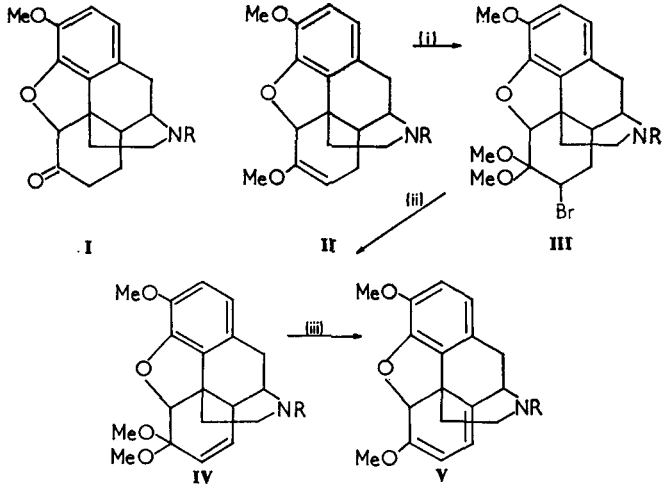
References

Croxatto, H. & Belmar, J. (1961). *Nature, Lond.*, **192**, 879–880.
Erspamer, V. & Glässer, A. (1963). *Brit. J. Pharmacol.*, **20**, 516–527.
Feldberg, W. & Lewis, G. P. (1963). *J. Physiol.*, **167**, 46–47P.
Parratt, J. R. (1964), *Brit. J. Pharmacol.*, **22**, in the press.

The synthesis of *N*-allylnorthebaine

SIR,—*N*-Allynorthebaine (V; R = $CH_2:CH\cdot CH_2$) is of major importance in the study of the structure-activity relationships of the morphine alkaloids and their derivatives. We now report the synthesis of *N*-allylnorthebaine, *N*-cyclopropylmethylnorthebaine, *N*-(t-butoxycarbonyl)northebaine, and of northebaine (V; R = H) itself.

O-Methylation of *N*-benzyloxycarbonyldihydronorcodeinone (I; R = $PhCH_2O\cdot CO$) with methyl sulphate and sodium t-butoxide gave the enol ether (II; R = $PhCH_2O\cdot CO$), which on treatment with triethylsilane in the presence of palladium chloride and triethylamine, followed by addition of methanol (Birkofer, Bierwith & Ritter, 1961), gave Δ^6-dihydronorthebaine (II; R = H), m.p. 153–154°. This product was converted into northebaine (V; R = H) [salicylate, m.p. 192·5 — 193·5° (decomp.)] by the route illustrated, with is analogous to that employed by Rapoport and his co-workers in the synthesis (Rapoport, Reist & Lovell, 1956) of thebaine itself from Δ^6-dihydrothebaine (II; R = Me) (Homeyer, 1956). Alkylation of northebaine with allyl bromide, or, better, alkylation of the ketal (IV; R = H) followed by treatment with anhydrous toluene-*p*-sulphonic acid in chloroform, gave *N*-allylnorthebaine (V; R = $CH_2:CH\cdot CH_2$)(salicylate, m.p. 185–187°). An alternative synthesis started from the ketone (I; R = $Bu^tO.CO$), itself obtained on treatment of dihydronorcodeinone (I; R = H) with t-butyl azidoformate (Schwyzer, Sieber & Kappeler, 1959; the reagent was prepared according to Carpino, Giza & Carpino, 1959). Further stages, analogous to those already described, led to *N*-(t-butoxycarbonyl)northebaine (V; R = $Bu^tO\cdot CO$), which on further treatment with toluene-*p*-sulphonic acid gave northebaine.



(i) MeOBr (ii) $EtMe_2COK$ (iii) p-$Me\cdot C_6H_4\cdot SO_3H$

O-Methylation of *N*-cyclopropanecarbonyldihydronorcodeinone gave the enol ether (II; R = cyclopropanecarbonyl), which was reduced with lithium aluminium hydride to *N*-cyclopropylmethyl-Δ^6-dihydronorthebaine (II; R = cyclopropylmethyl). This compound was converted into *N*-cyclopropylmethylnorthebaine (V; R = cyclopropylmethyl) [salicylate, m.p. 197–198·5° (decomp.)] by methods already outlined.

The ketals (IV; R = H and R = $Bu^tO{\cdot}CO$) were surprisingly unstable, partial conversion to the corresponding thebaine analogues (V; R = H and R = $Bu^tO{\cdot}CO$) occurring during isolation. In contrast, the ketal (IV; R = cyclopropylmethyl) is stable in the absence of acid.

Satisfactory analytical and infra-red spectral data were obtained for all new compounds except the unstable ketal (IV; R = $Bu^tO{\cdot}CO$), which was characterised by the infra-red absorption of freshly-prepared material.

Additional spectral confirmation of structures was obtained for the new thebaine analogues (V) (ultra-violet absorption at 285 mμ in EtOH) and for Δ^6-dihydronorthebaine (II; R = H) and norcodeinone dimethyl ketal (IV; R = H) [nuclear magnetic resonance: $\tau(CDCl_3)$ 5·19 (5 — H), 5·31 (7 — H), 6·18 (3 — OMe) and 6·54 (6 — OMe), and 4·43 (7 — H + 8 — H), 5·28 (5 — H), 6·16 (3 — OMe), 6·55 (6 — OMe) and 6·89 (6 — OMe), respectively].

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References

Birkofer, L., Bierwith, E. & Ritter, A. (1961). *Ber. dtsch. chem. Ges.*, **94**, 821–824.
Carpino, L. A., Giza, C. A. & Carpino, B. A. (1959). *J. Amer. chem. Soc.*, **81**, 955–957.
Homeyer, A. H. (1956). *J. org. Chem.*, **21**, 370.
Rapoport, H., Reist, H. N. & Lovell, C. H. (1956). *J. Amer. chem. Soc.*, **78**, 5128.
Schwyzer, R., Sieber, P. & Kappeler, H. (1959). *Helv. chim. acta*, **42**, 2622–2624.

Effects of smooth muscle stimulants and their antagonists upon potassium ion uptake and release in strips of guinea-pig ileum

SIR,—Born & Bülbring (1956), using the guinea-pig taenia coli, noted that spontaneous rhythmic activity was associated with increased outward flux of $^{42}K^+$. Stretching, histamine and acetylcholine had the same effect. Adrenaline, however, increased only the inward rate of movement of $^{42}K^+$ in 13 out of 24 preparations. Using a potassium-rich bath solution, Durbin & Jenkinson (1959, 1961) found that in the guinea-pig taenia coli, carbachol increased both inward and outward fluxes of $^{42}K^+$; both effects were abolished by atropine. Hurwitz (1960), using pilocarpine, found that $^{42}K^+$ release was increased and its uptake reduced. The effect on efflux was blocked by cocaine. Using the longitudinal smooth muscle layer of the guinea-pig ileum, Weiss, Coalson & Hurwitz (1961) showed that pilocarpine, acetylcholine and potassium-rich Tyrode's solution increased $^{42}K^+$ release. The two former also decreased $^{42}K^+$ influx. Calcium-free Tyrode's solution eliminated the contractile response to