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Preparation of 3-(3′-,4′-Hydroxyphenyl)sydnones

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3-(3′-,4′-Hydroxyphenyl)sydnones were prepared by dealkylation of 3-(3′-,4′-alkoxyphenyl)sydnones with concentrated sulfuric acid at room temperature in a range of 59 to 86% yield.

INTRODUCTION

Sydnone compounds are typical mesoionic compounds. The nature of mesoionic character and biological activities have drawn much attention. Some sydnone compounds are well known to show pharmacological activities.[1-5]

In this paper we present a general and efficient method for synthesizing 3-(3′-,4′-hydroxyphenyl)sydnones from corresponding 3-(3′-,4′-alkoxyphenyl)sydnones. Biological tests of the title compounds were also examined.

RESULTS AND DISCUSSION

In general, nitrosation of amino group is one of the key steps in sydnone preparation.[6] However, in the case of hydroxyphenylsydnones such reactions are restricted because the phenolic compounds readily undergo nitrosation at the hydroxyphenyl group. In contrast, 3-(3′-,4′-alkoxyphenyl)-sydnones can be synthesized from corresponding alkoxylaniline so that the desired 3-(3′-,4′-hydroxyphenyl)-sydnones might be prepared from dealkylation of corresponding 3-(3′-,4′-alkoxyphenyl)sydnones.

Ordinarily, alkoxybenzenes can be cleavaged by acid-catalyst into their corresponding hydroxybenzenes. The rate of hydrolysis can even be accelerated in the presence of nucleophiles such as Br^- or I^-.[7,8] However, the sydnone ring is very labile under such reaction conditions. Thus, dealkylation of 3-(3′-,4′-alkoxyphenyl)sydnones was performed in concentrated sulfuric acid at room temperature and the results are shown in Table 1.

Table 1 indicates that while the R group is methyl, the hydrolysis reaction was not proceeded at all. In contrast, benzylic substituent received the best yield. Accordingly, we suggest this dealkylation reaction may be progressed in an S_N1 mechanism so that the yield of reaction follows the direction of the stability of carbonium ions:

$$\overset{\oplus}{\text{Ph}}\text{CH}_2\text{-} > \text{CH}_3\overset{\oplus}{\text{C}}\text{HCH}_3 > \text{CH}_3\text{CH}_2\text{CH}_2\overset{\oplus}{\text{C}}\text{H}_2\text{-}$$

$$> \text{CH}_3\overset{\oplus}{\text{C}}\text{H}_2\text{-} >> \overset{\oplus}{\text{C}}\text{H}_3\text{-}$$

In the case of ortho substituted phenylsydnone, the above hydrolysis reaction could not be proceeded. Thus, 3-(2′-ethoxy-3′-nitrophenyl)sydnone was recovered from concentrated sulfuric acid. Surprisingly, under similar reaction conditions the 3-(2′-ethoxyphenyl)sydnone was obtained as sodium [3-(3′-sydnonyl)-4-ethoxy]benzenesulfonate in a yield of 40%. These results might suggest that the steric effect prevents the protonation reaction from occurring at the alkoxy group. Thus, the ethoxyl group serves as an activator to accelerate a sulfonation reaction on the benzene ring.

In addition, 3-(4′-hydroxyphenyl)sydnones (**Ia**) can also be obtained by dealkylation and deacetylation of the corresponding 4-acetyl-3-(4′-ethoxyphenyl)sydnones in a cold concentration of sulfuric acid.

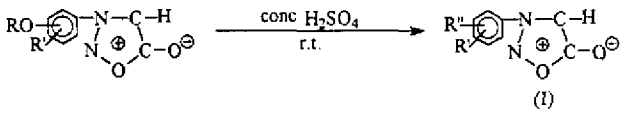
According to the biological tests, 3-(3′-hydroxyphenyl)sydnone shows some collagen induced inhibition platelet aggregation activity.

EXPERIMENTAL SECTION

General

Melting points were taken on a Yanaco MP-J3 apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Brucker AC-250 instrument. Mass spectra were obtained on a JEOL JMS-D100 instrument, and IR spectra were recorded on a Hitachi 270-30 spectrometer with sample as KBr discs. Microanalysis was performed on a rapid ana-

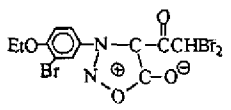
Table 1. The Yields of 3-(Hydroxyphenyl)sydnones(I) from 3-(Alkoxyphenyl)sydnones



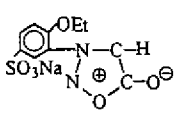
(I)

R-	R'-	R''-	yields (%)
4'-Et	H-	4'-OH	61
4'-n-Bu	H-	4'-OH	76
4'-i-Pr	H-	4'-OH	80
4'-$PhCH_2$	H-	4'-OH	86
4'-Me	H-	4'-MeO	no reaction
4'-Me	2'-MeO-	4'-MeO	no reaction
4'-Et	3'-Br-	4'-OH	72*[1]
4'-Et	2'-NO_2-	4'-OH	68
3'-Et	H-	3'-OH	59
3'-Et	4'-NO_2-	3'-OH	61
2'-Et	H-		40*[2]
2'-Et	3'-NO_2-	2'-EtO	no reaction

*[1] *from*



*[2] *from*



lyzer (Heraeus CHNO).

Raw Materials

3-(4'-ethoxyphenyl)sydnone,[9] 3-(2'-ethoxyphenyl)-sydnone,[10] 3-(4'-methoxyphenyl)sydnone,[10] 3-(2',4'-dimethoxyphenyl)sydnone,[11] 3-(2'-ethoxy-3'-nitrophenyl)-sydnone,[12] 3-(3'-ethoxy-4'-nitrophenyl)sydnone,[12] 4-dibromoacetyl-3-(4'-ethoxy-3'-bromophenyl)sydnone,[13] and 4-acetyl-3-(4'-ethoxyphenyl)sydnone[14] were prepared according to methods in the literature.

3-(4'-n-butoxyphenyl)sydnone

3-(Alkoxyphenyl)sydnone was prepared by a method similar to that by which 3-phenylsydnone is prepared from alkoxyanilines.[15] In a 500 mL round bottomed flask were placed 24 g (253 mmol) chloroacetic acid and 100 mL water. The acid was neutralized by careful, slow addition of 10% aqueous sodium hydroxide solution with shaking and cooling. To the solution of sodium chloroacetate was added 41.3 g (250 mmol) 4-n-butoxyaniline, and they were refluxed for 2 h. After cooling, the reaction mixture was neutralized with sodium hydroxide and extracted with toluene to remove unreacted 4-n-butoxyaniline. Upon addition of hydrochloric acid to the reaction solution, 38 g (68%) of 4-n-butoxyphenylglycine was separated out. Then, nitrosation with 12 g (174 mmol) sodium nitrate gave 25 g (58%) nitroso-compound. Cyclodehydration of this nitroso-compound by 75 mL acetic anhydride at room temperature for 2 days, gave a crude 3-(4'-n-butoxyphenyl)sydnone. Recrystallization from 95% ethanol gave 16 g (69%) of pure 3-(4'-n-butoxyphenyl)sydnone as pale brown crystals with mp 87-89 °C. IR (KBr); 3120 cm^{-1} (ν_{C-H} of sydnone ring), 1732 cm^{-1} ($\nu_{C=O}$ of sydnone ring). MS (70 eV); *m/z* 234 (M^+, 6.4%), 240 (M^+-NO, 94%), 176 (M^+-NO-CO, 100%). ^1H NMR (Acetone-d_6); δ = 7.85 (d, J = 9.2 Hz, 2H, 3-aryl-C-2), 7.20 (d, J = 9.2 Hz, 2H, 3-aryl-C-3), 7.20 (s, 1H, C-H of sydnone ring), 4.14 (t, J = 6.2 Hz, 2H, O-$\underline{CH_2}CH_2CH_2CH_3$), 1.95-1.34 (m, 4H, O-$CH_2\underline{CH_2}\underline{CH_2}CH_3$), 0.98 (t, J = 7.3 Hz, 3H, O-$CH_2CH_2CH_2\underline{CH_3}$). Anal. calcd for $C_{12}H_{14}N_2O_3$: C, 61.53; H, 6.02; N, 11.96%. Found: C, 61.60; H, 6.30; N, 11.96%.

3-(4'-Isopropoxyphenyl)sydnone

3-(4'-Isopropoxyphenyl)sydnone was prepared from 4-isopropoxyaniline in a manner similar to that mentioned above. Recrystallization from 95% ethanol afforded 3-(4'-Isopropoxyphenyl)sydnone as brown crystals with mp 82-83 °C. IR (KBr); 3130 cm^{-1} (ν_{C-H} of sydnone ring), 1730 cm^{-1} ($\nu_{C=O}$ of sydnone ring). MS (70 eV); *m/z* 220 (M^+, 2%), 190 (M^+-NO, 20%), 162 (M^+-NO-CO, 69%) 120 (M^+-NO-CO-C_3H_6, 100%). ^1H NMR (Acetone-d_6); δ = 7.84 (d, J = 9.1 Hz, 2H, 3-aryl-C-2), 7.18 (d, J = 9.1 Hz, 2H, 3-aryl-C-3), 7.20 (s, 1H, C-H of sydnone ring), 4.79 (septet, J = 6.0 Hz, 1H, $(CH_3)_2CH$-), 1.36 (d, J = 6.0 Hz, 6H, $(CH_3)_2CH$-). Anal. calcd for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72%. Found: C, 60.02; H, 5.45; N, 12.61%.

3-(4'-benzyloxyphenyl)sydnone

Similarily 3-(4'-benzyloxyphenyl)sydnone was obtained from 4-benzyloxyaniline. Recrystallization from 95% ethanol afforded 3-(4'-benzyloxyphenyl)sydnone as pale yellow needles with mp 158-159 °C. IR (KBr); 3140 cm^{-1} (ν_{C-H} of sydnone ring), 1735 cm^{-1} ($\nu_{C=O}$ of sydnone ring). MS (70 eV); *m/z* 268 (M^+, 1%), 238 (M^+-NO, 9.4%), 210 (M^+-NO-CO, 44%) 120 (M^+-NO-CO-C_7H_6, 6%), 91 (tropylium ion, 100%). ^1H NMR (Acetone-d_6); δ = 7.91 (d, J = 9.1 Hz, 2H, 3-aryl-C-2), 7.46-7.28 (m, 5H, phenyl), 7.33 (d, J = 9.1 Hz, 2H, 3-aryl-C-3), 7.32 (s, 1H, C-H of sydnone ring), 5.28 (s, 2H, CH_2). Anal. calcd for $C_{15}H_{12}N_2O_3$: C, 67.16; H, 4.51; N, 10.44%. Found: C, 67.26; H, 4.38; N, 10.45%.

3-(3'-Ethoxyphenyl)sydnone

3-(3'-Ethoxyphenyl)sydnone was prepared from 3-ethoxyaniline as mentioned above. After recrystallization from 95% ethanol, 3-(3'-ethoxyphenyl)sydnone was ob-

tained as light brown needle crystals with mp 111-112 °C. IR (KBr); 3150 cm^{-1} (ν_{C-H} of sydnone ring), 1780 cm^{-1} ($\nu_{C=O}$ of sydnone ring). MS (70 eV); *m/z* 206 (M^+, 11%), 176 (M^+-NO, 20%), 148 (M^+-NO-CO, 100%). ^1H NMR (DMSO-d_6); δ = 7.77 (s, 1H, C-H of sydnone ring), 7.69-7.22 (m, 4H, C-H of phenyl ring), 4.15 (q, *J* = 7.0 Hz, 2H, $-CH_2-$), 1.36 (t, *J* = 7.0 Hz, 3H, $-CH_3$). Anal. calcd for $C_{10}H_{10}N_2O_3$: C, 58.24; H, 4.89; N, 13.59%. Found: C, 58.15; H, 4.85; N, 13.59%.

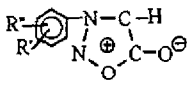
Dealkylation of 3-(alkoxyphenyl)sydnone

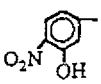
A typical procedure for the preparation of 3-(hydroxyphenyl)sydnone from the corresponding 3-(alkoxyphenyl)sydnone was as follows: to an ice-cooled concentrated sulfuric acid (20 mL), 2.0 g (9.7 mmol) of 3-(4′-ethoxyphenyl)sydnone was added step by step with stirring. After stirring with cooling 1 h, the reaction mixture was allowed to stand at room temperature for 24 h. Then, the reaction mixture was poured into crushed ice. The crude product was filtered and recrystallized from 95% ethanol to afford 1.1 g (61%) of 3-(4′-hydroxyphenyl)sydnone (**Ia**) as light brown crystals with mp. 255-257 °C. The physical properties are shown in Table 2.

Following treatment of 3-(4′-n-butoxyphenyl)-sydnone, 3-(4′-isopropoxy)sydnone and 3-(4′-benzyloxyphenyl)sydnone in the same way as described in the above procedure, **Ia** was obtained in 76%, 80%, and 86% yields respectively. The mp and IR spectra are in line with the authentic sample.

While 3-(3′-ethoxyphenyl)sydnone, 3-(4′-ethoxy-3′-nitrophenyl)sydnone, 3-(3′-ethoxy-4-nitrophenyl)sydnone, 4-acetyl-3-(4′-ethoxyphenyl)sydnone, and 4-dibromoacetyl-3-(4′-ethoxy-3′-bromophenyl)sydnone were treated by the above procedure, corresponding 3-(3′-,4′-hydroxyphenyl)sydnone was obtained in a yield of 95%, 61%, 68%, 62% and 72%, respectively. Its physical properties are shown in Table 2.

Table 2. The Physical Properties of 3-(Hydroxyphenyl)sydnones(I)



Compound No.	R″ / R′	mp (°C)	crystal type	IR (KBr) cm^{-1}	MS (70 eV) *m/z*	NMR (DMSO/$CDCl_3$)	Elementary Analysis Found (Calcd)
Ia		255-257	light brown fluffy crystals	3400-2800 (ν_{OH}) 1750 ($\nu_{C=O}$)	178 (M^+, 16) 148 (M^+-NO, 24) 120 (M^+-NO-CO, 100)	7.62 [s, 1H, C(4)-H] 7.81-6.96 (m, 4H, phenyl ring) 10.50 (s, 1H, -OH)	C: 53.98 (53.93); H: 3.36 (3.37); N: 15.75 (15.73).
Ib		208-209	light brown granular crystals	3400-3000 (ν_{OH}) 1750 ($\nu_{C=O}$)	178 (M^+, 18) 148 (M^+-NO, 25) 120 (M^+-NO-CO, 100)	7.72 [s, 1H, C(4)-H] 7.58-7.06 (m, 4H, phenyl ring) 10.38 (s, 1H, -OH)	C: 53.81 (53.93); H: 3.36 (3.37); N: 15.75 (15.73).
Ic		168-170	brown needles	3268 (ν_{OH}) 1767 ($\nu_{C=O}$)	223 (M^+, 4) 193 (M^+-NO, 13) 165 (M^+-NO-CO, 100)	7.50 [s, 1H, C(4)-H] 8.68-7.45 (m, 3H, phenyl ring)	C: 42.92 (43.06); H: 2.32 (2.26); N: 18.77 (18.83).
Id		169-170.5	brown needles	3262 (ν_{OH}) 1764 ($\nu_{C=O}$)	223 (M^+, 6) 193 (M^+-NO, 15) 165 (M^+-NO-CO, 100)	7.45 [s, 1H, C(4)-H] 8.68-7.50 (m, 3H, phenyl ring)	C: 42.91 (43.06); H: 2.35 (2.26); N: 18.76 (18.83).
Ie		184-186	light brown fluffy crystals	3400-2900 (ν_{OH}) 1719 ($\nu_{C=O}$)	258 (M^+, 5) 256 (M^+, 5) 226 (M^+-NO, 18) 198 (M^+-NO-CO, 100)	7.27 [s, 1H, C(4)-H] 8.14-7.34 (m, 3H, phenyl ring) 10.10 (s, 1H, -OH)	C: 37.38 (37.38); H: 2.05 (1.96); N: 10.90 (10.90).

Sodium[3-(3′-sydnonyl)-4-ethoxyl]benzenesulfonate

To an ice-cooled concentrated sulfuric acid (15 mL), 1 g (4.8 mmol) of 3-(2′-ethoxyphenyl)sydnone was added gradually with stirring. After standing 2 days at room temperature, the reaction mixture was poured into cold water. Sodium hydroxide solution was then added to get a white precipitation. After recrystallization from ethanol, 0.6 g (40% yield) of sodium[3-(3′-sydnonyl)-4-ethoxyl]benzenesulfonate was obtained as white plates, mp 275-277 °C. IR (KBr); 3100 cm^{-1} (ν_{C-H}), 1750 cm^{-1} ($\nu_{C=O}$). ^1H NMR (DMSO-d_6); δ = 1.29 (t, J = 7.0 Hz, 3H, $-CH_3$), 4.20 (q, J = 7.0 Hz, 2H, $-OCH_2-$), 7.43 (s, 1H, C(4)-H), 7.88-7.30 (m, 3H, aryl-H). Anal. calcd for $C_{10}H_{11}N_2O_7NaS$: C, 36.81; H, 3.37; N, 8.59%. Found: C, 36.75; H, 3.38; N, 8.60%.

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Key Words

3-(3′-,4′-Hydroxyphenyl)sydnone; 3-(3′-,4′-alkoxyphenyl)sydnone; Dealkylation.

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