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Metabolic Fate of Thalidomide in Rats*¹

The metabolic fate of thalidomide is of great interest from the pharmacological point of view, because its teratogenic action could be due to any of the metabolites. Several papers have appeared recently on its metabolism.¹⁻⁵⁾ This paper reports the biological oxidation of thalidomide labelled with ¹⁴C in one of the carbonyl groups of the glutarimide moiety and the excretion pattern of the drug with ¹⁴C in the phthaloyl moiety.

The ¹⁴C-thalidomide was prepared by the modified Beckmann's method. The positions of the radioactive carbon (*) are illustrated by the following formulae.



The chemical and radiochemical purity was determined by radiopaperchromatography*² and the melting point, elemental analysis, and infrared and ultraviolet spectra also supported the purity.

The results of measurement of expiratory radioactive carbon dioxide in rats following a single oral dose are shown in Table I.

TABLE I.

	Rat weight (g.) male	Experimental period (hr.)	Radioactivity of ¹⁴ CO ₂ obtained (d.p.m.)	Rate of decar- boxylation %
Ex. 1	300	11	7.4 × 10 ³	0.05
Ex. 2	300	11	2.7 × 10 ⁴	0.08

*¹ This paper was partly reported at the 19th Annual Meeting of Pharmaceutical Society of Japan (Tokyo, April 5, 1964).

*² Solvent: (1) *n*-AmOH-Pyridine-H₂O, 7:7:6. (2) DMF-MeOH-H₂O, 20:70:5.

1) R. Beckmann: *Arzneimittel-Forsch.*, **12**, 1095 (1962); *Ibid.*, **13**, 185 (1963).

2) R. D. MacKenzie, W. R. McGrath: *Proc. Soc. Exptl. Biol. Med.*, **109**, 511 (1962).

3) R. L. Smith, *et al.*: *Life Science*, **7**, 333 (1962).

4) J. W. Faigle, *et al.*: *Experientia*, **18**, 389 (1962).

5) R. T. Williams: *Lancet*, **1**, 723 (1963).

The specific activity of ^{14}C -thalidomide (I) was $0.8\ \mu\text{c. per mg.}$, and administration dose was $8.6\ \text{mg.}$ and $14.8\ \text{mg.}$ in the experiment 1 and 2, respectively. The expiratory carbon dioxide by the animal was absorbed in sodium hydroxide solution and the resulting sodium carbonate was changed into barium carbonate, and then the precipitated barium carbonate was collected, and dried. A fraction of the pulverized precipitates was put in the vial for counting the radioactivity of the collecting carbon dioxide.

The measurement of ^{14}C was made in a mixture of thixine and toluene solution containing PPO and POPOP with a liquid scintillation counter.*³

From the result it would be possible to speculate the formation of compounds (II~VI) are negligible in experimental animals, if any, and it might be concluded that thalidomide is excreted before the glutamic acid formation occurs *in vivo* and the path way shown in Fig. 1 is probably minor in rats. If the formation of glutamic acid itself took place as a result of hydrolysis of thalidomide to some extent during this experiments, radioactive carbon dioxide could be detected.

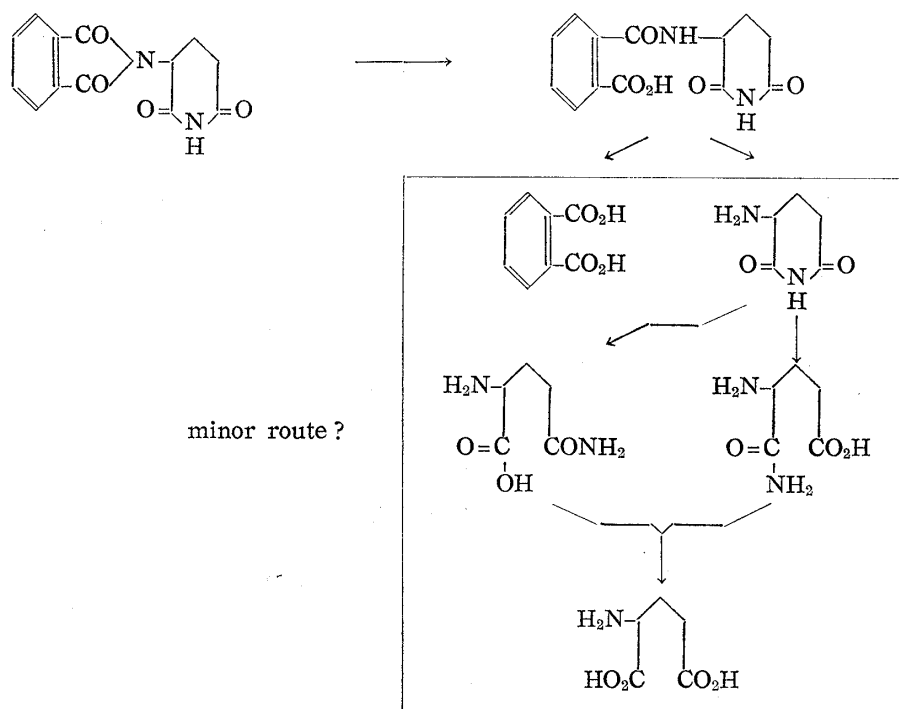
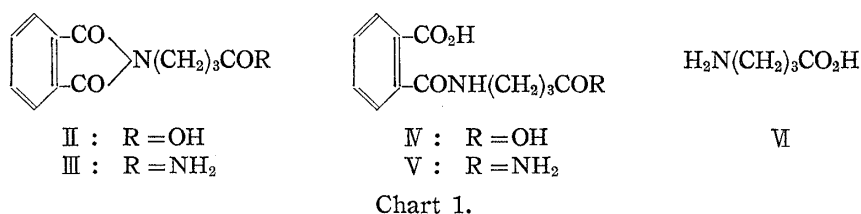


Fig 1. Metabolic Path Ways of Thalidomide in Rat

On the other hand, experiments with ^{14}C -thalidomide (I') tagged in the phthalloyl moiety showed that most of the radioactivity is excreted in the urine and faeces after a single orally administration into rats of $20\ \text{mg. per kg.}$ The results are shown in Table II.

*³ Tri-Carb. Model 314 E was used.

TABLE II.^{a)}

	Rat (hr.)	A	B	C	D	E	Average values (%)
urine	0~24	33.7	19.3	30.6	61.9	63.0	40.2
	24~48	0.5	11.7	2.7	0.5	1.4	3.6
	48~72	0.4	0.6	2.0	0.2	0.7	0.8
	72~96	0.3	0.0	0.2	0.0	0.3	0.2
	0~96	34.9	31.6	35.5	62.6	65.4	46.0
faeces	0~24	51.3	52.0	29.4	27.4	34.3	38.9
	24~48	8.7	11.9	19.1	0.1	0.4	8.0
	48~72	2.4	0.2	11.7	0.2	0.3	2.9
	72~96	0.9	0.0	0.2	0.1	0.4	0.3
	0~96	63.3	64.1	60.4	27.8	35.4	50.2
recovery (%)		98.2	95.7	95.9	90.4	100.8	96.2

a) The specific activity was $0.7\mu\text{c.}$ per mg. and the drug was given orally as a 0.5% solution. Urine was collected and concentrated, a fraction of the urine was plated and counted. The samples of faeces were pulverized and a fraction of the powder was plated and counted for radioactivity. All samples were corrected for self-absorption by a gas flow counter.

Most of faecal radioactivity was due to unchanged thalidomide, and from chromatographic behaviors the radioactivity in the urine was supposed to be metabolites of thalidomide. The distribution patterns were very similar to those found by other workers.¹⁻⁵⁾ No significant organ-specific affinity could be observed.

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