the prefix as ergokryptine[4]) only through the substitution of the L-leucine residue by the L-isoleucine residue.

As would be expected from the trivial difference in chemical structure α- and β-ergokryptine and dihydro-α- and dihydro-β-ergokryptine respectively correspond with one another extensively in their pharmacological activity. The pharmacological comparison covered the main actions of the ergot alkaloids namely the adrenolytic activity[5], the action on uterus motility[6], serotonin antagonism[7] and the influence on vascular tone[8]. β-Ergokryptine is somewhat more active than α-ergokryptine.

No statistically significant difference was established in the pharmacological activity of dihydro-α-ergokryptine and dihydro-β-ergokryptine.

A detailed account of the experimental results will be given elsewhere.

*Zusammenfassung.* Es wird die Isolierung eines neuen Isomeren des Ergokryptins beschrieben, das sich von diesem nur durch den Ersatz des Leucin-Restes durch den Isoleucin-Rest im Peptidteil des Moleküls unterscheidet. Das neue Isomere soll als β-Ergokryptin und das früher beschriebene Alkaloid als α-Ergokryptin bezeichnet werden. Die beiden Isomeren, ebenso ihre Dihydro-Derivate, unterscheiden sich pharmakologisch nur ganz unwesentlich.

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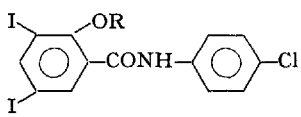
## A New Compound Effective Against Acute Fascioliasis in Sheep

Although adult *Fasciola hepatica* infections in sheep can be treated by available products, acute fascioliasis continues to be a costly problem. Some fasciolicides are ineffective against the immature flukes. Most require the administration of high dose levels to produce even a moderate response. Unfortunately a very narrow therapeutic index at these levels makes their use hazardous to the sheep under field conditions.

In our search for a new fasciolicide, efficacy against immature worms and a high therapeutic index under field conditions were major objectives. From a series of 70 candidates, 2-acetoxy-4′-chloro-3,5-di-iodobenzanilide, SYD-230 (I, R = $COCH_3$), was chosen because it fulfilled these requirements. The compound was prepared by condensing 3,5-di-iodosalicylic acid with *p*-chloroaniline to give 4′-chloro-3,5-di-iodosalicylanilide (I, R = H). Subsequent acetylation gave SYD-230 which crystallized from aqueous dimethylformamide or acetone as white needles, m.p. 215–216 °C. 2-Acetoxy-4′-chloro-3,5:di-iodobenzanilide has a theoretical elementary composition for $C_{15}H_{10}ClI_2NO_3$ of C, 33.27; H, 1.86; N, 2.59; Cl, 6.55; I, 46.87. Found: C, 33.30; H, 1.94; N, 2.48; Cl, 6.52; I, 46.83. It has strong IR-absorption peaks (KBr disc) at 3290, 1770, 1657, 1535, 1575, 1600, 1490, 1190, 830 $cm^{-1}$. Its UV-spectrum exhibits a maximum at 262 nm (methanol).




(I)

The activity of SYD-230 against immature and mature *F. hepatica* was assessed in approximately 1000 grazing sheep. In a number of experiments, infections were induced by the administration of metacercariae in gelatin capsules. Drug effectiveness was measured by quantitative fecal egg counts made before 2–8 weeks after dosing, or by live fluke counts at autopsy. Effectiveness is expressed as percentage reduction in egg output or live flukes, when compared with untreated controls.

The Table shows results from a typical slaughter experiment to determine the activity of SYD-230 against immature *F. hepatica* in sheep dosed with 300 metacercariae.

Infections with adult *F. hepatica* were reduced 98–100% by a single oral dose of SYD-230 at 25 mg/kg.

In sheep carrying natural *Haemonchus contortus* infections, activity greater than 95% was found against adult worms after a single oral dose at 25 mg/kg. There was no significant activity against *Ostertagia* spp., *Trichostrongylus colubriformis* or *Nematodirus* spp.

The $LD_{50}$ of SYD-230 in sheep was approximately 420 mg/kg by the rumenal route; 1600 mg/kg by the abomasal route. When administered orally as a 4% aqueous suspension, by conventional drenching equipment, to normal or stressed (heavily parasitized, advanced pregnancy,

| Drug | Dose level mg/kg | Age of fluke (weeks) | % effectiveness |
|---|---|---|---|
| SYD-230 | 60 | 4 | 31 |
| | 90 | 4 | 83 |
| | 32 | 6 | 67 |
| | 48 | 6 | 97 |
| $CCl_4$ | 120 | 4 | 35 |
| | 180 | 4 | 35 |
| | 64 | 6 | 0 |
| | 96 | 6 | 6 |

drought-fed or food and/or water deprived) sheep, the drug had at least a 7–8-fold therapeutic index at the 25 mg/kg level; at least a 3–4-fold index at the 40 mg/kg level.

The safety and efficacy of SYD-230 was confirmed in the field. During trials carried out under a variety of climatic and geographic conditions in Australia, 12,755 sheep were drenched at 25 mg/kg. Of 22 deaths, only 2 were judged to be drug-related. The other deaths were attributed to enterotoxemia, other clostridial toxins, the consequences of the parasitic infections or drought conditions encountered in Australia during the period of testing the drug. Among 1572 sheep dosed at 50 mg/kg, there were 12 deaths of which 3 were probably drug-related. The high efficacy of the drug against immature and mature *F. hepatica* was confirmed in these statistically designed field trials. The superiority of SYD-230 over carbon tetrachloride has been demonstrated in outbreaks of acute fascioliasis. Details of these experiments will be published at a later date.

*Zusammenfassung.* 2-Acetoxy-4'-chlor-3,5-dijodbenzanilid zeigte eine hohe Wirksamkeit gegen junge und gereifte *F. hepatica* and *H. contortus* in Schafen bei einer oralen Dosis von 25 und 40 mg/kg. Die gute Verträglichkeit der Verbindung in Schafen ergab sich aus Feldversuchen in Australien.

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## The Lipid Composition of Frog Retinal Rod Outer Segments

Retinal rod outer segments are derived from the plasma membrane of a neuron, the rod cell[1]. They may, therefore, provide a relevant macromolecular model for neuron plasma membranes, just as myelin may for oligodendrocyte plasma membranes. The paracrystalline structure of outer segments makes them amenable to examination by X-ray diffraction as well as electron microscopy; consequently, circumstances are especially favorable for determining their biochemical architecture by correlated chemical techniques[2]. This article describes studies of the lipid composition of chloroform-methanol extracts of intact dark-adapted outer segments of the leopard frog.

*Materials and methods.* All operations were done under dark-room conditions and retinas and outer segments were kept at 0 °C as much as possible. Retinas dissected from dark-adapted large male frogs (*Rana pipiens*) were suspended in frog Ringer's solution in a 3 ml tube (1 or 2 retinas/1 ml). The tube was held flexibly by its top while the lower end was stroked repeatedly with a finger or wet piece of rubber tubing, to cause the retinas to spin rapidly in the saline. After 3 min, another 1 ml of saline was added and the agitation continued for 2 min. This simple technique effectively freed outer segments from rod inner segments and produced fewer free nuclei and less debris than any other method of detachment tried[3]. The retinas and retinal fragments were allowed to settle for 10 min. The outer segments in the supernatant fluid were pipetted off, combined, and passed through Nitex mesh 25 $\mu$ in diameter (Tobler, Ernst and Traber, Inc., New York). In some experiments 10 $\mu$ Nitex was also used. The outer segments were sedimented in 2 min at half speed on an International Clinical Centrifuge (1500 rpm, 350 *g*) and washed with saline. The red pellet consisted predominantly of intact rod outer segments, the chief contaminant being large nuclei. Ten retinas yielded 2–3 million outer segments (hemacytometer count). A series of 19 pellets, totalling 30 million outer segments, provided 7 mg of lipids.

The pellets were extracted with chloroform-methanol (2:1, v/v) in the dark for several days at 4 °C. The extracts were combined and washed to remove non-lipid contaminants[4,5]. The residues from the pellets were then extracted with chloroform-methanol-concentrated. HCl (200:100:1, v/v) to solubilize any polyphosphoinositides present[6,7] and these acid extracts were combined.

Analyses for protein and lipid hexose were performed as previously described[5]; cholesterol was assayed in the non-saponifiable fraction by the method of Glick et al.[8]. Individual phospholipids were determined on the weighed solids of the washed chloroform-methanol extract by successive chemical hydrolyses and separation of the hydrolysis products by paper chromatography and electrophoresis according to Dawson et al.[9]; for comparison, lipids were also extracted from frog retinas and the phospholipids and cholesterol similarly analyzed.

*Results and discussion.* The outer segment preparations contained a high percentage of lipid, two-thirds of which was phospholipid (Table I). Lesser amounts of glycolipid and cholesterol were present. The molar ratio of phospholipid-glycolipid-cholesterol was 1:0.33:0.13. Examination of the non-saponifiable fraction by thin layer chromatography (silica gel G, $CHCl_3$ solvent) confirmed the presence of cholesterol and revealed 4 additional spots as yet unidentified[10]. Chemical evidence for glycolipids in rod outer segments has not been reported before, but their presence was suggested by Lillie[11] on the basis of histochemical staining reactions. The outer segments resembled mito chondria, chloroplasts and myelin in containing appreci-

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