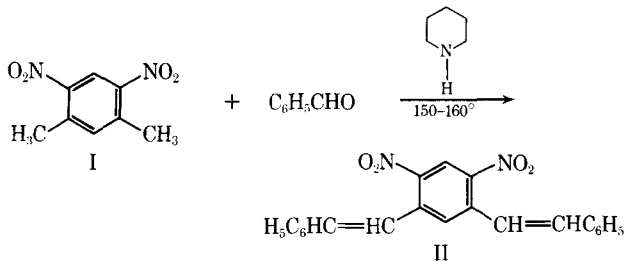
Preparation and Biological Activity of Substituted 1,3-Distyryl-4,6-dinitrobenzenes

Keyphrases □ 1,3-Distyryl-4,6-dinitrobenzenes—synthesis □ Cytotoxic, antimicrobial activity—1,3-distyryl-4,6-dinitrobenzenes

Sir:

In 1931, it was shown by Ruggil *et al.* (1) that one molecule of 4,6-dinitro-1,3-xylene (I) condensed with two molecules of benzaldehyde to give 1,3-distyryl-4,6-dinitrobenzene (II) (Scheme I). As an extension of this approach, we studied the condensation of a variety of



Scheme I

substituted aromatic aldehydes with 4,6-dinitro-1,3-xylene. The condensations were conducted by heating under reflux a solution of the appropriate aromatic aldehyde (0.2 mole), Compound I (0.1 mole), and piperidine (10 ml.) for 20–90 min. at 150–160°. The reaction mixture was diluted with a large volume of benzene or 75% ethanol, and the crystalline products (III) (Table I) were isolated by filtration and drying. The yields of 1,3-distyryl-4,6-dinitrobenzenes ranged between 40 and 60% and furnished satisfactory elemental (C, H, and N) analyses.

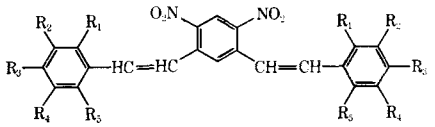
These compounds were examined for their antimicrobial activities (2). In these tests, the microorganisms were grown in agar media. The compounds to be tested were dissolved in acetone at concentrations of 1 mg./ml. and applied to paper disks of 13-mm. diameter. After incubation, the diameters of the zones of growth inhibition were measured. The compounds which showed significant antimicrobial activity are given in Table I.

Some of these compounds were also subjected to L-1210 *in vitro* assay for cytotoxic activity (3). In these screening experiments, the samples were weighed (about 5–10 mg.) into glass homogenizers (12-ml. size) sterilized with 0.1 ml. of 70% ethanol and about 0.1 ml. dimethylsulfoxide (DMSO) was added to help solubilize. The sample was ground with sterile water to make a suspension containing L-1210 leukemic cells. The tubes were stoppered and incubated at 37° for 3 days; then cell counts were made on each tube by a Coulter counter. The percent inhibition and the ID_{50} values were calculated. Values of 1 or less for ID_{50} were considered potentially

Table II—Cytotoxic Activity of Compounds III*f* and III*g*[a]

Compound		ID_{50}
III*f*	R_2 = OCH_3, R_3 = OH	0.188
III*g*	R_2 = OH, R_3 = OCH_3	0.648

[a] See Table I for Structure III.



III

Table I—Chemical and Biological Activity Data of Compounds III[a]

Test Organism	Compounds				
	III*a* R_1 = OH, R_5 = NO_2	III*b* R_1 = OCH_3	III*c* R_2 = NO_2	III*d* R_1 = OC_2H_5, R_2 = OCH_3	III*e* R_1 = Cl
	Zones of Inhibition, mm.				
Bacillus subtilis	29	25	25	17	29
Bacillus cereus	19	18	17		18
Staphylococcus aureus	25	22	23	17	25
Mycobacterium phlei	25	25	25	16	24
Bacillus subtilis (synthetic agar)	42	40	37	30	34
Escherichia coli (synthetic agar)	25	25	24		25
Propionibacterium thonii	37	32	33	16	30
Trigonopsis variabilis	21	20	21	17	22
Glomerella cingulata			20		
Chlorella vulgaris	30	22	25		20
Melting point	207–208°	218–219°	300°	161–162°	228–229°

[a] All R groups are H unless otherwise specified.

active. Only the compounds given in Table II showed significant cytotoxic activity.

(1) P. Ruggil, A. Zimmerman, and R. Thouvay, *Helv. Chim. Acta*, **24**, 1250(1931).
(2) L. J. Hanka, *Abstracts, Int. Congr. Chemother., Proc., 5th*, **B 912**, 351(1967).
(3) H. H. Buskirk, *Proc. Tissue Culture Ass.*, **20**, 23(1969).

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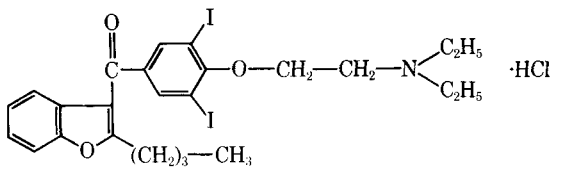
Observations on the Micelle Formation of 2-Butyl-3-benzofuranyl-4-[2-(diethylamino)ethoxy]-3,5-diiodophenyl Ketone Hydrochloride (SK&F 33134-A) by NMR Spectroscopy

Keyphrases □ 2-Butyl-3-benzofuranyl-4-[2-(diethylamino)ethoxy]-3,5-diiodophenyl ketone hydrochloride (SK&F 33134-A)—micelle formation □ Critical micelle concentration—SK&F 33134-A □ NMR spectroscopy—micelle formation determination

Sir:

In recent years, several papers (1–3) have dealt with the use of high-resolution NMR for the determination of CMC. In our laboratories, we have used NMR to show the existence of micelles in a 5% aqueous solution of SK&F 33134-A(I).[1] Micelle formation has not previously been reported for this system.



I

All measurements were carried out with a Jealco C60H NMR spectrometer equipped with a variable temperature probe. Spectra were recorded at temperatures ranging from 25 to 95°. Figure 1 illustrates the NMR spectrum for a 5% solution of SK&F 33134-A in D_2O at 25°. There are no sharp resonance lines as one would expect under normal conditions. Instead, there is a large broadening effect of all resonance lines. We attribute this broadening to dipolar interaction in the micellar structure where molecular motion is se-

[1] Marketed as Cordarone by Labaz Laboratories in several European countries.

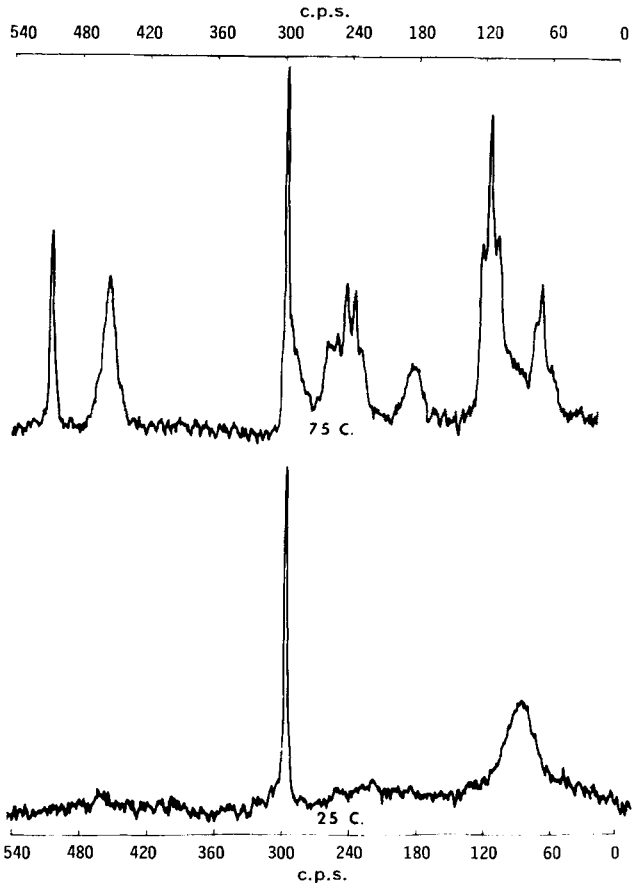


Figure 1—*NMR spectra for a 5% solution of SK&F 33134-A in D_2O at 25 and 75°, respectively.*

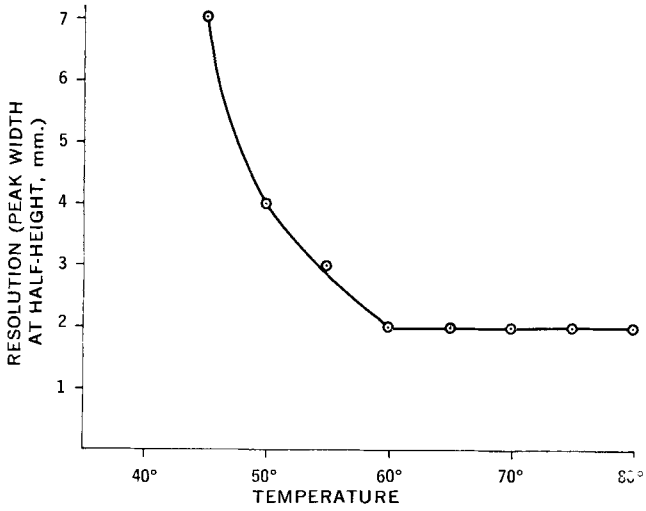


Figure 2—*A plot showing the effect of temperature on the resolution (peak width at half-height) at 504 c.p.s. for a 5% solution of SK&F 33134-A in D_2O.*