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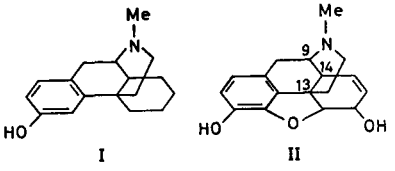
Optical rotatory dispersion characteristics of (−)-3-hydroxy-*N*-methylmorphinan and (−)-morphine

SIR,—The relative configurations of (−)-3-hydroxy-*N*-methylmorphinan (I, levorphanol) and (−)-morphine (II) are of interest in view of the established stereoselectivity of the analgesic receptor towards many classes of analgesics (Beckett & Casy, 1965). In the absence of direct chemical methods, the use of optical rotatory dispersion (o.r.d.) data (Crabbé, 1965) offers the most promising physical method for the stereochemical correlation of (−)-I and (−)-II. The following results were obtained using a Polarmatic 62 photo-electric spectropolarimeter. The o.r.d. curve of (−)-morphine base (*c*, 0·02% in ethanol, 0·05 dm cell) showed a negative Cotton effect, $[\phi]^{25}_{340}-1499$, $[\phi]^{25}_{303}-4123$, $[\phi]^{25}_{291}-5620$ (trough), $[\phi]^{25}_{281}+4120$ (inflection), $[\phi]^{25}_{256}+13490$ (peak), $[\phi]^{25}_{244}-30240$ (limit of measurement); the curve for (−)-morphine hydrochloride was similar with trough characteristics, $[\phi]^{25}_{290}-5223$. Bobbitt, Weiss & Henessian (1959), using a less sensitive spectropolarimeter, recorded the o.r.d. curves of morphine, codeine and dihydrocodeine in dioxane and observed negative Cotton effects with troughs near 300 mμ in each case; values beyond 298 mμ could not be obtained. The o.r.d. curve of levorphanol base (*c*, 0·01% in ethanol, 0·05 dm cell) also showed a negative Cotton effect, $[\phi]^{25}_{400}-3375$, $[\phi]^{25}_{313}-15520$, $[\phi]^{25}_{290}-40460$ (trough), $[\phi]^{25}_{288}-33050$ and $[\phi]^{25}_{278}-35780$ (fine structure, absent in the salt), $[\phi]^{25}_{268}+16190$ (peak); in 0·1N hydrochloric acid-ethanol, trough and peak characteristics were $[\phi]^{25}_{291}-45320$ and $[\phi]^{25}_{270}+18880$ respectively.



I II

The negative Cotton effects of (−)-I and (−)-II are attributed to the optically active phenolic chromophore because the Cotton effect mid-points (near 286 mμ for morphine and 280 mμ for levorphanol) are close to the phenolic ultraviolet absorption maxima of the two compounds [morphine λ_{max} 285 (base), 288 mμ (salt); levorphanol λ_{max} 284 (base), 283 mμ (salt) in ethanol]. Differences in the o.r.d. curves of I and II, viz. characteristics at wavelengths below 280 mμ and the lower $[\phi]^{25}_{291}$ (trough) value for (−)-II, probably arise as a result of the presence in (−)-II of optically active chromophores (additional to the phenolic function) that are absent in (−)-I, a compound of simpler structure.

Since the sign of a Cotton effect is governed chiefly by the stereochemical environment of the responsible optically active chromophore (Crabbé & others, 1965), the identity of sign noted for Cotton effects in (−)-I and (−)-II provides strong evidence for the configurations of the C-9, 13 and 14 asymmetric centres of (−)-morphine being the same as those of the corresponding centres of levorphanol. Portoghese (1966, quoting unpublished data) reports that the o.r.d. curves of some (−)-phenolic benzomorphan derivatives exhibit Cotton effects which also have the same sign as that of morphine. Hence, the results of o.r.d. studies substantiate previous conclusions of configuration based upon work involving stereoselective adsorbents (Beckett & Anderson, 1960).

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Note added in proof. Weiss & Rull (1965) report Cotton effects (by circular dichroism measurements) of similar sign near 260μ) for (—)-3-methoxy-*N*-methylmorphinan, dihydrodesoxycodeine and tetrahydrodesoxycodeine, results which provide further evidence of configuration in morphinan derivatives.

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Excretion of a glucuronide conjugate of 3-hydroxyphenyltrimethylammonium

SIR,—We have found that, after intramuscular injection of neostigmine in the rat, about 50% of the dose is excreted in the urine unchanged, a high proportion of the remainder being metabolized in the liver and excreted in the urine as 3-hydroxyphenyltrimethylammonium (Roberts, Thomas & Wilson, 1963, 1965a,b). We anticipated that some of this phenolic metabolite might be excreted as a conjugated product (described by Williams, 1959), but the paper electrophoresis technique we used did not enable us to establish this point.

Further investigation using [^{14}C]3-hydroxyphenyltrimethylammonium by intramuscular injection into rats showed that when the urine was examined by a modification of the electrophoresis procedure (Veronal buffer pH 7·0, 0·05M), two peaks of radioactivity were obtained. One of these peaks corresponded with a concurrently run authentic sample of 3-hydroxyphenyltrimethylammonium, the other was tentatively assumed to be the glucuronide conjugate of this compound. This assumption was confirmed by incubating samples of urine with β-glucuronidase ("Ketodase", Warner & Co.) and when these were subjected to paper electrophoresis, only the peak for 3-hydroxyphenyltrimethylammonium was identified.

Using this procedure urine was collected from rats for periods up to 24 hr after intramuscular injection of [^{14}C]3-hydroxyphenyltrimethylammonium. Fig. 1