

LETTERS TO THE EDITOR

Ethinyl Oestradiol

SIR,—It has recently been reported by Pheasant¹ that ethinyl oestradiol occurs in two polymorphic forms, the commonly encountered form melting at 146°C. and the other at 183°C. On the other hand Ehmann and Wettstein² state that the substance m.pt. 146°C. contains half a molecule of water which is removed by drying at 95°C./0.01 mm. for two hours to give the anhydrous form, m.pt. 183°C. In view of these conflicting reports, we have investigated the matter ourselves with the following results.

A sample of our material m.pt. 146°C. dried to constant weight at 50° to 60°C./12 mm. and then heated on the steam-bath for 5 hours at 0.01 mm. showed a loss in weight of 2.2 per cent. (theory for $\frac{1}{2}$ H₂O, 2.95 per cent.) but no change in m.pt. An attempt was then made to obtain the higher melting form according to the instructions of Pheasant¹. This author stated that when certain samples of pharmaceutical grade ethinyl oestradiol, which melted at 146°C. but did not give a perfectly clear melt, were subjected to sustained heating at 150° to 160°C., resolidification took place to give acicular crystals, m.pt. 183°C. A sample of our material held for 2½ hours at 150° to 160°C. showed no such physical change. It was observed, however, that our material gave an absolutely clear melt and it therefore seemed probable that the change observed by Pheasant was initiated by the presence of a small amount of the higher melting form in the original material. A number of batches of ethinyl oestradiol was therefore re-examined but none was found to behave in the manner described. An impure sample from mother-liquors, however, partially melted in the region of 140°C., resolidified and melted again at 180°C. A portion of pure material m.pt. 146°C. heated to 150°C. and seeded with a fragment of the 180°C. melting solid, solidified immediately and melted again at 183°C. Furthermore a sample of the 146°C. melting material dissolved in a little acetone, treated with light petroleum (40° to 60°C.) to give a milky and seeded with a little of the high-melting solid, gave a crystalline precipitate which after drying in vacuum overnight at room temperature, melted at 183°C.

It would appear from the above results, therefore, that Pheasant is correct in ascribing the existence of the two forms to polymorphism.

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REFERENCES

1. Pheasant, *J. Amer. chem. Soc.*, 1950, **72**, 4303.
2. von Ehmann and Wettstein, *Pharm. Acta Helvet.*, 1950, **25**, 297.