacement on the species NO₂X (which may be an ion-pair), and leading to predominant ortho substitution. This direct interaction is superimposed upon a normal pattern produced by free nitronium ions in the reaction medium.

A specific interaction appropriate to protonated acetyl nitrate (coordination of its electrondeficient carbonyl carbon to the lone pair of the substituent) is not acceptable in view of the similar positional selectivities shown by protonated acetyl nitrate (which is the active species in nitric acid – acetic anhydride mixtures, cf. Bordwell and Garbisch (9)) and nitronium tetrafluoroborate; a postulate of linear coordination between free nitronium ion and substituent lone-pair electrons (7) is also unacceptable, since all sources of nitronium ion should then behave similarly (6).

Acetanilide also exhibits reagent-dependent orientation in nitration; nitric and sulfuric acids yield paranitroacetanilide as major product, while with nitric acid – acetic anhydride, orthonitration is favored (10). If Taylor's rationalization is correct, nitration of acetanilides by preformed nitronium salts should yield substituted ortho-nitroacetanilides as the predominant products. This paper reports, *inter alia*, a test of Taylor's proposal for reagent-dependent orientation in nitrations.

We have examined the distribution of products

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obtained in the nitrations of a series of eight substituted acetanilides, using three different nitrating systems: nitric acid-sulfuric acid, nitric acid-acetic anhydride, and nitronium tetrafluoroborate in acetonitrile. Some competitive nitrations of toluene and acetanilide were also examined.

Experimental

Microanalyses were carried out by the Schwarzkopf Microanalytical Laboratory, Woodside, New York. Melting points were measured on a Fisher-Johns apparatus or on a Kofler "Heizbank", and are corrected. Infrared spectra were recorded on a Beckman IR-8 spectrophotometer; samples were examined as suspensions in potassium chloride disks. Proton magnetic resonance spectra were recorded with Varian A-60A or HA-100 spectrometers. Signals are expressed in parts per million from tetramethylsilane, present as an internal reference. Gas-liquid chromatographic analyses were made on an Aerograph A-90P3 instrument with a thermal conductivity detector. Helium was used as the carrier gas, and the analytical column used was 6 ft \times 1/4 in 5% silicone SE-30 partitioning phase supported on 60-80 mesh chromosorb P coated with dimethyldichlorosilane. All nitronium-salt nitrations were carried out in a dry box in an atmosphere of purified dry nitrogen.

Starting Materials

The acetanilides were prepared by standard methods from commercial samples of the corresponding anilines. Their melting points were identical with literature values and their nuclear magnetic resonance (n.m.r.) spectra indicated no contamination by isomeric compounds. Nitronium tetrafluoroborate was supplied by K. and K. Laboratories, Plainview, New York.

General Procedures for Nitrations

(a) By Nitric Acid - Acetic Anhydride

A solution of nitric acid (d, 1.52, 6 ml) in acetic an-hydride (15 ml), prepared at 15-20°, was cooled to -5° and added to a saturated solution of the substituted acetanilide (10 g) in acetic anhydride at 0°, over 15 min. The solution was kept at 0° for 1 h and was poured onto ice. The resulting mixture was extracted with benzene and washed free of acid, and subjected to adsorption chromatography on basic alumina (benzene as eluent), followed by crystallization from ethanol; alternatively, the washed benzene extract was concentrated and injected directly into the inlet port of the gas-liquid chromato-graph (column temperature 170-190°); the proportions of the isomeric products were determined by comparison of peak areas and relative retention times with those of authentic samples. Identities were further checked by gas-liquid chromatography of the nitroanilines obtained by hydrolysis of the crude mixture of nitroacetanilides. The results are summarized in Table I.

(b) In Nitric Acid – Sulfuric Acid

The substituted acetanilide (5.0 g) was dissolved in sulfuric acid (d, 1.84, 10 ml) and was cooled to 0° , and a mixture of nitric acid (d, 1.42, 10 ml) and sulfuric acid

TABLE I

Nitration of acetanilides by nitric acid - acetic anhydride

| Cult at it was t | 5-Sul 2-Nitro | bstituted acetanilide | |
|------------------|------------------|--------------------------|------------|
| in | Yield | Melting | Ortho:para |
| acetanilide | (%)* | point °C | ratio† |
| Nil | 72 | 93(93)‡ | 4.2 |
| 3-Br | 57 | 138(139) | 8.5 |
| 3-Cl | 62 | 118(120) | 9.0 |
| 3-F | 77 | 90§ | 9.1 |
| 3-I | 63 | 158 | 5.0 |
| 3-OMe | 56¶ | 125(125) | 4.0 |
| 3-Me | 58 | 87(87) | 4.5 |

*Of crystallized product. *Determined by gas-liquid chromatography. ‡Literature melting points are given in parentheses. \$Anal. Calcd. for $C_8H_7FN_2O_3$: C, 48.89; H, 3.56; N, 14.14. Found: C, 48.88; H, 3.81; N, 13.88. ||Anal. Calcd. for $C_8H_7IN_2O_3$: C, 31.40; H, 2.15; N, 8.95. Found: C, 31.05; H, 2.38; N, 8.78. *[In addition to the 5-methoxy-2-nitroacetanilide, 11% of 3-methoxy-4-nitroacetanilide, m.p. 164° (lit. 165°) was obtained.

(d, 1.84, 13 ml) was added at 0°; the mixture was kept

at 0° for 1 h and poured into water. The resulting mixture was extracted with benzene and washed free of acid, and the extract was evaporated and the residue was crystallized from ethanol, or the benzene extract was concentrated and injected for gas-liquid chromatographic analysis as above. The results are summarized in Table II.

(c) With Nitronium Tetrafluoroborate

The acetanilide (1 g) was dissolved in acetonitrile (10 ml) and the solution was cooled to -30° . Finely powdered nitronium tetrafluoroborate (1 g) was added slowly at such a rate that the temperature did not rise above -10° . After 30 min, the reaction mixture was poured into cold water, and the precipitated nitroacetanilides were collected, washed, and dried. Yields were virtually quantitative (greater than 90%) for the nitrations of acetanilide, 3-fluoroacetanilide, 3-chloroacetanilide, and 3-iodoacetanilide, and the ortho:para ratios (established, as above, by gas-liquid chromatography) exceeded 10.

Atypical Nitrations Nitroacetanilides

Nitroacetanilides were unaffected by nitric acid - acetic anhydride at 0°. Reaction at 50-55° using the general conditions specified above yielded 2,5-dinitroacetanilide (4.5 g), m.p. 122° (lit. m.p. 121°) and 1,3-dinitrobenzene (0.5 g), m.p. 88° (lit. m.p. 90°) (infrared and n.m.r. spectra identical with an authentic sample) from 3-nitroacetanilide. In similar reactions with 2- and 4-nitroacetanilides, adsorption chromatography (basic alumina, with benzene as eluent) gave small amounts (0.2 g) of the corresponding dinitrobenzenes as the most rapidly eluted materials. The 1,2-dinitrobenzene was identical in m.p. (118°), infrared and n.m.r. spectra with an authentic sample, while the 1,4-dinitrobenzene had m.p. 172° (lit. 172°) and its n.m.r. spectrum in deuteriochloroform showed a single peak at 8.60 p.p.m.

N-Methylacetanilide

Four grams of material was nitrated at 25° for 12 h using the general conditions of part (a) above. Chromatog-

General

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| Substituent in acetanilide | Major product | Yield (%)* | Melting point °C | Ortho:para ratio† |
|----------------------------------|---------------------------------|---------------|---------------------|----------------------|
| Nil | 4-nitroacetanilide | 75 | 216(216)t | 0.05 |
| 3-Cl | 3-chloro-4-nitroacetanilide | 60 | 141(145) | 0.04 |
| 3-F | 3-fluoro-4-nitroacetanilide | 52 | 1748 | 0.04 |
| 3-OMe | 3-methoxynitroacetanilide | 50 | 164(165) | 0.05 |
| 3-Br¶ | 3-bromo-4-nitroacetanilide | 40 | 145** | 0.08 |
| 3-Br | 4,6-dinitro-3-bromoacetanilide | 60 | 166†† | _ |
| 3-Me | 4,6-dinitro-3-methylacetanilide | 50 | 103(103) | |

| TABLE | Π |
|-------|---|
|-------|---|

Nitrations of acetanilides in sulfuric acid

*Recrystallized product. †By gas-liquid chromatography. ‡Literature melting points are in parentheses. §Anal. Found: C, 48.70; H, 3.50. ||Reaction period: 12 min at 0°. **Anal. Calcd. for C₈H,BrN₂O₃: N, 10.73. Found: 11.02. ††Anal. Calcd. for C₈H,BrN₂O₃: N, 13.82. Found: 13.55.

| TAB | LE | III | |
|-----|----|-----|--|
| | | | |

| Competitive | nitration | experiments |
|-------------|--|-------------|
| | TT++++++++++++++++++++++++++++++++++++ | *********** |

| Reagent | Ortho:para ratio of Reagent Substrate A products | | Substrate B | Ortho :para ratio of products | Relative yields of nitration products (NO ₂ ·A/NO ₂ B) |
|--|--|---|--|-------------------------------------|--|
| HNO ₃ – Ac ₂ O NO ₂ BF ₄ in MeCN HNO ₃ – H ₂ SO ₄ | acetanilide acetanilide acetanilide | $\begin{array}{c} 4.5 \pm 0.5 \\ 3.5 \pm 0.5 \\ < 0.05 \end{array}$ | toluene toluene <i>p</i> -nitrotoluene | 1.32 ± 0.10 1.30 ± 0.10 | $\begin{array}{c} 0.22 \pm 0.05 \\ 1.70 \pm 0.10 \\ 0.22 \pm 0.03 \end{array}$ |

raphy on alumina (benzene as eluent) yielded 4-nitro-N-methylacetanilide (2.8 g), m.p. 150° (lit. m.p. 152-153°) after crystallization from methanol. No ortho-isomer could be detected.

Competitive Nitrations

Equimolar mixtures of the substrates indicated in Table III were nitrated competitively using the conditions outlined above in the general procedures for nitrations, except that the amount of nitric acid or nitronium salt was decreased to 0.10 mole per mole of combined substrates, and the nitronium salt was dissolved in acetonitrile before addition to the substrates (also in acetonitrile). A reaction temperature of 0° was used. The crude nitroacetanilides and nitrotoluenes were collected together with unreacted substrates, after separation from unreacted toluene by chromatography on alumina, and were dissolved in acetic acid- d_4 : the composition of the mixtures was established by integration of the n.m.r. signals from the methyl protons of the acetamido and the methyl groups. The relevant chemical shifts (in Hz from tetramethylsilane) were: 2-nitroacetanilide, 136.0; 4-nitroacetanilide, 133.0; 2-nitrotoluene, 152.0; 4-nitrotoluene, 145.0; 2,4-dinitrotoluene, 160.0. Analysis of control mixtures of known composition showed that this method was accurate to $\pm 3\%$. The ortho:para ratios obtained in the nitrations of single compounds were also checked by the n.m.r. integration method, and the results are assembled in Table III.

Attempted Synthesis of N-Nitroacetanilide

N-Nitrosoacetanilide, m.p. 50° (10.0 g), in chloroform (30 ml) was added to a mixture of 30% hydrogen peroxide (6.8 g) and trifluoroacetic anhydride (6.8 g), and the mixture was stirred vigorously for 12 h. The mixture was extracted with sodium bicarbonate, and the residue was dried and chromatographed on alumina using chloroform as eluent. Acetanilide (3.5 g, 47%), m.p. 113° (identical (m.p., mixture m.p., infrared spectra) with an authentic sample) was obtained from the eluted solution on evaporation.

Discussion

Structures of Nitration Products

In most cases, the structures of the major nitration products of the acetanilides obtained using the various reagents were evident from the correspondence of their melting points, and the melting points of the nitroanilines obtained by hydrolysis, with literature values; nuclear magnetic resonance spectra (see section (d) below) gave further supporting evidence. The new 5-halogeno-2-nitroacetanilides (the fluoro- and iodo-compounds) were further identified by the fact that their infrared spectra showed the following strong bands in common with those of the known bromo and chloro compounds: 3350 cm⁻¹ (v_{NH}), 1695 cm⁻¹ (v C=O), 1493 and 1333 cm⁻¹ (asymmetric and symmetric N-O vibrations), and 865, 845, 820, and 748 cm⁻¹ (δ_{C-H} , out-of-plane); this resemblance in major spectral features is to be expected since the heavy halogen atoms have little effect on the vibrations in the rest of the molecule.

However, there is some uncertainty regarding the nature of the nitration products of 3-methoxyacetanilide. Reverdin and Widmer (11) found that nitration by 70% nitric acid at 65° gave two methoxynitroacetanilides, of melting points 125° and 165°, in 65% overall yield, which were hydrolyzed to the corresponding anilines, m.p. 129° and 169°; these were assigned as the 5-methoxy-2-nitro- and 3-methoxy-4-nitro compounds. More recently, Dyall and Pausacker (12) assigned the methoxynitroacetanilide of m.p. 125° as 3-methoxy-4-nitroacetanilide, and describe 3-methoxy-4-nitroaniline as having m.p. 131°. After hydrolysis of their nitration mixture, they obtained a compound, m.p. 157°, which was assigned as 3-methoxy-2,4dinitroaniline on the basis of a strong infrared absorption band at 830 cm^{-1} , supposedly characteristic of 1,2,3,4-tetrasubstitution. However, Bellamy (13) warns that absorption in this region is "a feature of aromatic nitro compounds, which should not be forgotten when attempts are made to recognize ring-substitution arrangements by the δ —CH frequencies in this region".

We find that the methoxynitroacetanilide of m.p. 125° (obtained as the major product from acetyl nitrate nitration of 3-methoxyacetanilide at 0°) is 5-methoxy-2-nitroacetanilide; the corresponding amine has m.p. 131° . 3-Methoxy-4-nitroacetanilide, m.p. 164° , is also obtained, and yields the corresponding amine, m.p. 169° , on hydrolysis. Definite chemical proof of structure for 5-methoxy-2-nitroaniline is provided by its conversion to 5-methoxybenzofuroxan, m.p. 116° , by oxidation with iodosobenzene diacetate in benzene (cf. Pausacker and Scroggie (14)).

The infrared spectrum of the 3-methoxy-4nitroaniline showed all the absorption bands quoted for "3-methoxy-2,4-dinitroaniline", and this product should therefore be withdrawn from the literature.

Positional and Substrate Selectivities

The general trend of the results is in agreement

with expectations based on Taylor's proposal of $S_N 2$ displacement on a species NO₂X; the 3-substituted acetanilides give predominant ortho substitution with acetyl nitrate and with nitronium tetrafluoroborate, while with mixed nitric and sulfuric acids, where *free* nitronium ions are present, predominant para substitution is observed.

The question remains whether the reaction of an acetanilide with a nitrating agent of NO_2X type occurs as in Scheme 1, path (a) (where the electron pair on oxygen is the effective nucleophile) or as in path (b) (where the electron pair on carbonyl oxygen is the nucleophile (cf. Norman and Radda (15)).

If path (a) is accepted, then there is some evidence that the π -complex represented as an intermediate stage between the reagents Ph·NHAc and NO₂X and the σ -complex for orthonitration should not be depicted as the conjugate acid of the hypothetical N-nitroacetanilide, since attempts to synthesize N-nitroacetanilide by peroxy-acid oxidation of N-nitrosoacetanilide (cf. Emmons and Ferris (16)) led to fragmentation to acetanilide in good yield, with no detectable ring-nitration. However, as a referee points out, the conditions for the fragmentation and the normal nitration reactions are not comparable.

If path (b) is accepted, then we must postulate that the O-nitrated intermediate does not form in highly acid media, since the oxygen atom will be protonated (for evidence of the predominant O-protonation of amides, see Gillespie and Birchall (17)). However, the protonated acetamido group will continue to exert a +R effect at the para position, thus accounting for the observed paraorientation.

The small changes in positional selectivity with temperature and with the nature of the nitrating reagent NO₂X are in the expected directions, although scarcely outside experimental reproducibility. Thus, Taylor (5, 6) noted that the ortho:para ratio in the nitration of biphenyl decreases with increasing temperature, in agreement with the differences noted for the nitronium tetrafluoroborate nitrations at -10and 0°, while at 0°, acetyl nitrate appears to give a slightly greater positional selectivity than nitronium tetrafluoroborate (Table III), possibly reflecting the greater ease of displacement in the ion-pair.

The relative reactivities of toluene and acet-

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anilide towards the nitrating agents would be of interest, and some experiments were carried out seeking this information. The significance of the results with nitronium tetrafluoroborate is questionable, since the reactions are very rapid (Ciaccio and Marcus (18)) found that the rate constant for nitration of nitrobenzene by nitronium tetrafluoroborate in acetonitrile at 24° was $0.111 \text{ mole}^{-1} \text{ min}^{-1}$), and kinetic control is not certain. However, acetanilide is apparently more reactive than toluene towards nitration by nitronium tetrafluoroborate, and with acetyl nitrate, where kinetic competition was probably observed, toluene is somewhat more reactive. When toluene and acetanilide were allowed to compete for small amounts of nitric acid in sulfuric acid, the toluene was dinitrated to a considerable extent, implying that toluene is far more reactive than the conjugate acid of acetanilide; in confirmation, a competitive experiment with *p*-nitrotoluene and acetanilide using mixed nitrating acids indicated that these compounds were of the same order of reactivity. Once again, however, kinetic competition is not assured under the conditions used.

The results probably allow order-of-magnitude assignments of total reactivity as compared with benzene, as follows: toluene, 25 (1–4); acet-anilide/NO₂BF₄, 50; acetanilide/AcONO₂, 5; *p*-nitrotoluene, 10^{-7} ; conjugate acid of acet-anilide, 10^{-8} .

Formation of Dinitrobenzenes from Nitroacetanilides

The formation of small proportions of the corresponding dinitrobenzenes on treatment of the three nitroacetanilides with acetyl nitrate at $50-55^{\circ}$ may be explained by postulating that

the acetamido group is *N*-nitrosated by nitrosonium ion (perhaps generated by dissociation of N_2O_4 into NO^+ and NO_3^- (19)), then rearranging to the diazoacetate, in turn giving the corresponding diazonium ion, which then undergoes nucleophilic displacement by nitrite ion. This sequence is admittedly speculative, but resembles that suggested previously for the replacement of the acetamido group by bromine using hydrobromic acid – nitric acid (19).

Nuclear Magnetic Resonance Spectra of Nitroacetanilides and Nitroanilines

The spectra of the various nitroacetanilides and nitroanilines obtained from the preparative selective nitrations were sufficiently characteristic for direct assignment of structure. In most cases, the spectra were analyzed as ABX systems (20), and the individual proton chemical shifts were extracted (100 MHz spectra were recorded for compounds where the ABX approximation was not valid at 60 MHz). The shifts are listed in Table IV.

It is to be expected that the acetamido group will exhibit anisotropic deshielding effects at the ortho positions (cf. Carter (21)), but will exert a net shielding effect at meta and para positions; Carter finds that the chemical shifts for the ring protons in acetanilide are shifted from the value for benzene (7.33 p.p.m.) as follows: (+ designates downfield, - upfield shift) ortho-, +0.16; meta-, -0.08; para-, -0.28. Accepting qualitative effects in this order, and using the parameters already available for many other substituents (22, 23), then the ring proton chemical shifts listed in Table IV are consistent in every case with the assigned structures. Further, we have shown (24) that the

(b)

(a)

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 TABLE IV

 Chemical shifts for substituted nitroanilines and nitroacetanilides

| | | Ring substituents or ring proton signals at position* | | | | | | | |
|-----------------------------------|-----------------|---|-------------|-----------------|-------------|-------------|-----------------|--|--|
| Solvent | 1 | 2 | 3 | 4 | 5 | 66 | Other signals | | |
| CDCl ₃ | NHAc | NO_2 | 8.03(-0.17) | 7.60(-0.17) | Br | 9.00(+1.23) | Acetyl, 2.27 | | |
| Ae_2CO-d_6 | NHAC | NO_2 | 8.15(-0.05) | 7.80(+0.03) | Br | 8.85(+1.08) | Acetyl, 2.37 | | |
| DCl ₃ | NHAc | NO_2 | 8.63(-0.52) | NO_2 | Br | 9.37(+1.40) | Acetyl, 2.33 | | |
| CDCl ₃ | NHAc | NO_2 | 8.10(-0.16) | 7.07(-0.49) | CI | 8.82(+1.26) | Acetyl, 2.25 | | |
| MSŌ | NH2 | NO_2 | 7.98(-0.28) | 6.63(-0.93) | Cl | 7.08(-0.48) | Amino, 7.67 | | |
| DCl ₃ | NHĀc | NO_2 | 8.30(+0.04) | 6.87(-0.36) | F | 8.67(+1.44) | Acetyl, 2.33 | | |
| | NHAc | NO_2 | 7.92(-0.11) | 7.50(-0.44) | I | 9.23(+1.29) | Acetyl, 2.27 | | |
| DCl ₃ | NHAc | NO_2 | 8.03(0.19) | 6.50(-0.61) | OMe | 8.28(+1.17) | Acetyl, 2.20 | | |
| MSŎ | NH_{2} | NO_2 | 7.92(-0.30) | 6.22(-0.89) | OMe | 6.45(-0.66) | Amino, 7,43 | | |
| OMSO | NH_{2} | NO_{2} | 7.90(-0.25) | 6.21(-1.16) | Me | 6.40(-0.97) | Amino, 7,40 | | |
| OMSO | NH | NO_{2}^{2} | 8.73(-0.37) | NO ₂ | Me | 6.90(-0.68) | Amino, ca. 8.00 | | |
| OMSO | NH ₂ | 6,70(Ő,86) | ČΙ | NO_2^{-} | 7,78(-0,48) | 6.55(-0.87) | -, | | |
| Ae ₂ CO-d _c | NHÃC | 8.13(+0.57) | Cl | NO ₂ | 8.07(-0.19) | 7.67(+0.25) | Acetvl, 2,17 | | |
| MSO | NH ₂ | 6.55(-0.68) | F | NO ₂ | 7.83(-0.43) | 6.47(-0.85) | Amino, 6,95 | | |
| Ae CO-de | NHAc | 8.32(+0.55) | Br | NO ₂ | 8.05(-0.15) | 7.80(+0.29) | Acetvl. 2.17 | | |
| | NHAC | 7.78(+0.67) | OMe | NO ₂ | 7.88(-0.36) | 6.78(+0.40) | Acetyl, 2, 20 | | |
| JMSO | NH | 6.33(-1.04) | Me | NO ₂ | 7.85(-0.30) | 6.40(-0.90) | Amino, 6.39 | | |

*Quantities in parentheses are substituent shifts assigned to the 1-substituent.

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amino proton chemical shifts of substituted anilines in dimethyl sulfoxide are dependent upon the nature and orientation of substituents; here again the observed shifts are consistent with the assigned structures.

It is possible to isolate the effects of the amino or acetamido groups on the various ring proton resonances by assuming that the effects of all other substituents are additive, so that the difference between the observed signal positions and that for benzene (7.33 p.p.m.) arises from the constant specific effects of the other substituents, together with the effect of the amino or acetamido group. The residual shift when the other substituents are taken into account is then assignable to the amino or acetamido group, and the quantities in parentheses in Table IV are these residual shifts.

The shielding effects of the amino group for the 2-nitroanilines in dimethyl sulfoxide are 0.25-0.37 p.p.m. for the 3-proton, 0.89-1.16 p.p.m. for the 4-proton, and 0.48-0.97 p.p.m. for the 6-proton; for the 4-nitroanilines, the effects at the 2- and 6-protons range from 0.68 to 1.04 p.p.m., and at the 5-proton, from 0.30-0.48 p.p.m. For a series of substituted anilines in deuteriochloroform,⁵ the mean shifts assignable to the amino group were: 2-proton, 0.82; 3-proton, 0.20; 4-proton, 0.72; 5-proton, 0.27; 6-proton, 0.67 p.p.m., so that the amino group effects in dimethyl sulfoxide are quite consistent with those noted for deuteriochloroform solutions.

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The acetamido group in the 2-nitroacetanilides shields the 4-proton by 0.17-0.61 p.p.m., and the 3-proton by a smaller amount (ranging from a deshielding of 0.04 p.p.m. to shielding of 0.19 p.p.m.; the abnormal shielding noted for 5-bromo-2,4-dinitroacetanilide is ascribed to twisting of the 4-nitro group out of the ring plane under the influence of the adjacent bromine). The 6-proton is drastically deshielded (1.17-1.44 p.p.m.), and it is suggested that this effect reflects the existence of a strong intramolecular hydrogen bond between nitro oxygen and acetamido hydrogen, so that the acetamido group is constrained into a conformation with the carbonyl group cis to, and coplanar with, the benzene ring, as in structure 1. The 6-proton in the substituted 2-nitroacetanilides is thus in the deshielding zone of the acetamido carbonyl group. The ortho-deshielding effects are much greater in the planar 2-nitroacetanilides of Table IV than in the non-planar (21, 25) parent acetanilide, and these large shifts are regarded as presumptive evidence for strong intramolecular hydrogen-bonding. Independently, Rae, Sternhell, and their co-workers⁵ have reached similar conclusions; the n.m.r. method provides unequivocal indications of the presence of such bonds in suitable 2-substituted acetanilides (contrast the extensive infrared spectroscopic study by Dyall and Kemp (26), where no unique test for intramolecular hydrogen bonding could be established).

It is considered likely that part of the driving force for the ortho-nitrations depicted in Scheme 1 paths (a) and (b) is this strong hydrogenbonding interaction between nitro group and acetamido hydrogen; in support of this contention, in the acetyl nitrate nitration of Nmethylacetanilide, where the hydrogen-bonding interaction is eliminated, 4-nitro-N-methylacetanilide is the major reaction product.

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NOTES

Chemistry of diarylazoalkanes. I. Synthesis of p,p'-disubstituted azocumenes and their decomposition products^{1,2}

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p,p'-Disubstituted azocumenes were prepared from the requisite p-substituted cumylamines, p-XC₆H₄C(CH₃)₂NH₂, X = CH₃, CH₃CH₂, (CH₃)₂CH, (CH₃)₃C, or Br, by treatment with iodine pentafluoride. The major products from thermal decomposition were dicumyls, along with minor amounts of cumenes and α -methylstyrenes. Syntheses of the corresponding authentic materials are described.

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The availability in this laboratory of a convenient, new method (1-3) for synthesis of *p*-substituted cumylamines (α,α -dimethylbenzylamines) suggested the use of these compounds as starting materials for preparation of the corresponding *p*,*p*'-disubstituted azocumenes (1) via oxidative coupling (4, 5). In keeping with our general interest in the behavior of radical species,



 $X = H, CH_3, CH_3CH_2, (CH_3)_2CH, (CH_3)_3C, Br$

the azo derivatives were desired as precursors for the generation of cumyl-type radicals (for a recent paper in the series, see ref. 6). This note deals with the synthesis and characterization of the azocumenes and their decomposition products.

A description is provided elsewhere of the requisite amines which were obtained by sidechain amination of cumenes with trichloramine aluminium chloride -t-butyl bromide (2, 3). Conversion to the p, p'-disubstituted azocumenes was accomplished by adaptation of the directions of Nelsen and Bartlett (5) for the preparation of azocumene (1, X = H) from cumylamine and iodine pentafluoride. The decomposition points, extinction coefficients at 367 mµ, elemental analyses, and yields for the five new azo compounds are listed in Table I. The decomposition temperature is dependent upon the rate of heating. Since only one run was carried out in each case, the yields, which refer to analytically pure material, undoubtedly could be improved. A study of the effect of the para substituents in the azocumenes on rate of decomposition, activation energy, and product distribution is presented in another report (7).

Nelsen and Bartlett (5) established that the major (94–95%) product from the thermal decomposition of azocumene was dicumyl (2, X = H), with the minor ones, cumene (3, X = H), and α -methylstyrene (4, X = H), resulting from disproportionation of cumyl radicals. Thermal degradation of the substituted analogues in solution gave similar results, >77% (usually >90%) coupling, accompanied by the

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| p,p'-X,X- | Melting point | | | | Calcd. (%) | | Found (%) | | | |
|---|---|--|---------------------------------|---|---|---------------------------------------|--------------------------------------|---|---------------------------------------|------------------------------|
| X = | (decomp.) °C | ε _{367 mµ} | yield | Formula | С | н | N | С | Н | N |
| H Methyl Ethyl sopropyl -Butyl Bromo | 88.8-90* 92-95 36.5-38 55-57.2 93.5-97.5 109.6-110 | 47.3† 49.5 52.4 51.7 54.2‡ 66.5 | 21 10 17 8 9§ 22 | $\begin{array}{c} C_{20}H_{26}N_2\\ C_{22}H_{30}N_2\\ C_{24}H_{34}N_2\\ C_{26}H_{38}N_2\\ C_{18}H_{20}N_2Br_3\end{array}$ | 81.63 81.95 82.23 82.48 2 50.96 | 8.84 9.62 9.78 10.12 4.75 | 9.52 8.69 7.99 7.40 6.61 | 81.54 81.79 82.18 82.22 50.87 | 8.80 9.23 9.81 10.26 4.70 | 9.60 8.82 7.88 6.60 |

TABLE I p,p'-Disubstituted azocumenes

*Literature (5) m.p. 86.9-88.7°. †Literature (5) e 44. ‡For material decomposing at 89.5-95°. §Plus a second crop, m.p. 89.5-95° (decomp.) (7% yield). ||Br: Calculated, 37.68. Found, 37.84.



disproportionation side reaction (7). Authentic samples of the expected products were either purchased or synthesized for use in identification of products by gas-liquid partition chromatography analysis. Only two of the compounds are treated in detail (p,p'-dibromo- and p,p'-diethyldicumyl) since the others are found in the prior literature.

Experimental⁶

p, p'-Disubstituted Azocumenes

The procedure of Nelsen and Bartlett (5) was used with the indicated modifications. Since iodine pentafluoride decomposes in water (8), the methylene chloride solvent and pyridine were distilled from calcium hydride. Also, the reaction flask was baked overnight in an oven at 200° before use. For the sake of convenience, at the completion of reaction and after water had been added, sufficient ether was introduced to ensure that the organic phase would comprise the upper layer during subsequent work-up. Although methylene chloride or ether was used in the earlier studies (5) as the recrystallization solvent, we found that hot pentane dissolved the azo compounds leaving a brown, insoluble material which could be removed by filtration. If this procedure did not work efficiently, washing the crude solid with small amounts of methanol dissolved the dark impurity leaving the azo compound as a tan powder which could then be recrystallized from pentane or methylene chloride (Table I). Decomposition points were determined in a capillary tube with a heating rate of $1-2^{\circ}/\text{min}$.

Decomposition Products from the Azocumenes p-Substituted Cumenes

p-Cumene was obtained from Eastman Organic Chemicals Department.

p-Ethylcumene—Treatment of cumene with acetyl chloride and aluminium chloride gave p-isopropylacetophenone (9) which was converted to p-ethylcumene by the Huang-Minlon modification of the Wolff-Kishner reduction (10a). The product, b.p. 194-196° (742 mm), lit. (10b) b.p. 193° (744 mm), was essentially free of the other isomers according to infrared and gas-liquid partition chromatography (g.l.p.c.) analyses. Attempts to prepare the compound by direct alkylation (10b) gave a mixture of isomers not easily separable by distillation.

p-Isopropylcumene was obtained from the Aldrich Chemical Company.

p-t-Butylcumene—-Cumene was alkylated with *t*-butyl alcohol in 85% sulfuric acid (11). After work-up, the product was distilled through a column packed with glass helices, b.p. 219-224° (748 mm), lit. (11) b.p. 220° (746 mm). Infrared and g.l.p.c. analyses indicated good purity. p-Bromocumene was obtained from Columbia Organic Chemicals Company.

p-Substituted α -Methylstyrenes

4-Methyl-a-methylstyrene-This compound, prepared by dehydration of *p*-tolyldimethylcarbinol with potassium hydrosulfate (12a), was obtained in 43% yield after redistillation at atmospheric pressure from sodium, b.p. 185–186.5°, n_D^{27} 1.5316, lit. (12a) b.p. 187°, lit. (12b) $n_{\rm D}^{20}$ 1.5350.

4-Ethyl-α-methylstyrene—The desired material resulted when the distillation of 4-ethylphenyldimethylcarbinol (13), prepared from acetone and the Grignard reagent of

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⁶Decomposition points (uncorrected) were determined with a Thomas-Hoover or Mel-Temp capillary tube apparatus. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tennessee. The ultra-violet spectra were obtained with a Cary recording spectrophotometer model 14.

4-Isopropyl-a-methylstyrene was obtained from Aldrich Chemical Company.

4-t-Butyl-a-methylstyrene-A mixture of saturated aqueous oxalic acid (50 ml) and 4-t-butylphenyldimethylcarbinol (15) (9.63 g, 0.05 mole) was refluxed for 21 h. The organic layer was separated and washed with water, 2% sodium hydroxide, and then water until the washings were neutral. A small amount of ether was added initially to aid the separations. After removal of solvent from the dried solution, the olefin was distilled, 5.6 g, b.p. 102-105° (11 mm), n_D^{28} 1.5192–1.5194. An additional 1.2 g of product was obtained by extracting the combined aqueous phases. The combined fractions were stored over sodium and redistilled to give 5.45 g (60% yield) of the desired material, b.p. $92-94^{\circ}$ (8 nnn), n_{D}^{27} 1.5194–1.5200, lit. (14) b.p. 98° (5 nn), n_{D}^{20} 1.523.

4-Bromo-a-methylstyrene-The procedure involved dehydration of 4-bromophenyldimethylcarbinol (17) with aqueous oxalic acid as described in the preceding section, 48% yield, b.p. 109–116° (12 mm), $n_{\rm D}^{23}$ 1.5818–1.5822, lit. (18) b.p. 108–110° (11 mm), $n_{\rm D}^{12}$ 1.5835, lit. (19) b.p. 58–60° (1.8 mm), $n_{\rm D}^{20}$ 1.5778, lit. (20) b.p. 114.5–117.5° $(24 \text{ mm}), n_{\rm D}^{20} 1.5834.$

p,p'-Disubstituted Dicumyls

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p,p'-Dimethyldicumyl-This compound was synthesized in 3% yield according to the method of Farmer and Moore (21), m.p. 154.5-158°, lit. (22) m.p. 157°.

p,p'-Diethyldicumyl-The preparation was first attempted by the method described for p, p'-dibromodicumyl. The product, which showed three peaks in g.l.p.c. analysis, was presumed to include coupled side products resulting from abstraction of hydrogen from methylene of the ethyl group.

An alternative pathway was therefore employed. In a flask fitted with a reflux condenser and magnetic stirring bar were placed 20 ml of benzene and 0.5 mmole of p,p'-diethylazocumene. The flask was purged with nitrogen and immersed in an oil bath at 85° for 3 days. After removal of most of the solvent by distillation, a brown solid comprised the residue after evaporation for 2 days in air. A solution of this material in absolute ether on evaporation for 5 days in air to remove the disproportionation products gave a light-brown solid (0.095 g, 0.33 mmole), m.p. 73.5-75.2°. The nuclear magnetic resonance spectrum (Varian A60) in carbon tetrachloride with tetramethylsilane internal standard showed the methyl singlet superimposed on the methyl triplet at δ 1.28, the methylene quartet centered at δ 2.59, and the aromatic region centered at δ 6.92. These groups of peaks were in the ratio, 18:4:8, in agreement with that expected for p, p'-diethyldicumyl.

Anal. Calcd. for C222H30: C, 89.79; H, 10.21. Found: C, 89.53; H, 10.31.

The g.l.p.c. retention time was the same as that for the last of the three peaks obtained from injection of the products from the photolysis reaction.

p,p'-Diisopropyldicumyl-A literature pathway (21)

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provided the hydrocarbon in 3% yield, m.p. 134-135.5°, lit. (23) m.p. 134–135°.

p,p'-Di-t-butyldicumyl-Use of a prior technique (21) gave a 7% yield of product, m.p. 221-225°, lit. (15) m.p. 225°.

p,p'-Dibromodicumvl—This compound was prepared by a photolytic method developed in this laboratory (16). The apparatus consisted of an outer pyrex reaction vessel equipped with thermometer, nitrogen inlet, condenser, and an inner pyrex insert containing a GE H100-A 4/T mercury lamp. The outer glass jacket of the lamp was removed to allow insertion into the apparatus. Since di-t-butyl peroxide shows a broad, regularly increasing absorption from 2200-3400 Å (24), the wavelengths emitted by the lamp which are effective for peroxide decomposition were 3022, 3131, and 3341 Å.

The photolysis apparatus was charged with 0.16 mole of peroxide, 0.64 mole of p-bromocumene, and 150 ml of benzene. After a 2 h purge with nitrogen, the mixture was then photolyzed for 25 h at the reflux temperature. Heat for reflux was supplied by the lamp itself, and the desired reflux rate was maintained by passing a stream of air over the light source. Following removal of solvent by rotary evaporation, three recrystallizations of the brown. solid residue from absolute alcohol gave a colorless product, m.p. 174-175.2° (10% yield).

Anal. Calcd. for C₁₈H₂₀Br₂: C, 54.79; H, 5.07; Br, 40.13. Found: C, 54.32; H, 4.98; Br, 40.10.

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The alkaline decomposition of *o*-phthalaldehyde di-*p*-toluenesulfonylhydrazone

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The Bamford-Stevens reaction of o-phthalaldehyde di-p-toluenesulfonylhydrazone gives N-(3,4dihydrophthalazinyl)p-tolylsulfone. The product is synthesized by an independent method.

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The alkaline decomposition of tosylhydrazones³ of aldehydes and ketones has been extensively used for the synthesis of olefins (1) and some novel cyclic compounds (2).

The Bamford-Stevens reaction of benzaldehyde tosylhydrazone (1a, 1c) under aprotic conditions (3) yields an aryl carbene which dimerizes to trans-stilbene in high yield. Very little is known about the alkaline decomposition of ditosylhydrazones (1a) under aprotic conditions. The ditosylhydrazone of o-phthalaldehyde (1) could yield a dicarbenoid (4) species (2) and hence benzocyclobutadiene (3) (5) or some interesting unsaturated macrocyclic compounds.

o-Phthalaldehyde ditosylhydrazone (1) was prepared by mixing o-phthalaldehyde and ptoluenesulfonylhydrazine in a 1:2 ratio in ethanol. The use of acetic acid as solvent (6) gave a colored solution. Heating a solution of 1 in dimethyl formamide at 120°, or in diethyl Carbitol at 160°, with either sodium methoxide or sodium hydride gave N-(3,4-dihydrophthalazinyl) ptolylsulfone (4) in 5-30% yield, as the only new substance isolated.⁴ No products derived from benzocyclobutadiene (3) (5) could be detected in the reaction product. Cava and Stein (7) have obtained a similar product by the reaction of phthalaldehydic acid tosylhydrazone with excess acetyl chloride in methanol.



The product 4 was also synthesized by the method of Lemal and Fry (8). Phthalazine (5) was reduced with lithium aluminium hydride to 3,4-dihydrophthalazine (6), and the crude product was treated directly with *p*-toluenesulfonyl chloride in freshly distilled sulfolane and triethylamine.

Dornow and Bartsch (1b) have reported the formation of sulfones from diazoalkanes and aldehyde tosylhydrazones and hence the conversion of 1 to 4 is not surprising. A likely precursor of 4 may involve a monocarbene resulting from loss of one tosylhydrazone group

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Theories adults's Department of Chemistry, Tork University, Toronto 12, Ontario. ³Tosyl = Ts = p-toluenesulfonyl. ⁴Ditolyldisulfide and sodium p-tolylsulfinate were also formed as side products (see refs. 1c, 9).