THE DETERMINATION OF PHENADOXONE

By W. H. C. Shaw and J. P. Jefferies

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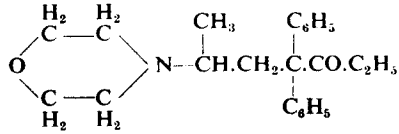
Recently *dl*-6-morpholino-4:4-diphenylheptan-3-one has been introduced as an analgesic of high potency. It has the following constitution:



I

The non-proprietary name phenadoxone has been assigned to it by the General Medical Council; it is marketed in this country as its hydrochloride under the name "Heptalgin." In American literature it has been mentioned as heptazone. Phenadoxone hydrochloride is administered orally as tablets or by injection in 1 per cent. aqueous solution.

Among possible physical methods of analysis, an approximate polaro-

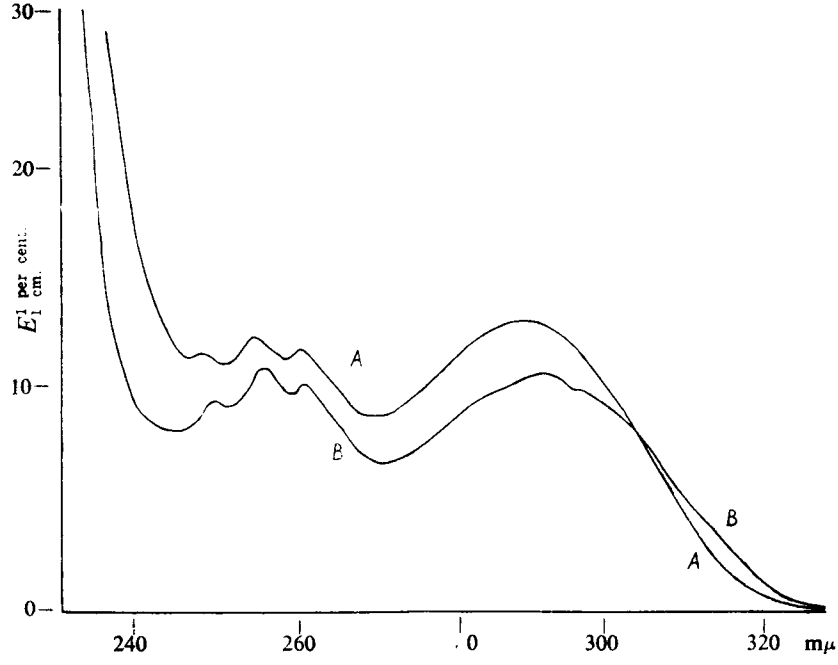


Fig. 1. Ultra-violet Absorption spectra for Phenadoxone Hydrochloride. A, in water $E_{1\text{ cm.}}^{1\text{ per cent.}}$ 13·6 at 259 mμ, 14·2 at 292·5 mμ. B, in alcohol $E_{1\text{ cm.}}^{1\text{ per cent}}$ 12·0 at 260 mμ, 11·8 at 294·5 mμ. ("Uvispek" photometer, concentration 0·1 per cent. w/v. 0·5 cm. cell.)

graphic assay has been described by Page and King[1] who also give details of a colorimetric method applicable to dilute solutions. The melting-point of phenadoxone hydrochloride (approximately 225°C. with decomposition), though useful for identification, is of no great value as a criterion of purity.

A. *Ultra-violet Absorption.* Phenadoxone hydrochloride solutions absorb selectively in the ultra-violet region. The absorption spectra in water and in absolute ethanol are shown in Figure 1. Two main maxima are obtained in each solvent, at 259 mμ and 292·5 mμ in water and at 260 mμ and 294·5 mμ in ethanol.

The extinction values ($E_1^{1\%}_{1\,cm.}$) at the maxima are low; nevertheless they provide the basis for a satisfactory method of assay in the absence of other substances showing absorption at the same wavelengths. In practice it has been found more convenient to use the maximum at the longer wavelength for purposes of quantitative assessment.

B. *Chemical Analysis.* Consideration of the structure of phenadoxone suggests that determination of nitrogen or ionisable chlorine or a reaction involving the ketone group might be the possible basis for a chemical method of analysis. Of these, the first two may readily be carried out by conventional methods, but they have obvious disadvantages. The carbonyl group has been found non-reactive towards the usual ketone reagents, perhaps from steric hindrance by the two phenyl groups attached to the adjacent carbon atom. Other possible methods include base extraction, as applied to the closely related methadone hydrochloride (amidone hydrochloride)[2], but phenadoxone is an exceedingly weak base,

TABLE I

ANALYSIS OF PHENADOXONE HYDROCHLORIDE AND RELATED SUBSTANCES BY THE PICROLONATE METHOD

Sample	Weight taken g.	Weight of picrolonate g.	Apparent phenadoxone hydrochloride per cent.	Corrected m.pt. of residue °C.
A. Purified phenadoxone hydrochloride	0·1494	0·2375	100·0	205·5 to 206·0
	0·2037	0·3231	99·9	205·5 to 206·0
	0·2018	0·3208	100·1	205·7 to 206·1
	0·2493	0·3962	100·0	205·7 to 206·2
B. Commercial phenadoxone hydrochloride	0·2004	0·3175	99·7	205·0 to 206·2
	0·2083	0·3301	99·8	205·0 to 206·0
C. Crude nitrile (II)	0·1999	0·3419	107·7*	About 220*
	0·2039	0·3663	113·2*	„ 223*
D. A+3 per cent. of crude nitrile (II)	0·2050	0·3269	100·4	204·0 to 204·6
	0·2057	0·3289	100·7	204·0 to 204·8
E. Crude ketimine dihydrochloride (III)	0·2008	0·2729	85·6*	200·0 to 200·8
	0·2043	0·2792	86·1*	199·0 to 200·2
F. A+10 per cent. of crude ketimine dihydrochloride (III)	0·1980	0·3109	98·9	205·0 to 205·3
	0·2018	0·3169	98·9	204·9 to 205·2
G. Purified isophenadoxone (IV) ...	0·1995	0·3156	99·6	242·5 to 243·7
H. A+5 per cent. of *iso*phenadoxone (IV)	0·2093	0·3325	100·1	201·3 to 202·8
	0·2059	0·3277	100·2	201·5 to 202·6

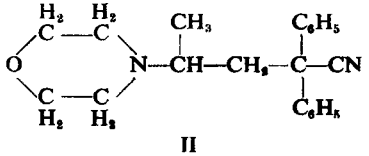
* Results variable

so that the usual titration procedure for completing base-extraction analyses is inapplicable. Among the derivatives of potential value for gravimetric analysis, the picrate (m.pt. 154° to 156°C., recryst.) does not precipitate well from aqueous solutions, but the picrolonate is sparingly soluble in water and crystallises quantitatively under suitable conditions.

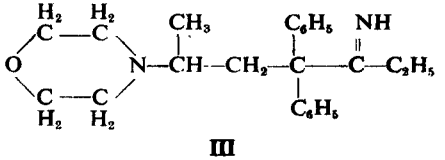
Determination as Picrolonate

Experimental: A sample of *dl*-phenadoxone hydrochloride was recrystallised twice from ethanol and dried to constant weight at 100°C. Analysis of the purified material gave C, 71·0; H, 7·64; N, 3·61; ionisable chlorine, 9·08; $C_{23}H_{29}O_2N.HCl$ requires C, 71·2; H, 7·79; N, 3·61; ionisable chlorine, 9·14 per cent.; m.pt. 225° to 226°C. (with decomposition). The picrolonate method detailed below was applied to this material with the results given in Table I (sample A). Analysis of the precipitate gave C, 64·1; H, 6·05; N, 10·86; $C_{33}H_{37}O_7N_5$ requires C, 64·3; H, 6·06; N, 11·38 per cent. The results given for sample B are typical of those obtained on material of commercial quality.

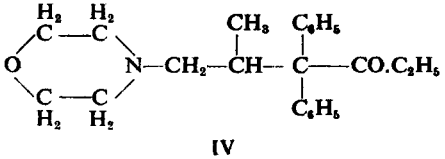
Consideration of the method of manufacture described by Attenburrow *et al.*[3] suggests that the impurities most likely to be encountered in commercial phenadoxone are the nitrile (II), the dihydrochloride of the ketimine (III) and possibly the hydrochloride of an isomer of phenadoxone (IV) (*iso*phenadoxone). The effect of the addition of small proportions of these compounds is demonstrated in the results on samples D. F and H.



II



III



IV

With some slight modifications the ultra-violet absorption and picrolonate methods described have been successfully applied to the analysis of tablets and of solutions for injection. Comparative results are given in Table II.

TABLE II

ANALYSIS OF PREPARATIONS OF PHENADOXONE HYDROCHLORIDE

Preparation	Prepared strength	Proportion of phenadoxone hydrochloride found		
		Ultraviolet absorption analysis (calc. from λ (max.) 292·5 mμ)	Picrolonate method	Ionisable chlorine (corrected for chlorine content of excipients)
Solution for injection	0·950 per cent. w/v	0·97 per cent. w/v	0·955 per cent. w/v	—
	1·049 " "	1·07 " "	1·06 " "	—
	1·0 " "	1·03 " "	1·01 " "	—
	1·0 " "	1·02 " "	1·01 " "	—
Tablets	10 mg./tablet	—	10·0 mg./tablet	9·8 mg./tablet
		—	9·7 " "	9·5 " "
		—	9·8 " "	9·9 " "
		—	10·0 " "	10·0 " "

PROCEDURE

Reagents. I. *Picrolonic Acid Solution.* Dissolve 1·5 g. of picrolonic acid in 500 ml. of boiling water and filter if necessary.

II. *Water saturated with phenadoxone picrolonate.* Filter when required for use.

Dissolve about 0·2 g., accurately weighed, in 100 ml. of water. Heat to boiling and add, with stirring, 100 ml. of picrolonic acid solution that has been heated to about 80°C. Continue boiling and stirring for 5 minutes. Set aside for not less than 12 hours. Filter through a tared No. 3 sintered glass crucible and wash the residue with a total of 100 ml. of water saturated with phenadoxone picrolonate. Dry at 100°C., allow to cool and weigh. Each g. of residue is equivalent to 0·6300 g. of $C_{23}H_{29}O_2N,HCl$.

Determine the melting point of the residue. Insert at 190°C. and heat at the rate of 3°C. per minute (m.pt. of pure picrolonate, approximately 206°C.).

DISCUSSION

Consideration of the results obtained with pure materials and elementary analysis of the precipitate indicate the presence of 1 molecule each of phenadoxone and picrolonic acid. The compound may be dried satisfactorily at 100°C. It is, however, very slightly soluble in water, though apparently there is no loss in the mother liquors.

Many other basic substances form insoluble compounds with picrolonic acid, and a check on the melting-point of the precipitate is necessary for identification. The ketimine dihydrochloride (III) is readily hydrolysed by dilute acids to give phenadoxone hydrochloride, and this reaction also takes place to some extent during the assay. The presence of closely related substances, other than this compound in small quantities, has been shown to affect either the weight of precipitate obtained or the melting-point of the residue or both.

The authors are indebted to Miss R. P. Russell for carrying out the spectroscopic examinations and to Miss H. King for the micro-analyses.

SUMMARY

1. Spectroscopic absorption data in the ultra-violet region are presented for solutions of phenadoxone hydrochloride in water and in absolute alcohol.

2. A chemical method of analysis, involving precipitation of sparingly soluble phenadoxone picrolonate under standardised conditions, has been devised, and the behaviour of closely related compounds during the assay has been studied.

3. With suitable modification, the ultra-violet absorption and picrolonate methods described have been applied successfully to the analysis of preparations of phenadoxone hydrochloride.

REFERENCES

1. Page and King, *Analyst*, 1950, **75**, 71.
2. "*New and Non-official Remedies*," 1950, 612.
3. Attenburrow, Elks, Hems and Speyer, *J. chem. Soc.*, 1949, **114**, 510.

DISCUSSION

The paper was presented by MR. W. H. C. SHAW.

The CHAIRMAN observed that the methods described appeared to be much more satisfactory than the old base extraction method, and it was interesting to note that picrolonic acid was now being employed in quantitative estimations.

DR. R. E. STUCKEY (London) said he noted that the author had used an aqueous solution of phenadoxone in the determination of the ultra-violet absorption data. It might be expected from the formula that the hydrochloride in solution would result in the addition of a proton to the nitrogen atom which in turn would modify the absorption spectrum. In view of the fact that the substance was a weak base had the author observed whether the acidity of the solution affected the ultra-violet absorption curves?

DR. W. MITCHELL (London) referred to the analytical figures in Table I which showed the presence of 3 per cent. of crude nitrile was not disclosed and asked what percentage of that and other impurities could be detected by a determination of melting-point. He suggested that although the ketone group did not react with normal reagents the use of Girard-type reagents might be considered.

DR. G. FOSTER (Dartford) asked whether, in view of the fact that it was necessary to use boiling water in the preparation of picrolonic acid solutions, the authors had considered the use of the sodium salt instead. He also asked whether they had any experience of the detection of phenadoxone in organs and body fluids.

MR. SHAW, in reply, said that the ultra-violet absorption curves in acid solutions of different *p*H values had been examined. The addition of hydrochloric acid down to *p*H 1 had shown no experimentally detectable

difference in the maxima obtained. There was a tendency for both the two main maxima to rise in solutions of phenadoxone in concentrated hydrochloric acid, but that was unimportant because such solutions were not used in practice. The melting-points had been determined by direct comparison with a pure sample so that small discrepancies were immediately detectable. He welcomed the suggested use of Girard T reagent and observed that that had been employed in polarographic analysis for the detection of ketones which themselves were not readily reducible. The estimation of phenadoxone in body fluids was most readily accomplished by polarographic methods and such a method had been used for urine.