BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN VOL. 43 1135—1138 (1970)

Formation of 4-Hydroxycarbostyrils in the Reaction of Carbon Suboxide with Aromatic Amines

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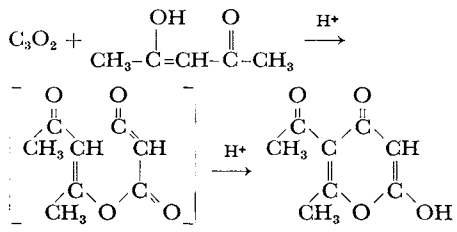
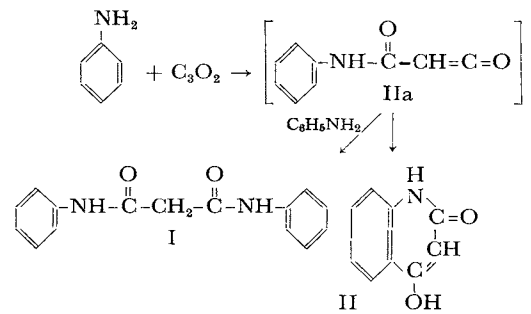
(Received July 18, 1969)

The reactions of carbon suboxide with aromatic amines were found to give various 4-hydroxycarbostyril derivatives. The reaction between aniline and carbon suboxide usually gives malonanilide. However, it was found that the reaction of aniline with carbon suboxide in ether in the presence of aluminum chloride produced phenylcarbamoylacetic acid in a good yield and that cyclization to 4-hydroxycarbostyril occurred when the solvent was replaced by benzene before the decomposition of the reaction mixture with water. The solvent effect on the formation of 4-hydroxycarbostyrils and the possible reaction mechanism were discussed.

The reaction between carbon suboxide and several enolizable ketones have been reported to give pyrone and pyronopyrone derivatives.[1-3] In our recent publications,[3,4] we have reported the reaction of carbon suboxide with acetylacetone in the presence of sulfuric acid, thus producing 3-acetyl-6-hydroxy-2-methyl-4-pyrone. The reaction includes the cyclization of the *O*-acetylated ketenic intermediate to the pyrone, as is indicated below:



It has been reported that the reaction of carbon suboxide with aniline[5] gave malonanilide (I) quantitatively. In this case, the reaction may proceed *via* the *N*-acylated ketenic intermediate (IIa), which may be expected to produce 4-hydroxycarbostyril (II) if the intramolecular cyclization occurs.



In the present paper, we wish to report on the formation of various 4-hydroxycarbostyril derivatives in the reaction of carbon suboxide with aromatic amines.

1) E. Ziegler and H. Bieman, *Monatsh. Chem.*, **93**, 34 (1962).

2) F. Haadetzky and E. Ziegler, *ibid.*, **97**, 398 (1966).

3) A. Omori, N. Sonoda, S. Okano and S. Tsutsumi, *Tetrahedron Lett.*, **1968**, 3647.

4) A. Omori, N. Sonoda and S. Tsutsumi, *J. Org. Chem.*, **34**, 2480 (1969).

5) L. H. Reyerson and K. Kobe, *Chem. Rev.*, **7**, 479 (1930).

Results and Discussion

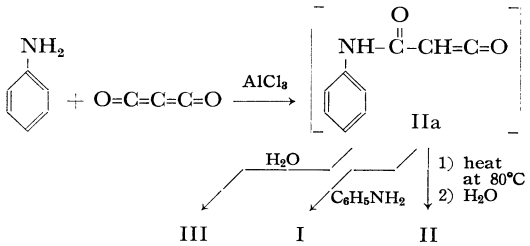
Reaction with Aniline. The reaction of carbon suboxide with aniline in ether gave I quantitatively. The presence of a catalytic amount of sulfuric acid did not affect the reaction, and no II was obtained. A further attempt with aluminum chloride in carbon disulfide failed to give either II or phenylcarbamoylacetic acid (III), only I was isolated. However, the reaction of carbon suboxide with aniline in the presence of aluminum chloride in ether at room temperature gave III in a 78% yield when the reaction mixture was decomposed with water. On the other hand, II was obtained in a 17.3% yield when, before the decomposition of the reaction mixture with water, benzene was used in the place of ether and the benzene solution was refluxed at 80°C. The structures of II and III were confirmed by comparison with authentic samples in terms of their mass, infrared, and ultraviolet spectra. The results obtained in the reaction of carbon suboxide with aniline are summarized in Table 1.

Table 1. Reaction of carbon suboxide with aniline under various conditions

Reactant $C_6H_5NH_2$/ C_3O_2	Solvent	Catalyst	Reaction temp.	Product (yield)
1/1	CS_2	$AlCl_3$	r. t.	I (95%)
1/2	CS_2	$AlCl_3$	r. t.	I (100%)
1/2	Et_2O	none	r. t.	I (100%)
1/2	Et_2O	H_2SO_4	r. t.	I (100%)
1/2	Et_2O	$AlCl_3$	r. t.	III (78%)
1/3	$Et_2O \rightarrow C_6H_6$	$AlCl_3$	80°C	II(17.3%)

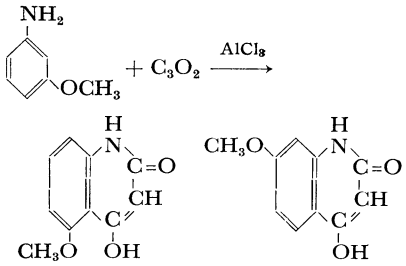
* Mole ratio

A possible reaction path for the formation of II is illustrated below. The first step in the reaction is considered to be the *N*-acylation to give an *N*-acylated intermediate (IIa), which, on cyclization, gives II and which, on reaction with one molecule of aniline and with water, gives I and III respectively.

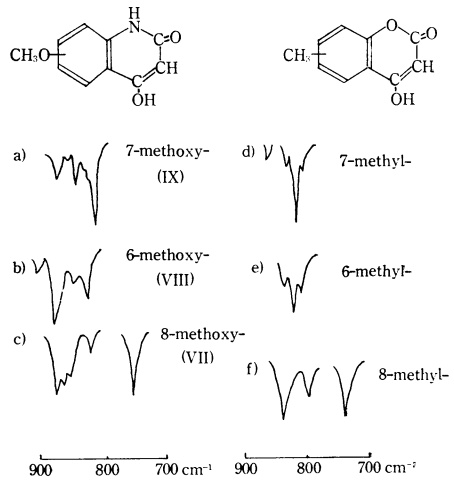


As is shown in Table 1, the solvent effect on the reaction with aniline is remarkable. In the first two cases in Table 1, I was formed quantitatively in carbon disulfide with aluminum chloride. However, in ether III was produced in a 78% yield under similar conditions. The reason for this solvent effect is that aluminum chloride may be catalytically inactive for the formation of I due to the formation of a complex ($Et_2O \rightarrow AlCl_3$); since no such complex is formed when carbon disulfide is used, it is thought that the activity of aluminum chloride remains such as to give I.

Reaction with Anisidines. The reaction of carbon suboxide with *o*,- *p*-, and *m*-anisidines (IV, V, and VI respectively) gave 4-hydroxy-methoxycarbostyrils in 29—67% yields under conditions similar to those used in the case of aniline. In the reaction with IV, 4-hydroxy-8-methoxycarbostyril (VII) was obtained in a 28.5% yield. With V, 4-hydroxy-6-methoxycarbostyril (VIII) was obtained in a 58.7% yield. The structures of VII and VIII were confirmed by comparison with authentic samples in terms of their infrared, ultraviolet, and mass spectral data. In the reaction of carbon suboxide with VI, a carbostyril derivative (mp 330°C) (IX) was obtained. In this case, 4-hydroxy-5-methoxy- and/or 4-hydroxy-7-methoxycarbostyril would normally be expected.



The structure of IX was examined by a comparison of its infrared and ultraviolet spectra with



IR spectra of carbostyrils IR spectra of coumarins

Fig. 1. The IR spectra between 900 cm^{-1} and 700 cm^{-1} of carbostyrils and coumarins.

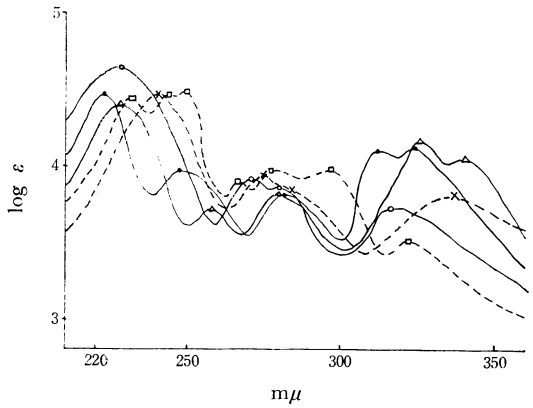
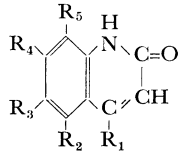


Fig. 2. The UV spectra of carbostyril derivatives.



1) $R_1,R_2,R_3,R_5=H$, $R_4=CH_3$ (—△—△)
2) $R_1=OH$, $R_2,R_3,R_4=H$, $R_5=OCH_3$ (—□—□)
3) $R_1=OH$, $R_2,R_4,R_5=H$, $R_3=OCH_3$ (—×—×)
4) $R_1=OH$, $R_2,R_3,R_4,R_5=H$ (—○—○)
5) IX (—●—●)

those of other 4-hydroxycarbostyril and 4-hydroxycoumarin derivatives (Fig. 1 and Fig. 2).

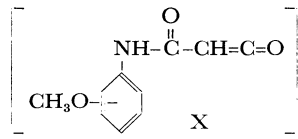
The 1,2,3-trisubstituted benzene rings of 4-hydroxy-methylcoumarin and 4-hydroxy-methoxycarbostyril show characteristic absorption bands due to hydrogen on the benzene ring between 800 cm^{-1} and 700 cm^{-1}. However, IX shows no absorption bands in this region, and the spectrum between 900 cm^{-1} and 800 cm^{-1} can be interpreted rather as that for the 1,2,4-trisubstituted benzene derivative. The spectral data of some 1,2,4-trisubstituted benzene derivatives related to 4-hydroxycarbostyril are also shown in Fig. 1. This speculation is also supported by the ultraviolet spectral data shown in Fig. 2. On the basis of these facts, the structure of IX was assigned to 4-hydroxy-7-methoxycarbostyril. The results obtained in the reactions of anisidines are shown in Table 2.

Table 2. Reaction of carbon suboxide with anisidines

Reactant	Solvent	Catalyst	Reaction temp.	Product (yield)
IV	$Et_2O \rightarrow C_6H_6$	$AlCl_3$	80°C	VII(28.5%)
V	$Et_2O \rightarrow C_6H_6$	$AlCl_3$	80°C	VIII(58.7%)
VI	$Et_2O \rightarrow C_6H_6$	$AlCl_3$	80°C	IX (66.8%)

The reaction path for the formation of 4-hydroxy-methoxycarbostyrils may also include the cyclization of the *N*-acylated intermediate (X).

The better yields of carbostyril derivatives from anisidines than from aniline may be ascribed to



the electron-donating effect of the methoxyl group on the benzene ring in X. In the case of VI, the steric interaction between the methoxyl group and the ketenic group in the intermediate may affect the course of cyclization so as to favor the production of the 7-methoxycarbostyril rather than the 5-methoxy derivative.

Experimental

Preparation of Carbon Suboxide. Carbon suboxide was prepared by the pyrolysis[6] of diacetyltartaric anhydride at about 700°C and trapped at −78°C (a dry ice-methanol bath), and it was purified by distillation from trap to trap. The identification was established by the preparation of malonanilide by means of a reaction with aniline.

Reaction of Carbon Suboxide with Aniline in Carbon Disulfide. Into a suspension of aluminum chloride (15.2 g, 0.14 mol) in carbon disulfide (15 m*l*), we stirred a solution of carbon suboxide (8.8 g, 0.14 mol) in carbon disulfide (20 m*l*) at −70°C under nitrogen. Then a solution of aniline (11.8 g, 0.14 mol) in carbon disulfide (50 m*l*) was stirred, drop by drop, into this reaction mixture over a period of one hour. The reaction mixture was then maintained at −70°C for 6 hr, at 0°C for 9 hr and at room temperature for 9 hr. The reaction mixture was then poured into ice-water. The solid (19.5 g, 95%) which was deposited was recrystallized from ethanol to give I, mp 225°C.

Reaction of Carbon Suboxide with Aniline in Ether. The same procedure as described above was applied using aluminum chloride (6.9 g, 0.05 mol), carbon suboxide (3.4 g, 0.05 mol), and aniline (1.7 g, 0.017 mol), and ether (170 m*l*) instead of carbon disulfide. The reaction mixture was poured into ice water. The ether layer was dried over anhydrous magnesium sulfate, and the solid residue was recrystallized from chloroform to give III (2.2 g, 78%); mp 128°C; ν_{max}^{KBr} 1730 (C=O), 1670 (–NH–C(=O)–) cm^{-1}; an acidic test by $NaHCO_3$ was positive.

Found: C, 60.25; H, 4.90; N, 7.86%. Calcd for $C_9H_9NO_3$: C, 60.33; H, 5.06; N, 7.82%.

4-Hydroxycarbostyril (II). The same procedure as described above was applied using aluminum chloride (6.5 g, 0.04 mol), carbon suboxide (3.3 g, 0.049 mol), aniline (1.5 g, 0.016 mol), and ether (250 m*l*). After mixing the reactants, benzene (150 m*l*) was added, drop by drop, to the mixture, and at the same time the ether was evaporated by warming. After the ether had been removed completely, the benzene solution was refluxed at 80°C for 4 hr and then poured into ice water. A yellow solid, extracted with methanol from the solid deposited, was recrystallized from ethanol to give II; 0.46 g (17.3%); mp 333—335°C (decomp.); ν_{max}^{KBr} 2900 (–OH, –NH), 1680 (C=O), 1600 (C=C)

6) E. Ott, *Ber.*, **47**, 2388 (1914).

cm^{-1}; λ_{max}^{EtOH} 228 (log ε, 4.64), 270 (3.91), 315 (3.74) mμ; enolic –OH (by $FeCl_3$ test); $C_9H_7NO_2$ (M^+, 161).

4-Hydroxy-8-methoxycarbostyril (VII). By the treatment of carbon suboxide (2.2 g, 0.032 mol) with *o*-anisidine (1.3 g, 0.011 mol) as has been described in the formation of II, VII was obtained; 0.58 g (28.5%); mp 243—243.5°C; ν_{max}^{KBr} 3200, 2950 (–NH, –OH), 1640 (C=O), 1600(C=C) cm^{-1}; λ_{max}^{EtOH} 231 (logε, 4.44), 243 (4.47), 249 (4.49), 266(3.91), 276(3.98), 286(3.98), 321(3.53) mμ; $C_{10}H_9NO_3$ (M^+, 191).

Found: C, 62.43; H, 4.95; N, 6.75%. Calcd for $C_{10}H_9NO_3$: C, 62.82; H, 4.75; N, 7.33%.

4-Hydroxy-6-methoxycarbostyril(VIII). By the treatment of carbon suboxide (2.8 g, 0.04 mol) with *p*-anisidine (1.7 g, 0.014 mol) in the presence of aluminum chloride (5.4 g, 0.04 mol) as has been described above, VIII was obtained; 1.52 g (58.7%); mp 305°C (decomp.); ν_{max}^{KBr} 3400, 2950(–NH, –OH), 1660(C=O), 1610(C=C) cm^{-1}; λ_{max}^{EtOH} 240 (logε, 4.45), 274(3.93), 283(3.86), 336(3.81) mμ; $C_{10}H_9NO_3$ (M^+, 191).

Found: C, 63.09; H, 4.70; N, 7.56%. Calcd for $C_{10}H_9NO_3$: C, 62.82; H, 4.75; N, 7.33%.

4-Hydroxy-7-methoxycarbostyril (IX). By the treatment of carbon suboxide (2.8 g, 0.04 mol) with *m*-anisidine (1.7 g, 0.014 mol) in the presence of aluminum chloride (5.4 g, 0.04 mol) as has been described above, IX was isolated; 1.73 g (66.8%); mp 330°C (decomp.); ν_{max}^{KBr} 3100, 2900(–NH, –OH), 1690, 1640 (C=O), 1615(C=C) cm^{-1}; λ_{max}^{EtOH} 222 (logε, 4.47), 247 (3.98), 281(3.84), 311(4.10), 323(4.12) mμ; $C_{10}H_9NO_3$ (M^+, 191).

Found: C, 63.21; H, 4.69; N, 7.92%. Calcd for $C_{10}H_9NO_3$: C, 62.82; H, 4.75; N, 7.33%.