administering the morphine in such a way that the animals receive adequate doses of the drug at frequent enough intervals to reach and maintain the desired levels of tolerance and physical dependence. This can be done by repeated daily injections, but this consumes too much time, both in administering the doses and in the time (weeks) it takes for tolerance and dependence to develop. A more convenient alternate procedure is to implant a pellet of morphine subcutaneously, thus allowing a continual gradual release of the drug. Maggiolo and Huidobro (1) have reported such a technique utilizing a pellet of pure morphine base compressed at high pressure. While this pellet proved useful for their studies, it released drug very slowly (25% of the dose in 8 days and 50% in 16 days).

Way *et al.* (2, 3) produced morphine tolerance and dependence in mice by subcutaneously injecting increasing doses of morphine three times a day for 3 consecutive weeks; but from a time-convenience standpoint, they were interested in using the pellet implantation method. However, with the Maggiolo-Huidobro pellet, the mice developed the desired level of tolerance and dependence too slowly. By using a modified formulation developed by these laboratories, Way *et al.* could induce a high degree of tolerance and physical dependence in 2 or 3 days (the modified pellet released 25–50% of the drug in the first 2 days after implantation). Since the publication of the Way articles, we have received a number of requests for manufacturing details. Therefore, the purpose of this Communication is to provide these formulation details pertaining to the experimental products utilized in the previously published paper emanating from these laboratories. For each tablet:

Morphine, purified powder	0.075 g.
Microcrystalline cellulose (Avicel)	0.075 g.
Fumed silicon dioxide (Cab-O-Sil)	0.00075 g.
Calcium stearate	0.0015 g.

Directions: Screen the morphine, microcrystalline cellulose, fumed silicon dioxide, and calcium stearate through 60-mesh screen. Slug using 1.91-cm. (0.75-in.) FFBE punch and die, obtaining thin, firm wafers. Screen, No. 16 mesh, *via* Stokes oscillating granulator. Mix well in a twin shell blender. Compress *via* Colton tablet press model 330:

Tablet weight	0.152 g.
Tablet hardness	15 Strong-Cobb Units
Tablet thickness	3 mm.

Because of the possibility of particle segregation in the hopper of the tablet press, the slugging step was introduced. This is especially important in view of the small batch sizes produced.

The determining factor in selecting microcrystalline cellulose as the diluent was the desire to control pellet density or hardness. Because morphine is soluble in tissue fluids and cellulose is not, it is reasonable to expect that, after some initial rapid release of the drug, the absorption rate would become constant as soon as the material at the surface of the pellet has dissolved. While it is quite possible that other materials could also give the desired effect, the microcrystalline cellulose was chosen because: (*a*) it is easily compressed to varying degrees of density while providing a physically stable pellet; (*b*) it proved a satisfactory vehicle for providing a reasonably constant absorption rate for the drug; and (*c*) its physical characteristics are such that after 5 days' implantation the pellet remained as a semisolid palpable mass, facilitating easy removal from the animal.

This work suggests that microcrystalline cellulose is a possible vehicle for long-term implantation pellets for human use, provided, of course, it proves to be safe from a toxicity standpoint. Preliminary information suggests that microcrystalline cellulose may be relatively innocuous since implantation of pellets in mice containing no morphine elicited no overt toxic effects. Whether or not the body can adequately eliminate the cellulose from the tissues remains to be seen.

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Rearrangement of Chloramphenicol-3-monosuccinate

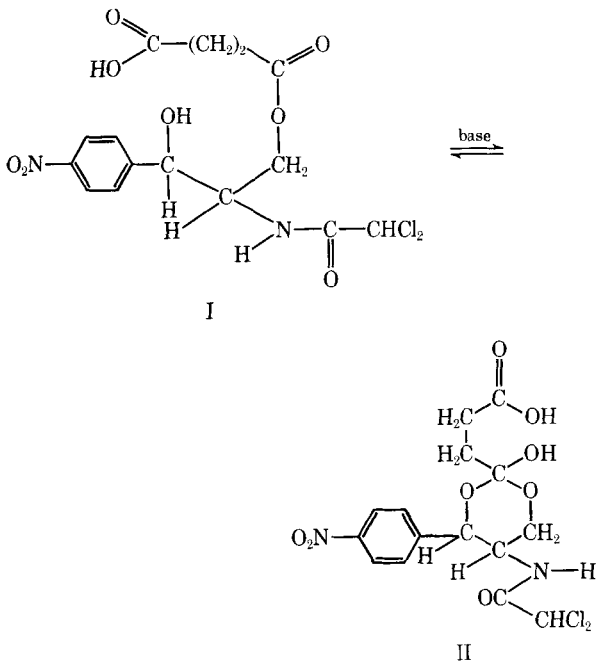
Keyphrases ☐ Chloramphenicol-3-monosuccinate—rearrangement ☐ Chromatography, liquid–liquid, thin-layer—separation, analysis ☐ NMR spectroscopy—structure ☐ Optical rotatory dispersion—identity ☐ IR spectrophotometry—structure

Sir:

Investigation of the behavior of aqueous solutions of chloramphenicol-3-monosuccinate (I) indicated that at pH's near neutrality the compound is incapable of independent existence but rather exists as an equilibrium mixture of itself and a different molecular form. This report concerns the isolation and characterization of the rearranged compound. Details of the chemistry of this process will be reported in a subsequent communication.

Components of the equilibrium mixture were separated by reverse phase liquid–liquid chromatography using a fatty acid *N,N'*-dimethylamide[1] on silanized diatomaceous earth[2] as stationary phase and 0.05 *N*

[1] Hallcomid M-18, The C. P. Hall Co., Akron Ohio.
[2] Celite 545, Johns-Manville, New York, N. Y.



Scheme I

HCl as eluent. TLC using silica plates with an acidic developer indicated that the isolated material was a single entity which could be converted to I by treatment with base (see Scheme I).

Spectral and kinetic evidence suggest that the rearranged material is a cyclic hemi-*ortho* ester (II) of the type postulated as an unstable intermediate in 1–3 acyl migrations (1, 2).

Structural determination was primarily achieved by using NMR. A comparison of the NMR spectra of I with II revealed certain significant differences in the chemical shifts and splitting patterns of several protons (Table I).

The peak positions for the amide nitrogen, the aromatic ring protons, and the $CHCl_2$ hydrogen were identical in both linear and cyclic form. The peak position of the C(1)—H proton in the cyclic compound is 57 c.p.s. downfield from that of the linear form. The deshielding effect produced on esterifying a hydroxyl group on the proton or the protons on the carbon holding the hydroxyl group is well documented (3). Also for the cyclic ester, the splitting of the C(2)—H hydrogen by the C(1)—H and the two C(3)—H protons gives a quartet centered at 4.44 p.p.m. The two hydrogens on C(3) have shifted upfield to 3.7 p.p.m. as a pair of overlapping doublets, where in the linear form these three protons form a complex multiplet.

Table I—Chemical Shift Values (p.p.m.) Using D_6Acetone for Solvent, TMS as Internal Standard

Proton	Chemical Shift (p.p.m.) Chloramphenicol-3-monosuccinate	Chemical Shift (p.p.m.) Cyclic Succinate
C_1—H	5.26	6.23
C_2—H	4.4	4.44
C_3—H_2	4.4	3.7
C_3—OH	6	—
—$(CH_2)_2$—	2.63 (singlet)	2.7 (A_2B_2)
ring—H_4	7.95 (A_2B_2)	7.95 (A_2B_2)
N—H	7.46	7.46
CCl_2—H	6.35	6.35

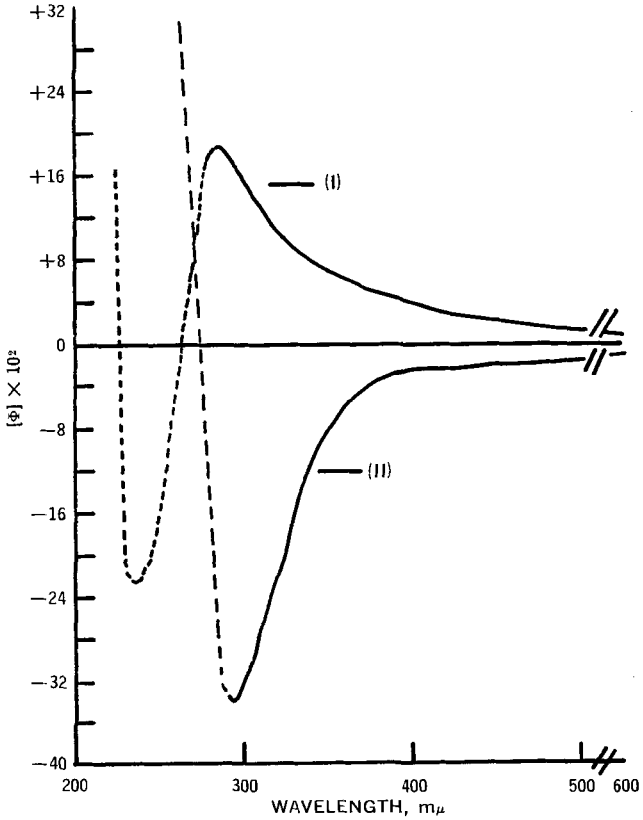


Figure 1—*The ORD curves of chloramphenicol-3-monosuccinate (I) and the cyclic hemi-*ortho *ester (II). Anhydrous ethanol is the solvent. Dashed portion of lines indicates areas of high absorbance.*

The succinate methylene protons in the cyclic *ortho* ester do not give rise to a singlet as is the case in the linear molecule. The signal for these hydrogens in the cyclic compound is an A_2B_2 system which arises from a pair of overlapping triplets. It is thought that different electronic effects associated with sp^2 and sp^3 hybridized carbon atoms adjacent to the succinate methylenes cause splitting of signal.

Additional evidence for the proposed cyclic isomer was obtained from IR and optical rotatory dispersion (ORD) data. Whereas the IR spectrum for I showed three distinct carbonyl absorptions at 1690, 1718, and 1745 $cm.^{-1}$, the spectrum for II showed only two carbonyl peaks at 1690 and 1745 $cm.^{-1}$. This apparent loss of ester carbonyl absorption and a change in absorbance in the C—O—C stretch region in the IR spectrum of II could be explained on the basis of the cyclic isomer (II).

The ORD curve for the cyclic and linear ester is shown in Fig. 1. Due to high absorption of both compounds below a wavelength of 280 mμ, this region is an approximation based on repeated determinations and several dilutions. Linear chloramphenicol-3-monosuccinate shows a positive Cotton effect, whereas the cyclic ester shows a negative Cotton effect. The ORD curves of o^1-acetylated chloramphenicol-3-monosuccinate and o^1-dichloroacetylchloramphenicol-3-mono-

succinate also shows a negative Cotton effect. Esterification of the secondary hydroxyl group is associated with a change in optical rotation resulting in a negative ORD curve for the o^1-ester compound whose ORD curve prior to esterification was positive. Also characteristic of esterification of the o^1-hydroxyl group is a paramagnetic shift of the C(1)—H. Both of these phenomena were observed in the rearrangement of chloramphenicol-3-monosuccinate.

Complete migration of the succinyl function was ruled out on the basis of NMR and chemical data. Complete migration would have given a terminal hydroxyl. No peak corresponding to that for the C(3)—OH proton of chloramphenicol was observed. Chemical evidence indicated that the 0 → 0 migration product was incapable of existence in equilibrium with chloramphenicol-3-monosuccinate under experimental conditions.

Attempts to acetylate or methylate the isomeric compound resulted in complex reaction mixtures, presumably due to the breakdown of the cyclic structure by the reacting anion. All spectral and chemical evidence support the proposed structure.

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Covalent Addition of *N*-Chlorosaccharin to Cyclohexene

Keyphrases □ *N*-Chlorosaccharin—cyclohexene addition □ Cyclohexene—*N*-chlorosaccharin addition □ *N*-(2-Chlorocyclohexyl)-saccharin—synthesis, structure, formation rate □ IR—identification, structure □ NMR—identification, structure □ UV—rate of formation

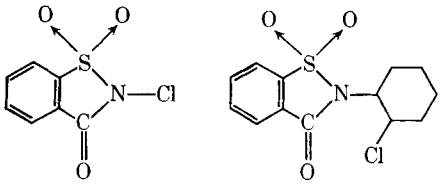
Sir:

It has recently been reported (1) that *N*-chloro-*N*-methylethanesulfonamide will add covalently across the >C=C< double bond of 1-hexene under photoirradiation. In similar, but apparently more facile, reactions, *N,N*-dichlorobenzenesulfonamide (2) and *N*-aryl-*N*-halosulfonamides (3) will add covalently to cyclohexene. Because *N*-chloro compounds are used as chlorinating and oxidizing agents for a wide variety of compounds, additional reactions of the above type must be expected to occur if the molecules to be chlorinated contain unsaturated groups.

Table I—Rate Constants for the Covalent Addition of *N*-Chlorosaccharin to Cyclohexene in Carbon Tetrachloride at 25°

[Cyclohexene]$_{added}$ × 10 *M*	[*N*-Chlorosaccharin]$_{added}$ × 10^4 *M*	$10^2 k_{obs.}$ sec^{-1}	$10^2 k_1$ M^{-1} $sec.^{-1}$
4.96	6.30	1.69	3.41
3.22	10.00	1.16	3.60

We have recently discussed (4) the possible usefulness of *N*-chlorosaccharin (I) as an organochlorinating agent on the basis of its low chlorine potential in water and its solubility and stability in a variety of organic solvents. However, we now present evidence that I will also covalently add to cyclohexene in a facile reaction at room temperature to yield *N*-(2-chlorocyclohexyl)-saccharin (II).



I II

When I (400 mg.) was added to cyclohexene (15 ml.) at 25°, it gradually dissolved and simultaneously a white powder crystallized out of solution. After recrystallization from acetone–water, this powder had m.p. 171–172.5° and the same elemental analysis as II. (Found: C, 52.07; H, 4.86; Cl, 11.94; N, 4.78; S, 10.97. II, $C_{13}H_{14}NClSO_3$, requires C, 52.0; H, 4.67; Cl, 11.85; N, 4.67; S, 10.70.) Its structure was confirmed by NMR and IR spectroscopy. Its NMR spectrum showed the presence of 4 benzene protons and 10 cyclohexene protons, but no cyclohexene-ethylene protons were evident. The IR spectrum of the compound was consistent with that of Structure II and contained a strong band at the carbonyl-stretching frequency region. This latter piece of evidence ruled out the possibility that an O—C bond existed between saccharin and cyclohexene. The product did not release iodine from aqueous solutions of potassium iodide, thereby indicating that it was not in equilibrium with *N*-chlorosaccharin and that its chlorine was fixed and no longer "active."

The rate of formation of the adduct was determined by measuring changes in UV absorbance at 270 mμ after carbon tetrachloride solutions of I and cyclohexene (which had been equilibrated at 25.0 ± 0.2°) were mixed in a 1-cm. spectrophotometer cell. The rate of change of absorbance was first order when [cyclohexene]$_{added}$ was much greater than [I]$_{added}$ and pseudo first-order rate constant, $k_{obs.}$, values were calculated. At two different cyclohexene concentrations the value of $k_{obs.}/[\text{cyclohexene}]_{added} = k_1$ was constant and thus