THE PREPARATION AND MEASUREMENT OF THE SURFACE ACTIVITY OF A SERIES OF 4-ALKYL-1,1'-SPIROBIPIPERIDINIUM BROMIDES

BY J. THOMAS AND D. CLOUGH

From the Department of Pharmacy, University of Manchester

The preparation of a series of 4-alkyl-1,1'-spirobipiperidinium bromides is described. The measurement of the surface tension of aqueous solutions of these quaternary salts is reported. Within the concentration ranges studied none of the spiran quaternary compounds form micelles. The relationship between micelle formation of quaternary ammonium ions and antibacterial activity is discussed.

THE general problems associated with structure-activity interpretations of the antibacterial actions of aqueous solutions of quaternary ammonium compounds can be divided into two main groups. The first is the factors involved in transferring a quaternary ammonium ion from the environment of the water molecules of the solution to a "receptor" area on the bacterial cell. The second is the factors involved in the mechanism by which death of the cell is brought about once the quaternary ammonium ions are adsorbed onto the "receptors". For an understanding of the first problem the nature of aqueous solutions of quaternary ammonium ions and the nature of, and factors involved in, the adsorption of these compounds onto an anionic type "receptor" require to be studied.

Quaternary ammonium compounds are not typical electrolytes in that the ions are not randomly distributed among the water molecules but are concentrated at interfaces and also tend to become associated in micelles. The formation of micelles is a limiting factor on the activity of quaternary ammonium salts because it limits the effective concentration of monomolecular form available for adsorption onto the bacterial "receptors" (Cella and others, 1952). The surface activity of quaternary ammonium ions is a useful property in their antibacterial actions in that higher concentrations of ions are present in the region of the bacterial "receptors" than in the bulk of the solution although it has been shown that surface activity *per se* is not necessarily accompanied by activity (Stacey and Webb, 1947). It is clear that the relationship between chemical structure and micelle formation of quaternary ammonium compounds in aqueous solution is an important part of the overall structure-activity relationships of the antibacterial action of these ions.

If micelle formation could be prevented or reduced, such bactericidal activity in an homologous series would move further along the series. Hartley (1941) showed that the critical micelle concentration of dialkyl ethers of dihydric phenols was greater than the critical micelle concentration of the monoalkyl compound containing the same number of carbon atoms. The bactericidal activities of dialkyldimethylammonium bromides have been compared with alkyltrimethylammonium bromides by Davis and others (1949). They found that in the twin-chain series beginning with dihexyldimethylammonium bromide and ending with

didodecyldimethylammonium bromide, bactericidal activity increased with increasing chain length, whereas with the single-chain compounds bactericidal activity reached a maximum when there were 18 carbon atoms in one chain. In the twin-chain series a total of 24 carbon atoms did not appear to be the limit. A limiting factor with the twin-chain compounds was their low solubility in water.

Thomas (1961 a, b) and Thomas and Starmer (1961) have used spiran quaternary compounds, in which the stereochemistry is "rigid" and known, to investigate the factors involved in the adsorption of quaternary ammonium ions onto anionic-type "receptors". Since the physico-chemical properties of quaternary ammonium salts in solution play an important part in their antibacterial action, then data on the surface activity, critical micelle concentration and solubility of the spirans are needed for structure-activity studies. Because of the control over the shape of the ions which the spiran system allows it may be possible to use this type of structure for studying the relationship between critical micelle concentration, solubility and stereochemistry.

A series of 4-alkyl-1,1'-spirobipiperidinium bromides (I) has now been prepared and the surface tensions of their aqueous solutions determined.

$$R\text{—}\underset{\text{I}}{\overset{+}{N}}\text{—}\quad Br^- \qquad R = alkyl$$
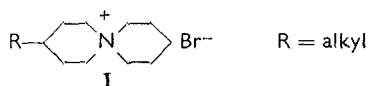
<div align="center">EXPERIMENTAL</div>

Chemical

All melting points were determined on a Kofler block and are corrected.

Diethyl tetrahydropyran-4,4-dicarboxylate was prepared essentially by the method of Gibson and Johnson (1930) by condensing di(2-chloro-ethyl) ether (214 g., 1·5 mole) with diethyl malonate (520 g., 3·25 mole) in super-dry ethanol (1 litre) with sodium (69 g., 3 mole) dissolved in it. The product was isolated by fractionation under reduced pressure. Two fractions were collected: diethyl malonate b.p. 89° at 14 mm., yield 192 g., and diethyl tetrahydropyran-4,4-dicarboxylate b.p. 136° at 14 mm., yield 193 g. (56 per cent based on the di(2-chloroethyl) ether).

Tetrahydropyran-4,4-dicarboxylic acid was prepared by hydrolysis of diethyl tetrahydropyran-4,4-dicarboxylate (115 g., 0·5 mole) with potassium hydroxide (62 g., 1·1 mole) dissolved in ethanol (500 ml., 95 per cent). The free acid was isolated by diluting the mixture with water, removing the ethanol by distillation, acidifying the solution with hydrochloric acid and extracting with ether in a continuous extractor for 8 hr. Yield 83 g. (95 per cent).

Tetrahydropyran-4-carboxylic acid was prepared from tetrahydropyran-4,4-dicarboxylic acid (100 g.) by decarboxylation at 180°. The product was distilled under reduced pressure b.p. 152–154° at 20 mm., and crystallised to a white solid. Yield 73 g. (95 per cent). Recrystallised from ethyl methyl ketone m.p. 88°. Found: C, 55·2; H, 7·7. $C_6H_9O_3$ requires C, 55·4; H, 7·7 per cent.

<div align="center">168</div>

Tetrahydropyran-4-carbonyl chloride. Tetrahydropyran-4-carboxylic acid (72 g.) was refluxed with thionyl chloride (120 ml.) for 1 hr. The product was isolated by distillation under reduced pressure b.p. 85° at 16 mm. Yield 80 g. (95 per cent).

Propyl tetrahydropyran-4-yl ketone. A Grignard reagent was prepared in the usual manner from propyl bromide (37 g., 0·3 mole) and transferred to a flanged flask (700 ml.) by connecting the two flasks with a glass tube and blowing the clear ethereal solution over with dry nitrogen. The flanged flask was fitted with a reflux condenser, dropping funnel and a mechanical stirrer. A Hinsberg-type stirrer made from nicrom wire

TABLE I

ALKYL TETRAHYDROPYRAN-4-YL KETONES AND THEIR 2,4-DINITROPHENYLHYDRAZONES

Alkyl radical	B.p. °C	Yield per cent	M.p. °C	2,4-Dinitrophenylhydrazones			
				Analysis (per cent)			
				Calculated		Found	
				C	H	C	H
Ethyl	100–102 at 11 mm.	60·2	148–149	52·17	5·59	51·9	5·5
Propyl	105–106 at 10 mm.	75·0	137–138	53·57	5·95	53·8	6·3
Butyl	124–125 at 15 mm.	69·0	98–99	54·85	6·28	54·9	6·4
Pentyl	130 at 10 mm.	66·0	84–85	56·04	6·59	56·3	6·8
Hexyl	146–148 at 10 mm.	53·0	61–62	57·15	6·88	56·9	7·0
Heptyl	162 at 15 mm.	56·0	61–62	58·16	7·14	57·9	7·2
Octyl	172–173 at 15 mm.	58·0	72–73	59·12	7·39	58·9	7·4
Nonyl	176–178 at 11 mm.	60·0	108	60·00	7·62	60·1	7·6
Decyl	192–193 at 13 mm.	56·0	74–75	60·82	7·83	60·5	8·1

fused to a glass rod was used to ensure efficient stirring and scraping of the vessel walls. Anhydrous cadmium chloride (28 g., 0·15 mole), which had previously been sifted through a No. 60 sieve and dried at 105° for 1 hr., was added with vigorous stirring and the mixture refluxed under nitrogen until a negative Gilman Grignard test was obtained. The ether was replaced by sodium-dried benzene (300 ml.), tetrahydropyran-4-carbonyl chloride (22·6 g., 1·6 mole) dissolved in sodium-dried benzene (100 ml.) was slowly introduced and the mixture refluxed for 30 min. with vigorous stirring to keep the insoluble material as a fine suspension in the benzene. The product was isolated by adding water followed by dilute hydrochloric acid and separating the benzene layer, which was washed in turn with water (50 ml.), sodium carbonate solution (50 ml. 10 per cent) and water (50 ml.) and then dried over anhydrous sodium sulphate. Distillation under reduced pressure gave 17·3 g. (75 per cent), b.p. 105–106° at 10 mm.

2,4-Dinitrophenylhydrazone, yellow plates from ethanol m.p. 137–138°. Found: C, 53·8; H, 6·3. $C_{15}H_{20}N_4O_5$ requires C, 53·6; H, 6·0 per cent. A list of n-alkyl tetrahydropyran-4-yl ketones and their 2,4-dinitrophenylhydrazone derivatives which were prepared is given in Table I.

4-*Butyltetrahydropyran.* Propyl tetrahydropyran-4-yl ketone (15 g.), potassium hydroxide (10 g.) and hydrazine hydrate (10 g.) were added to triethylene glycol (80 ml.) and the mixture heated on a steam-bath for 1 hr. A thermometer was then placed in the reaction mixture and the condenser set for distillation. The temperature of the mixture was raised to 190° and the distillate collected. The mixture was then maintained under reflux for 3 hr. and then allowed to cool. The previous distillate was added with water (100 ml.) and the mixture extracted with ether (3 × 50 ml.). The ethereal solution was dried over anhydrous

TABLE II

4-ALKYLTETRAHYDROPYRANS

Compound	Mol. formula	B.p. °C	Yield per cent
4-Propyltetrahydropyran	$C_8H_{16}O$	55–56 at 11 mm.	68·5
4-Butyltetrahydropyran	$C_9H_{18}O$	84–85 at 25 mm.	58·5
4-Pentyltetrahydropyran	$C_{10}H_{20}O$	83–84 at 15 mm.	50·0
4-Hexyltetrahydropyran	$C_{11}H_{22}O$	101–102 at 15 mm.	68·5
4-Heptyltetrahydropyran	$C_{12}H_{24}O$	122–124 at 13 mm.	64·5
4-Octyltetrahydropyran	$C_{13}H_{26}O$	130–132 at 10 mm.	57·0
4-Nonyltetrahydropyran	$C_{14}H_{28}O$	150–152 at 10 mm.	62·0
4-Decyltetrahydropyran	$C_{15}H_{30}O$	164–166 at 15 mm.	53·0
4-Undecyltetrahydropyran	$C_{16}H_{32}O$	178–180 at 13 mm.	67·0

calcium chloride and the product obtained by distillation under reduced pressure, b.p. 84–85° at 25 mm., yield 8·0 g. (58·5 per cent). A similar method was used to reduce a series of alkyl (ethyl to hexyl) tetrahydropyran-4-yl ketones but failed to reduce heptyl tetrahydropyran-4-yl ketone and higher homologues.

4-*Octyltetrahydropyran.* Heptyl tetrahydropyran-4-yl ketone (15 g.) and hydrazine hydrate (7 g.) were refluxed in absolute ethanol (100 ml.) for 1 hr. Triethylene glycol (80 ml.) and potassium hydroxide (10 g.) were then added and the ethanol removed. A thermometer was placed in the reaction mixture and the temperature raised to 190°, any distillate collected when the temperature was being raised from 120 to 190° being kept. The procedure was the same as that described for 4-butyltetrahydropyran from this point. 4-Octyltetrahydropyran b.p. 130–132° at 10 mm., yield 8·0 g. (57 per cent). A similar method was used to reduce heptyltetrahydropyran-4-yl ketone acid to nonyl tetrahydropyran-4-yl ketone but gave a low yield with the decyl homologue.

4-*n-Undecyltetrahydropyran* was prepared from decyl tetrahydropyran-4-yl ketone (10 g.) by the method described for 4-octyltetrahydropyran but substituting a mixture of benzene (10 ml.) and ethanol (90 ml.) for absolute ethanol in the first part of the reaction. 4-Undecyltetrahydropyran, b.p. 182–184° at 15 mm., yield 6·4 g. (68 per cent).

A list of 4-alkyltetrahydropyrans prepared is given in Table II.

1-*Bromo*-3-*(2-bromoethyl)-heptane*. 4-Butyltetrahydropyran (7 g.) was added to a mixture of hydrobromic acid (35 ml., 60 per cent solution) and concentrated sulphuric acid (2 ml.). The mixture was heated on a steam-bath for 5 hr. with occasional shaking. The cooled mixture was diluted with water (100 ml.), extracted with ether (2 × 50 ml.) and the ethereal extract washed in turn with water (50 ml.), sodium carbonate (50 ml., 10 per cent solution) and water (50 ml.) and then dried over anhydrous calcium chloride. The product was isolated by distillation under reduced pressure b.p. 148–150° at 13 mm., yield 9·8 g. (60 per cent).

Bisthiuronium dipicrate was prepared by heating the alkyl halide (0·5 g.) with thiourea (1 g.) in ethanol (20 ml.) for 20 min. on a steam-bath and then pouring the solution into an aqueous solution of picric acid (100 ml.

TABLE III
3-ALKYL-1,5-DIBROMOPENTANES AND THEIR BISTHIURONIUM DIPICRATES

n-Alkyl radical	B.p. °C	Yield per cent	Bisthiuronium dipicrate derivatives				
			M.p. °C	Analysis (per cent)			
				Calculated		Found	
				C	H	C	H
Propyl	147 at 17 mm.	64·0	135	36·66	3·89	36·5	3·8
Butyl	148 at 13 mm.	60·5	181	37·60	4·09	37·4	4·4
Pentyl	157 at 13 mm.	69·5	175	38·50	4·28	38·7	4·3
Hexyl	166 at 15 mm.	59·5	159	39·36	4·46	39·2	4·3
Heptyl	180 at 13 mm.	66·0	161	40·20	4·64	40·3	4·9
Octyl	188–190 at 10 mm.	42·0	148	41·00	4·81	40·9	5·1
Nonyl	203–205 at 16 mm.	78·0	107–108	41·80	4·97	42·1	5·3
Decyl	210 at 14 mm.	61·0	158	42·54	5·13	42·9	5·1

1 per cent). Recrystallisation of the precipitate twice from ethanol (50 per cent) gave yellow crystals m.p. 181°. Found: C, 37·4; H, 4·4. $C_{23}H_{30}N_{10}O_{14}S_2$ requires C, 37·6; H, 4·1 per cent.

A list of 3-alkyl-1,5-dibromopentanes and their bisthiuronium dipicrates prepared is given in Table III.

4-*Alkyl*-1,1′-*spirobipiperidinium bromides* were prepared by condensing 3-n-alkyl-1,5-dibromopentanes (1 mole) with piperidine (2 moles) by heating them under reflux in chloroform and then evaporating the solution to dryness. Sodium hydroxide (1 mole) solution was added and the solution again evaporated to dryness under reduced pressure on a steam-bath and the residue extracted with ethyl methyl ketone in a Soxhlet extractor, after which the product precipitated from the solvent. The salts were recrystallised from ethyl methyl ketone. A list of spiran quaternary ammonium compounds prepared is given in Table IV.

Surface Activity Measurements

The Wilhelmy plate method was used as it has been shown to be an accurate method for solutions of surface-active compounds (Padday and Russel, 1960).

Apparatus. A glass microscope cover slip was suspended from the beam of a torsion balance with wire. The balance was calibrated up to a 1,000 mg. in 2 mg. divisions and it could be adjusted so that when the blade was freely suspended in air it read zero. The width and thickness of blade were measured on the calibrated stage of a microscope. A 6 cm. crystallising dish was used to hold the solutions while measurements were taken.

Calibration of equipment. All the volumetric glassware used in the determinations were previously calibrated to N.P.L. class A standards.

Water (40 ml.) was pipetted into the clean dry basin and the height of the basin adjusted so that the blade did not touch the bottom when the torsion arm was free to move, but was not pulled out of the water when

TABLE IV

4-ALKYL-1,1'-SPIROBIPIPERIDINIUM BROMIDES

| Alkyl radical | M.p.* °C | Analysis (per cent) | | | | | |
| | | Calculated | | | Found | | |
		C	H	Br	C	H	Br
H	335–336	51·28	8·54	34·18	51·1	8·4	34·3
Propyl	287	56·50	9·42	29·00	56·35	9·7	28·9
Butyl	288	57·90	9·65	27·60	57·8	9·5	27·4
Pentyl	298	59·20	9·87	26·30	59·1	9·8	26·4
Hexyl	303	60·40	10·06	25·16	60·0	10·3	25·1
Heptyl	302	61·44	10·24	24·10	61·3	10·3	23·9
Octyl	300–301	62·43	10·40	23·12	62·5	10·4	23·0
Nonyl	298	63·33	10·54	22·22	63·2	10·4	22·1

* All the spiran quaternary compounds melt with decomposition and it was difficult to obtain consistent values. The following method was used to give reproducible values. A value was obtained by heating the block at 5°/min. The melting point of a new sample of salt was then obtained by starting from 5° below the first value and raising the temperature of the block at 2°/min. By this method it was possible to observe liquifaction before decomposition of the solid.

the torsion arm was restored to its zero position. The depth of the immersion of the blade at zero position was measured accurately. The basin was clamped in this position and provided that the same blade was used with 40 ml. of solution, the depth of immersion of the blade when the torsion arm was in its equilibrium position would be constant. Under these conditions the torsion balance reading is directly proportional to the surface tension of a solution of surface-active agent, assuming the variation in density with concentration is negligible over the range of concentrations studied.

Measurement of surface tension of pure liquids. The blade was cleaned in chromic acid, washed with distilled water and dried in an oven at 120°. Care was taken not to finger the blade at any time. The blade was suspended from the torsion arm and the balance adjusted to give a zero reading. Distilled water (40 ml.) was pipetted into the basin. From the weight now required to keep the torsion arm in its equilibrium position the surface tension of distilled water was calculated using the equation:

$$S.T. = \frac{g(W + \rho tah)}{2(t + a)}$$

g   = acceleration due to gravity.
W   = torsion balance reading in g.
ρ = density of liquid.
t   = width of blade in cm. = 1·9 cm.
a   = thickness of blade in cm. = 0·02 cm.
h   = depth of immersion of blade in cm. = 0·3 cm.

The experiment was repeated substituting in turn Analar benzene and pyridine for the water. The results obtained are given below.

	W g.	g./ml.	Surface tension dynes/cm.	Literature values dynes/cm. (International Critical Tables 1928)
Water	0·272	0·997	72·14	72·75
Benzene	0·1	0·877	28·1	28·9
Pyridine	0·136	0·982	37·6	38·0

Measurement of surface tension of solutions of spiran quaternary compounds. An approximately 10^{-2} M solution of spiran quaternary compound was accurately prepared. The solution (40 ml.) was pipetted into the basin and the surface tension of the solution determined as

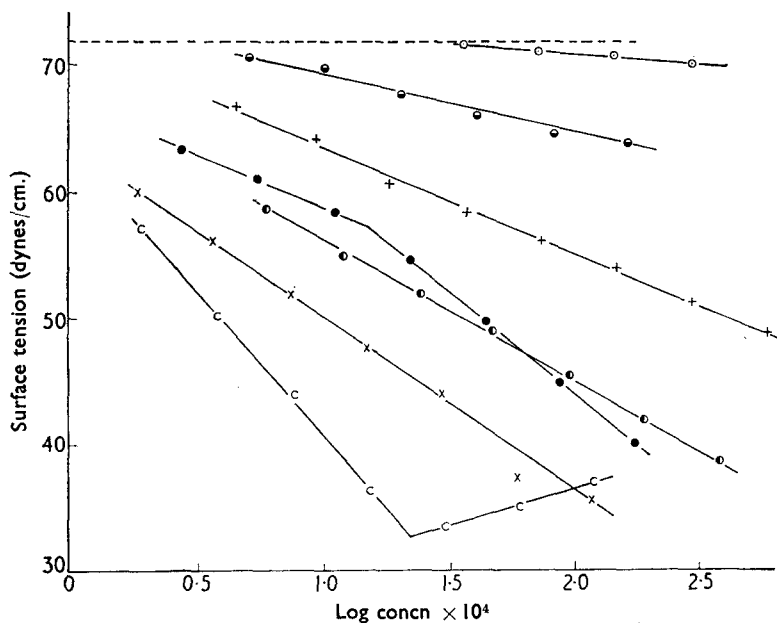FIG. 1. Surface tension/concentration curves for 4-alkyl-1,1′-spirobipiperidinium bromides and cetrimide.

⊙   1, 1′-Spirobipiperdinium bromide
◓   4-Pentyl-1,1′-spirobipiperidinium bromide
+   4-Hexyl-1,1′-spirobipiperidinium bromide
◖   4-Heptyl-1,1′-spirobipiperidinium bromide
×   4-Octyl-1,1′-spirobipiperidinium bromide
●   4-Nonyl-1,1′-spirobipiperidinium bromide
C   Cetrimide
- - -   Distilled water

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described above. The blade was then placed in chromic acid, washed with distilled water and dried at 120°. Some of the solution (20 ml.) was removed from the basin and distilled water (20 ml.) added using a clean pipette and the surface tension of this new solution taken after 2 min. This procedure was repeated several times so that a series of surface tension measurements at different concentrations was obtained. All the

TABLE V

SURFACE TENSION MEASUREMENTS OF 4-ALKYL-1,1'-SPIROBIPIPERIDINIUM BROMIDES AND CETRIMIDE. TEMP. 20°. DENSITY OF SOLUTIONS TAKEN TO BE 0·997 G./ML.

Alkyl radical	Conc. of soln. g. mole/litre	Torsion balance reading in mg.		Surface tension in dynes/cm. (mean)
		1st	2nd	
H	$2·964 \times 10^{-2}$	264		70·4
	$1·482 \times 10^{-2}$	266	266	70·9
	$7·410 \times 10^{-3}$	268	267	71·2
	$3·705 \times 10^{-3}$	270	269	71·8
Pentyl	$1·650 \times 10^{-2}$	239		64·0
	$8·250 \times 10^{-3}$	242	242	64·7
	$4·125 \times 10^{-3}$	248	248	66·2
	$2·062 \times 10^{-3}$	254	256	68·0
	$1·031 \times 10^{-3}$	262	263	70·0
	$5·155 \times 10^{-4}$	266	266	70·9
Hexyl	$5·848 \times 10^{-2}$	180		48·9
	$2·924 \times 10^{-2}$	190	190	51·4
	$1·462 \times 10^{-2}$	204	202	54·2
	$7·310 \times 10^{-3}$	210	208	56·3
	$3·655 \times 10^{-3}$	219	218	58·7
	$1·827 \times 10^{-3}$	226	228	60·9
	$9·135 \times 10^{-4}$	240	240	64·2
	$4·567 \times 10^{-4}$	250	250	66·8
Heptyl	$3·804 \times 10^{-2}$	140		38·7
	$1·902 \times 10^{-2}$	154	153	42·1
	$9·510 \times 10^{-3}$	166	168	45·6
	$4·755 \times 10^{-3}$	183	182	49·5
	$2·377 \times 10^{-3}$	194	194	52·5
	$1·188 \times 10^{-3}$	206	206	55·5
	$5·940 \times 10^{-4}$	218	220	58·9
Octyl	$1·177 \times 10^{-2}$	128		35·6
	$5·885 \times 10^{-3}$	136	134	37·4
	$2·942 \times 10^{-3}$	162	160	44·0
	$1·471 \times 10^{-3}$	172	180	47·6
	$7·355 \times 10^{-4}$	190	194	52·0
	$3·677 \times 10^{-4}$	207	211	56·3
	$1·838 \times 10^{-4}$	222	226	60·1
Nonyl	$1·755 \times 10^{-2}$	146		40·2
	$8·775 \times 10^{-3}$	165	165	45·1
	$4·387 \times 10^{-3}$	186	182	49·9
	$2·193 \times 10^{-3}$	204	202	54·7
	$1·096 \times 10^{-3}$	219	217	58·6
	$5·480 \times 10^{-4}$	228	228	61·2
	$2·740 \times 10^{-4}$	236	238	63·5
Cetrimide	$1·213 \times 10^{-2}$	134		37·1
	$6·065 \times 10^{-3}$	124	128	35·1
	$3·032 \times 10^{-3}$	121	120	33·6
	$1·516 \times 10^{-3}$	132	130	36·4
	$7·580 \times 10^{-4}$	162	160	44·0
	$3·790 \times 10^{-4}$	187	184	50·3
	$1·890 \times 10^{-4}$	214	211	57·2

glassware used was cleaned in chromic acid, washed with water and dried and then a duplicate series of results was obtained using the same original spiran quaternary solution. The temperature of the solution was 20°. After each series of determinations on a compound the cleanliness of the apparatus was checked by determining the surface tension of distilled water.

The surface tensions of solutions of the spiran quaternary compounds and cetrimide were determined in this manner. The results are given in Table V, and shown graphically in Fig. 1.

DISCUSSION

The reactions used to prepare the 4-alkyl-1,1'-spirobipiperidinium bromides were standard ones but a few points of detail arose during the work which are worthy of mention. In the preparation of alkyl tetra-hydropyran-4-yl ketones from the carbonyl chloride and alkyl cadmium salts, the stirring employed was found to have a marked influence on the yields. It is necessary to maintain the particulate matter as a fine suspension throughout the reaction with constant scraping of the walls of the flask. By using a Hinsberg stirrer and carrying out the reaction in a flanged flask yields were improved from the 35 to 40 per cent region up to 70 to 75 per cent. The replacement of ether by benzene as described by Cason and Prout (1944) and Casson (1946) was also advantageous.

All the standard methods of reducing the alkyl tetrahydropyran-4-yl ketones to the hydrocarbon were examined and the Huang-Minlon (1946) modification of the Wolff-Kishner reaction was found to be the most efficient. The method worked well up to the hexyl homologue but when used with the heptyl one the original ketone was recovered unchanged. This was clearly due to the hydrazone not being formed and it was found that this was due to the ketone being practically insoluble in the triethylene glycol. This was overcome by preparing the hydrazone in ethanol and then replacing this solvent with triethylene glycol for the subsequent stage of the reaction. This modification worked for the higher homologues, except decyl tetrahydropyran-4-yl ketone, for which only a 4 per cent yield was obtained. The reason for this low yield was that the hydrazone was insoluble in ethanol and triethylene glycol and co-distilled with the ethanol and condensed as a white solid in the condenser. It was found that the addition of a mixture of ethanol and benzene kept the hydrazone and triethylene glycol in one phase for a sufficient time to prevent co-distillation and a high yield of 4-decyltetrahydropyran resulted.

A number of methods of opening the tetrahydropyran ring were tried, including one reported by Kaluszyner and Galum (1961) in which hydro-bromic acid was prepared *in situ* from sodium bromide and sulphuric acid. However, yields were not as high as desired. It was found that an important factor which governed yields was the degree of charring which occured and so the mildest conditions which would open the ring were used. A mixture of hydrobromic acid (60 per cent solution) and sulphuric acid on a steam-bath was found to produce yields of 60 per cent with little charring (Thomas, 1954).

The preparation of spiran quaternary ammonium compounds has been studied in detail by Thomas (1954, 1957). It was found that the most satisfactory method was to react a substituted 1,5-dibromopentane (1 mole) with a cyclic amine (2 moles) in a solvent such as chloroform. The reactions involved are shown in Fig. 2, from which it can be seen that there are two possible products formed either by an intramolecular cyclisation (*a*) or an intermolecular cyclisation (*b*). When the concentration of reactants is below 5 per cent of the total volume of reaction mixture an intramolecular cyclisation occurs giving the required spiran. Since, of the two possible products, one is a dimer of the other, elemental

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analysis will not distinguish between them. Final proof of which type of compound was formed under conditions of high dilution was obtained by molecular weight determination (Thomas, 1957).

FIG. 2

The results of the surface activity measurements are given in Table V and Fig. 1. Over the concentration range studied there is a linear relationship between the log of concentration and surface tension for all the homologues except the nonyl compound. It is difficult to see why this compound was anomalous. None of the spiran quaternary compounds showed the characteristic break in its surface tension/concentration curve which occurs at the critical micelle concentration of surface-active agents. The curve for cetrimide is included for comparison. It is concluded that micelles are not formed by spiran quaternary compounds over the concentration range studied. The 1,1'-spirobipiperidinium ion consists of two piperidinium rings linked at right angles by a common nitrogen atom. Assuming that the two piperidinium rings are in the chair form, the structure of the 1,1'-spirobipiperidinium ion is as indicated in II. The fixed and "rigid" structure of the two piperidinium rings

II

results in a large bulk of the ion being situated around the positively charged nitrogen atom. It has been shown that increase in bulk around the nitrogen atom leads to an increase in the critical micelle concentration

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(Cella and others, 1952), although increases in the critical micelle concentration of 4-n-alkyl-1,1'-spirobipiperidinium bromides were greater than were expected from the work of Cella. Increase in bulk around the nitrogen atom also leads to a decrease in solubility in long-chain quaternary ammonium compounds (Kuhn and Westphal, 1940; Niederl and Weingarten, 1941). This effect was seen with the spirans. The lower homologues were very soluble in water but their solubility in water at 20° fell rapidly as the series was ascended above the heptyl homologue. Hartley (1941) suggested that the lack of micelle formation could be the main factor causing low solubility and this idea is supported by the results obtained with the spiran quaternary compounds.

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