THE ANALYSIS OF POLDINE METHYL METHOSULPHATE BY INFRA-RED SPECTROSCOPY

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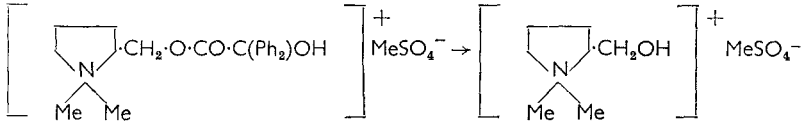
An assay of the drug poldine methyl methosulphate (Nacton, 2-benziloyloxymethyl-1,1-dimethylpyrrolidinium methyl sulphate) is described, based on absorption measurements in the infra-red region of the spectrum. Absorption bands at 5·72, 7·79, 8·13, 9·84, 13·60 and 14·23 μ may be used, the first of which, however, is favoured. The method is no less accurate, and is quicker and more informative than that of Singleton and Wells, with which it is compared. The calculation of drug purity from an absorption band at one wavelength and the use of the ratio of drug purities calculated from the other bands is discussed in relation to standardisation.

The only published method for the assay of poldine methyl methosulphate (Nacton, 2-benziloyloxymethyl-1,1-dimethylpyrrolidinium methyl sulphate) is that of Singleton and Wells (1960). Their method depends on the formation of an ammonium cobaltithiocyanate complex which is extracted by chloroform for absorption measurements at 322 mμ.

The use of the infra-red region of the spectrum, however, might be expected to offer an additional advantage in that several absorption bands, corresponding to different parts of the drug molecule, may be used to obtain further information about the purity of the preparation. It is suggested that the simultaneous use of several bands in this manner merits consideration in drug standardisation. The assay has been devised for the examination of samples taken from bulk supplies of the pure material.

The drug (I) can hydrolyse to give 2-hydroxymethyl-1,1-dimethylpyrrolidinium methyl sulphate (II) and benzilic acid (III), from which it must be distinguished.



I II

+ HO·C(Ph₂)·CO₂H

III

Preliminary investigations showed that presentation of the samples in potassium bromide discs gave variable spectra, and while potassium chloride discs gave better results, they were not adequate for quantitative analysis. The use of a solvent is limited by solubility and absorption considerations, to acetonitrile, in which, however, II is sparingly

soluble (about 0·1 per cent w/w). This limitation is not serious since the drug concentration in acetonitrile is about 2 per cent, and only small amounts of II are likely to be present.

The ester carbonyl absorption band of the drug at 5·72μ is used for assay. Benzilic acid (III), if present, can interfere at this wavelength, but this source of error is readily eliminated by treatment of the assay solutions with sodium bicarbonate before their spectra are obtained.

Experimental and Discussion

Reagents

A.R. sodium bicarbonate (stored over phosphorus pentoxide).

Acetonitrile. B.D.H. analytical reagent grade was used.

Assay Procedure

The drug sample is pulverised in an agate vibration ball mill for 3 min. An accurately weighed portion of the sample of about 60 mg. is weighed into a 10 ml. centrifuge tube to which is added 200 mg. of sodium bicarbonate* and sufficient acetonitrile to make a 2·0 per cent w/w solution of the drug. A control solution without the drug is also prepared. The well-stoppered solutions are allowed to stand, with occasional shaking, for a minimum of 20 min., after which the solutions are centrifuged, transferred to a matched pair of 0·2 mm.† path length cells with sodium chloride windows and scanned in a Grubb Parsons G52A double beam grating spectrometer.

Reference spectra of solutions up to 3 per cent w/w of the pure drug in acetonitrile were thus obtained in the 5–15μ region. Careful standardisation of instrumental conditions was maintained, viz. loop gain, slit width programme and transmission. The spectra are shown in Fig. 1.

The major bands in the spectrum of the drug (I) and their probable assignments are (Bellamy, 1958):

5·72 μ	stretching of	ester C=O group.
7·99 μ	,,	pyrrolidine ring C–N bond.
8·13 μ	,,	ester C–O bond.
9·84 μ	,,	absorption mainly involving S–O of the methylsulphate ion (by analogy with HSO_4^-, Miller and Wilkins, 1952 c.f. also Chihara 1960).
13·60 μ, 14·23 μ	out of plane	C–H bond deformation of monosubstituted benzene ring.

It is noticeable that the spectrum of compound III contains absorption bands which interfere with the 5·72, 9·84, 13·60 and 14·23 μ absorption bands of the drug, whilst the spectrum of compound II contains absorption bands which interfere with those of the drug at 7·99, 8·13 and 9·84 μ.

Removal of compound II is difficult, and without the preliminary sodium bicarbonate treatment to remove benzilic acid (III) it appears

* Fig. 2 shows that bicarbonate treatment has no effect on standard solutions of the pure drug.

† Path length was determined by the method of Smith and Miller (1944).

unlikely that a satisfactory assay procedure could be devised. Only the bands at 5·72 μ and possibly 13·60 μ remain for consideration for assay purposes. The former is preferable since it is stronger, sharper and further from a solvent absorption bands.

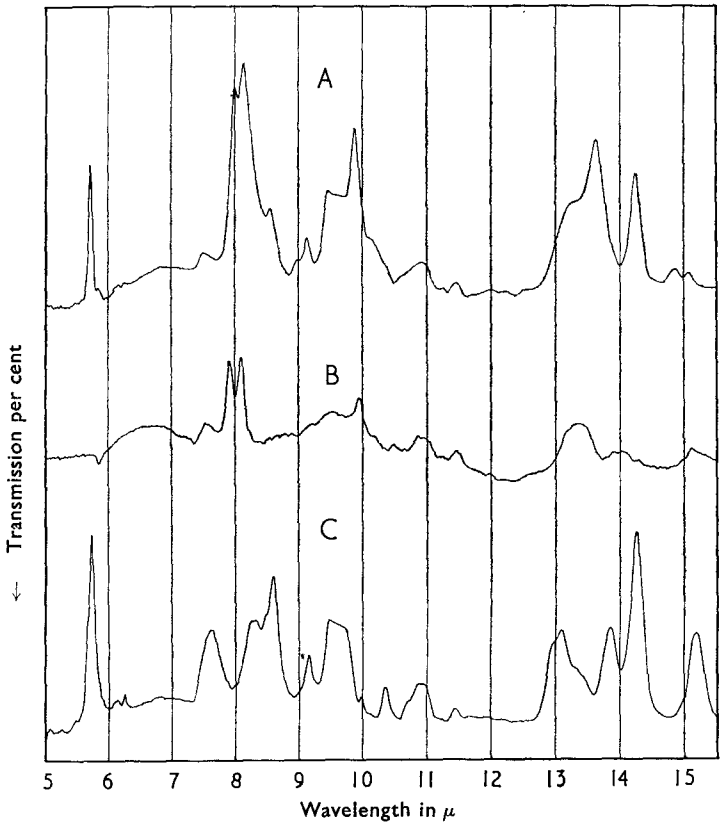


FIG. 1. Infra-red spectra of poldine methyl methosulphate and its hydrolysis products.

A. Poldine methyl methosulphate (2 per cent in acetonitrile.)
B. 2-Hydroxymethyl-1,1-dimethylpyrrolidinium methyl sulphate saturated solution in acetonitrile ($\simeq$ 0·1 per cent w/w).
C. Benzilic acid (2·3 per cent in acetonitrile.)

These reference spectra were used to obtain the absorbances of the various concentrations at the wavelengths of the major bands. Figs. 2 and 3 show plots of unit absorbance (A_s) against concentration. Unit absorbance is calculated thus:

$$A_s = \frac{1}{p}\left(\log_{10}\frac{1}{T} - \log_{10}\frac{1}{t}\right) = \frac{1}{p}\log_{10}\left(\frac{t}{T}\right)$$

where: p = the cell path length (0·212 mm. in the present work).
T = transmittance at the band peak.
t = transmittance at 5·30 μ.

For baseline correction the transmittance at several wavelengths was examined: that at 5·30 μ gave the most reproducible results.

This correction allows for any differences in light scattering, reflection and cell window thickness since both beams of the spectrometer are balanced and the path lengths of the cell are made the same. The very small absorption by the solvent in the regions used greatly facilitates the assay. These factors make it unnecessary to use a geometric construction, as suggested for example by Beaven, Johnson, Willis and

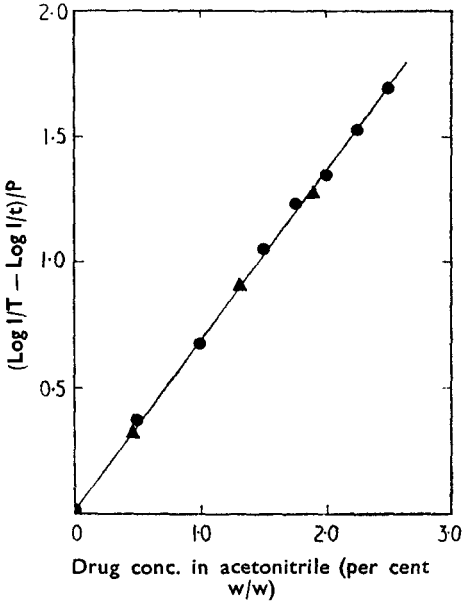


FIG. 2. Calibration curve obtained from absorption measurements at 5·72 μ.
▲, Solution treated with $NaHCO_3$.

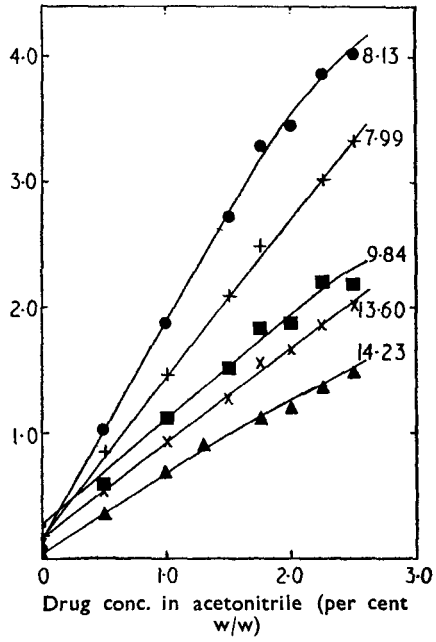


FIG. 3. Calibration curves obtained from absorption measurements at the wavelengths shown (in μ).

Miller (1961), for corrections involving measurements at several wavelengths and the measurement at 5·30 μ is used directly.

The method was tested by assaying known mixtures of the pure drug and compound II or III or both. The mixtures were prepared by mixing the weighed components in an agate mortar using a vibration mill: the 5·72 μ band was used in the absorbance calculation (see above).

The results of these tests (Tables I–II) show an error of $\pm$1·6 per cent with no significant trend.

The method was compared with that of Singleton and Wells (1960); six unknown samples were assayed by two operators, each using one of the methods. The differences between these two (Table III) are about $\pm$1·6 per cent.

TABLE I

ASSAY OF DRUG IN PRESENCE OF COMPOUNDS II AND III

Mixture	Drug per cent	Drug found per cent	Difference
Compound III			
1	100·00	101·3	+1·30
2	97·56	96·3	−1·26
3	94·67	95·6	+0·93
4	91·12	92·5	+1·38
Compound II			
1	100·00	101·3	+1·30
5	97·38	97·7	+0·32
6	94·79	94·3	−0·49
7	89·38	88·7	−0·68

Preliminary work on the assay of the drug in tablets indicates that other substances in the formulation interfere with the 5·72 μ absorption band; calculations based on use of the 7·99 μ band appear to give more consistent results than the 8·13 or 9·84 μ bands.

TABLE II

ASSAY OF DRUG IN PRESENCE OF MIXTURES OF COMPOUNDS II AND III

Mixture	Drug per cent	Compound III per cent*	Drug found per cent	Difference
1	100·0	0	101·3	+1·3
8	87·94	6·47	88·3	+0·36
9	89·09	4·89	89·4	+0·31
10	88·87	7·86	89·8	+0·93
11	87·10	2·69	85·5	−1·6
12	83·60	5·12	82·4	−1·2
13	95·30	2·43	96·4	+1·1
14	93·04	2·69	91·5	−1·54

* The balance is made up of the percentage of II present.

Additional Information on Drug Purity

This may be obtained from the other major absorption bands as follows.

An approximately 2 per cent w/w solution of the sample in acetonitrile is made up accurately and the spectrum run in the 5–15 μ region under the same standardised conditions as used for preparing the calibration curves. Sodium bicarbonate is omitted. The percentage purity of the sample is then calculated on each of the six major wavebands using the calibration curves of Figs. 2 and 3.

TABLE III

COMPARISON OF INFRA-RED AND ULTRA-VIOLET ASSAY METHODS

Sample No.	Per cent drug found in assay		
	Infra-red method operator 1	Ultra-violet method operator 2	Difference
A1	99·3	99·0	+0·3
A2	100·0	100·5	−0·5
A3	100·0	101·2	−1·2
B1	99·0	99·9	−0·9
B2	98·5	99·8	−1·3
B3	99·0	99·9	−0·9

The results obtained from the spectra of the ternary mixtures before treatment with sodium bicarbonate (Table IV) show a considerable variation in the apparent purity.

TABLE IV

DEPENDENCE OF APPARENT PURITY OF DRUG ON ABSORPTION BAND USED FOR CALCULATION

Mixture	Composition of mixture (per cent)			Apparent per cent purity of drug in mixture wavelength of absorption bands used					
	Drug	Compound II	Compound III	5·72 μ	7·99 μ	8·13 μ	9·84 μ	13·60 μ	14·23 μ
8	87·94	6·47	5·59	95·0	96·1	90·4	89·0	82·1	93·5
9	89·09	4·89	6·02	91·7	92·4	90·5	86·0	78·9	81·6
10	88·87	7·86	3·27	95·5	91·0	89·7	87·3	80·8	87·6
11	87·10	2·69	10·21	89·3	96·4	90·0	85·0	80·0	80·0
12	83·60	5·12	11·29	86·3	88·8	88·4	82·0	73·4	78·4
13	95·30	2·43	2·27	96·0	96·4	94·6	88·6	83·9	82·3
14	93·04	2·69	4·27	93·0	95·4	92·5	84·3	80·9	77·5
15	86·88	10·4	2·72	94·5	87·6	86·6	87·1	76·2	89·9

The intensity of the absorption bands at 8·13 μ and 5·72 μ is increased by the presence of compounds II and III respectively. The ratio (r) of the purities calculated from the absorbance at these wavelengths, therefore, should be a function both of the relative amounts of these compounds present and also of the concentration of the drug. For practical purposes in this assay, however, this relationship may be expressed in a two dimensional form (Fig. 4 and Table V).

TABLE V

EFFECT OF COMPOUNDS II AND III ON RATIO OF PURITIES FROM BANDS AT 5·72 μ AND 8·13 μ

Mixture	Drug per cent	Drug per cent from 5·72 μ / Drug per cent from 8·13 μ	Per cent compound III / Per cent compound II
16	86·9	1·09	3·82
11	88·9	1·06	2·40
9	88·0	1·05	1·16
14	95·3	1·01	1·07
1	100·0	1·00	—
10	89·1	1·01	0·83
15	93·0	1·00	0·63
13	83·6	0·98	0·45
12	87·1	0·99	0·26

For the bands at 14·23 μ and 7·99 μ the ratio (r) is apparently very sensitive to the presence of up to 2 per cent of the compounds. If this ratio is plotted against the true purity of the drug (Fig. 4), the curves obtained pass through minima at about 95 per cent purity and rise steeply to the theoretical value of 1·0 for the pure drug.

This kind of ratio can be very useful in problems associated with nearly pure materials.

It can readily be shown that if the assay procedure gives variations of around ±1·5 per cent when applied repetitively to the same sample, then the resulting variation in the ratio is about ±0·04 per cent,

so that the use of such a ratio will tend to offset the variations in procedure and instrumentation invariably occurring from laboratory to laboratory.

In general, it is felt advantageous to assay the purity of a drug using one absorption band, and, to calculate a ratio, using two other carefully selected absorption bands. The choice of these bands depends on the nature of the problem for which the assay is required.

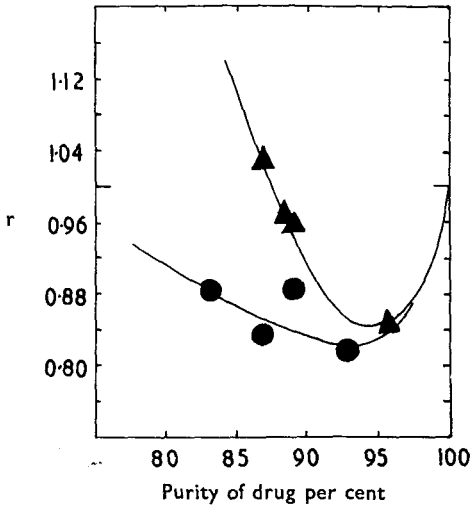


FIG. 4. The effect of compounds II and III on the purity ratio r calculated from absorption measurements at 7·99 and 14·23 μ.

● Compound II predominant. ▲ Compound III predominant.

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