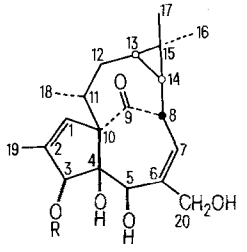
2,6-dimethylundecanoate. 7 other residues were not identified. Thus, the ingenol esters **6** have the structures given in



6: R= $COCH(CH_2)_3CHCH_2CH_3$ (CH_3, CH_3)
$COCH(CH_2)_6CH_3$ (CH_3)
$COCH(CH_2)_3CHCH_2CH_2CH_3$ (CH_3, CH_3)
$COCH(CH_2)_7CH_3$ (CH_3)
$COCH(CH_2)_3CH(CH_2)_3CH_3$ (CH_3, CH_3)
$COCH(CH_2)_8CH_3$ (CH_3)
tentatively
$COCH(CH_2)_3CH(CH_2)_4CH_3$ (CH_3, CH_3)

The occurrence of methyl substituted long chain fatty acids in higher plants is unusual[13]; to our knowledge the only branched long chain fatty acid derivatives isolated from plants are amides of 7-methyl-octanoic and 9-methyl-decanoic acid from Japanese *Capsicum*[14] and methyl-7-methyl-octanoate from hop[15].

Irritant and cocarcinogenic activities. The irritant doses 50 (ID_{50}) of the compounds isolated are given in Table I. For comparison, croton oil factor A_1 (TPA), the main irritant and cocarcinogen from croton oil[6], is used.

As compared to TPA the ingol esters **1** and **2** are not irritant on the mouse ear. The 12-deoxy-phorbol esters are relatively weak irritants and it is interesting to note that, within the variations of the assay, the ID_{50} of **3** is identical with that of the corresponding tigliate[8]. The mixture of ingenol acylates shows considerable irritant activity.

Cocarcinogenic activities were tested in the standard assay[6] on the back skin of mice using TPA for comparison. The results are given in Table II in terms of tumor rates and tumor yields, together with the mortality rates in each experiment. Pronounced necrosis of the skin is observed in the treated area after 2–3 applications of 12-deoxy-phorbol-13-isobutyrate-20-acetate (**4**) and -13-phenylacetate-20-acetate (**5**). Therefore, the mortality of animals in case of **4** and **5** is relatively high. A definite but weak cocarcinogenic effect is exerted by 12-deoxy-phorbol-13-angelate-20-acetate (**3**) (and, perhaps, by **5**). With the mixture of ingenol-3-acylates, the mortality is not exceptionally high. As can be seen from Table II (experiments 541 and 601), $p = 0.1$ μMoles of the mixture appear to be equipotent to $p = 0.01$ μMoles of TPA.

Zusammenfassung. Aus «Euphorbium», dem luftgetrockneten Latex von *Euphorbia resinifera* Berg, wurden 2 neue Ester des tri- und makrozyklischen, polyfunktionellen Diterpens Ingol, 2 neue und ein bereits bekannter Ester des tetrazyklischen polyfunktionellen Diterpens 12-Desoxy-phorbol sowie ein Gemisch von neuen Estern des tetrazyklischen polyfunktionellen Diterpens Ingenol isoliert. Das Gemisch der Ingenolester enthält langkettige, methylverzweigte Fettsäuren. Alle isolierten Ester wurden auf irritierende Wirkung am Mäuseohr und auf cocarcinogene Wirkung an der Rückenhaut der Maus geprüft.

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6 August 1974

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[17] S. K. is grateful to the Alexander-von-Humboldt-Stiftung for a fellowship. Firma E. Merck, Darmstadt, kindly provided the 'Euphorbium' used in our investigation.

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The Analgesic Action of 1-Fluorocodeine

It is well known[1] that introduction of substituents into the aromatic ring of morphine (**1**), codeine (**2**), and their congeners leads to a marked decrease in analgesic effect. For instance, 1-chloro- and 1-bromocodeine show only about $^1/_2$ of the potency of the parent (**2**), and the activity of 1-acetocodeine is likewise markedly smaller than that of (**2**)[1]. A priori, this decrease in pharmacological effect due to the halogen atoms could be caused by their bulk, which might interfere with the proper attachment of the molecule to a binding site on a receptor, or by their electronegativity, which would influence the charge distribution in the aromatic ring, and through this the analgesic action; the diminished effect of 1-acetocodeine could be explained in a similar manner.

To decide between these alternatives, we have prepared the hitherto unknown 1-fluorocodeine (**3**). Since the atom of fluorine is hardly larger than that of hydrogen (van der Waals radii[2]: H, 1.2; F, 1.35 Å), its steric effect should be minimal compared to that of other substituents, which are all significantly larger[2] (e.g. Cl, 1.80; Br, 1.95 Å); on the other hand, this most electronegative of all atoms

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[2] L. PAULING, *The Nature of the Chemical Bond*, 3rd. edn. (Cornell University Press, Ithaca, New York 1960), p. 260 and 91.

should exert a powerful electronic influence upon the aromatic ring. In addition, it could provide an acceptor site for hydrogen bonding. Examination of the analgesic activity of (**3**) should thus yield information upon the relative importance of steric vs. inductive influences.

1-Fluorocodeine (**3**) was prepared from 1-aminocodeine[3] via the diazonium fluoroborate, which was obtained as a yellowish powder on carrying out the diazotization in a 1:2 mixture of fluoroboric acid and ethanol. Schiemann-reaction[4], i.e. pyrolysis of this salt, gave acceptable yields (~ 30%) of (**3**) only if performed on a small scale (100–200 mg). However, the method of KIRK and COHEN[5] for photochemical decomposition of diazonium fluoroborates in 50% aqueous fluoroboric acid provided the desired (**3**) in similar yields on a 0.5–1.0 g scale. The compound was isolated by column chromatography on SiO_2 (Merck, 70–350 mesh) with chloroform and chloroform-acetone-diethylamine (5:1:0.5) as eluants; it was purified by recrystallization from acetone-hexane. Colorless crystals, m.p. 176–179°; mol. wt. 317 (mass spec.; calc. for $C_{18}H_{20}NO_3F$, 317). 1-Fluorocodeine had the expected spectroscopic characteristics; the splitting of the NMR-signal from the proton at C-2 into a doublet (1H; δ 6.41, $J = 12$ Hz) by the adjacent fluorine conclusively identifies the compound[6].

The (**3**) obtained by either thermal or photochemical decomposition of the fluoroborate was sometimes accompanied by varying amounts of (**2**); similar replacement of the diazonium group by hydrogen has been observed in other instances[7].

Pharmacological investigation of (**3**) gave the results summarized in the Table. Analgesic activity was determined by the hot-plate method[8]. Clearly, neither the pain-relieving effect nor the other observed parameters were significantly different from those of (**2**). This finding strongly suggests that the decrease in analgesic potency found[1] on introduction of substituents on the aromatic ring of (**2**) and its relatives is caused by the bulk of these substituents; their inductive effect seems to have no detectable influence.

The binding of (**3**) to the narcotics receptor of rat brain has been measured[9] by Dr. WERNER A. KLEE, whom we wish to thank for permission to quote his findings. The dissociation constants oberved for (**3**), (**2**), and (**1**) are 7×10^{-7}, 8×10^{-7}, and 3×10^{-9} *M*, respectively. Here, again, the behavior of (**3**) is thus not significantly different from that of (**2**)[10].

Zusammenfassung. Das bisher unbekannte 1-Fluorcodein wurde durch Schiemann-Reaktion aus 1-Aminocodein dargestellt. Es ist nahezu ebenso stark analgetisch wirksam wie Codein, und wird fast ebenso stark an den Morphin-Rezeptor des Rattengehirns gebunden. Diese Befunde zeigen, dass die früher beobachtete verringerte Aktivität von 1-Chlor-, 1-Brom-, und 1-Acetocodein auf die Raumbeanspruchung der Substituenten zurückzuführen ist.

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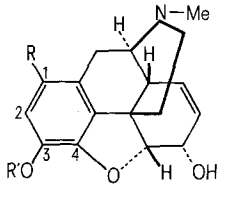

(**1**): R = R' = H
(**2**): R = H, R' = Me
(**3**): R = F, R' = Me

Table I

		1-Fluoro-codeine (*2*)	Codeine (*3*)
ED_{50} (mg/kg)		7.9	7.5
Onset of action		4.0	3.4
Peak of action	(min after	22.8	12.4
Duration of action	administration)	118.8	108.7

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[6] 1-Fluorodihydrocodeine was prepared in analogous fashion from 1-aminodihydrocodeine. Mol. wt. 319 (mass spec.). It was not obtained crystalline.
[7] Cf., e.g., T. KAMETANI, T. SUGAHARI, F. SATOH and M. YAGI, Chem. Commun. *1968*, 1398; J. chem. Soc. (C), *1969*, 520.
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[9] For the method used, see W. A. KLEE and R. A. STREATY, Nature, Lond. *248*, 61 (1974).
[10] The authors are much indebted to Dr. EVERETTE L. MAY, Laboratory of Chemistry, NIAMDD, for the pharmacological data, and to Dr. K. L. KIRK of the same laboratory for the photochemical experiments.
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Hypersensitivity to Lysergic Acid Diethylamide (LSD-25) and Psilocybin in Essential Headache[1]

The brain modulation of the pain input is partly controlled by monoamines, mainly by 5-hydroxytryptamine (5-HT)[2,3]. An impairment of the modulation following a deficiency of 5-HT, has been recently hypothesized in the mechanism of migraine and other essential headaches (EH)[4,5]. According to the supersensitivity phenomenon, a deficiency of 5-HT could induce an increased reactivity of the specific brain receptors to the same

[1] This study has been carried out with a grant from the National Council of Research, Rome, Italy.
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