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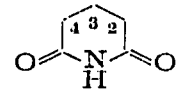
R_F values of some glutarimides

Various derivatives of glutarimide (I) have been shown to possess biological activities (Table I)[1,2] and a few of these are employed in medical practice. As part of an investigation of the metabolic fate of some glutarimides in animals, a study was made of their chromatographic properties.



(I)

All paper chromatograms were carried out with Whatman No. 1 grade. Some papers were impregnated with liquid paraffin (4% in hexane), olive oil (20% in

TABLE I

MAIN PHARMACOLOGICAL ACTION OF THE GLUTARIMIDES USED IN THE STUDY

	Compound	*Pharmacological action*
I	Glutarimide	None
II	3,3-Dimethyl glutarimide	Convulsive
III	3-Ethyl-3-methyl glutarimide (Bemegride)	Convulsive
IV	2,4-Dicyano-3-ethyl-3-methyl glutarimide	None
V	3-Isopropyl-3-methyl glutarimide	Convulsive
VI	3,3-Di-*n*-propyl glutarimide	Hypnotic
VII	2-Phenyl-2-ethyl glutarimide (Glutethimide)	Hypnotic
VIII	2-*p*-Aminophenyl-2-ethyl glutarimide (Aminoglutethimide)	Anticonvulsive
IX	2-Phenyl-2-diethylaminoethyl glutarimide hydrochloride (Phenglutarimide)	Parasympatholytic

TABLE II

R_F VALUES (× 100) OF SOME GLUTARIMIDES ON CELLULOSE PAPER

Glutarimide	*Solvent systems**																			
	S_1	S_2	S_3	S_4	S_5	S_6	S_7	S_8	S_9	S_{10}	S_{11}	S_{12}	S_{12}**	S_{13}	S_{14}	S_{15}	S_{16}	S_{17}	S_{18}	S_{19}
I	70	62	83	74	68	77	50	68	66	56	92	68	78	67	60	57	20	100	31	100
II	84	72	84	84	—	75	84	74	90	84	—	89	24	80	84	—	100	98	74	96
III	100	71	83	86	81	86	84	74	91	85	100	86	100	84	85	85	100	100	90	76
IV	—	—	—	40	—	89	—	—	63	87	83	97	—	84	88	67	85	96	3	93
V	89	67	81	—	—	89	91	67	95	89	100	91	—	86	86	—	97	100	100	—
VI	91	—	60	100	91	93	100	80	96	—	100	97	—	88	97	90	100	98	100	63
VII	91	76	60	86	84	83	98	80	93	90	97	90	100	82	91	86	97	100	100	10
VIII	84	70	71	—	5	86	—	72	72	80	97	75	—	73	74	97	87	96	15	80
IX	64	68	65	56	71	86	68	72	64	56	—	—	78	61	57	53	11	98	5	94

* S_1 = *n*-propanol–water (4:1), 4 h; S_2 = methanol–petroleum ether 40–60° (1:1), 5 h; S_3 = *n*-hexanol–water (1:1), 7 h; S_4 = benzyl alcohol–water (1:1), 7 h; S_5 = methanol–chloroform (1:1), 5 h; S_6 = ethanol–0.9% (w/v) sodium chloride (1:1), 6 h; S_7 = ethanol–0.2 *N* HCl (1:1), 7 h; S_8 = methanol–pyridine–water (1:20:5), 4 h; S_9 = *n*-butanol–acetic acid–water (12:3:5), 7 h; S_{10} = *n*-butanol–ethanol–water (3:1:1), 10 h; S_{11} = *n*-butanol–dimethyl formamide–water (15:4:1), 8 h; S_{12} = isobutanol–acetic acid–water (4:1:1), 12 h; S_{13} = *tert.*-butanol–acetic acid–water (4:1:1), 24 h; S_{14} = *tert.*-butanol–acetic acid–water (4:1:1), 17 h; S_{15} = isopropanol–ethyl acetate–water (2:1:3), 4 h; S_{16} = toluene–acetic acid–water (10:5:4), 1 h; S_{17} = chloroform–acetic acid–water (1:2:1), 8 h; S_{18} = carbon tetrachloride–acetic acid–water (1:2:1), 7 h; S_{19} = sodium chloride 10% (w/v), 2 h.

** Cellulose phosphate paper.

acetone[3]) or tributyrin (10 % in acetone). All compounds were applied to the sheets in amounts of 100 μg by the window technique[4] and they were located with the hypochlorite reagent of GRIEG AND LEABACK[5]. Thin-layer chromatographic separation was made on alumina (Merck) plates, 50 μ thick, prepared with a Camag thin-layer chromatographic spreader and activated at 150° for 1 h. Alkaline solvent systems could not be used because the glutarimides, especially the 2-substituted derivatives, hydrolyse above pH 8. Ascending chromatography was used in all experiments and the data are tabulated in Tables II, III and IV.

By the use of any two of four solvent systems it was possible to distinguish between the glutarimides, the most useful being toluene–acetic acid–water (10:5:4), carbon tetrachloride–acetic acid–water (1:2:1), aqueous sodium chloride (10 %, w/v)

TABLE III

R_F VALUES (× 100) OF SOME GLUTARIMIDES ON IMPREGNATED CELLULOSE PAPER

Glutarimide	*Solvent systems* *				
	S_1 **	S_{20} ***	S_{21} ***	S_{22} §	S_{23} §
I	69	54	83	80	87
II	86	61	—	72	70
III	81	64	84	50	68
V	—	65	86	35	—
VI	—	66	79	5	3
VII	—	63	76	2	4
VIII	—	—	—	20	20
IX	65	68	88	83	87

* S_1 = *n*-propanol–water (4:1), 24 h; S_{20} = methanol–water (1:1), 8 h; S_{21} = acetic acid–water (1:1), 8 h; S_{22} = 0.066 *M* sodium phosphate pH 7.3, 1 h; S_{23} = 0.066 *M* sodium phosphate pH 8.0, 1 h.
** Paper impregnated with liquid paraffin.
*** Paper impregnated with olive oil.
§ Paper impregnated with tributyrin.

TABLE IV

R_F VALUES (× 100) OF SOME GLUTARIMIDES ON THIN-LAYER ALUMINA PLATES

Glutarimide	*Solvent systems* *							
	S_1	S_{11}	S_{14}	S_{22}	S_{24}	S_{25}	S_{26}	S_{26} **
I	80	87	87	98	69	—	—	—
II	85	89	95	92	70	—	—	—
III	87	88	92, 74 ***	90	73, 65 ***	95	79	62
VII	86	94, 85 ***	87	93, 71 ***	70	95	82	68
VIII	85	88	86	90	70	—	—	—
IX	77	85	78	95	67	95	75, 11 ***	14

* S_1 = *n*-propanol–water (4:1), 2 h (time for 5 in. rise of solvent front); S_{11} = *n*-butanol–dimethyl formamide–water (15:4:1), 2.5 h; S_{14} = *tert.*-amyl alcohol–acetic acid–water (4:1:1), 10 h; S_{22} = 0.066 *M* sodium phosphate pH 7.3, 1 h; S_{24} = methanol, 0.75 h; S_{25} = chloroform–methanol (1:1), 0.5 h; S_{26} = chloroform–acetone (9:1), 1 h.
** Plate activated at 180° for 3 h.
*** Formation of double spots.

and, on paper impregnated with tributyrin, 0.066 *M* sodium phosphate, pH 7.3. With these solvents compact spots of reproducible R_F were obtained. The systems isobutanol–acetic acid–water (4:1:1) and *tert.*-butanol–acetic acid–water (4:1:1) gave good resolution but required longer times for development. *n*-Butanol–acetic acid–water (12:3:5) was also an efficient system and has been found to separate the metabolites of Bemegride[6].

Development of the alumina chromatoplates with chloroform or chloroform–benzene (1:1) resulted in the appearance of multiple spots with the compounds used. This was also observed with a number of other solvents for a few of the glutarimides (Table IV). All of the spots were well resolved and the compounds were easily detected in amounts of 1–10 μg by the hypochlorite reagent and by the alkaline hydroxylamine spray of SHEPPARD *et al.*[7]. This is particularly useful, because the 3-substituted glutarimides are not readily located by the latter reagent on paper chromatograms. The detection of glutethimide, in these small quantities, by the hydroxylamine reagent on alumina plates may be of importance in forensic investigations. Barbiturates, which may be present with the glutarimide in biological specimens taken for toxicological analysis, do not interfere with the reaction.

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