Summary

5-Methyl-7-methoxy-*s*-triazolo[1,5-*a*]pyrimidine (IVa) was prepared by the reaction of the 7-chloro compound III with sodium methoxide at below room temperature. The property of the 7-alkoxy derivatives (IVa and IVb) was examined and it was discovered that the alkyl group of these derivatives undergoes rearrangement to the ring nitrogen at 3- and 4-positions. In order to determine the structure of the products being obtained by above rearrangement, the reaction of ethyl acetoacetate with 5-alkylamino-*s*-triazoles (XIVa and XIVb) and 4-alkyl-5-amino-*s*-triazoles (XVa and XVb) which were prepared from 1-alkyl-2-aminoguanidinium sulfates (XIIa and XIIb), was investigated.

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15. Toyozo Uno and Koichiro Miyajima : Determination of Surface-active Agents. V.*2 Volumetric Determination of Ethylene Oxide Content in Nonionic Surface-active Agent.*3

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Among the numerous methods for the determination of the ethylene oxide content in nonionics, the titrimetric method has been disregarded. Steele and Berger[1] reported a method using the cloud point of an aqueous solution. Karabinos[2] titrated the solution of nonionics with 5% phenol until opalescence appeared, and this method had been improved by Greenbald[3] and Lloyd.[4] Morgan[5] determined ethylene oxide condensates by cleaving the ethylene oxide bond with hydroiodic acid to ethylene iodide and ethylene.

Gravimetric methods using precipitating reagents, such as potassium ferrocyanate,[6] barium chloride and heteropolic acid,[7~10] or sodium tetraphenylborate[11~13] (STB) were also studied and reported by many workers. However, the procedures are complicated and required so much time for determination. In the preceding papers,[14~16] the volu-

*1 Yoshida-konoe-cho, Sakyo-ku, Kyoto (宇野豊三, 宮島孝一郎).

*2 Part IV : Yakugaku Zasshi, **82**, 1017 (1962).

*3 This work was presented at Kinki local meeting of Pharmaceutical Society of Japan, held on November, 1961.

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metric determinations of ionic surface-active agents with a precipitating reagent as a titrant and pH dye as an indicator were reported. In the present work, a similar attempt was made with nonionics of alkyl and aralkyl polyoxyethylene condensates using STB as a titrant, and Congo red as an indicator in the presence of barium chloride.

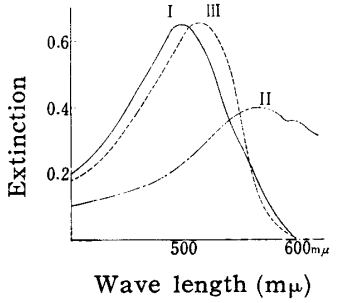

Fig. 1. Absorption Spectra of Congo Red in Water and in the Solution of Nonionics

I : 2 ml. of 0.0001*M* CR and 8 ml. of H_2O (pH : 5.8)
II : 2 ml. of 0.0001*M* CR and 8 ml. of H_2O (pH : 2.8)
III : 2 ml. of 0.0001*M* CR and 8 ml. of 0.01*M* NP 40 solution (pH : 2.8)

As shown in Fig. 1, Congo red (CR) in acid (pH : 2.8) and alkaline (pH : 5.8) media (Curves I and II) has an absorption maximum at 500 and 570 mμ, respectively. The absorption maximum at 500 mμ is due to the pentamer of CR and the monomer band is at about 497 mμ.[17] The absorption spectrum of CR in the solution of nonionics is curve III, which has an absorption maximum at 515 mμ above pH 2.5 and no spectral change is observed upon the addition of barium chloride solution. However, the acidic color of CR gradually appears at pH 2.4 and the absorption maximum shifted to 570 mμ at pH 2.3. The relationship between the concentration of the solution of nonionics and the shift of the absorption maximum from 500 mμ to 515 mμ is shown in Fig. 2.

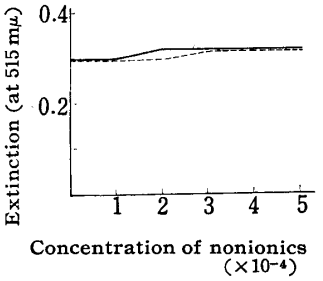

Fig. 2. Relationship between the Color Change of CR and the Concentration of the Solution of Nonionics

—— NP 10 and NP 20
------ NP 30 and NP 40

To 1 ml. of 0.0001*M* CR solution, 9 ml. of various concentrations of nonylphenol of ethylene oxide condensates are added and the extinctions at 515 mμ were measured. A shift of absorption maximum from 500 mμ to 515 mμ took place at more than 2×10^{-4} molar concentration on nonylphenol containing 10 units of ethylene oxide (NP 10) and 20 units of ethylene oxide (NP 20), but at more than 3×10^{-4} molar concentration on NP 30 and NP 40. These values mean also that 1 mole of CR combines with 20 moles of NP 10 and NP 20, and 30 moles of NP 30 and NP 40. According to the report of Nakagawa,[18] CMC of nonionics is about 10^{-4} molar concentration. In order to make the relationship between these values and the CMC clear, the solubilization of Sudan III was studied. However, a clear solubilization point could not be obtained, because of the Poisson distribution of ethylene oxide condensates.[19,20]

When 0.01*M* STB solution was added to the solution of nonionics which was adjusted to pH 3 with hydrochloric acid after an addition of 2 drops of 0.001*M* CR solution and 2 ml. of 0.1*M* barium chloride, the precipitate of nonionics-barium STB was

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20) Y. Masada, T. Yamamoto, T. Shimotori : Yukagaku, **7**, 8 (1958).

gradually formed and CR adsorbed in the precipitate turned to bluepurple from pink at the end point.*4 In this procedure, the color of CR was changed by an addition of one or two drops of 0.01*M* STB solution in the absence of barium chloride. A mixture of STB and barium chloride therefore cannot be used as a titrant for the same reason. Based on these facts, the procedure described in Experimental part was established after an investigation of various conditions. The results obtained using this procedure are shown in Fig. 3.

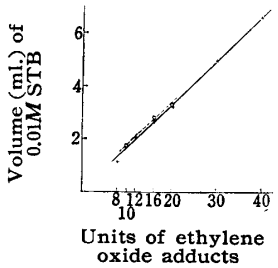

Fig. 3. Relationship between the Units of Ethylene Oxide and the Volume of STB

Sample solution : 10 ml. of 0.001*M* NP and 0.001 *M* LA solution
Titrant : 0.01*M* STB solution
—— Ethylene oxide adducts of nonylphenol
------ Ethylene oxide adducts of lauryl alcohol

As shown in Fig. 3, a linear relationship was observed between the volume of STB and the units of ethylene oxide in nonionics independent from differences of lipophilic radicals. Ten ml. of 0.001*M* NP 10 reacts with 1.7 ml. of 0.01*M* STB, that is, 1 mole of STB combines 6 moles of ethylene oxide. For the determination of polyethylene glycol (PEG) and nonionics containing less than 8 units of ethylene oxide, this method cannot be applicable, because of the appearance of the acidic color of CR on the adjustment of the solution to pH 3 with hydrochloric acid. However when these compounds were mixed in nonionics with more than 10 units of ethylene oxide, they combined with STB and the consumption of STB increased almost in the same ratio. In the case of ionic surfactants, the lower the CMC of the surfactant was, that is, the longer the alkyl chain was, the lower the concentration which could be titrated.

This tendency was not so obvious in nonionics as in ionic surfactants. As to the ionic surfactants, the coloration change of indicator took place mainly in the water phase. However in this titration, CR was adsorbed into the precipitate, in which the color changed. Therefore, the water phase was almost decolored. The mechanism of this titration seems to be as follows. CR combined with nonionics is included in micells and is protected from an attack of hydrogen ion. If oxygen of the ether bond became positively charged forming an oxonium salt,[21] electric repulsion might occur between hydrogen ion and the oxonium cation and CR in the micell would be stabilized. During the course of the titration, the nonionics combined with STB, miscell is destroyed and finally the acidic color of CR appeared.

Experimental

(I) **Method**——(1) Materials and reagents. Nonionics : Nonionics were prepared by the reaction of ethylene oxide gas and either nonylphenol or lauryl alcohol at 140° under pressure and the units of ethylene oxide condensates were determined by an increase of weight in the reaction mixture. Therefore, the units of ethylene oxide means the averaged value. The chemical properties of these nonionics were measured by ordinary methods, which are shown in Table I.

PEG : PEG was manufactured by Sanyo Yushi Co., Ltd.

STB : About 3.43 g. of Dotite Kalibor (Donin Chemical Co. Ltd.) was dissolved in H_2O to make 1 L., and 2 g. of $Al(OH)_3$ were added if necessary to remove turbidity, and filtered after stirring for 5 min.

*4 At the end point, another two phenomena were observed. (1) Coagulation of the precipitate, and (2) disappearance of foams.

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Table I. Properties of Ethylene Oxide Condensates

Compouds	Cloud point (°C)	Acid value	Hydroxyl value
NP 8[a)]	26.5	1.01	118.3
NP 10	62.5	1.00	88.3
NP 12	77.8	0.94	77.8
NP 16	99.5	1.04	70.4
NP 20	123.5	0.98	44.3
NP 30	128.0	0.71	35.7
NP 40	128.5	0.93	31.0
LA 10[b)]	86.0	0.95	87.5
LA 15.4	122.5	0.98	71.3
LA 20	124.5	1.03	45.6

a) Nonylphenol with 8 units of ethylene oxide.
b) Lauryl alcohol with 10 units of ethylene oxide.

The first 20 ml. of filtrate were discarded and a clear solution was used for the titration. The pH value of this solution was around 6.5.
Congo red : Congo red (Merck Co. Ltd.) was dissolved in H_2O to make a 0.001*M* solution.
Barium chloride : $BaCl_2 \cdot 2H_2O$ (J. T. Baker Chemical Co.) was dissolved to make 0.1*M* solution.

(2) Determination of standard STB solution. To 20~25 ml. of STB solution 2~3 drops of *N* $AlCl_3$ solution and about 2.5 times as much amount of 0.02*M* KCl solution as STB in molar ratio, were added and filtered through a sintered glass filter (No. 4) after standing for 20 min. On drying at 120°C for 3 hr., the weight of precipitates $K[B(C_6H_5)_4]$ was measured and the factor of STB was calculated.

(3) Procedure. To 10~20 ml. of 0.001*M* sample solution measured accurately, 1~2 drops of 0.001*M* CR solution and 2 ml. of 0.1*M* $BaCl_2$ solution were added and this solution was adjusted to pH 3 with HCl. This solution was titrated with standard 0.01*M* STB solution*[5] with mechanical stirring with a magnetic stirrer, until pink color turns to blue-purple.

(II) Disccusion of Conditions——(1) Effect of the hydrogen ion concentration. As the color change of CR is observed at the pH range between 3.0~5.2, it is impossible to titrate at a pH of 5.2 and higher because the color change does not occur. When the pH is between 3.0~5.2, the color does not change sharply. As shown in Table II, better results were obtained at pH 3.0~2.5. As the acidic color of CR appears prior to the titration at pH of 2.4 and lower, the titration cannot be carried out.

Table II. Effect of the Hydrogen Ion Concentration

pH Value		Volume (ml.) of 0.01*M* STB
Before Titration	After Titration	
3.25	3.40	7.00
2.90	3.20	6.70
2.76	2.90	6.65
2.70	2.86	6.65
2.65	2.80	6.63
2.50	2.60	6.65
2.38	2.46	6.65
2.30	(impossible for titration)	

Sample : 20 ml. 0.001*M* NP solution.
Titrant : 0.01*M* STB solution.

(2) Results obtained when the volume of 0.1*M* $BaCl_2$ solution was varied. As mentioned above, no spectral change of CR in the solution of nonionics was observed upon the addition of 2 ml. of 0.1*M* $BaCl_2$ solution, but the titration cannot be carried out without addition of $BaCl_2$ solution. As shown in Table III, when less than 0.4 ml. of 0.1*M* $BaCl_2$ solution is added to 10 ml. of 0.001*M* NP 30 solution, coagulation of the precipitate was not observed and the color change of CR was not sharp. Better results were obtained by the addition of more than 0.5 ml. of 0.1*M* $BaCl_2$ solution. Therefore, the volume of 0.1*M* $BaCl_2$ solution is fixed with 2 ml. to every 10 ml. of 0.001*M* solution of nonionics.

(3) Effect of the concentration of the solution.

*[5] The end point was easily recognized by the use of a STB solution at 10 times higher concentration than the sample solution.

Table III. Effect of the Concentration of Barium Chloride

Volume (ml.) of 0.1*M* $BaCl_2$	Volume (ml.) of 0.01*M* STB	Note
0.1	1.0	does not coagulate
0.2	2.2	〃
0.3	4.85	〃
0.4	5.16	coagulates
0.5	5.16	〃
1.0	5.16	〃
2.0	5.16	〃
5.0	5.16	〃
10.0	5.16	〃

Sample solution : 10 ml. of 0.001*M* NP 30 solution.
Titrant : 0.01*M* STB solution.

Table IV. Effect of the Concentration of the Solution

Compounds	Concentration of the solution (*M*)			
	0.01	0.001	0.0005	0.00025
NP 8	1.13	1.13	—	—
NP 10	1.70	1.70	—	—
NP 16	2.71	2.70	—	—
NP 20	3.25	3.25	—	—
NP 30	5.16	5.14	2.53	—
NP 40	6.65	6.65	3.33	
Titrant	0.1*M* STB solution	0.01*M* STB solution	0.01*M* STB solution	—

Sample solution : 10 ml. of nonylphenol with ethylene oxide adducts solution.

As shown in Table IV, titration could be carried out at about 0.001*M* concentration. The relation between the units of ethylene oxide and the concentration of nonionics applicable to titration is not so obvious as ionic surfactants. The color change of two steps near the CMC was not observed in nonionics. These facts seem to be due to the difference of the structure of the micells and the purity of surfactants.

(4) Results obtained when PEG and NP 6 solution were added.

Table V. Results obtained when PEG or NP 6 was added

Compounds added (1 ml. of 0.01*M* solution)	Volume (ml.) of 0.01*M* STB	
	(10 ml. of 0.001*M* NP 20)	(10 ml. of 0.001*M* NP 40)
PEG 300	4.17 (1.02)	7.73 (1.08)
PEG 600	5.55 (2.40)	9.03 (2.38)
PEG 1540	9.05 (5.90)	12.48 (5.83)
NP 6	3.91 (0.76)	7.38 (0.73)
None	3.15 —	6.65 —

Samples : 10 ml. of 0.001*M* NP 20 or NP 40 solution.
1 ml. of 0.01*M* PEG or NP 6 solution.
Titrant : 0.01*M* STB solution.

As described before, titration could not be carried out, with PEG or NP 6 alone, but when they were mixed in nonionics containing more than 10 units of ethylene oxide, STB combined with these compounds in nearly the same ratio, as seen in Table V. Therefore, this method is not applicable for determining nonionics which are contaminated with PEG or nonionics with ethylene oxide of low molar condensates.

(5) Indicator. Any other dyes useful for this titration could not be discovered. A similar spectral change was observed with Benzopurpurin 4B, however the color change was not so sharp as that of CR. Methyl Orange, Bromophenolblue, Thymolblue, and Tropaeoline OO also could not be used for this titration because of the appearance of the acidic color on the adjustment of pH values of the solution of nonionics.

The authers express their thanks to Mr. S. Okada and Sanyo Yushi Co. Ltd. for a supply of nonionics and PEG.

Summary

A new volumetric determination of ethylene oxide content in nonionics was established with sodium tetraphenylborate as a titrant using Congo red as an indicator. This method can be applied to nonionics containing more than 10 units of ethylene oxide. A linear relationship between the units of ethylene oxide and the volume of sodium tetraphenylborate was obtained that six units of ethylene oxide combined with one mole of sodium tetraphenylborate. The accuracy of this titration is about ±3%.

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16. Toyozo Uno and Koichiro Miyajima: Determination of Surface-active Agents. VI.*2 On the Composition of Nonionics-Barium-Tetraphenylborate Complex.*3

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In the preceding paper,*2 the titrimetric determination of ethylene oxide content in nonionics using barium chloride, sodium tetraphenylborate (STB) and Congo red was described. Nonionics containing ethylene oxide was reported not to combine with various kinds of precipitating reagents, such as heteropolic acid and barium chloride[1] or potassium bismuth iodide[2] stoichiometrically. Recently, similar results were obtained with polyethyleneglycol-barium-tetraphenylborate complex by Seher.[3] On the other hand, Schönfeldt reported that 6 units of ethylene oxide combined with 1 mole of potassium ferrocyanate.[4] From the titrimetric results,*2 6 moles of ethylene oxide combined with 1 mole of STB. To make clear this relationship between the units of ethylene oxide in nonionics and the precipitating reagent, several methods were examined using ethylene oxide adducts of nonylphenol and it was concluded that 6 units of ethylene oxide combined 1 mole of STB and 0.5 mole of barium in nonionics with 10~40 units of ethylene oxide.

(1) Determination of ethylene oxide contents by Morgan's method.[5] To determine ethylene oxide contents in nonionics used in the previous work,*2 Morgan's method was employed with following modifications: (a) The Kirsten's reagent containing twice volumes of hydriodic acid was used instead of hydriodic acid alone. (b) Nitrogen gas was used instead of carbon dioxide as a carrier gas.

Results of these determination are shown in Table I. Ethylene oxide content (%) agreed with those obtained by calculation based on the hydroxyl values.

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*2 Part V. This Bulletin, **11**, 75 (1963).

*3 This paper was presented at Kinki branch meeting of Pharmaceutical Society of Japan, November, 1961.

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