Studies on *N*-Halo Alicyclic Aryl Sulphonamides: *N*-Chloro-*d*-Camphor-β-sulphonyl Aryl and Alkyl Amides, Their Reactivity and Rearrangement in Protic and Aprotic Media

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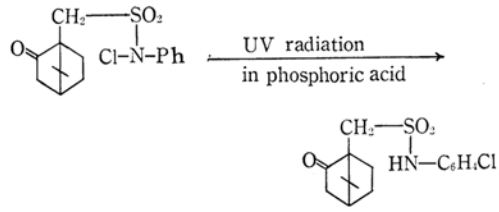
In cross-over experiments *N*-chlorosulphonamides chlorinated anisole.

Orton rearrangement of *N*-chloroacylanilides to *C*-chloroacylanilides has been reported applicable to *N*-chloroarylsulphonyl phenylamides in protic and aprotic solvents,[1,2] although in certain cases the *N*-chlorine becomes more acidic and labile and does not chlorinate the sulphonamide molecule.[3] In this communication the behaviour of *N*-chlorine attached to an alicyclic sulphonyl aryl and alkyl-amides will be reported.

N-Chloro-*d*-camphor-β-sulphonyl phenyl, (*o*-, *m*-, and *p*-)tolyl, (*o*-, *m*- and *p*-)chlorophenylamides and *N*-chloro-*d*-camphor-β-sulphonyl methyl, ethyl and *n*-butyl amides are fairly stable and can be kept in dry non-polar solvents for a week at room temperature.

N-Chloroacetanilide is known to rearrange to *o*- and *p*-chloroacetanilide in dry state by the action of heat,[4] light,[5,6] also in aqueous[7,8] and non-aqueous solvents[9,10] catalysed by UV radiation.[11] *N*-Chloro-*d*-camphor-β-sulphonanilides are fairly stable towards the action of heat and light in the dry state and are not transformed into *C*-chloro-sulphonamides. In protic solvents such as acidified ethyl alcohol, *N*-chlorosulphonanilides yield nuclear chlorinated products (Table 2). Methyl and chloro substituted phenyl sulphonamides also yield nuclear chlorinated products. In all the transformations in different media, whether protic or aprotic, only one chlorine substituted sulphonanilide has been recovered. Best yield at the products without side reactions were obtained in glacial acetic acid. In case of a (+I), CH_3-substituted phenyl sulphonamide, the substitution of chlorine follows the usual orientation rule. An alicyclic system adjacent to the sulphonyl group which is susceptible to chlorine attack at the α-position has not been chlorinated and always the phenyl nucleus is attacked. The products isolated were purified by fractional crystallisation and analysed (Table 2). *N*-Methyl, ethyl and *n*-butyl derivatives of *N*-chloro-*d*-camphor-β-sulphonamides in acidified ethyl alcohol yield the parent sulphonamides. When air was bubbled through alcoholic solution of the *N*-chlorosulphonamides, chlorine gas escaped along with air. In "cross-over" experiments all these *N*-chloro derivatives gave *p*-chlorinated anisole.

N-Chloro-*d*-camphor-β-sulphonyl phenylamide, when exposed to UV radiation in phosphoric acid (under the usual conditions of Hofmann-Löffler reaction)[12] did not form cyclic compound incorporating $-SO_2-$ group in the ring and *d*-camphor-β-sulphonyl-*p*-chlorophenylamide was obtained. Under similar conditions *N*-methyl and *N*-ethyl-*N*-chloro-*d*-camphor-β-sulphonamides yielded the parent sulphonamides:



N-Chloro-*N*-*n*-butyl-*d*-camphor-β-sulphonamide underwent Hofmann-Löffler reaction when exposed to UV radiation and yielded *d*-camphor-β-sulphonyl pyrrolidinoamide.

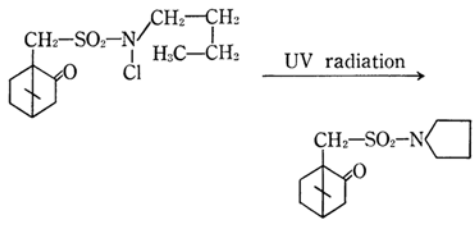


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TABLE 1

Compound		Mp °C	% Nitrogen Found	% Nitrogen Calcd
d-Camphor-β-sulphonyl methyamide,	$C_{11}H_{19}NO_3S$	54	5.52	5.71
d-Camphor-β-sulphonyl ethylamide,	$C_{12}H_{21}NO_3S$	78	5.35	5.41
d-Camphor-β-sulphonyl *n*-butylamide,	$C_{14}H_{25}NO_3S$	66	4.78	4.87

TABLE 2. *N*-CHLORO DERIVATIVES AND THEIR REARRANGED PRODUCTS IN ETHYL ALCOHOL (HCl)

	Compound: *N*-Chloro-*d*-camphor-β-sulphonyl-	Mp °C	% Active chlorine Found	% Active chlorine Calcd	Rearranged product: *d*-Camphor-β-sulphonyl-	Mp °C	Analysis Observed	Analysis Calcd
1	Phenylamide $C_{16}H_{20}ClNO_3S$	78	11.02	11.97	4-Chlorophenylamide	141	S 9.39 N 3.98	9.37 4.10
2	*o*-Tolylamide $C_{17}H_{22}ClNO_3S$	95	9.64	10.33	4-Chloro-2-methyl phenylamide	115	S 9.04 N 3.90	9.00 3.94
3	*m*-Tolylamide $C_{17}H_{22}ClNO_3S$	96	9.73	10.33	2-Chloro-5-methyl phenylamide	126	S 9.10 N 3.92	9.00 3.94
4	*p*-Tolylamide $C_{17}H_{22}ClNO_3S$	105	9.88	10.33	2-Chloro-4-methyl phenylamide	105	S 9.03 N 3.90	9.00 3.94
5	*o*-Chlorophenyl-amide $C_{16}H_{19}Cl_2NO_3S$	66	9.25	9.50	2, 4-Dichloro phenylamide	135	S 8.99 N 19.52	8.88 19.58
6	*m*-Chlorophenyl amide $C_{16}H_{19}Cl_2NO_3S$	87	9.02	9.50	2, 5-Dichloro phenylamide	129	S 8.94 Cl 19.39	8.88 19.58
7	*p*-Chlorophenyl amide $C_{16}H_{19}Cl_2NO_3S$	153	9.12	9.50	2, 4-Dichloro phenylamide	134	S 8.89 Cl 19.46	8.88 19.58
8	Methylamide mp 54°C $C_{11}H_{18}ClNO_3S$	42	12.25	12.70	Methylamide	54	The mixed melting points of these compounds did not show any depression with the authentic ones.	
9	Ethylamide mp 78°C $C_{12}H_{20}ClNO_3S$	64	12.01	12.12	Ethylamide	78		
10	*n*-Butylamide mp 66°C $C_{14}H_{24}ClNO_3S$	49	9.98	11.01	*n*-Butylamide	66		

No *N*-bromosulphonanilide has yet been reported. All attempts to prepare *N*-bromosulphonanilide resulted *C*-bromo products. It appears that *N*-bromosulphonanilides are highly reactive and rearrange even at 0°C to form nuclear brominated products. *N*-Bromo derivative of *d*-camphor-β-sulphonyl ethylamide possesses a reactivity similar to the *N*-chloro derivative and does not form any cyclic compound even when subjected to free radical reaction.[13]

Experimental

d-Camphor-β-sulphonyl, *N*-Aryl and Alkylamides; $C_{10}H_{15}OSO_2NHR$. *d*-Camphor-β-sulphonyl phenyl, (*o*-, *m*- and *p*-)tolyl and (*o*-, *m*- and *p*-)chlorophenylamides were prepared by condensation of *d*-camphor-β-sulphonyl chloride with aniline, (*o*-, *m*- and *p*-)toluidines and (*o*-, *m*- and *p*-)chloroanilines according to the method described by Singh *et al.*[14,15] *N*-Alkyl sulphonamides were prepared by condensation of *d*-camphor-β-sulphonyl chloride with methyl, ethyl and butylamines in 1 : 2 molar proportions. The products obtained gave the following analysis (Table 1).

***N*-Chloro Derivatives of Sulphonamides, $C_{10}H_{15}\overset{Cl}{\underset{|}{N}}OSO_2R$.** *N*-Chloro derivatives of *d*-camphor-β-sulphonanilides were prepared with an excess (*ca.* 2 mol) of hypochlorous acid in chloroform solution.[16] *N*-Chloro derivatives of *d*-camphor-β-sulphonyl alkylamides were prepared by chlorinating a clear alkaline solution (1% KOH) of the sulphonamide at 0°C. The

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precipitate obtained was crystallised from chloroform and petroleum ether mixture (1 : 1). The active chlorine was determined iodometrically in alcoholic medium acidified with acetic acid. The observed values together with the melting points are recorded in Table 2. All the *N*-chloro compounds are fairly stable in the absence of moistrue. They are highly soluble in benzene, chloroform, carbon tetrachloride and acetone, fairly so in ethyl alcohol, methyl alcohol, acetic acid and acetic anhydride and sparingly soluble in ether and petroleum ether.

Rearrangement *In Ethyl Alcohol.* Two grams of *N*-chloro derivative was taken in 75 m*l* ethyl alcohol with 3—4 drops of hydrochloric acid. The rearrangement was complete within 48 hr, yield 40—45%. At 75—80°C the rearrangement completed in about 4 hr, yield 20—30%. A purified product after preliminary investigation was analysed (S and N), and was hydrolysed by concentrated hydrochloric acid in a sealed tube at 135—140°C in a bomb furnace. The product obtained was made alkaline, the liberated amine was extracted with ether and was identified by usual qualitative procedure. The acid part isolated as its sodium salt was converted in the chloride (mp 67°C). The products of the rearrangement are recorded in Table 2.

In Glacial Acetic Acid (AnalaR). *N*-Chloro-*d*-camphor-β-sulphonylanilides yielded same products as in ethyl alcohol (yield, 50—55% at room temperature). The rearrangement was effective at 100°C within 12 hr, yield 25—30%. *N*-Chloro-*d*-camphor-β-sulphonylalkylamides showed chlorine activity for more than two months. When refluxed, they yielded parent sulphonamides after 30 hr. Fractional distillation of the liquid portion yielded some monochloroacetic acid.

In Trichloroacetic Acid and Chlorobenzene (Aprotic). *N*-Chloro derivative (2 g) was taken in 50 m*l* of 0.6 N solution of trichloroacetic acid in dry chlorobenzene. It was refluxed on water bath and it took about 20 hr to complete the rearrangement. Yield 30—35%.

In Acetic Anhydride and Sulphuric Acid. *N*-Chloro-compound (2 g) was taken in pure dry acetic anhydride (19 m*l*) and sulphuric acid (1 m*l*) and kept at room temperature. The reaction mixture did not show any test for active chlorine after three days. Same products were isolated as mentioned for alcohol medium in Table 2. Yield 30%.

Reaction with Anisole. *N* - Chloro - *d* - camphor- β - sulphonyl phenylamide 5 g in 50 m*l* of ether was refluxed with 2 m*l* of anisole for 2 hr. The liquid portion was hydrolysed with 48% hydrobromic acid; the fraction obtained at 217°C was benzoylated in the cold and the derivative obtained melted at 93°C; *p*-chlorophenyl benzoate $ClC_6H_4OBz_3(p)$ melts at 93°C. *d*-Camphor-β-sulphonyl phenylamide (50%) and *d*-camphor-β-sulphonyl-*p*-chlorophenylamide (10—15%) were also isolated.

Bromo Derivatives. *N*-Bromo-derivatives of *d*-camphor-β-sulphonyl ethylamide and *p*-toluenesulphonyl methylamide were precipitated by treating the potassium sulphonamide solution with bromine water 0°C, washed with cold water and crystallised from chloroform and ether mixture (1 : 1).

N-Bromo-*p*-toluene sulfphonyl methylamide melted at 75°C (active bromine. Fround: 29.96%. Calcd for $C_8H_{11}BrNO_2S$: 30.84%).

N-Bromo-*d*-camphor-β-sulphonyl ethylamide melted at 107°C (active bromine; Found: 22.86%. Calcd for $C_{12}H_{20}BrNO_3S$: 23.64%).

N-Bromo derivatives of alkyl sulphonamides were treated with acidified alcohol (HCl), glacial acetic acid and acetic anhydride+sulphuric acid, when only the parent sulphonamides were obtained from these solution.

Attempts to prepare *N*-bromo derivatives of sulphonanilides by the above method or by shaking a chloroform solution of the sulphonanilide with hypobromous acid in the cold (0°C) lead to *C*-brominated sulphonanilide.

Free Radical Reaction. *N* - Chloro - *d* - camphor - β - sulphonyl-*n*-butylamide (0.04 mol) in 30 m*l* of 90% phosphoric acid was irradiated in a quartz flask with UV light. The reaction was complete in about six hours. The solution was made alkaline with potassium hydroxide and left for half an hour. The insoluble portion was crystallised from alcohol, mp 85°C. Mixed melting point with *d*-camphor-β-sulphonyl pyrrolidinoamide did not give a depression. This pyrrolidinoamide was prepared by condensation of *d*-camphor-β-sulphonyl chloride and pyrrolidine in dry state, and crystallised from 50% alcohol, mp 87°C (Found: S, 10.68; N, 4.49%. Calcd for $C_{14}H_{23}NO_3S$: S, 10.63; N, 4.91%)).

Similar attampts of cyclisation of *N*-chloro-*N*-methyl and *N*-ethyl-*d*-camphor-β-sulphonamides yielded the parent sulphonamides.

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