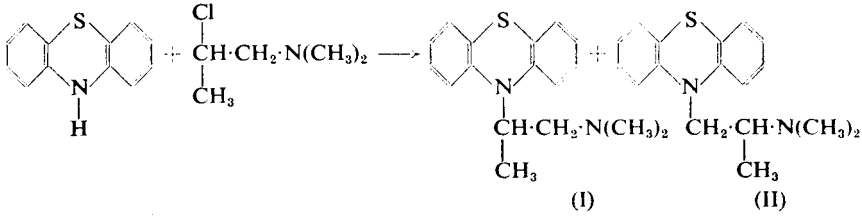
LETTER TO THE EDITOR

The Identity of Certain Antihistamine Drugs

SIR,—Some confusion arose in early investigations concerning both the analgesic drug methadone[1] and the antihistamine drug promethazine,[2] owing to uncertainties in their structure. The preparation of both drugs includes a stage at which a condensation with 1-dimethylamino-2-chloropropane[3] is carried out in the presence of sodamide as acid binding agent, and it is now well known that condensations of this type can produce isomeric products of which, in the case of promethazine, it is the "abnormal" one (II) which predominates.



As a result of work by Charpentier and his colleagues[2,4,5] promethazine (the isomer forming the less soluble hydrochloride) has been assigned the structure *N*-(2-dimethylamino-2-methylethyl) phenothiazine (II), and *iso*promethazine the structure of *N*-(2-dimethylamino-1-methylethyl)phenothiazine (I).

The purpose of this letter is to present certain facts which may help to clarify this subject further, particularly in regard to the true structure of the product lergigan which has hitherto been described[6,7] as having the structure (I).

We thought it of interest to re-examine some of the pharmacological properties of pure promethazine hydrochloride (phenergan) and its isomer. The product lergigan was included in these experiments for comparative purposes, since there was chemical and physical evidence showing that lergigan was in fact identical with promethazine (II), and not *iso*promethazine (I).

In the first place, conversion of the methanol- (and ether-) soluble, basic material from lergigan tablets (manufactured by Aktiebolaget Recip, Sweden), to picrate in methanolic solution gave a 50 per cent. yield of yellow needles, m.pt. 164° C. (Maquenne block), identical with an authentic sample of promethazine picrate.[8]

Secondly, the infra-red spectrum of the total crude, ether-soluble, basic material from lergigan tablets in 1 per cent. carbon disulphide solution, has been shown to be indistinguishable in the region 7·7 μ to 11·5 μ from that of promethazine base (total ether-soluble base from pure promethazine hydrochloride, m.pt. 230° to 232° C. in a sealed evacuated capillary). Both spectra were distinctly different from the infra-red spectrum of a sample of pure *iso*promethazine base, kindly provided by Professor R. Paul (Société des Usines Chimiques Rhône-Poulenc). We are very grateful to Mr. R. L. Warren (Courtauld Institute of Biochemistry, The Middlesex Hospital) for these comparative determinations of spectra.

For the pharmacological experiments, samples from the following sources were used: (*a*) promethazine hydrochloride (m.pt. as above) taken from an ordinary production batch; (*b*) *iso*promethazine hydrochloride (m.pt. 193° to 194° C. in a sealed evacuated capillary) kindly provided by Professor R. Paul;

(*c*) lergigan base (as used for the infra-red spectrum determination), dissolved in dilute hydrochloric acid. Assays were carried out on the isolated guinea-pig ileum. The pharmacological effects of lergigan and promethazine were indistinguishable, and both could be readily differentiated from *iso*promethazine. Thus lergigan was equally as active as promethazine in antagonising the stimulant effects of both histamine and acetylcholine. But though lergigan and promethazine had the same activity as *iso*promethazine against the effects of histamine, either of the former compounds was 20 to 24 times more active than *iso*promethazine in antagonising the effects of acetylcholine. This formed a ready means of distinguishing between them.

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REFERENCES

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2. Charpentier, *C.R. Acad. Sci., Paris*, 1947, **225**, 306.
3. Schultz and Sprague, *J. Amer. chem. Soc.*, 1948, **70**, 48.
4. Charpentier and Ducrot, *C.R. Acad. Sci., Paris*, 1951, **232**, 415.
5. Charpentier, Gailliot and Gaudechon, *ibid.*, 1951, **232**, 2232.
6. Halpern and Briot, *C.R. Soc. Biol.*, 1950, **144**, 887.
7. Reuse, *Arch. int. pharmacodyn.*, 1952, **89**, 117.
8. Charpentier, *private communication.*

ABSTRACTS (*continued from p.* 278).

BACTERIOLOGY AND CLINICAL TESTS

Skin Disinfectants, Testing of. P. Story. (*Brit. med. J.*, 1952, **2**, 1128.) Strains of *Staphylococcus pyogenes*, *Bacterium coli*, *Pseudomonas pyocyanea* and *Proteus vulgaris* isolated from wound swabs were used as test organisms. 6 circular areas 4 cm. in diameter were outlined on the forearm or thigh and 1 drop of bacterial suspension spread over 5 of these areas, which were left to dry. The first 4 circles and the uninoculated area were treated with disinfectant, applied fairly freely. The areas were sampled after ½, 1, 2 and 5 minutes, by placing a glass ring over the test area, adding 5 ml. of sterile water, rubbing for 15 seconds with a glass spreader and taking 1 ml. of the fluid for viable counting. All the test organisms were penicillin-resistant, and penicillin was added to the culture medium to suppress growth of normal skin flora. In experiments on quaternary ammonium compounds the recovered organisms were mixed with sterile milk before cultivation, to neutralise the bacteriostatic action of the chemical. A disinfectant was considered satisfactory when not more than 1 colony grew per plate, and since at least 10,000 organisms were recovered from each staphylococcal control area, this involved the death of at least 99·9 per cent. of bacteria. Solutions in industrial methylated spirit containing 1 per cent. of iodine, 1 per cent. of cetrimide or 0·1 per cent. of dynium chloride killed all bacteria within 30 seconds. Industrial methylated spirit alone was a satisfactory disinfectant in 30 seconds and 1 per cent. of aqueous iodine was satisfactory against *Ps. pyocyanea* in 30 seconds. A 1 per cent. aqueous solution of domiphen bromide (bradosol), 2 per cent. aqueous cetrimide and 0·1 per cent. zephiran in 50 per cent. ethanol were not consistently effective even when left in contact with the bacteria on the skin for 5 minutes. G. B.