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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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

pilocarpine, but not the increased $^{42}K^+$ release, while cocaine reduced both contractile response and $^{42}K^+$ efflux, due to potassium-rich bath fluid. Chujyo & Holland (1962) have shown that pilocarpine decreased $^{42}K^+$ uptake and increased its release in tubular segments of guinea-pig ileum. In 1956, Lembeck & Strobach showed that in the cat small intestine acetylcholine increased potassium (K^+) release: an effect counteracted by atropine and papaverine, but not by cocaine. Histamine and stretching had no effect but neostigmine and

TABLE 1. DRUG EFFECTS UPON $^{42}K^+$ UPTAKE AND RELEASE IN STRIPS OF GUINEA-PIG ILEUM

Drug	Dose (per ml)	Effect on $^{42}K^+$ release*	Effect on $^{42}K^+$ uptake*	Change in residual content of potassium*
Acetylcholine chloride	0·1 mg	Increased (8) $P < 0.001$	Decreased (16) $P < 0.001$	Decreased (8) $0.001 < P 0.01$
Carbachol	3 μg	Increased (8) $P < 0.001$	Decreased (16) $P < 0.001$	Decreased (8) $0.02 < P < 0.05$
Histamine acid phosphate	10 μg	Increased (8) $P < 0.001$	Decreased (16) $P < 0.001$	Decreased (8) $0.02 < P < 0.05$
5-Hydroxytryptamine creatinine sulphate	10 μg	Increased (8) $P < 0.001$	Decreased (16) $P < 0.001$	No change (8) $0.60 < P < 0.70$
Barium chloride	1 mg	Increased (8) $P < 0.001$	Decreased (16) $P < 0.001$	No change (8) $0.05 < P < 0.10$
Papaverine sulphate	0·2 mg	Decreased (8) $P < 0.001$	Decreased (16) $P < 0.001$	No change (8) $0.90 < P$
Lysergic acid diethylamide	10 μg	No change (8) $0.60 < P < 0.70$	No change (16) $0.80 < P < 0.90$	No change (8) $0.70 < P < 0.80$
Atropine sulphate	10 μg	No change (8) $0.40 < P < 0.50$	No change (16) $0.30 < P < 0.40$	No change (8) $0.80 < P < 0.90$
Mepyramine maleate	10 μg	No change (8) $0.50 < P < 0.60$	No change (16) $0.60 < P < 0.70$	No change (8) $0.80 < P < 0.90$
Adrenaline hydrogentartrate	0·5 mg	No change (8) $0.80 < P < 0.90$	No change (16) $0.05 < P < 0.10$	No change (8) $P = 0.80$
Acetylcholine chloride	10 μg	Depression of Acetylcholine increased release (9)	—	No change (9)
Atropine sulphate + Acetylcholine chloride	2 μg + 10 μg	$P < 0.001$		$0.40 < P < 0.50$
Histamine acid phosphate	1 μg	Depression of Histamine-increased release (9)	—	No change (9)
Mepyramine maleate + Histamine acid phosphate	0·2 μg + 1 μg	$0.001 < P < 0.01$		$0.50 < P < 0.60$
5-Hydroxytryptamine creatinine sulphate	10 μg	Depression of 5-Hydroxytryptamine-increased release (8)	—	No change (8)
Lysergic acid diethylamide + 5-Hydroxytryptamine creatinine sulphate	2 μg + 10 μg	$0.01 < P < 0.02$		$0.70 < P < 0.80$
Barium chloride	1 mg	Depresssion of Barium Chloride-increased release (8)	—	No change (8)
Papaverine sulphate + barium chloride	0·2 mg + 1 mg	$P < 0.001$		$0.10 < P < 0.20$

* Figures in parentheses indicate the number of paired strips of guinea-pig ileum used.

tetramethylammonium also increased K^+ release. Pilocarpine, nicotine, suxamethonium and decamethonium also did so, but irregularly. The studies of Tobain & Fox (1956) and Headings & Rondell (1962) suggest that, in dog arteries noradrenaline causes both increased uptake and release of K^+.

Using strips of isolated guinea-pig ileum and Krebs' solution (Banerjee & Lewis, 1963), we have also noted that acetylcholine increases release and depresses uptake of $^{42}K^+$; carbachol, histamine, 5-hydroxytryptamine and barium chloride have similar effects. Adrenaline had no statistically significant effect on $^{42}K^+$ uptake or release, but out of 16 uptake experiments the test-preparation showed a higher count than the control in 13 cases. Of the drug antagonists only papaverine sulphate, which significantly decreased both $^{42}K^+$ uptake and release (Banerjee & Lewis, 1963), had an effect. Atropine depressed the increased release of $^{42}K^+$ due to acetylcholine. Mepyramine, papaverine and lysergic acid diethylamide respectively antagonised the increased $^{42}K^+$ release due to histamine, barium chloride and 5-hydroxytryptamine (Table 1). These results support the findings of the workers cited above on potassium release, differing from Durbin & Jenkinson (1959, 1961) who used depolarized muscle on the effects of carbachol on $^{42}K^+$ uptake.

The results indicate that, at the doses used, drug antagonists have no apparent effects upon release or uptake of $^{42}K^+$, but are able to prevent the characteristic effects of the agonist. When the potassium remaining in the tissue following the release experiments was estimated flame photometrically, it was found that acetylcholine-treated muscles showed a highly significant fall. Significant falls were also shown by tissues which had been treated with carbachol and histamine (Table 1).

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