

Reaction of N-Bromosuccinimide with 8-Aminoquinoline

New Micro-Determination of 8-Aminoquinoline

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(Received May 29, 1974)

N-Bromosuccinimide 와 8-Aminoquinoline 의 反應에 對하여

8-Aminoquinoline 의 새로운 微量定量法

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(1974년 5월 29일 수리)

Summary

In the presence of 2N hydrochloric acid, N-bromosuccinimide reacts with 8-aminoquinoline to yield 5,7-dibromo-8-aminoquinoline in aqueous medium. This reaction proceeds readily and quantitatively at room temperature. The mechanism of this reaction is investigated in this work. A new titrimetric method for the micro-determination of 8-aminoquinoline by the use of N-bromosuccinimide is described.

The proposed method is quite simple, rapid and yet shows relatively high accuracy over the suggested range. The experimental error does not exceed ± 1.78 per cent. Results are reported for the comparative analysis of 8-aminoquinoline by the proposed method and by bromimetry.

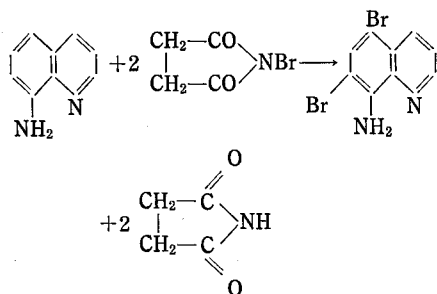
Introduction

Both 8-quinolinol (oxine)¹⁻²⁾ and quinoline-8-thiol (thioxine)³⁻⁵⁾ are useful organic reagents

in chemical analysis. Many articles concerning each of them have been published. Comparison of their different chemical properties based on their different coordinate atoms, i.e., O, N, vs.

S, N, in the cyclic structure has been investigated⁶⁾. 8-aminoquinoline which has a similar cyclic structure to them is a N, N-coordination reagent and its chemical property lies between aliphatic property⁷⁾ of ethylenediamine and aromatic one of 1, 10-phenanthroline. Albert⁸⁾ investigated the basicity of 8-aminoquinoline and Steck et. al.⁹⁾ studied the ultraviolet absorption spectra of this compound. Recently, gravimetric determination of copper¹⁰⁾ and spectrophotometric determination of palladium,¹¹⁾ iron,¹²⁾ manganese,¹³⁾ chromium (VI)¹⁴⁾ and vanadium(V)¹⁴⁾ by the use of 8-aminoquinoline have been reported. And several derivatives of 8-aminoquinoline have been used as great therapeutic agents in the remedy of malaria¹⁵⁾. Concerning the determination of 8-aminoquinoline, there appears to be no report done except for the bromimetric method presented by Yamamoto et al.,¹⁶⁾ adopting a back-titration. However, this method is not discussed thoroughly enough from an analytical point of view, and the procedure is somewhat tedious, time- and material-consuming.

Present investigation deals with the reaction of N-bromosuccinimide with 8-aminoquinoline and micro-determination of 8-aminoquinoline by using N-bromosuccinimide standard solution as a titrant. This method is based on the fact that aqueous solution of 8-aminoquinoline is readily and quantitatively brominated by N-bromosuccinimide in the presence of 2N hydrochloric acid at room temperature and N-bromosuccinimide is reduced irreversibly to succinimide, as represented by the following equation.



N-bromosuccinimide¹⁷⁻¹⁹⁾ which involves monovalent bromine has been used as a selective oxidizing agent²⁰⁾ and brominating agent. Using

this reagent, the determination of ascorbic acid²¹⁾, isoniazid,²²⁾ and hydroquinone²³⁾ etc. were reported. There seems to be no paper concerning the reaction of N-bromosuccinimide and 8-aminoquinoline. Therefore the author carried out an experiment to verify the reaction quantitatively. The reaction product was isolated and identified with 5, 7-dibromo-8-aminoquinoline by comparing the melting point, mixed melting-point determination with an authentic specimen, elementary analysis, IR absorption spectrum and NMR spectrum with those of an authentic specimen.

The proposed method described here is quite simple, rapid and accurate compared with bromimetry.

Experimental

Reagents 8-aminoquinoline (Wako Pure Chemical Co. Japan)

0.01N N-bromosuccinimide (178 mg. per 100ml.) aqueous solution; this solution should be freshly prepared before use.

0.05 per cent w/v of indigocarmine aqueous solution as an indicator.

4N hydrochloric acid solution.

Bromine

Glacial acetic acid

All chemicals used in this experiment were reagent grade. Redistilled water was used in the experiment.

Apparatus A 5—ml. microburette graduated in 0.02—ml. was used for titration analysis.

Graduated pipets of 1—, 2—, 5—, and 10—ml. capacity.

Conical beakers of 25—, 50—, and 100—ml. capacity.

IR absorption spectra were recorded in a Beckman IR-12 spectrophotometer, using KBr pellets.

NMR spectra were measured at 100 MHz. on a Varian HA-100 D spectrometer using deuterated chloroform as solvent.

Reaction between N-bromosuccinimide and 8-aminoquinoline

Since 1 millimole of 8-aminoquinoline reacts

with 2 millimole of N-bromosuccinimide, a 0.14411 gm. portion of 8-aminoquinoline (0.001 mole) was dissolved with stirring in hot distilled water (about 50°C). After cooling, the volume was made up to 100 ml. by adding distilled water. To 8-aminoquinoline solution an equal volume of 4N hydrochloric acid solution was added in order to make the aminoquinoline solution 2 N acidity. On the other hand a 0.356 gm. portion of N-bromosuccinimide (0.002 mole) was dissolved in 100 ml. of hot distilled water. When the N-bromosuccinimide solution was cool, it was put into a burette and was added gradually to 8-aminoquinoline solution with shaking. Then the reaction mixture was poured slowly into about 1 liter of cold water while being stirred whereupon precipitation developed immediately in pale-yellow flocks. To enable the precipitates to settle down to the bottom of the vessel, the solution was allowed to stand over night. Then the precipitates were separated by ordinary filtration and washed thoroughly with cold water, until there was no chloride ion reaction when a 5 per cent silver nitrate solution was added. The filtrate which was designated as fraction A was reserved for identification of succinimide. Following this treatment, the precipitates were air-dried at room temperature to yield a yellow powder which was designated as compound I, having a melting point of 120°C.

Compound I was proved to be 5,7-dibromo-8-aminoquinoline by comparison of the melting point and mixed melting-point determination with an authentic sample, compound II (Described in the following paragraph.) The yield was 0.26848 gm. i.e., 88.96 per cent of the theoretical one.

Anal. - Calc. for $C_9 H_6 N_2 Br_2$: C, 35.79; H, 2.00; N, 9.27

Found: C, 36.2; H, 2.40; N, 8.95

Fraction A was distilled under reduced pressure using a water aspirator, and the solid residue was crystallized from benzene giving colorless crystals, having a melting point of 124°C to 125°C. This compound was proved to be succinimide by comparison of the melting point and mixed melting-point determination with an

authentic specimen.

Synthesis of 5, 7-dibromo-8-aminoquinoline

5, 7, -dibromo-8-aminoquinoline (compound II) as an authentic specimen for the confirmation of compound I, was synthesized according to the method described in Beilstein Organische Chemie²⁴⁾, as well as the method reported of Yamamoto et al.²⁵⁾. In a 50-ml. beaker, 0.5 gm. of 8-aminoquinoline was dissolved in 2.4 ml. of glacial acetic acid and in a 20-ml. beaker 1.110 gm. (0.36 ml) of bromine was dissolved in 5.2 ml. of glacial acetic acid. The bromine solution was put into a 10 ml. burette and added drop by drop slowly with vigorous stirring during additions into 8-aminoquinoline solution which was set in an ice bath. A sticky, reddish-yellow lumpy product was formed, which was dissolved in 35~40 ml. of warm concentrated hydrochloric acid to yield a reddish solution. The solution was poured slowly into about 1 liter of cold water with stirring, and precipitation occurred immediately in pale-yellow flocks. The precipitates were allowed to settle overnight, followed by filtration and washing thoroughly with cold water until there was no chloride ion reaction when a 5 per cent silver nitrate solution was added. The precipitates then were air-dried at room temperature, to yield a yellow powder which was designated as compound II, having a melting point of 120°C. The yield was 0.957 gm. i.e., 91.4 per cent of the theoretical one.

Anal-Cal. for $C_9 H_6 N_2 Br_2$: C, 35.79; H, 2.00; N, 9.27

Found: C, 35.7; H, 2.20; N, 9.00

Validity of reaction for quantitative determination

The following experiment was carried out to verify quantitatively the reaction between N-bromosuccinimide and 8-aminoquinoline, before applying the reaction to the determination of 8-aminoquinoline.

An accurately measured volume of solution containing 0.14411 gm. (1 millimole) of 8-aminoquinoline per 10 ml. was placed in a 50-ml. conical beaker, and an equal volume of 4 N hydrochloric

acid and 3 drops of 0.05% w/v indigocarmine were added. The mixture was titrated with 0.01 N N-bromosuccinimide solution, added drop by drop from a microburette, with gentle swirling after each addition. When the green color of the solution began to fade, titration was carried out slowly with continuous swirling. The end-point

was reached when the last drop of titrant discharged the green color of the sample solution. A similar series of experiments were performed with N-bromosuccinimide solution containing twice the number of molecules of solute as in the first solution. The results are given in Table 1.

Procedure The recommended procedure is as

Table I. Validity of the reaction for quantitative determination

Volume of 8-aminoquinoline solution(1m mole per 100ml), ml.	10	5	4	3	2	1
Titre of N-bromosuccinimide(1m mole per 100ml), ml.	20.05	10.02	8.04	6.04	4.03	2.02
Titre of N-bromosuccinimide(2m mole per 100ml), ml.	9.99	5.01	4.02	3.03	2.02	1.01

follows: to an accurately measured volume (e.g., 5ml.) of the 8-aminoquinoline solution in a 50-ml. conical beaker, add an equal volume, i.e., 5ml. of 4N hydrochloric acid and 3 drops of 0.05% w/v indigocarmine solution as an indicator. Titrate the mixture with 0.01N N-bromosuccinimide solution, adding it drop by drop from a microburette, with gentle swirling to mix after each addition. When the green color of the solution begins to fade, another drop is added and titration is continued slowly at a rate of 1 drop every 5 to 10 seconds with continuous swirling. The end-point is reached when the last drop of titrant discharges the green color of the solution completely, leaving it a yellow color. A blank experiment should be carried out simulta-

neously and this reading should be subtracted from the titre before calculation. The 8-aminoquinoline content of the sample solution is calculated from the expression
1ml. of 0.01N N-bromosuccinimide \equiv 0.72056mg. of 8-aminoquinoline

Effect of hydrochloric acid concentration in the solution The concentration of hydrochloric acid in the sample solution which would have a marked effect on the recovery of 8-aminoquinoline was examined. This experiment was performed according to the recommended procedure previously described by varying the concentration of hydrochloric acid from 0.5 N to 3.5 N; the results are given in Table II.

Indicator In order to choose the proper in-

Table II. Effect of hydrochloric acid concentration on the consumption of 0.01N N-bromosuccinimide

Concentration of hydrochloric acid, Normality	0.50	1.00	1.50	1.75	2.00	2.25	2.50	3.00	3.50
Occurrence of precipitate	+	+	+	+*	-	-	-	-	-
0.01 N-bromosuccinimide used, ml.	7.26	7.31	7.16	7.04	6.94	6.85	6.79	6.75	6.70
Found, mg	5.231	5.267	5.159	5.073	5.001	4.936	4.893	4.864	4.828
Error, %	4.62	5.34	3.18	1.46	0.02	1.28	2.14	2.72	3.44

* Very small amount of precipitate was occurred. Sample taken: 8-aminoquinoline 5 mg/5ml
Indicator: 0.05%w/v indigocarmine 3 drops

dicator to be employed in this titration analysis, three kinds of azo dye ²⁶⁾ which are commonly used in bromatimetry and bromimetry as an indicator, i.e., methyl orange, methyl red and

indigocarmine were examined. All three indicators showed almost the same results on the recovery of 8-aminoquinoline. However indigocarmine gave rather clear end-point,

Application of the Method

Determination of 8-aminoquinoline A 0.2 or 0.1 per cent solution of 8-aminoquinoline was prepared by dissolving 0.2 gm. or 0.1 gm. of pure 8-aminoquinoline in hot distilled water with stirring. After cooling the volume was adjusted to 100ml. by adding distilled water in a volume-

tric flask. 0.05 or 0.01 per cent solution of 8-aminoquinoline was prepared by diluting a 0.1 per cent solution of 8-aminoquinoline 2 times or 10 times with distilled water. The 8-aminoquinoline contents of the 0.2, 0.1 and 0.05 per cent solutions were then determined by the proposed method; the results of the analysis are shown in Table III. Only in the case of 0.01 per cent solution

Table III. Recovery of 8-aminoquinoline by the proposed method

Concentration of 8-aminoquinoline solution, % w/v	Volume of solution, used, ml.	8-aminoquinoline content, mg.	Titre of 0.01N N-bromosuccinimide solution, ml.	8-aminoquinoline found, mg.	Error, %
0.2	1	2	2.80	2.018	0.90
	2	4	5.55	3.999	0.02
	3	6	8.34	6.009	0.15
	4	8	11.12	8.013	0.16
	5	10	13.92	10.030	0.30
0.1	1	1	1.40	1.009	0.90
	2	2	2.81	2.025	1.25
	3	3	4.18	3.012	0.40
	4	4	5.54	3.992	0.20
	5	5	6.94	5.001	0.02
	6	6	8.35	6.017	0.28
	7	7	9.68	6.975	0.36
	8	8	11.11	8.005	0.06
	9	9	12.46	8.978	0.24
	10	10	13.88	10.001	0.01
0.05	1	0.5	0.70	0.504	0.80
	2	1.0	1.40	1.009	0.90
	3	1.5	2.10	1.513	0.87
	4	2.0	2.81	2.025	1.25
	5	2.5	3.46	2.493	0.28
	6	3.0	4.13	2.976	0.80
	7	3.5	4.83	3.480	0.57
	8	4.0	5.53	3.985	0.37
	9	4.5	6.24	4.496	0.09
	10	5.0	6.91	4.979	0.42

of 8-aminoquinoline,, 0.005N N-bromosuccinimide solution was used as a titrant. The results are given in Table IV.

The proposed method was compared with bromimetry reported by Yamamoto et al.¹²⁾ by titrating a 0.1 per cent solution of 8-aminoquinoline. In bromimetry, 0.01N potassium bromate-bromide solution as a titrant and 0.01 N sodium

thiosulfate solution as a back-titrant was used. Results of the comparative analysis are shown in Table V. Every result given in all tables is the average of at least duplicate or triplicate titration.

Results and Discussion

All results are summarized in Tables I to V. IR absorption spectra (KBr) of compound I and

Table IV. Microdetermination of 8-aminoquinoline by the proposed method
1ml. of 0.005 N N-bromosuccinimide \equiv 0.360278 mg. of 8-aminoquinoline

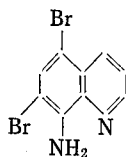
Volume of 8-aminoquinoline solution, used, ml.	8-aminoquinoline present, μ g.	Titre of 0.005N N-bromosuccinimide solution, ml.	8-aminoquinoline found, μ g.	Error, %
10	1,000	2.80	1008.778	0.88
9	900	2.53	911.508	1.28
8	800	2.26	814.233	1.78
7	700	1.97	709.748	1.39
6	600	1.69	608.870	1.47
5	500	1.40	504.389	0.88

Table V. Comparison of results by the proposed method and bromimetry

1ml. of 0.01 N N-bromosuccinimide \equiv 0.72056 mg. of 8-aminoquinoline
1ml. of 0.01 N bromine \equiv 0.36028 mg. of 8-aminoquinoline

Volume of 0.1% w/v 8-aminoquinoline solution taken, ml.	8-aminoquinoline content, mg.	With 0.01 N N-bromosuccinimide as titrant			With 0.01 N bromine as titrant		
		Titre ml.	8-aminoquinoline found, mg.	Error, %	Titre ml.	8-aminoquinoline found, mg.	Error, %
10	10	13.90	10.016	0.16	28.34	10.210	2.10
8	8	11.10	7.998	0.03	22.71	8.182	2.28
6	6	8.35	6.017	0.28	16.84	6.067	1.12
4	4	5.56	4.006	0.15	11.38	4.100	2.50
2	2	2.79	2.010	0.50	5.83	2.100	5.00
1	1	1.40	1.009	0.90	2.87	1.034	3.40
0.5	0.5	0.70	0.504	0.80	1.48	0.533	6.64

compound II: δ 5.4 (broad peak, $2H_8^*$) is assigned to amino group; 7.39 (quartet, $1H_3$, $J_{34}=8$ Hz, $J_{23}=4$ Hz) 7.71 (singlet, $1H_6$) 8.28 (doublet, $1H_4$, $J_{34}=8$ Hz, $J_{24}=1$ Hz) and 8.65 (doublet, $1H_2$, $J_{23}=4$ Hz, $J_{24}=1.7$ Hz) are assigned to aromatic protons.



5,7-dibromo-8-aminoquinoline

IR absorption spectrum and NMR spectrum of compound I are superimposable with those of compound II (See Fig. 1-a, 2-a and Fig. 1-b

compound II (5,7-dibromo-8-aminoquinoline) which was used as an authentic specimen for identification of compound I, are shown in Fig. 1-a and Fig. 2-a, respectively.

Characteristic IR absorption data for compound II: $\nu_{\text{max}}^{\text{KBr}}$ 3429, 3304 cm^{-1} (N-H stretching), 1610 cm^{-1} (N-H deformation), 1560, 1492, 1458 cm^{-1} (C=C and C=N vibration), and 868, 845, 808, 787 cm^{-1} (C-H deformation in ring).

NMR spectra (CDCl_3) of compound I and compound II are shown in Fig. 1-b and Fig. 2-b, respectively. Chemical shifts are parts per million (δ scale) downfield from tetramethylsilane, the internal standard.

Characteristic NMR spectrum data for com-

2-b). The melting point of compound I coincides with that of compound II and the mixed melting-point determination showed no melting-point depression. On the basis of these facts, the author concludes that compound I is entirely identical with compound II.

Although compound I was prepared from the strong acidic medium, it is evident that this compound exists not as hydrochloric acid salts but in a free state, since (1) this compound is sparingly soluble in water but easily soluble in organic solvents, e.g., methanol, ethanol, ether, chloroform, acetone and benzene, (2) from the IR absorption spectrum data of this compound, the N-H stretching of the amino group does not

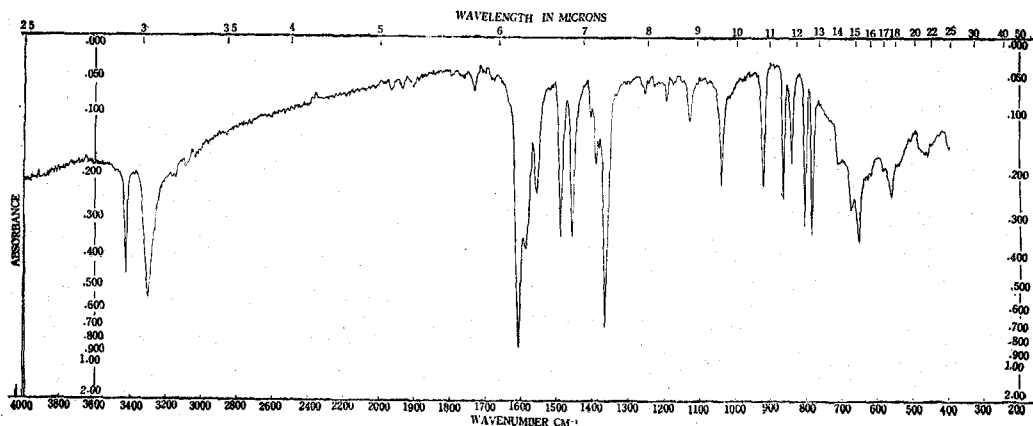


Fig. 1-a. IR absorption spectrum (KBr) of compound I

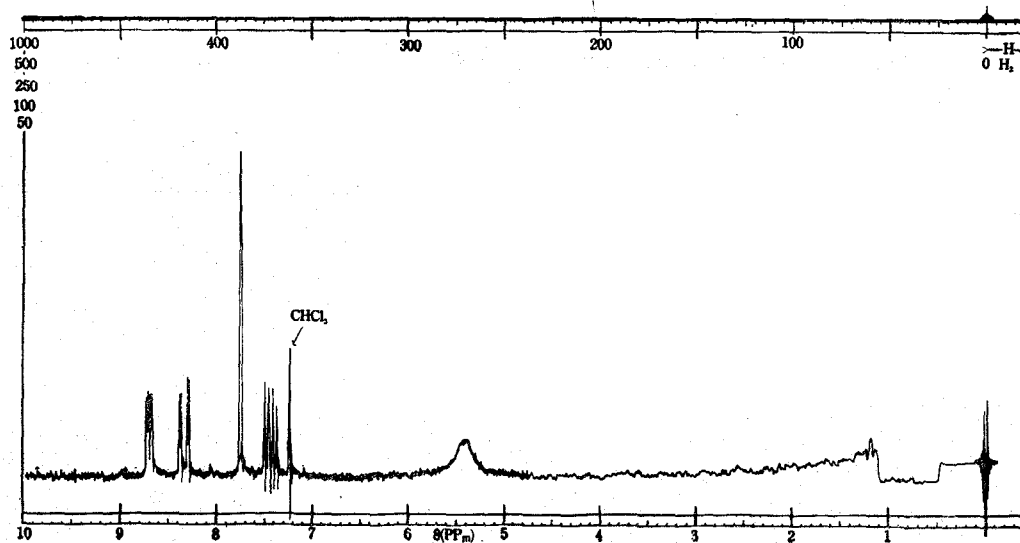


Fig. 2-a. IR absorption spectrum (KBr) of compound II

shift to near 3000cm^{-1} and its peak is not broad but rather sharp.²⁷⁻²⁸⁾

The results given in Table II show that the optimum concentration of hydrochloric acid in the titration process is 2 N. When below 1.5N of hydrochloric acid, precipitation occurred during titration which makes it difficult to detect the end point.

It was found that the reaction was stoichiometric in the presence of 2N hydrochloric acid at room temperature (See Table I).

The fact that 8-aminoquinoline reacts preferentially with N-bromosuccinimide before the latter decolorize indigocarmine which was added as an indicator at the beginning of the titration, provides a reliable titrimetric analysis for the determination of 8-aminoquinoline. The green color of the indicator remains unchanged until all 8-aminoquinoline present in the solution has reacted. The slightest excess of N-bromosuccinimide added, after all the aminoquinoline content has been consumed, will decolorize the dye.

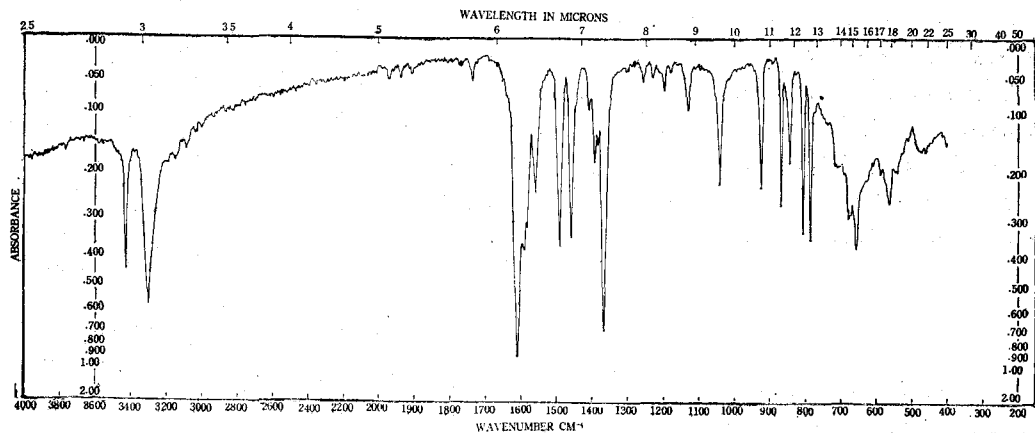


Fig. 1-b. NMR spectrum of compound I in CDCl_3 with an internal TMS standard.

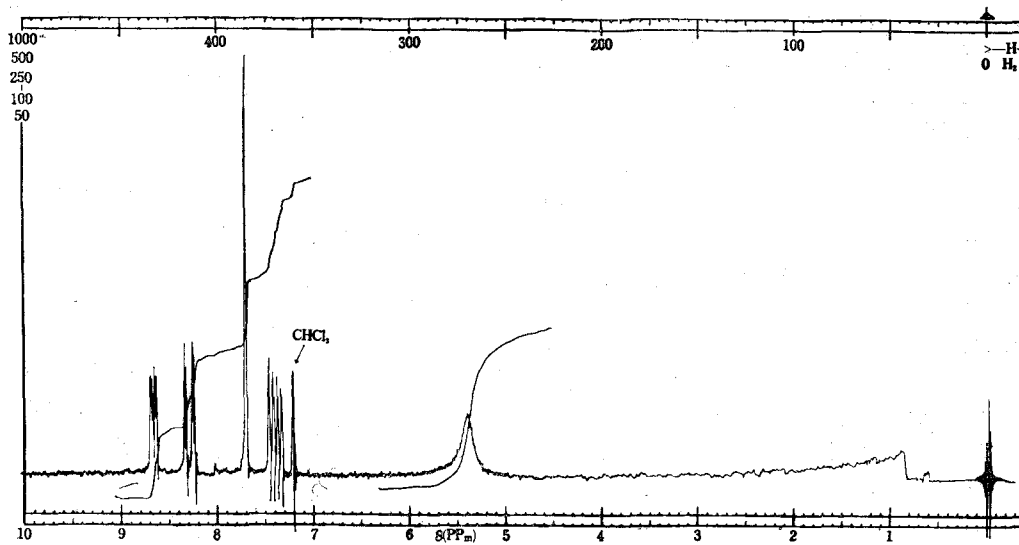


Fig. 2-b. NMR spectrum of compound II in CDCl_3 with an internal TMS standard.

The proposed method is simple, rapid and helpful discussion during this investigation. moreover excellent in accuracy and sensitivity.

요 약

Acknowledgement

The author thanks Prof. K.N. Shin for his

2N 염산의 존재 하에 N-bromosuccinimide 는 8-aminoquinoline 과 수용액 중에서 반응하여 5,7-

dibromo-8-aminoquinoline 를 생성한다.

이 반응은 실온에서 용이하게 또 정량적으로 진행 한다.

본 연구에서 이 반응기구가 검토되었으며 N-bromosuccinimide 를 사용하여 8-aminoquinoline 의 미량정량을 위한 새로운 적정법이 확립되었다.

본 분석방법은 간단하고 신속하며 주어진 정량 범위내에서 비교적 높은 정확성을 나타내며, 실험 오차는 $\pm 1.78\%$ 를 넘지않는다.

본 방법과 Bromimetry 에 의한 8-aminoquinoline 의 비교분석 결과도 보고한다.

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