Hindered *N*-Arylhydroxamic Acids from Arylamines *via* Nitroso-compounds

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Hindered aromatic nitroso-compounds, prepared by oxidation of the corresponding amines with *m*-chloroperoxybenzoic acid, were converted into *N*-arylhydroxamic acids which could be obtained only in poor yield or not at all by the conventional reduction of nitro-compounds.

We have previously reported the preparation of *N*-fluoren-4-ylacetohydroxamic acid [1] from 4-nitrofluorene in 4% yield. The formation of maleamic acids which were obtained as undesirable products in the oxidation of amines has since been eliminated as follows. The two-phase system of hydrogen peroxide and maleic anhydride in methylene chloride was stirred at 0° for 4 hr. The lower layer was then added to fresh methylene chloride. The peroxy-acid in the methylene chloride layer of this biphasic system, which contains no maleic anhydride, was titrated iodometrically and then used for the oxidation of the amine in the same way as the 0·350M-solution of *m*-chloroperoxybenzoic acid in ref. 2 and in the present work. Aromatic nitroso- and nitro-compounds were obtained by this procedure in yields of up to 80%. If the lower layer which contains the peroxymaleic acid is exposed to air, an exothermic reaction ensues after a short time. Care must therefore be taken that the lower layer remains covered with methylene chloride at all times.

The yield of *N*-fluoren-4-ylacetohydroxamic acid has now been increased to 62% by use of 4-nitrosofluorene as the starting material. Other acetohydroxamic acids have been prepared similarly from the appropriate nitroso-compounds. This method appears to be useful for the preparation of *N*-arylhydroxamic acids in which the nitrogen atom is in a hindered position. In these reactions, acetyl chloride is a better acetylating agent than acetic anhydride. Thus, 2-nitrosofluorene, when reduced in the presence of acetyl chloride, yielded *N*-fluoren-2-ylacetohydroxamic acid in 77% yield, whereas use of acetic anhydride alone gave 2,2′-azoxyfluorene as the main product, along with *N*-acetoxy-*N*-fluoren-2-ylacetamide (20%). Acetyl chloride apparently acetylates the intermediate hydroxylamine more rapidly than does acetic anhydride. The formation of azoxy-compound from the hydroxylamine and the starting material is thereby prevented.

The hindered nitroso-compounds were prepared by oxidation of the corresponding amines with *m*-chloroperoxybenzoic acid.[2] With the use of the stoicheiometrically required molar ratio of peroxy-acid to amine (2 : 1), different amines yielded varying amounts of nitroso-compound. Thus, fluoren-4-amine, 2-aminobiphenyl, 3-bromofluoren-2-amine, and 3-methoxyfluoren-2-amine gave nitroso-compounds in yields of 80, 52, 38, and 10%, respectively. These and other [3,4] data indicate that the yield of nitroso-compound increases as the nitrogen atom becomes increasingly hindered, whereas the yield of azoxy- and/or azo-compounds increases as

[1] Y. Yost and H. R. Gutmann, *J. Chem. Soc.* (*C*), 1969, 345.
[2] Y. Yost, *J. Medicin. Chem.*, 1969, **12**, 961.
[3] R. R. Holmes and R. P. Bayer, *J. Amer. Chem. Soc.*, 1960, **82**, 3454; R. Okazaki, T. Hosogai, E. Iwadare, M. Hashimoto, and N. Inamoto, *Bull. Chem. Soc. Japan*, 1969, **42**, 3611.
[4] H. R. Gutmann, *Experientia*, 1964, **20**, 128; L. Horner and W. Kirmse, *Annalen*, 1955, **597**, 70.

steric crowding at the nitrogen atom is decreased. In general, azoxy- and/or azo-compounds are the predominant products of the oxidation of primary aromatic amines in which the nitrogen atom is unhindered.

EXPERIMENTAL

M.p.s were taken with a Fisher–Johns apparatus. I.r. spectra were recorded with a Beckman IR-10 spectrophotometer and u.v. spectra with a Beckman DK-2 spectrophotometer. Silica gel GF_{254} for t.l.c. was obtained from Brinkmann Instruments, Inc., Westbury, New York.

2-Nitrosobiphenyl.—2-Aminobiphenyl (Aldrich) (4·91 g., 29·0 mmoles) in chloroform (40 ml.) at 0° was poured into a cold 0·176M-solution of *m*-chloroperbenzoic acid (60 mmoles) in chloroform. The solution was stirred at 0° for 15 min., then gradually brought to room temperature, and finally refluxed for 10 min. It was washed with 0·5N-sodium hydroxide, dried ($MgSO_4$), and evaporated. The residue was chromatographed on a column of alumina (neutral grade) packed with n-hexane. The compound was eluted with n-hexane to which increasing amounts of dichloromethane were added as the chromatography proceeded. Slow evaporation of the initial fractions yielded needles (2·0 g., 38%), which gave *2-nitrosobiphenyl*, m.p. 111—112° (from dichloromethane and n-hexane) (Found: C, 78·9; H, 4·85; N, 7·9. $C_{24}H_{18}N_2O_2$ requires C, 78·65; H, 4·95; N, 7·65%), $\lambda_{max.}$ (EtOH) 233 (log ε 4·20), 277 (3·72), 315 (3·67), and 770 (1·68) nm. Although the nitroso-group in this compound is in a hindered position, solid 2-nitrosobiphenyl appears to exist as a dimer, since it is colourless. In solution, the compound dissociates into monomeric units as indicated by the green colour and by absorption at 770 nm.

In another experiment 0·50 g. of the 2-aminobiphenyl was oxidized. The product was purified by t.l.c. on silica gel GF_{254} with n-hexane–benzene (2 : 1). The fastest-running band, R_F 0·5, yielded the product in 52% yield (determined spectrophotometrically at 233 nm.).

2,2″-Azobiphenyl.—2-Nitrosobiphenyl (100 mg., 0·55 mmole) in dichloromethane (2 ml.) was added to 2-aminobiphenyl (93 mg., 0·55 mmole) in acetic acid (4 ml.) and the mixture was heated on a steam-bath for 6 hr., then evaporated. The residue was applied to a plate (20 × 20 cm.) coated with silica gel GF_{254} (1 mm. thick), which was developed with n-hexane; the orange band, R_F 0·5, was removed. The product was eluted from the silica gel with ether and gave orange *needles* (30%), m.p. 135° (from n-hexane) (resolidifies and remelts at 144—145°) (Found: C, 86·0; H, 5·35; N, 8·3. $C_{24}H_{18}N_2$ requires C, 86·2; H, 5·4; N, 8·4%), $\lambda_{max.}$ (EtOH) 230 (log ε 4·50), 330 (4·20) and 450 (2·75) nm. A second band, R_F 0·3, yielded a trace of yellow material, $\lambda_{max.}$ (EtOH) 232, 315, and 425infl nm., presumably the geometric isomer.

3-Methoxy-2-nitrosofluorene.—3-Methoxyfluoren-2-amine [5] was oxidized with *m*-chloroperoxybenzoic acid and the product was isolated by column chromatography as described for 2-nitrosobiphenyl. The initial yellow fractions yielded mainly 3-methoxy-2-nitrofluorene,[5] identified by its i.r. spectrum. The subsequent green fractions yielded yellow-green *needles* (10%), m.p. 143° (decomp.) (from ethanol) (Found: C, 74·65; H, 5·15; N, 6·05. $C_{14}H_{11}NO_2$ requires C, 74·65; H, 4·9; N, 6·2%), $\lambda_{max.}$ (EtOH) 264 (log ε 3·77) and 360 (4·21) nm.

3-Bromo-2-nitrosofluorene.— 3-Bromofluoren-2-amine [6] (3·00 g., 11·5 mmoles) in chloroform (40 ml.) was oxidized with 0·1742M-*m*-chloroperbenzoic acid (23·2 mmoles) as described for 2-nitrosobiphenyl. The mixture was chromatographed on an alumina column packed with n-hexane and the chromatogram was developed with n-hexane–dichloromethane (8 : 1). The first yellow band yielded an orange compound (30 mg.) with u.v. and i.r. spectra similar to those of 3,3′-dibromo-2,2′-azofluorene. The solvent of the succeeding green fractions was allowed to evaporate at room temperature. The residue consisted of green needles and a few yellow needles. The latter, m.p. 127—131°, were separated manually and identified (i.r. spectrum) as 3-bromo-2-nitrofluorene (lit.,[7] m.p. 130—131°). The green product was recrystallized from ethanol (1·20 g., 38%); m.p. 148° (decomp.) (Found: C, 56·85; H, 2·9; Br, 29·45; N, 5·4. $C_{13}H_8BrNO$ requires C, 56·95; H, 2·95; Br, 29·15; N, 5·1%), $\lambda_{max.}$ (EtOH) 248 (log ε 3·91), 267 (3·81), and 375 (4·26) nm.

3,3′-Dibromo-2,2′-azofluorene.—3-Bromofluoren-2-amine [7] (74 mg., 0·28 mmole) in acetic acid (8 ml.) was added to 3-bromo-2-nitrosofluorene (77 mg., 0·28 mmole) in chloroform (4 ml.) and the solution was left overnight at 40°. The orange *precipitate* was collected and washed with hot ethanol (44 mg., 30%); m.p. 300° (decomp.) (Found: C, 60·65; H, 3·1; Br, 30·95; N, 5·6. $C_{26}H_{16}Br_2N_2$ requires C, 60·5; H, 3·1; Br, 30·95; N, 5·45%), $\lambda_{max.}$ ($CHCl_3$) 253 (log ε 4·30), 267infl (4·28), and 405 (4·52) nm.

N-Acetoxy-N-(3-bromofluoren-2-yl)acetamide.—3-Bromo-2-nitrosofluorene (400 mg., 1·46 mmole) in ethyl acetate (40 ml.), acetic anhydride (0·5 ml.), and acetyl chloride (1 ml.) was hydrogenated in the presence of 10% palladium–charcoal (30 mg.) and sodium acetate (150 mg.) until 1·5 mmoles of hydrogen had been consumed; the originally green solution had then become colourless. The catalyst was filtered off and the filtrate was concentrated. The concentrate was applied to two plates (20 × 20 cm.) coated with silica gel GF_{254} (1 mm. thick) and the chromatograms were developed with benzene–ethyl acetate (7 : 1). The product was located under u.v. light (2537 Å) as a fluorescence-quenching band (R_F 0·4), which was eluted from the silica with ether. The eluate was evaporated to 2 ml., diluted with warm n-hexane (4 ml.) and then cooled at 0° in a partly stoppered flask to yield tan prisms (80 mg.), m.p. 135—137° (Found: C, 56·4; H, 3·7; Br, 22·0; N, 4·1. $C_{17}H_{14}BrNO_3$ requires C, 56·7; H, 3·9; Br, 22·2; N, 3·9%), $\lambda_{max.}$ (EtOH) 273 (log ε 4·32), 296 (4·10), and 307 (4·13) nm., $\nu_{max.}$ (KBr) 1793 [(O)C=O] and 1692 [(N)C=O] $cm.^{-1}$. In an identical catalytic reduction of 3-bromo-2-nitrosofluorene the mixture was stirred with 8M-ammonium hydroxide for 12 hr. subsequent to the hydrogenation and was then extracted with 10% sodium hydroxide. Acidification of the extract and recrystallization of the crude product from ethanol–water gave *N-(3-Bromofluoren-2-yl)acetohydroxamic acid* (52%), m.p. 194—196° (Found: C, 56·5; H, 3·9; Br, 25·15; N, 4·65. $C_{15}H_{12}BrNO_2$ requires C, 56·6; H, 3·8; Br, 25·1; N, 4·4%), $\lambda_{max.}$ (EtOH) 271 (log ε 4·32), 298 (4·04), and 307 (4·10) nm., $\nu_{max.}$ (KBr) 3100 and 2860 (broad, OH) and 1640 (C=O) $cm.^{-1}$. The hydroxamic acid (10 mg.)

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[7] T. L. Fletcher and H. L. Pan, *J. Amer. Chem. Soc.*, 1956, **78**, 4812.

in ethyl acetate was reduced catalytically with 10% palladium–charcoal (15 mg.) at room temperature and atmospheric pressure to *N*-(3-bromofluoren-2-yl)acetamide.[7] When ethanol was used as the solvent in the catalytic reduction (5 hr.), the hydroxamic acid was first reduced to the *o*-bromo-amide. The latter was then debrominated quantitatively to *N*-fluoren-2-ylacetamide. The reduction and debromination were monitored by u.v. spectrophotometry.

N-*Fluoren*-2-*ylacetohydroxamic Acid*.—2-Nitrosofluorene [2,8] * (1·00 g., 5·12 mmoles) in ethyl acetate (80 ml.), triethylamine (0·10 ml.), acetyl chloride (0·7 ml.), and acetic anhydride (2 ml.) was hydrogenated at room temperature and atmospheric pressure over 10% palladium–charcoal (50 mg.) until 5·2 mmoles of hydrogen had been consumed; the originally green solution had then turned colourless. The product was isolated by the published procedure.[9] One crystallization yielded the pure product (0·95 g., 77%), m.p. 149—151° (lit.,[9] 143—144°; 20—30% from 2-nitrofluorene). The experiment was repeated without acetyl chloride. T.l.c. of the residue remaining after evaporation of the ethyl acetate yielded 2,2′-azoxyfluorene (34%), most of which precipitated during the reduction, *N*-acetoxy-*N*-fluoren-2-ylacetamide (20%), and *N*-fluoren-2-ylacetamide (22%). The yields were determined by u.v. spectroscopy and the compounds were identified by their u.v. spectra and R_F values.

N-Acetoxy-*N*-fluoren-2-ylacetamide, when subsequently chromatographed on silica gel with benzene apparently underwent acid-catalysed rearrangement; [10] material of R_F *ca.* 0·1 appeared on the chromatograms. The i.r. spectrum of this substance exhibited the NH, CO, and all other absorptions found in the spectra of *N*-3-acetoxy- and *N*-1-acetoxyfluoren-2-ylacetamide, and showed that the material consisted predominantly of the 3-isomer. Because of this rearrangement this method should not be used for the purification of *N*-acyloxy-*N*-arylamides which are unsubstituted *ortho* to the nitrogen atom.

We have also observed that when the developed chromatogram of an *N*-*ortho*-acetoxyfluoren-*x*-ylacetamide was left exposed to ambient conditions for 4 hr. and was then redeveloped, the original band, R_F *ca.* 0·3, yielded two bands of about equal intensity [*N*-(1-acetoxyfluoren-2-yl)acetamide, *N*-(3-acetoxyfluoren-2-yl)acetamide, and *N*-(2-acetoxyfluoren-3-yl)acetamide were tested]. The new, faster-moving band yielded the corresponding amidophenol as shown by u.v. and i.r. spectra and R_F value; the slower-moving band gave the applied compound. The difference in R_F values [ethyl acetate–benzene (1 : 1)] between these acetates (R_F *ca.* 0·3) and the respective phenols (R_F *ca.* 0·4) afforded good separation. The R_F values of phenols are generally smaller than those of the corresponding acetates, but the relative values were in these cases reversed, apparently because of chelation: $\nu_{max.}$ (KBr) *ca.* 25,000br cm.$^{-1}$ (OH). The lone pair of electrons of the nitrogen atom presumably forms a five-centred transition state with the carbonyl carbon atom of the vicinal acetoxy-group and thus facilitates the hydrolysis. This explanation was tested with *N*-(5-acetoxyfluoren-2-yl)acetamide, *N*-(7-acetoxyfluoren-2-yl)acetamide, and *N*-(1-acetoxyfluoren-4-yl)acetamide, which were not hydrolysed under the conditions described.

N-*Fluoren*-4-*ylacetohydroxamic Acid*.—4-Nitrosofluorene [1,2] (3·20 g., 16·5 mmols) in ethyl acetate (290 ml.), acetyl chloride (6·5 ml.), acetic anhydride (4 ml.), and triethylamine (0·6 ml.) was hydrogenated at room temperature and atmospheric pressure over 10% palladium–charcoal (320 mg.) until 16 mmoles of hydrogen had been consumed. The product, m.p. 152—154° (lit.,[1] 147—153° in 4·1% yield) was isolated as described previously (2·44 g., 62%).

The triethylamine in the catalytic reduction occasionally poisons the catalyst. This can be avoided by adding additional catalyst (after evacuation of hydrogen) or by using sodium acetate instead of triethylamine. The solubility of sodium acetate in ethyl acetate at 25° is 0·15% (w/v).

N-*Biphenyl*-2-*ylacetohydroxamic Acid*.—2-Nitrosobiphenyl (3·00 g., 16·4 mmoles) in ethyl acetate (300 ml.), acetic anhydride (4 ml.), and acetyl chloride (6 ml.) was hydrogenated at atmospheric pressure and at room temperature in the presence of 10% palladium–charcoal (120 mg.) and sodium acetate (see previous experiment) (2 g.) until 16·5 mmoles of hydrogen had been consumed. The catalyst was filtered off and the filtrate was stirred at room temperature overnight with 8M-ammonium hydroxide (80 ml.). The organic phase was extracted with 10% sodium hydroxide (7 × 10 ml.). The extract was cooled to 0° and acidified with conc. hydrochloric acid. The oily product which precipitated solidified when the mixture was stirred at 0° for 15 min. The crude product (2·6 g.), m.p. 155—157°, was dissolved in hot ethanol (50 ml.) and hot water (45 ml.) was added. Pale tan *prisms* were deposited when the solution was kept at 0° for 2 days (2·40 g., 64%), m.p. 156—157° (Found: C, 74·0; H, 5·75; N, 6·35. $C_{14}H_{13}NO_2$ requires C, 74·0; H, 5·75; N, 6·15%), $\lambda_{max.}$ (EtOH) 235 (log ε 4·22) nm., $\nu_{max.}$ (KBr) 3210 and 2850 (broad, OH) and 1645 (C=O) cm.$^{-1}$. The organic phase was evaporated, and the residue was chromatographed as described for the purification of 2-nitrosobiphenyl. The fastest-running fractions yielded starting material (8%) and the tail fraction gave *N*-biphenyl-2-ylacetamide (12%), identified by its u.v. spectrum, R_F value, and m.p.

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* 2-Nitrosofluorene, when prepared and purified by recrystallization from n-hexane as described in refs. 2 and 8, often contains 2,2′-azoxyfluorene. The latter is insoluble in ethanol and can be eliminated by heating the crude 2-nitrosofluorene in ethanol to about 65° and by filtration (gravity) of the hot mixture.

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