Derivatives of Morphine: the Structure of Pentachloro-oxy- and -ethoxycodides; an Unusual Addition Reaction to an Aromatic Ring

By U. EISNER, T. J. BATTERHAM, and U. WEISS*
(*National Institute of Arthritis and Metabolic Diseases, Bethesda, Maryland* 20014)
and ISABELLA L. KARLE
(*Naval Research Laboratory, Washington, D.C.* 20390)

DURING their research on halogeno-morphides and -codides, Small, Faris, and Mallonee[1] investigated the action of cold sulphuryl chloride on morphine and a few of its congeners. Morphine itself was unaffected, codeine, β-chlorocodide, and α-chloromorphide yielded resins, but α-chlorocodide (I) gave a crystalline base, pentachloro-oxycodide (II), whose empirical formula, $C_{18}H_{20}NO_3Cl_5$, suggested that it was formed by the addition, to (I), of four atoms of chlorine, and one of oxygen. Since (II) proved quite intractable, forming a resin on contact with warm dilute acid or on attempted hydrogenation, nothing further was established about this product of an obviously unusual reaction.

We have confirmed the formation and empirical formula of (II), which was obtained as silky needles from hexane or cyclohexane. It was homogeneous on t.l.c. (silica gel, 3% MeOH in $CHCl_3$).

Spectroscopic data (no absorption band above 210 mμ; no n.m.r. signals in the aromatic region) conclusively showed that (II) no longer contains the aromatic ring of (I); i.r. bands ascribable to carbonyl or enol ether[2] groups are likewise absent, although a band due to hydroxyl was observed [ν(OH) 3600 cm.$^{-1}$].

The exceeding sensitivity of (II) to most agents frustrated attempts to establish its structure by chemical means, only minute yields of crystalline products being obtained, at best, in a variety of reactions; futhermore, the thin, silky needles of (II) were unsuitable for the elucidation of its structure by X-rays. It was found, however, that quenching the reaction mixture with cold ethanol rather than ice[1] yielded a pentachloroethoxycodide† (III) analogous to (II) which, while similar to the latter in its behaviour towards chemical transformations, formed compact crystals from hexane, m.p. 183—184°, suitable for X-ray investigation.

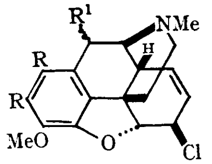
The X-ray analysis showed the space group to be $P2_12_12_1$ with cell dimensions $a = 13\cdot38$, $b = 9\cdot50$, and $c = 17\cdot58$ Å. The results of this investigation reveal that (III) has the highly unusual structure shown below; (II) is undoubtedly the analogous compound with R = H. The absolute configuration has not been established in this determination but is presumed to be the same as that of morphine.

Since (III) decomposes under the impact of X-rays, the analysis was conducted using numerous crystals, each of them being exposed for only short periods of time. X-ray induced chemical changes are not uncommon (see for example ref. 3).

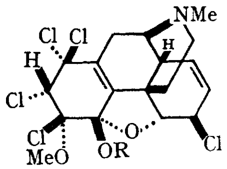
A minor by-product in the reaction of (I) with cold SO_2Cl_2 was assigned structure (IV) on the basis of its elemental analysis and n.m.r. spectrum; m.p. 156—158° (from benzene–hexane).

In an attempt to explore the process by which (II) is formed from (I), the action of limited amounts of SO_2Cl_2 in cold chloroform upon (I) was investigated. This yielded a mixture of (II) and the known[1,4] trichlorocodide (V), which could not be obtained completely pure. Neither this compound nor (IV) are likely to be intermediates in the formation of (II) or (III), which retain one hydrogen atom in ring A. The nature of the reaction of (I) to give (II) or (III) remains obscure; while it is well known that SO_2Cl_2 is an efficient agent for chlorination by a free radical[5] mechanism, addition to an aromatic nucleus by this reagent under such mild conditions appears to be unprecedented. Furthermore, the survival of groupings such as the α-chloromethoxy- and allylic *gem*-dichloro-groups of (II) and (III) during work-up involving exposure to dilute aqueous acid and ammonia seems quite surprising.

We thank Dr. K. H. Bell for help in the preparation and purification of (II) during early stages of this research.



(I) R = R¹ = H
(IV) R = R¹ = Cl
(V) R = Cl, R¹ = H



(II) R = H
(III) R = Et

(*Received, May 3rd,* 1968; *Com.* 535.)

---

† Satisfactory elemental analyses were obtained for (III) and (IV).

[1] L. Small, B. F. Faris, and J. E. Mallonee, *J. Org. Chem.*, 1940, **5**, 334.

[2] G. D. Meakins, *J. Chem. Soc.*, 1953, 4170; K. Nakanishi, "Infrared Absorption Spectroscopy"; Holden–Day, San Francisco and Nankodo Company, Ltd., Tokyo, 1962, p. 36.

[3] F. W. Comer, F. McCapra, I. H. Qureshi, and A. I. Scott, *Tetrahedron*, 1967, **23**, 4761.

[4] T. J. Batterham and U. Weiss, *Austral. J. Chem.*, 1965, **18**, 1863.

[5] *cf.* J. Sosnowsky, "Free Radical Reactions in Preparative Organic Chemistry," The McMillan Co., New York, 1964.