

Determination of Esters of Acetylenic Alcohols

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Various physical and chemical methods may be applied to the determination of acetylenic compounds, depending on the nature of the acetylenic group and on the presence of other functional groups in the molecule. The most general methods for acetylenic compounds are based on Raman and infra-red absorption spectra measurements (1), but these are not the most suitable for the type of compound under consideration. An ester of an acetylenic alcohol could be determined by reaction at either the acetylenic or the ester group, but the most specific method would be one in which both groups are involved. Actually, the acetylenic alcohols are quite volatile and can usually be steam-distilled. Thus the most useful procedure when dealing with esters of acetylenic alcohols is a preliminary hydrolysis and steam-distillation of the acetylenic alcohol. Then the acetylenic alcohol may be determined by any of the usual acetylene methods. If the acetylenic function is a terminal one, then an acetylde method is especially appropriate. In fact, the presence of an acetylde-forming reagent in the receiver during the steam distillation provides a means of trapping the otherwise volatile acetylenic compound.

The mono-esters of dicarboxylic acids with 3-methyl-1-pentynol-3 are ideally suited to the procedure just mentioned. The phthalate and succinate mono-esters have been studied and a method for their assay in pharmaceutical preparations was developed. The hydrolysis and steam-distillation of the acetylenic alcohol are accomplished simultaneously in a modified Pregl micro-Kjeldahl distillation apparatus. The steam is supplied from a steam generator having an internal electric heating coil, and the apparatus is flushed out at the conclusion of each determination by sucking back the reaction mixture and rinse water into a trap. The 3-methyl-1-pentynol-3 in the distillate is trapped in an alcoholic silver nitrate solution, which is then titrated with sodium hydroxide according to Method B of Siggia (2).

Interfering substances in this method are volatile alkaline compounds such as amines, for which correction could be easily made by a blank determination without silver nitrate. The problem of volatile alkaline materials has not been encountered, however, in the pharmaceutical preparations which have been studied. A problem which may be encountered in assays of the amounts of mono-ester present in various compositions is the interference of neutral acetylenic substances. The di-ester as well as the free alcohol may be present; a relatively simple extraction method has been devised for the determination of the amounts of each of these for correction of the total acetylene results. Appreciable amounts of neutral acetylenic substances were found in the case of the mono-succinate, but not in the case of the mono-phthalate.

Apparatus

The principle item necessary for carrying out the described method is a specially modified Pregl type micro-Kjeldahl distillation apparatus. The fundamental principles involved in the modified apparatus are the same as in the Kjeldahl determination, so that the apparatus listed for this determination in catalogs (3) may be referred to for guidance. The unmodified apparatus could be used successfully, no doubt, but the apparatus which was actually used is more suitable for this particular determination. The points of difference will be listed:

1. The distillation flask is operated in a vertical position and the condenser is attached securely to it, also being in a vertical position.
2. The Kjeldahl-type trap is replaced by a plain bulb having a small outlet at the top leading directly to the condenser (one piece of glass). No joints or rubber tubing intervene in the path of the distillate.
3. The sample addition tube is about 1 cm. ID and is vertically aligned. The steam enters through a side-arm about 2 cm. below the opening, which is closed by a rubber stopper during the distillation. At about 3 cm. below the steam inlet there are several indentations which serve to hold up capsules while disintegration is taking place.

Experimental Procedure

A sample of the material to be assayed is ground up and mixed if necessary, and a portion containing about 0.3 to 0.4 Gm. of mono-ester is weighed out into a small beaker. The distillation apparatus is pre-heated by passing in steam for 5 to 10 minutes and then sucking back. The rubber stopper is removed from the addition tube so that the sample and reagents may be introduced. First, three drops of anti-foam (octanol or silicone) are put in, then the sample, with the aid of a funnel and a nichrome wire. Then the beaker, funnel, and wire are rinsed with ethanol (2 or 3 ml.). Finally, the funnel is removed and sodium hydroxide is added (ca. 5 ml. of 2 N solution). The steam trap drain being open, the stopper is replaced and the heat for the steam generator is turned up high. The receiver, a 125 ml. erlenmeyer flask containing 20 ml. of alcohol (#30) and 15 ml. of silver nitrate solution (100 grams per liter), is put in place with the delivery tube barely submerged. When the steam trap is hot, the drain is closed and steam is passed at 80 volts to heat up the entry tube. (Note: The voltages are given for guidance, but only apply exactly to the particular apparatus used.) When the entry tube is hot, the voltage is reduced to 70 and the reaction mixture is heated up. By pinching the rubber tubing at the steam inlet a few times, the entry tube may be washed out by the reaction mixture. Then the voltage is reduced to 67 when the reaction mixture is hot and the ethanol begins to come over. The timing for the 30-minute distillation is begun at this point. After the ethanol has distilled over, the voltage must be gradually reduced to 63 to

control foaming. For a few minutes the foaming must be carefully watched and the steam trap drain opened if necessary. When the foaming diminishes, the voltage is gradually raised to 67 and left there for the remainder of the 30-minute distillation. For the last five minutes, the delivery tube is raised out of the liquid in the receiver and rinsed off on the outside. When the distillation time is completed, the current is shut off and the apparatus cleaned out by sucking back deionized water. The mixture in the receiver is then titrated with standard sodium hydroxide (ca. 0.1 N) using a mixed indicator (Note 2). The end-point is taken as the place where there is no longer a pinkish tinge to the cloudy solution; the color is a bluish gray. The concentration value of the sodium hydroxide which is used in calculation of the results is that determined with the same indicator. The stoichiometry is one equivalent of sodium hydroxide per mole of mono-ester.

Notes on the Procedure

1. The anti-foam agents are needed only when certain excipients are present. Raw material is sufficiently pure that foaming is not serious.
2. The mixed indicator is a solution of methyl red (0.1%) and methylene blue (0.05%) in alcohol. Six drops are used.
3. The pH at the equivalence point is 3.5; the color change apparently corresponds to this point, the indicator being affected by the presence of the silver ion.

For determination of the neutral acetylenic substances, a sample containing one gram of mono-ester is dissolved in 25 ml. of ethyl acetate, unless there is insoluble material, in which case 40% more is dissolved in 35 ml. and allowed to settle so that 25 ml. of clear supernatant solution may be used. The ethyl acetate solution is extracted successively with sodium bicarbonate (25 ml. of 5% solution), sodium carbonate (5 ml. of 5% solution), and water (three times of 5 ml. each). The free acetylenic alcohol is extracted out with silver nitrate (10 ml. and 5 ml. of 100 grams per liter solution) and collected in a 125 ml. erlenmeyer flask. After two washes of 10 ml. water each, these being combined with the silver nitrate extracts, the whole is titrated with sodium hydroxide as in the fundamental procedure of the first paragraph. It has been found that a recovery of about 90% is obtained in the case of 3-methyl-1-pentynol-3.

The ethyl acetate solution remaining after the extraction of the acetylenic alcohol is evaporated to dryness by an air jet. The non-volatile di-ester remaining is titrated in the usual manner after addition of 15 ml. of alcohol (#30) followed by 10 ml. of the silver nitrate solution.

Results

Some typical results for the two parts of the procedure are shown in Tables I and II.

TABLE I

Fundamental procedure:— Mono-ester plus di-ester and free alcohol.

3-methyl-1-pentyn-3-yl acid phthalate			3-methyl-1-pentyn-3-yl acid succinate		
Raw material (pure)	100.5 % 100.5 100.1 101.1	0.0 0.0 —0.4 +0.6	Individual capsules No. 7140 (½ Gm.)	97.8 % 97.8 97.2 97.4	—0.3 +0.4 —0.2 0.0
Av. 100.5 %		S.D. ± 0.4	Av. 97.4 %		S.D. ± 0.3
Tablets No. 206854B (84.2 %)	84.1 85.0 84.0 84.8	—0.4 +0.5 —0.5 +0.3			
Av. 84.5 %		S.D. ± 0.5			

TABLE II

Neutral acetylene procedure:— Di-ester and free alcohol only.
Mole percent.

3-methyl-1-pentyn-3-yl acid phthalate		3-methyl-1-pentyn-3-yl acid succinate			
Tablets No. 206854B	Free Alcohol	Amount H ₂ O	Tempera- ture	Free Alcohol	Di-ester
	0.3				
	Di-ester	0.9 %	25°C	0	4.8
	0.3			4½	5.3
		4.7 %	25°C	4	7.7
			37°C	4	9.7
					1.8
					7.8

The results show a degree of precision and accuracy which is quite good for a pharmaceutical control method. In addition, the procedure has been found to be quite practicable in the routine assay of the 3-methyl-1-pentyn-3-yl acid phthalate which is the active ingredient in a veterinary anthelmintic tablet currently being marketed. Though only a rather special class of esters of acetylenic alcohols has been studied, it is anticipated that the procedure could be extended to many other classes of this type of compound by the introduction of some simple modifications.

Literature Cited

1. BELLAMY, L. J. 1954. The Infra-red Spectra of Complex Molecules. John Wiley and Sons, Inc., New York, page 49 et seq.
2. SIGGIA, S. 1949. Quantitative Organic Analysis via Functional Groups. John Wiley and Sons, Inc., New York, page 54.
3. Scientific Glass Apparatus Company, Inc., Bloomfield, New Jersey. Catalog J-52, item JM-2980, page 364.