magnitude of this effect in man must remain speculative pending appropriately designed clinical trials.

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Received April 8, 1968.
Accepted for publication May 27, 1968.

Keyphrases

Aspirin hydrolysis—rat small intestine
Everted intestine—experimental technique
Hydrolysis, aspirin—concentration effect
Enzymes, intestinal—aspirin hydrolysis effect

A Cardioactive Steroidal Iodoacetate

Sir:

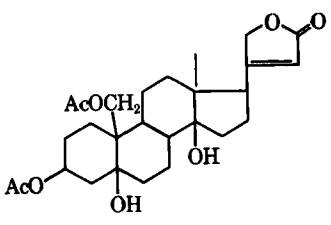
Empirical relationships between the chemical constitution and biological activity of cardiac glycosides and aglycones, *e.g.*, I, have been tabulated (1), and the unsaturated lactone at C-17 appears essential for activity. Moreover, it seems likely that these cardiotonic substances act through inhibition of enzyme systems involved in ion transport (2).

The chemical basis for the essentiality of the lactone is unknown. Portius and Repke (3) have proposed that the α,β-unsaturated carbonyl *Wirkguppierung* is a proton acceptor in hydrogen bonding, whereas Glynn (4) has postulated that addition of essential sulfhydryl groups to the unsaturated center may be involved. We have evaluated the last suggestion by the preparation of analogs.

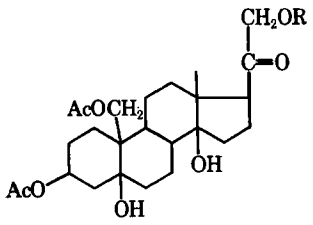
The reaction of II with chloroacetic anhydride at 55° produced the corresponding 21-chloroacetate ester m.p. 109–111°, $[\alpha]_D$ + 51°[1] which on treatment with sodium iodide in acetone solution gave the iodoacetate III, m.p. 150–155°, $[\alpha]^{20}$ + 49°.

Biological evaluation was performed in the usual way (6) in cats under chloralose-urethan anesthesia. A volume of 1 ml. of 47.5% alcohol containing 0.4 mg. of drug was injected at 3-min. intervals into the femoral vein. The effect of the drug was observed by EKG and blood-pressure readings recorded on a Grass polygraph. The following lethal doses were determined (LD ± SE in mg./kg.): III (1.37 ± 0.26), IV (7) (15.59 ± 2.28). The high activity of III indicates that the lactone ring is not an essential feature for a cardioactive compound.

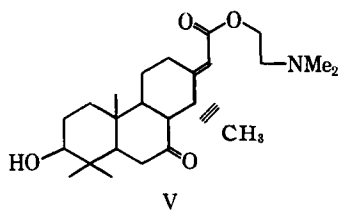
Iodoacetates are known to react with nucleophiles, such as sulfhydryl groups. Thus a reasonable explanation for the great difference in potency of the iodoacetate III relative to the acetate IV is that alkylation of an essential nucleophilic



I



II, R = H
III, R = $COCH_2I$
IV, R = $COCH_3$



V

Strophanthidiol 3, 19-diacetate (I) (5) in ethyl acetate solution was allowed to react with ozone at −70°, and the resulting ozonide was decomposed with zinc dust in acetic acid. Isolation of the product afforded 3β, 5β, 14β, 19, 21-pentahydroxypregnan-20-one 3,19-diacetate (II).

group on the receptor is required for drug action. This is in harmony with the concept that the unsaturated lactone performs a similar function by addition of the nucleophile to the double bond. Cavallito and Haskell (8) have described such

[1] Satisfactory analyses have been obtained for all new compounds in this paper.

reactions between unsaturated lactones and reagents containing sulfhydryl groups. On the other hand, the difference in activity of the iodoacetate III and the acetate IV argues against a hydrogen bonding role for the lacetone carbonyl group.

The cardiotonic activity of cassaine V (9) (LD 1.15 mg./kg.), may be explained in a similar manner, as the α,β-unsaturated ester in this material is also a potential electrophilic reagent. In both cases, the function of the polycyclic portion of the molecule is presumably to induce an inhibitory specific conformational perturbation (10) in the enzyme. This is indicated by the known biological consequences of structural variations in this part of the molecule (1), as well as by the fact that simple unsaturated lactones (11) and simple sulfhydryl reagents (12) are dissimilar from cardiac glycosides in their effects.

The extension of these studies to other electrophilic analogs is in progress.

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Received March 20, 1968.
Accepted for publication May 10, 1968.

This work was supported in part by a grant (HE 09578) from the National Heart Institute, U. S. Public Health Service.
We thank Dr. Bertram Katzung for advice concerning biological testing.

Keyphrases

Steroidal iodoacetate
Cardioactivity—steroidal iodoacetate
Lactone rine—cardioactive compounds

Books

REVIEWS

Treatise on Analytical Chemistry. Part III: *Analytical Chemistry in Industry.* Vol. 1. Edited by I. M. KOLTHOFF, P. J. ELVING, and F. H. STROSS. Interscience Publishers, Inc., 605 Third Ave., New York, NY 10016, 1967. xxiv + 455 pp. 17 × 24.5 cm. Price $17.50.

The well-known and respected "Treatise on Analytical Chemistry" series edited by Kolthoff and Elving by now has reached encyclopedic proportions. However, when it came to Part III "Analytical Chemistry in Industry" the editors, as they state in the Preface, deferred for industrially important analytical methods and procedures to Snell and Hilton's even larger "Encyclopedia of Industrial Chemical Analysis" by the same publishers. Therefore, the first volume of Part III with F. Stross as co-editor addresses selected topics to the organization builder, the laboratory designer, the production controller, and the safety conscious among others. The pharmaceutical analyst should approach this volume forewarned that there are few specific references to the pharmaceutical industry. The student eager to explore the attractiveness of industrial employment should be told that the treatise is a "comprehensive account" but comprehensiveness is not apt to stimulate the imagination or inspire enthusiasm. Where is the analytical Watson to write "The Double Focus?"

About individual contributions the following should be briefly reported: In "Analytical Chemistry and the Analytical Chemist in Industry" Royer and Maricle are of the opinion that "analytical chemistry, without doubt, entered industry through the Control Laboratory." In "Methodology of Industrial Analysis" Spauschus makes the excellent point that "the contributions of the analytical chemist to a research program will be most effective if he is given the opportunity to participate while the program is being planned." In "Organization of Analytical Chemistry in the Industrial Research Laboratory" Kirklin makes very cogent comments on the controversial question whether to submit samples for reanalysis "openly" or "blindly." Kirklin also presents a plethora of organization charts but wisely states that "changes in details of organization are made frequently in accordance with the demands of the work." He should have added "and of problems of personality." In "Organization for Analytical Chemistry in Production Control" the same