THE ISOLATION OF A METABOLITE OF β-ETHYL-β-METHYLGLUTARIMIDE (NP 13)

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The use of β-ethyl-β-methylglutarimide and 2 : 4-diamino-5-phenylthiazole in the treatment of patients suffering from barbiturate intoxication has been recently reported[1]. While the mode of action of these compounds is not yet understood, their efficacy in the relief of comatose conditions caused by excessive doses of barbiturates is being demonstrated.[2]

Recently, a patient was admitted to hospital in a coma, the cause of which was provisionally diagnosed to be barbiturate poisoning. A sample of urine obtained by catheter was brought to this laboratory for analysis and it was reported to contain relatively large amounts of phenobarbitone. The patient remained in a coma for 9 days and was treated during this time with several injections of β-ethyl-β-methylglutarimide and the thiazole derivative. For 17 days all urine samples, except those which were contaminated by fæcal material, were preserved for examination. Subsequent information confirmed that the patient had consumed at least 100 grains of phenobarbitone.

Examination of Urine

The pooled daily urine samples obtained by catheter were acidified and submitted to ether extraction in two 3-litre continuous extractors. The first samples were extracted for 36 hours, after which the ether was replaced with a fresh sample and the extraction continued for a further 12 hours. This last ether was found to have extracted a small amount of material, so all subsequent extraction occupied between 50 and 60 hours. The daily volumes received during the period of coma were about 1·5 litres, but this was later reduced owing to fæcal contamination.

Samples of urine and serum taken on the 6th to 8th days after the initial ingestion of the drug were examined spectrophotometrically[3]. These tests indicated that a compound having an intact barbiturate ring was still present in both fluids. The ultra-violet absorption curves for these days, however, showed the appearance of a small maximum in the vicinity of 230 mμ. No significance was attached to this minor peak at the time because, in ammoniacal solution, β-ethyl-β-methylglutarimide was found to display a maximum absorption at 230 mμ. The thiazole derivative was also found to have an absorption, but the magnitude of the absorption was fairly constant over the range of wavelength used and it should not, therefore, obscure the absorption of the other compounds.

The ether from the continuous extractors was spontaneously evaporated and the remaining water removed from the residues in a vacuum desiccator. A deep-brown oil remained, the total weight of which was 3·778 g.

Purification of Residues

Purification methods such as recrystallisation were found unsatisfactory because of the solubility of the pigmented material. A small amount of the crude material was submitted to counter-current distribution using 25 transfers. The system chosen was *n*-butanol as the stationary phase and 5N ammonia as the mobile phase. Although the separation effected was not sharp, spectrophotometric examination showed that the residue consisted of several different substances.

The whole of the residue from the ether extractions was dissolved in chloroform and transferred to a chromatographic column filled with alumina. Elution was continued with chloroform and the eluate collected in successive 10 ml. portions which were evaporated and weighed. The pigmented material remained stationary at the top of the column. On plotting the weights of the residues obtained in successive 10 ml. volumes of eluate (in weighed evaporating dishes) against the volume number, a graph was obtained in which four maxima appeared. The residues constituting these maxima on the curve were pooled according to the following scheme:

Dishes combined	*Residue number*	*Weight after purification (mg.)*
1 to 11		nil
12 to 34	1	38
35 to 60	2	—
61 to 116	3	68
117 to 210	4	210

Examination of Residues

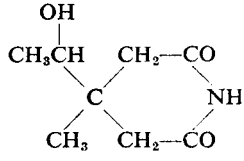
Residue 1 was a pale-yellow gum-like substance which, on purification by sublimation under reduced pressure, was found to be unchanged β-ethyl-β-methylglutarimide, melting point 119 to 121° C.

Residue 2 was, from spectrophotometric and melting point evidence, transitional between residues 1 and 3 and was too small to allow the use of separation techniques.

Residue 3 was white in colour and appeared fairly pure. The absorption in ultra-violet light gave a curve with a maximum at 230 mμ and identical in shape with that given by β-ethyl-β-methylglutarimide. However, the melting point range was 91 to 99° C. and this range could not be reduced after two sublimations under reduced pressure. Recrystallisation of the material from light petroleum (B.pt. 60–80° C.) yielded crystals melting at 99° C. and the compound had an elementary composition corresponding to β-ethyl-β-methylglutarimide with one additional oxygen atom.

Analysis, found: C, 56·66; H, 7·88; N, 8·19 per cent.
$C_8H_{13}NO_3$ requires C, 56·14; H, 7·60; N, 8·18 per cent.

The purified compound gave a positive iodoform reaction and was evidently an hydroxy-derivative of β-ethyl-β-methylglutarimide, the hydroxy-group being situated on the β-ethyl substituent. The metabolite would therefore have the structure (I) shown below.



(I)

The metabolite was found to be more soluble in water than was NP 13 and less soluble in organic solvents. It was probably this compound which caused the original ether extraction of the urine to be prolonged.

Residue 4 was found to consist mostly of unchanged phenobarbitone.

Summary

1. β-Ethyl-β-methylglutarimide is being tested by the Department of Pharmacology of this University for its action in the relief of barbiturate coma.

2. A metabolite has been isolated from the urine of a patient receiving treatment with β-ethyl-β-methylglutarimide. The metabolite was found to be the hydroxy-derivative of the substituted glutarimide, the hydroxy-group being situated on the ethyl side-chain.

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References

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3. McCallum, *J. Pharm. Pharmacol.*, 1954, **6**, 733.