is typical of other 4-deoxyphorbol diesters with a primary hydroxyl group at C-20 (7–9). Mass spectral and NMR observations permitted the assignment of these ester functions as tiglic and isobutyric acids (9, 11). The tiglic group was assigned to C-12 because a fragment ion in the mass spectrum of I at *m/e* 401 indicated the loss of an acyloxy radical rather than a whole acid substituent from the molecular ion, an effect that was noted previously in phorbol 12,13-diesters (12). In contrast, as indicated by the fragment ion at *m/e* 412, the C-13 isobutyric substituent left the molecule of I as an acid (12). Confirmation of these assignments was achieved using a selective hydrolysis procedure in which the C-12 substituent of I was less susceptible to hydrolysis than the C-13 substituent (8). This procedure resulted in the formation of II, in which the tiglyl substituent was detected by NMR and mass spectral analyses.

Esters of 4-deoxyphorbol appear to be rare in the plant kingdom, having been described previously in *Euphorbia tirucalli* (7, 8) and *E. biglandulosa* (9). The irritant principle I in *S. grantii* is the first representative in this series to be esterified with two short-chain acids.

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N-Demethylation of Dextromethorphan

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Abstract □ In addition to providing an efficient synthesis of 3-methoxymorphinan hydrochloride, the use of 2,2,2-trichloroethyl chloroformate in the *N*-demethylation of dextromethorphan led to the isolation of two novel zinc salts of 3-methoxymorphinan.

Keyphrases □ Dextromethorphan—*N*-demethylation to yield 3-methoxymorphinan hydrochloride and two novel zinc salts of 3-methoxymorphinan □ Antitussives—dextromethorphan, *N*-demethylation to yield 3-methoxymorphinan hydrochloride and two novel zinc salts of 3-methoxymorphinan □ 3-Methoxymorphinan—synthesis by *N*-demethylation of dextromethorphan

A sample of 3-methoxymorphinan (V) recently was required in these laboratories for pharmacological evaluation. Compound V is one of the three known metabolites of dextromethorphan (3-methoxy-*N*-methylmorphinan, I) (1, 2), a clinically useful antitussive agent. This report describes a new synthesis of V from I and the isolation of novel zinc salts of V.

EXPERIMENTAL[1]

Synthesis of 1,3,4,9,10,10a-Hexahydro-6-methoxy-2*H*-10,4a-(iminoethano)phenanthrene-11-carboxylic Acid 2,2,2-Trichloroethyl Ester (II)—Dextromethorphan hydrobromide monohydrate[2] (27.8 g, 75.0 mmoles) was partitioned between chloroform and a solution of 5.7 g of potassium hydroxide in water. The organic layer was separated, dried (sodium sulfate), and concentrated to leave a viscous oil, which solidified upon standing to yield 20.4 g (100%) of I, mp 107–110°; IR (mineral oil): 1610 cm^{-1}. TLC on silica gel with chloroform–methanol (9:1) gave a single spot at $R_f \simeq 0.1$.

To a solution of I (8.14 g, 30.0 mmoles) in 100 ml of benzene was added 2,2,2-trichloroethyl chloroformate[3] (6.99 g, 33.0 mmoles). After refluxing for 1 hr, the solution was concentrated to leave 14.6 g of crude II as a viscous oil; IR (mineral oil): 1710 (C=O) cm^{-1}; NMR (deuterochloroform): δ 4.70 (s, 2H, OCH_2); mass spectrum (70 ev, electron impact): *m/e* 431 (molecular ion). TLC on silica gel with chloroform–methanol (9:1) gave a single spot at $R_f \simeq 0.8$.

Synthesis of 3-Methoxymorphinan Tetrachlorozincate (IV)—To a solution of II (12.7 g, 29.3 mmoles) in 100 ml of 90% acetic acid was added 5 g of powered zinc. An exotherm followed. After 20 min, TLC indicated completeness of the reaction, and the mixture was filtered. The filtrate was concentrated to a white solid, which was triturated with ether and collected to yield 3-methoxymorphinan tetraacetatozincate (III), mp 157–167° (glass); NMR (deuterochloroform and dimethyl sulfoxide-d_6): δ 7.20–7.00 (m, 1H, aromatic), 6.87–6.68 (m, 2H, aromatic), 3.80 (s, 3H, OCH_3), 3.30–3.00 (m, 3H, $CHNHCH_2$), and 2.06 (s, ~6H, acetate ions); mass spectrum (70 ev, electron impact): *m/e* 257 (molecular ion). TLC on silica gel with chloroform–methanol (9:1) gave a single spot at $R_f \simeq 0.15$.

Crude III (10.0 g) was dissolved in 2000 ml of chloroform, and dry hydrogen chloride gas was bubbled through the solution for 10 min. The solution was concentrated, and the resulting oil partially crystallized upon standing under ether. Trituration with a small volume of isopropanol

[1] Melting points are uncorrected. IR spectra were recorded with a Perkin-Elmer model 727B spectrophotometer. NMR spectra were obtained with a Varian EM360A spectrometer. Mass spectra were recorded with a Finnigan model 4023 gas chromatograph–mass spectrometer (electron impact and chemical ionization) at 70 ev. Combustion analyses for carbon, hydrogen, nitrogen, chlorine, and zinc were performed by Dow Analytical Laboratories and Galbraith Laboratories, Knoxville, Tenn.

[2] Dow Chemical Co., Indianapolis, Ind.

[3] Aldrich Chemical Co., Milwaukee, Wis.

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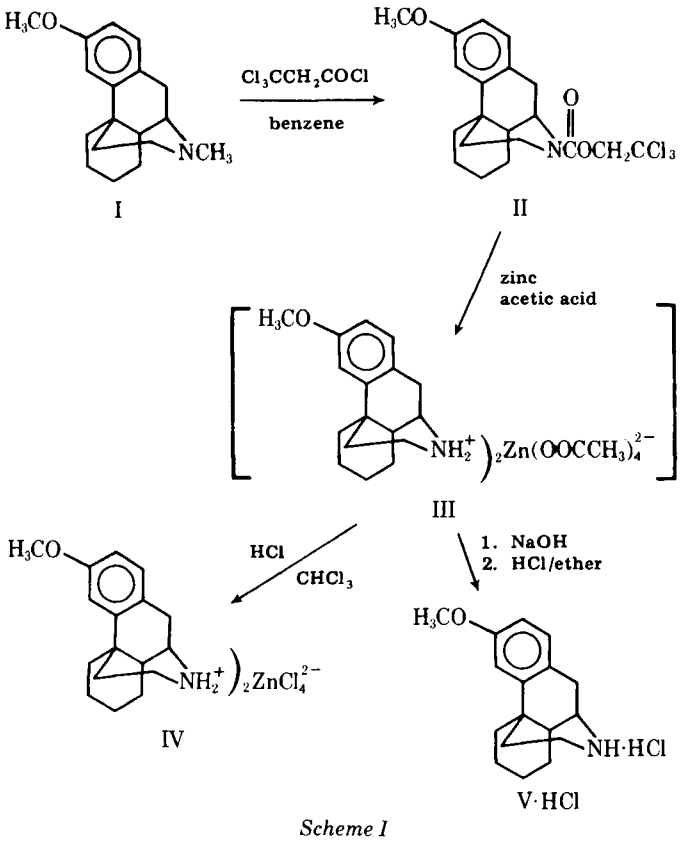

Scheme I

effected complete crystallization. Recrystallization of this material twice from isopropanol–ethyl acetate gave 2.19 g of IV, mp 191–192°; IR (mineral oil): 3200–2750 (NH_2^+), 1600, 1505, 1235, and 1030 cm^{-1}; NMR (dimethyl sulfoxide-d_6): δ 9.07 (broad s, 2H, NH_2^+, deuterium oxide exchangeable), 7.30–7.10 (m, 1H, aromatic), 6.96–6.77 (m, 2H, aromatic), and 3.78 (s, 3H, OCH_3). TLC on silica gel with chloroform–methanol (9:1) gave a single spot at $R_f \simeq 0.15$.

Anal.—Calc. for $C_{34}H_{48}Cl_4N_2O_4Zn$: C, 56.40; H, 6.68; Cl, 19.59; N, 3.87; Zn, 9.03. Found: C, 56.52; H, 6.54; Cl, 19.40; N, 3.70; Zn, 8.94.

Synthesis of 3-Methoxymorphinan (V) Hydrochloride—Crude III (21.8 g, 26.7 mmoles) was dissolved in chloroform and treated with 75 ml of 1 *N* NaOH. A flocculent white precipitate was removed by filtration. The organic phase of the filtrate was separated, dried (sodium sulfate), and concentrated to yield 10.5 g (77%) of V as a viscous oil; IR (neat): 1610, 1490, 1240, 1040, and 745 cm^{-1}; NMR (deuterochloroform): δ 7.15–6.95 (m, 1H, aromatic), 6.88–6.64 (m, 2H, aromatic), and 3.79 (s, 3H, OCH_3).

A solution of the free base (10.0 g, 38.8 mmoles) in ether–ethyl acetate was treated with ethereal hydrogen chloride until oiling no longer occurred. Scratching produced a white solid, which was collected, washed with ether, and air dried to yield 9.30 g (81%) of V, mp 249–250.5° (methanol–ether–ethyl acetate) [lit. (3) mp 253.5–255°]; IR (mineral oil): 3100–2400 (NH_2^+), 1610, 1510, 1245, 1040, and 900 cm^{-1}; NMR (dimethyl sulfoxide-d_6): δ 9.55 (broad s, 2H, NH_2^+, deuterium oxide exchangeable), 7.26–7.05 (m, 1H, aromatic), 6.95–6.73 (m, 2H, aromatic), and 3.75 (s, 3H, OCH_3).

RESULTS AND DISCUSSION

N-Demethylation of I was accomplished previously using phenyl chloroformate (followed by hydrolysis of the resulting carbamate) (3) or cyanogen bromide (4). 2,2,2-Trichloroethyl chloroformate was considered an attractive potential reagent for this *N*-demethylation since it is mild and was previously employed for the demethylation of tertiary methylamines. Yields are high for *N*-demethylation using this reagent; morphine was demethylated in 75% yield with 2,2,2-trichloroethyl chloroformate (5). Demethylation with 2,2,2-trichloroethyl chloroformate generally leads to fewer side reactions and a cleaner product than does demethylation with cyanogen bromide. The use of ethyl or phenyl chloroformate for demethylation requires a strong acid or strong base for hydrolysis of the intermediate carbamates, whereas 2,2,2-trichloroethyl chloroformate does not.

Accordingly, dextromethorphan (I) was treated with 2,2,2-trichloroethyl chloroformate to produce II. Treatment of an acetic acid solution of II with zinc dust produced a material that was partially characterized and assigned as the zinc tetraacetate salt of 3-methoxymorphinan (III). This remarkable salt (mol. wt. 818.30) was soluble in chloroform and displayed an elution position on a silica gel TLC plate using chloroform–methanol (9:1) as the eluent. Spectral data were in accord with the structural assignment for III (Scheme I). However, the structure of III was clearly indicated by its conversion to the zinc tetrachloride salt of 3-methoxymorphinan (IV).

Treatment of a chloroform solution of III with dry hydrogen chloride yielded a white solid, which, when recrystallized twice from isopropanol–ethyl acetate, displayed a sharp melting point at 191–192°. An aqueous solution of this material, when treated with aqueous silver nitrate, produced a voluminous, white precipitate. Spectral data for this material were in accord with Structure IV and were similar to those recorded for III. Elemental combustion analysis established the structure of the zinc salt as IV. Correct analyses for carbon, hydrogen, nitrogen, chlorine, and zinc were obtained. These analyses could be obtained only if the salt was dried under vacuum at 60°. Drying at 40 or 80° led to incorrect analyses, presumably due to insufficient removal of volatile substances and decomposition, respectively.

The tendency for 3-methoxymorphinan (V) to associate with zinc produced two salts (III and IV), whose identification was subordinate to the preparation of the desired metabolite (V). However, it is speculated that the ability of at least one metabolite of dextromethorphan to complex with zinc (and perhaps other trace metals) may be intimately associated with the pharmacology displayed by I.

Associated zinc was separated readily from III by partitioning between chloroform and aqueous base. The chloroform layer then contained noncomplexed V, which was isolated and treated with dry hydrogen chloride to produce 3-methoxymorphinan (V) hydrochloride. The overall yield of V·HCl from I was ~70%.

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