J. Pharm. Pharmac., 1973, **25**, 993–995 *Received June* 8, 1973

A note on the chemical change of pentazocine in aqueous acidic media

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Pentazocine decomposes in the acidic conditions used to hydrolyse glucuronides. The structure of the decomposition product was identified as 2′-hydroxy-2-(3-methyl-3-hydroxy-butyl)-5,9-dimethyl-6,7-benzomorphan. Pentazocine is stable when incubated at 37°, pH 5·0, and can be stored in biological fluids without drug loss.

Acid hydrolysis is frequently used to hydrolyse conjugates of a drug before the detection or determination of the drug in biological fluids. One of the metabolites of pentazocine in man is a glucuronide (Berkowitz & Way, 1970). However, the acidic conditions used to hydrolyse glucuronides (Yey & Woods, 1970) will decompose pentazocine (El-Muzati & Way, 1971); the structure of the product is now reported.

METHODS

Gas-liquid-chromatography (g.l.c.) was carried out using a Perkin-Elmer Model F11 Gas Chromatograph (F.I.D.): Hitachi Perkin-Elmer Model 159 recorder. Column and conditions: 2 meter $\frac{1}{4}''$ o.d. glass tubing, 2·5% SE 30 on Chromosorb G (80–100 mesh) A.W. DMCS treated; oven temperature 200°; injection block temperature 220°; nitrogen carrier gas, flow rate 60 ml min^{-1}; hydrogen and air pressure 15 lb $inch^{-2}$ and 20 lb $inch^{-2}$ respectively.

Mass spectrometry (m.s.). Mass spectra were obtained at 70 eV using an A.E.I. M.S.902 mass spectrometer running at a source temperature of 220°. Samples were introduced via the direct inlet system of the mass spectrometer. The elemental composition of ions encountered in the fragmentation of the molecules were confirmed by accurate mass measurements at a resolving power of 20 000. Mass spectra of g.l.c. peaks were obtained at 70 eV using a Perkin-Elmer Model 270 gas chromatograph mass spectrometer (column 2·5% SE 30 on Chromosorb G, helium carrier gas).

Nuclear magnetic resonance spectroscopy (nmr). Nmr spectra were recorded in D_2O using a Perkin-Elmer R–10 nmr spectrometer plus a Northern Scientific 544 CAT. T.M.S. as the internal standard.

Infrared spectroscopy. Infrared spectra were recorded as Nujol mulls using a Unicam SP 200 infrared spectrometer.

Thin layer chromatograph (t.l.c.). T.l.c. was on 0·5 mm thick Silica Gel G plates (glass 20 × 20 cm.) activated for 1 h at 110°. The solvent systems used were: A, ethyl acetate–triethylamine (9:1); B, acetic acid–ethyl acetate–acetone (3:5:5). T.l.c. spots were visualized by Dragendorff's reagent and iodine vapour.

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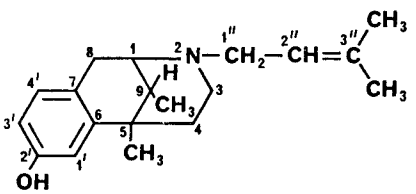
Reaction of pentazocine with acid media. Pentazocine hydrochloride (2 g) was dissolved in N hydrochloric acid (30 ml) and heated in a water bath (90°) for 2 h. The pH of the ice cooled solution was carefully adjusted to pH 9·0 with 10% ammonia solution, and then extracted with freshly distilled ether (5 × 20 ml). The ethereal extract was concentrated and analysed by g.l.c. and t.l.c.; on g.l.c. and t.l.c., pentazocine, (I) and a second compound (II) were detected. After preparative t.l.c. (solvent system A), the band corresponding to II was scraped off, extracted with diethylether and the compound crystallized as the hydrochloride.



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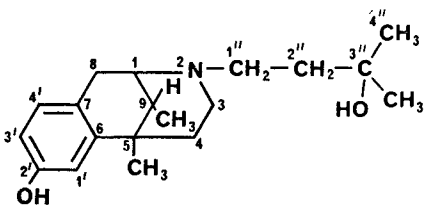

II

RESULTS AND DISCUSSION

The evidence for the structure of the product (II) obtained from pentazocine being 2′-hydroxy-2-(3-methyl-3-hydroxy-butyl)-5,9-dimethyl-6,7-benzomorphan is as follows:

(i) II had t.l.c. and g.l.c. characteristics indicating it to be more polar than pentazocine (I), i.e. t.l.c.: system A, R_F 0·45; system B, R_F 0·19 (I—R_F 0·62 and 0·33 respectively): g.l.c. retention time (Rt) 20·5 min (I—Rt, 13·7 min). On reaction with acetic anhydride, II gave two acetyl derivatives (acetyl I and acetyl II, g.l.c. evidence) whereas I gave only one acetyl derivative (2′-acetylpentazocine). Acetyl I was identified as the phenolic acetyl of II and acetyl II as the diacetyl derivative of II since the g.l.c. retention time of acetyl I relative to that of II was identical to that of morphine or pentazocine (I) relative to their corresponding phenolic acetyl derivatives (Rt—acetyl I, 24·4 min; morphine, 21·5 min; 3-acetylmorphine, 25·9 min and 2′-acetylpentazocine, 16·4 min) and the g.l.c. retention time of acetyl II relative to that of II was identical to that of morphine relative to that of diacetylmorphine (Rt—acetyl II, 37·1 min and diacetylmorphine 38·7 min).

(ii) The mass spectrum of II exhibited a molecular ion (M^+) of *m/e* 303 ($[C_{19}H_{29}O_2N]^+$ by accurate mass) indicating the addition of a molecule of water to I to give II (M^+ of I = *m/e* 285). Unlike the mass spectra of other *N*-3-methylallyl derivatives of benzomorphans (e.g. I and its *trans* alcohol and *trans* acid metabolites), no "nor-ions" or ions characteristic of their subsequent fragmentation (see Vaughan & Beckett, 1973) were present in the spectrum of II which indicated the absence of an *N*-allylic substituent in II: "Nor-ions" (*m/e* 217 in pentazocine and its metabolites) are formed from *N*-3-methylallyl compounds upon electron impact by a hydrogen rearrangement mechanism which is dependent on an intact allylic system (Vaughan, 1972). The base ion in the spectrum of II (*m/e* 230; $[C_{15}H_{20}ON]^+$ by accurate mass) was formed by α-fission of the molecular ion, as was indicated by metastable transition ions: this is characteristic of *N*-alkyl benzomorphans and

morphinans when the alkyl substituent lacks an olefinic bond (Mendelbaum & Ginsburgh, 1966). A tertiary alcohol group in II was indicated by the presence of *m/e* 59 ions ($[C_3H_7O]^+$ by accurate mass) in its m.s. (I lacks *m/e* 59 ions in its m.s.).

(iii) The infrared of II confirmed the absence of an allylic *N*-substituent (C=C stretching in I 1670 cm^{-1}).

(iv) II had an intact benzomorphan nucleus since proton resonances identical to those in I were present in its nmr spectra (*H* aromatic, τ 3·2^m; 9- CH_3 τ 9·1^d, J = 6Hz; 5-CH_3 τ 8·6^s; 3-CH_2 τ 6·85^m and 1″ -CH_2 τ 6·2^m). II differed from I in the absence of an olefinic proton resonance (2″ —C*H* = τ 4·7^m in I) and a six proton resonance (τ 8·6^s), attributed to two equivalent methyl groups, replaced the doublet of the two methyl groups attached to the terminal olefinic carbon in I (6*H* τ 8·1^d, J = 4·5 Hz). Additionally, II had proton resonances (2″ -CH_2, τ 6·6) attributable to the resonance of a CH_2 group β to a tertiary hydroxyl group.

Compound II has a structure sufficiently similar to the known metabolites of I to cause problems in a study of the pharmacokinetics of pentazocine. Although pentazocine is unstable to heat in aqueous acid media, no degradation occurred when I was incubated at pH 5·0 (37° in Walpoles acetate buffer), stored in urine (pH 4·0–8·0 for 10 days at 4°) and stored in 0·1N HCl (3 h at 20°), indicating that biological fluids containing pentazocine can be stored without drug loss. Pentazocine glucuronide should be hydrolysed in biological fluids by β-glucuronidase rather than by acid hydrolysis.

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