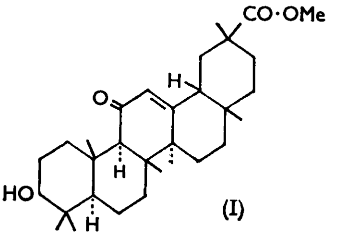
1230. *Halogenolysis of Methyl Glycyrrhetate with Lithium Iodide–Dimethylformamide*

By P. D. G. Dean

STERICALLY hindered methyl esters can be converted into the corresponding acids by heating with lithium iodide or bromide in pyridine,[1] 2,6-lutidine,[2] or 2,4,6-collidine.[2] The mechanism involves nucleophilic attack by the halide ion on the methyl carbon atom. A very good solvent for bimolecular nucleophilic substitution by halide ions is dimethylformamide;[3] accordingly, the halogenolysis of a methyl ester by halide ions has been examined using this solvent. The ester used for a comparative series of experiments was methyl glycyrrhetate (I) as the amount of halogenolysis could be followed easily by thin-layer chromatography of the mixture of acid and ester followed by spectrophotometric estimation of the separated components, making use of the absorption band due to the αβ-unsaturated ketone grouping. In each case the halogenolysis of methyl glycyrrhetate was carried out at the boiling point of the solvent used. The results (Table) indicate that lithium iodide–dimethylformamide is a satisfactory reagent. It also has a practical advantage over lithium iodide–collidine since the reaction mixture may be poured into water and acidified, and the product extracted with ether.



(I)

Nucleophile	Solvent	Time of hydrolysis	% Hydrolysis
LiI	Pyridine	8 hr.	30
LiI	2,6-Lutidine	8 hr.	100
LiI	2,4,6-Collidine	8 hr.	100
LiI	*N*-Methyl-2-pyrrolidone	3 hr.	86
LiI	Dimethylformamidc	1½ hr.	100
LiBr	,,	4 hr.	100
LiF	,,	24 hr.	0
LiOH	,,	16 hr.	100
NaI	,,	16 hr.	40

Experimental.—For thin-layer chromatography (t.l.c.) Kieselgel H was used, and elution was with ethyl acetate. Reactions were carried out in a stream of nitrogen at the boiling point of the solvent. The percentage of halogenolysis was estimated by removing with a syringe a portion of the reaction mixture, which was placed in water (5 c.c.). The resulting solution was acidified with hydrochloric acid and extracted with ether (3 × 20 c.c.). The extract was examined by t.l.c. The plates were sprayed with water, and the areas corresponding to the ester and halogenolysis product were scraped off, and extracted with ether (3 × 30 c.c.). The extracts were evaporated to 1 c.c., made up to 5 c.c. in each case, and the relative ultraviolet absorption at 2430 Å determined. All solvents were dried and the lithium halides were dried at 100°/1 mm. for 2 days prior to use.

Halogenolysis of Methyl Glycyrrhetate. The ester (100 mg.) in dimethylformamide (15 c.c.) was heated under reflux in an atmosphere of nitrogen with lithium iodide (500 mg.) for 2 hr. The reaction mixture was cooled, poured into water (15 c.c.), acidified to litmus with dilute hydrochloric acid, and extracted with ether. The extract was washed thrice with water, dried, and evaporated, to give a solid which was crystallised from acetic acid to give glycyrrhetic acid, m. p. 300—305°, as plates. Examination of the solid by t.l.c. showed only one spot when sprayed with a 10% solution of phosphomolybdic acid in ethanol and the plate heated at 100° for 5 min.

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[*Received, May* 18*th*, 1965.]

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[1] E. Taschner and B. Liberek, *Roczniki Chem.*, 1956, **30**, 323.

[2] F. Elsinger, J. Schreiber, and A. Eschenmoser, *Helv. Chim. Acta*, 1960, **43**, 113.

[3] A. J. Parker, *Quart. Rev.*, 1962, **16**, 163.