Reduction Studies of Various Substituted Carbostyrils

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This study was undertaken to determine the value of complex metal hydrides as reducing agents for certain functional groups when they are a part of the carbostyril ring system. Sodium borohydride has been found capable of reducing 4-formylcarbostyrils to the corresponding alcohols, carbostyrilcarboxaldehyde anils to the corresponding secondary amines and several carbostyrilnitroalkenes to the carbostyrilnitroalkanes without attacking the heterocyclic or homocyclic rings of the carbostyril.

The ease of oxidation of 1,4-dimethylcarbostyril and 4-methylcarbostyril to the corresponding 4-formylcarbostyrils with selenium dioxide has been demonstrated in past work. (1) (2) The 1-methyl-4-formylcarbostyril has previously been converted to the alcohol by reduction with aluminum isopropoxide. (1) In this study the reduction was carried out with sodium borohydride in methanol in a much more efficient manner. When 4-formylcarbostyril was reduced in the same manner, a 92% yield of 4-hydroxymethylcarbostyril was obtained.

Several anils of the 1-methyl-4-formylcarbostyril have been prepared by Cook and Flanders. (3) When 1-methyl-4-formylcarbostyril-p-phenylanil was treated with sodium borohydride, an 85% yield of 1-methyl-4-(p-biphenylaminomethyl)carbostyril was obtained.

Evidence from the infrared absorption studies of this reduction shows that the anil was converted to the secondary amine without attack on the ring. An absorption spectra of the reduced product revealed the presence of the –NH– stretching band at 3500 cm^{-1} and the –NH– deformation band at 1530 cm^{-1}. Evidence is also found from the spectra that no reduction took place in the rings of this compound. A moderate band at 876 cm^{-1} is related to the one out-of-plane hydrogen of the heterocyclic ring while a strong band at 757 cm^{-1} is indicative of the four adjacent hydrogens in the homocyclic ring. A moderate band at 839 cm^{-1} is due to the two adjacent hydrogens in the anil phenyl ring and two strong bands at 771 cm^{-1} and 707 cm^{-1} indicates the monosubstituted phenyl ring on the para position of the anil ring. In a similar type of reduction 1-methyl-4-(p-(diethylamino)phenylaminomethyl)carbostyril was prepared in 53% yield from 1-methyl-4-formylcarbostyril-p-diethylaminoanil.

1-(1'-Methyl-4'-carbostyril)-2-nitroethanol and 1-(1'-methyl-4'-carbostyril)-2-nitropropanol have been previously prepared by Cook and Stamper. (1) The present method describes an improved method of preparation of these compounds. These alcohols were converted to 1-(1'-methyl-4'-carbostyril)-2-nitroethene and 1-(1'-methyl-4'-carbostyril)-2-nitro-1-propene by dehydration with acetic anhydride in pyridine. The method of Schecter, Ley and Roberson (4) was used to reduce the olefinic bond of these compounds to the saturated nitro derivatives. 1-(1'-Methyl-4'-carbostyril)-2-nitroethane was obtained in 16% yield and had a melting point of 139-140.5° while 1-(1'-methyl-4'-carbostyril)-2-nitropropane was recovered in 15% yield and had a melting point of 115.5-116.5°.

Several attempts were made to carry out reductions on the functional groups attached to the carbostyril ring using lithium aluminumhydride.

In each case the lactam group of the heterocyclic ring was also attacked resulting in a mixture of products which were not identified.

Experimental

1-Methyl-4-formylcarbostyril was prepared by the method of Cook and Stamper (1) and was found to melt at 179-180°.

4-Formylcarbostyril. This compound was prepared as described by Yunghans (2) but has not been previously reported in the literature. Ten grams (0.063 moles) of 4-methylcarbostyril was added to 100 ml. of diphenyl ether and heated to 185°. While the solution was stirred, 7.77 g. (0.07 moles) of selenium dioxide was added portionwise. Stirring and heating was continued for two hours. The hot diphenyl ether was decanted from the selenium and diluted with 200 ml. of ligroin (b. p. 100-120°). Upon cooling in ice, a light yellow solid precipitated. When recrystallized from a benzene-ethanol mixture, 8 g. (72.7%) of light yellow crystals, m.p. 267°, was obtained.

Anal. Calcd. for $C_{10}H_7O_2N$: N, 8.09%. Found: N, 8.21%.

1-Methyl-4-hydroxymethylcarbostyril. Four grams (0.026 moles) of 1-methyl-4-formylcarbostyril was dissolved in 100 ml. of methanol and cooled in an ice-bath. Four grams of sodium borohydride (0.106 moles) was added to the solution in small portions. The reaction mixture was shaken throughout the addition. When the reaction had subsided, it was hydrolyzed with 10% hydrochloric acid. A white powder was recovered from the solution upon evaporation. Recrystallization of this product from 130 ml. of hot water gave 4.4 grams (97.7%) of the desired alcohol with a m.p. of 185-187.5°. Cook and Stamper reported a m.p. of 187-188°.

4-Hydroxymethylcarbostyril. Three grams of 4-formylcarbostyril (0.019 moles) was dissolved in 50 ml. of methanol and with vigorous stirring was reduced with 1.0 g. of sodium borohydride. After hydrolysis with 10% hydrochloric acid and evaporation to dryness, 3.2 g. of a white powder was obtained. Upon recrystallization from ethanol, 2.8 g. (92%) of the product melting at 271-272° was obtained. Sorter has reported a m.p. of 265°.

Infrared Absorption Bands (in Nujol): 3350 cm^{-1} (m—broad), 1650 (s), 1093 (s), 857 (m) and 753 (s).

1-Methyl-4-formylcarbostyril-p-phenylanil. This compound was prepared by the method of Cook and Flanders (3) from the 1-methyl-4-formylcarbostyril and p-phenylaniline. When crystallized from ethanol and a small amount of water, yellow crystals melting at 156-157° (dec.) were obtained.

Anal. Calcd. for $C_{23}H_{18}N_2O$: N, 8.28%. Found: N, 8.27%.

1-Methyl-4-formylcarbostyril-p-diethylaminoanil. This compound was prepared as described by Cook and Flanders. (3) The melting point was 171-172°.

1-Methyl-4-(p-biphenylaminomethyl)carbostyril. Four grams (0.0123 moles) of 1-methyl-4-formylcarbostyril-p-phenylanil was placed in 80 ml. of methanol and 0.6 g. (0.013 moles) of sodium borohydride was added to

the solution. After the initial reaction had subsided, the mixture was heated on the steam bath for five minutes. During the reaction a white precipitate formed and with the addition of 20 ml. of water to the solution, the product was completely precipitated. The product was washed with water, dried, and then dissolved in sufficient hot benzene. The product from the benzene weighed 3.6 g. (85.7%) and melted at 209-210°.

Anal. Calcd. for $C_{23}H_{20}N_2O$: N, 8.23%. Found: N, 8.19%.

Infrared Absorption Bands (in Nujol) 3500cm^{-1} (w), 1660 (s), 1530 (m), 876 (m), 839 (m), 757 (s), 771 and 707 (s).

A *picrate* of this compound was obtained and found to melt at 166-167.5°.

Anal. Calcd. for $C_{29}H_{23}N_5O_8$: N, 12.30% Found: N, 12.41%

1-Methyl-4-(p-(diethylamino)phenylaminomethyl)carbostyril. One gram (0.0029 moles) of 1-methyl-4-formylcarbostyril-p-diethylaminoaril was dissolved in 20 ml. of methanol. In a manner similar to the preparation of 1-methyl-4-biphenylaminomethyl)carbostyril, 0.75 g. of sodium borohydride (0.029 moles) was added rapidly to the methanol solution. When the reaction was complete and the product recovered, recrystallization from ethanol gave 0.58 g. of a substance melting at 160-161°. The yield was 54%.

Anal. Calcd. for $C_{21}H_{25}N_3O$: N, 12.54% Found: N, 12.70%

1-(1'-Methyl-4'-carbostyril)-2-nitroethanol. Twenty grams (0.106 moles) of 1-methyl-4-formylcarbostyril was dissolved in 500 ml. of boiling ethanol. A mixture of 40 ml. of nitromethane and 8 ml. of diethylamine was added to the boiling solution. After standing for 4-5 hours, the product was formed and recovered from the solution by filtration. A yield of 17 g. (64%) with a m.p. of 175-177° was recovered. When this product was recrystallized from ethanol the m.p. was found to be 184-184.5° (dec.). A previous reported m.p. for this compound on a Fisher-Johns melting block was 168-170°. When a sample of this compound was melted on the Fisher-Johns block, it was found to melt at 172-173° (dec.).

Infrared Absorption Bands (in Nujol): 3360 cm^{-1} (m), 1645 (s), 1580(s), 1550 (s), 1325 (w), 1278 (w), 1115 (m), 1055 (m), 887 (m), and 761 (s).

1-(1'-Methyl-4'-carbostyril)-2-nitropropanol. The condensation of 1-methyl-4-formylcarbostyril and nitroethane was carried out in the same manner as described by Cook and Stamper. (1) The product melted at 174-176° and was obtained in 65% yield.

1-(1'-Methyl-4'-carbostyril)-2-nitroethene. Ten grams (0.04 moles) of 1-(1'-methyl-4'-carbostyril)-2-nitroethanol was dissolved in 100 ml. of warm pyridine and arranged for reflux. Sixty milliliters of acetic anhydride was added to the mixture and brought to boiling for three minutes. Upon cooling the solution, long orange-yellow needles precipitated. The mixture was poured into 350 ml. of ice water and stirred. The precipitate was collected and found to melt at 191-197°. After recrystallization from acetone, the product melted at 215-217° (dec.). The yield was 8.5 g. (91.4%).

Anal. Calcd. for $C_{12}H_{10}N_2O_3$: N, 12.17% Found: N, 12.24%

1-(1'-Methyl-4'-carbostyril)-2-nitro-1-propene. In a manner similar to the preceding preparation, 2.5 g. of the 1-(1'-methyl-4'-carbostyril)-2-nitropropanol was converted to the olefin. The precipitate obtained weighed 2.0 g. (86%) and melted at 181-182°.

Anal. Calcd. for $C_{13}H_{12}N_2O_3$: N, 11.48% Found: N, 11.55%

Infrared Absorption Bands (in Nujol): 1675 cm^{-1} (s), 1600 (m), 1525 (m), 1328-1322 (m), 929 (w), 865 (w) and 758 (s).

1-(1'-Methyl-4'-carbostyril)-2-nitroethane. Nine grams (0.039 moles) of 1-(1'-methyl-4'-carbostyril)-2-nitroethene was dissolved in 1 liter of methanol and cooled in ice. With stirring vigorously, 10 g. (0.264 moles) of sodium borohydride was added to the solution. After the reaction was complete, the solution was neutralized with 10% hydrochloric acid. The solution changed from a red color back to a yellow color upon acidification. The solution was then concentrated to 75 ml. by heating under a vacuum and filtered hot to remove a small amount of tar. After cooling 3 g. of a tan precipitate, m.p. 130-137.5°, was obtained. The precipitate was recrystallized from water. One-half gram (16.5%) of the pure product, m.p. 139-140.5°, was obtained.

Anal. Calcd. for $C_{12}H_{12}N_2O_3$: N, 12.06% Found: 12.09%

Molecular Weight Calculated 232.2 Found: 234

Infrared Absorption Bands (in $CHCl_3$ against a $CHCl_3$ reference cell) 3080 cm^{-1} (w), 1665 (s), 1600 and 1565 (s), 1460 (m), 1380 (m), 1330 (w) and 887 (w).

1-(1'-Methyl-4'-carbostyril)-2-nitropropane. One gram of 1-(1'-methyl-4'-carbostyril)-2-nitro-1-propene was placed in 50 ml. of methanol and reduced with sodium borohydride in much the same manner as the preceding preparation. After recrystallization of the product from alcohol, 0.15 g. (14.9%) of the pure substance was obtained. It melted at 115-116.5° (dec.).

Anal. Calcd. for $C_{13}H_{14}N_2O_3$: N, 11.38% Found: N, 11.25%

Molecular Weight Calculated: 246.2 Found: 244

Literature Cited

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