plete oxidation to carbon dioxide. It is possible that there is an equilibrium between the four formally prototropic systems ('3 carbon' C=C—C—H, 'keto-enol' C=C—O—H, 'imino-enamine' C=C—N—H and 'amido-imidol' O=C—N—H) discernible in the end rings of the structures (II), (III), (IV). In this event, the structure of stercobilin might vary according to its chemical environment, and it is perhaps significant that Fischer[5] effected a higher degree of hydrogenation in acid- than in alkaline-solution. We have not, however, detected the production of any ketonic fractions such as would be expected from structures like (II) and (III) and, apart from the invariable presence of a small, non-mobile fraction, stercobilin behaves as an individual on paper chromatography and in counter-current distribution.

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C. H. Gray
D. C. Nicholson

Department of Chemical Pathology,
King's College Hospital Medical School,
Denmark Hill,
London, S.E.5.

Nov. 10.

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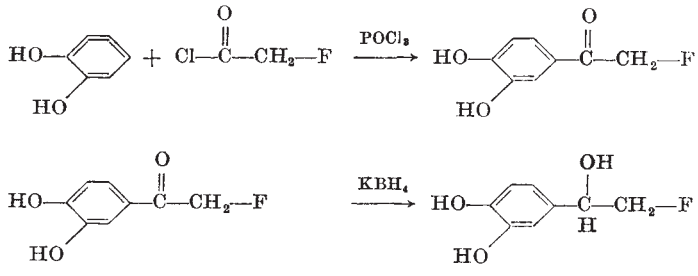
Fluoroarterenol: a Fluorine Isostere of Norepinephrine

In an investigation of the enzymatic methylation of norepinephrine, certain of the isosteres of this neurohormone, designed as antagonists of this system, have been synthesized. This communication deals with D,L-3,4-dihydroxy-(α-fluoromethyl)benzyl-alcohol, fluoroarterenol, its synthesis and biological properties.



3,4-Dihydroxyphenacylfluoride was prepared as follows. To 40 gm. of catechol in 150 ml. of benzene was added 25 gm. of phosphorus oxychloride and 25 gm. of fluoroacetyl chloride[1]. The reaction mixture was refluxed overnight. After the solvent was removed under reduced pressure, the residue was dissolved in boiling water, treated with charcoal and filtered; on cooling, the product crystallized out. This material was recrystallized from water. Yield, 20 gm.; melting point, 185° uncorr.; calculated for $C_8H_7O_3F$: C, 56·47; H, 4·26; F, 11·18; found: C, 56·11; H, 4·12; F, 11·90 per cent.

D,L-3,4-Dihydroxy-(α-fluoromethyl)benzylalcohol was prepared from this fluoride. 10 gm. of 3,4-dihydroxyphenacyl fluoride was suspended in 75 ml. of water, and a drop of concentrated sodium hydroxide was added. To this solution was added slowly 3·3 gm. of potassium borohydride with vigorous stirring. The temperature of the reaction mixture was maintained at 50° C. The reaction was completed in half an hour and dilute hydrochloric acid was added to *p*H 3·6. The water was stripped off under reduced pressure and the residue was treated with warm peroxide-free ethyl ether to extract the product from the potassium chloride and boric acid which resulted in the reaction. The extract was stripped free of ether under reduced pressure and the crude product was recrystallized from a mixture of ethyl acetate/chloroform. Yield, 8·7 gm.; melting point, 107°–110° C. (dec.) uncorr.; calculated for $C_8H_9O_3F$: C, 55·81; H, 5·23; F, 11·05; found: C, 55·17; H, 5·25; F, 11·73 per cent.

The mean arterial dog blood pressure was determined with a mercury manometer connected to the cannulated femoral artery of an animal anæsthetized with nembutal. While both *l*-epinephrine and *l*-norepinephrine bitartrate produced the expected pressor amine effect, fluoroarterenol in concentrations as high as 0·1 mgm./kgm. produced no change in the blood pressure of the dog. When, however, the animal was treated with the adrenolytic agent 'Dibenamine' (20 mgm./kgm.), fluoroarterenol (0·1 mgm./kgm.) produced a marked *depressor* effect similar to that produced by epinephrine (0·001 mgm./kgm.) and in contrast to norepinephrine (which produced the pressor effect in this preparation).

The effect of fluoroarterenol on the rabbit intestine was determined using the method described by Burn[2]. The isolated intestine from a freshly killed rabbit was placed in a 10-ml. chamber attached to a hooked hypodermic needle (which functioned also as an inlet for oxygen gas), and suspended from a writing lever. The preparation was permitted to relax in Ringer–Locke solution maintained at 35° C. All test material was added to the chamber at this temperature and dilutions made with Ringer–Locke solution. After each test addition to the bath, the preparation was washed three times with Ringer-Locke solution.

With 0·1 mgm./c.c. fluoroarterenol, marked relaxation of the isolated intestine, comparable to the effect produced by 0·002 mgm./c.c. of epinephrine or 0·004 mgm./c.c. of *l*-norepinephrine, was observed.

The non-pregnant rat uterus was employed to investigate the effect of fluoroarterenol on the contractions produced with acetylcholine. The uterus from a freshly killed rat was suspended in a chamber as described above. The Ringer–Locke solution used was prepared according to Burn[2]. The bath was aerated with a stream of oxygen, and its temperature was maintained at 30° C. The volume was 10 ml.

Contraction of the uterus was obtained by the addition of 0·25 γ/c.c. of acetylcholine. The test material was introduced into the bath and 30 sec. later acetylcholine was added. Both *l*-epinephrine (0·05 γ/c.c.) and *l*-norepinephrine bitartrate (5·0 γ/c.c.) showed the expected suppression of the acetylcholine-

induced contraction of the rat uterus. In contrast, fluoroarterenol in concentrations of 0·05 mgm./c.c. did not suppress the contractions in this preparation. However, at this concentration fluoroarterenol almost completely prevented the effect of norepinephrine and epinephrine on the rat uterus. Simultaneously introducing both fluoroarterenol (0·05 mgm./c.c.) and *l*-epinephrine (0·05 γ/c.c.) or *l*-norepinephrine bitartrate (5·0 γ/c.c.) into the bath permitted an almost maximal acetylcholine-induced contraction of the rat uterus.

Based mainly on the work of Gaddum[3] and Blaschko[4], the idea has been advanced that some adrenergic effects of derivatives of β-phenylethylamine are due to the inhibition of amine oxidase by these substances. Presumably, then, the inhibitors showed adrenergic effects due to their sparing action on the oxidative deamination of epinephrine. Since this may also account for the above physiological effects of fluoroarterenol, this substance was examined for its effect on liver amine oxidase.

The enzyme preparation employed was prepared as described by Blaschko, Richter and Schlossmann[4] using guinea pig liver as the source. The substrate was *l*-epinephrine. With this system, concentrations of fluoroarterenol as high as 100 $\mu M/3$ ml. ($5{\cdot}6 \times 10^{-2}\ M$) did not inhibit the oxidation of epinephrine.

These results indicate that the fluorine isostere of norepinephrine has pharmacological activity which cannot be accounted for on the basis of its interference with amine oxidase inactivation of epinephrine. The isostere had no observable effect on the highly specific rat uterus preparation, but its competition with the epinephrine and norepinephrine activity suggests that it can associate with the specific receptors with which the pressor amines normally react. The effect of fluoroarterenol on the 'Dibenamine' dog preparation and on the rabbit intestine preparation appears to be a direct action, but evidence presented here is equivocal.

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J. H. Fellman

Division of Neurology,
University of Oregon Medical School,
Portland 1, Oregon.

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X-Ray Diffraction Patterns and Alpha–Beta Transformation of a Protein extracted from the Human Epidermis

Recently, a fibrous protein has been extracted by one of us from the cellular portion of the human epidermis with 75 per cent lithium bromide[1]. The first observable microscopic change in the extracted epidermis was a disruption of tonofibrils and intercellular bridges; coincidentally, the protein appeared as an amorphous mass within the Malpighian layer and between the granular and horny layers[2]. When treated with 60 per cent acetone and 4 per cent acetic acid, the protein formed a gel. This gel could be dried as a film on silicone-coated glass. The present communication reports the results of an X-ray investigation of this substance.

X-ray diffraction diagrams of strips of the film were prepared with the beam perpendicular to the long axis of the strips and either parallel or perpendicular to the film surface, at a sample distance of 40 mm.

The two diagrams are identical, and show a strong, rather broad diffraction ring of about 5·15 A. and an extremely faint indication of a smaller ring of about 9·5 A. interplanar spacing. Intensive diffraction is present at small angle, near the primary beam (Fig. 1,*a*). The diagram shows no evidence of orientation, and from the diffuse character of the diffraction rings, it appears that the material is present in a low degree of crystallinity.

However, after immersion in cold water, the protein film became highly elastic and could be oriented by the extension method[3]. Strips of the protein 2–3 mm. wide were fixed in a clamp, immersed in cold water for 10 min. and stretched 200 per cent of their original lengths. The strips were held in the extended state for 1 hr. and allowed to contract in cold water for about 4 hr. until they reached constant length. At this time, 50 per cent contraction had occurred. The film had also become birefringent.

In parallel mount, the diagram (Fig. 1,*b*) of these strips consists of a diffuse outer scattering zone, at the inner edge of which a sharp ring of about 4·6 A. spacing can be seen with indications of higher intensities near the meridian. Close to the inside of this ring and fusing into it (forming a doublet) is a second, less distinct ring at about 4·7 A. Intense equatorial arcs of about 9·5 A. are present, extending at lower intensity through the meridian. The diagram is similar to that of 'regenerated α-keratin'[4–7] in the incompletely oriented state. With perpendicular mount, the same diffractions are principally present, but all evidence of orientation is absent. The innermost arcs are replaced by one continuous central disk. The different features of the diagrams in parallel and perpendicular mount indicate that the long axis of the molecules must have preferent orientation parallel to the surface of the film and random orientation in other planes, similar to that found with epidermal keratins[4].

For further comparison of the protein with keratin, its super-contraction and α–β transformation were investigated. Thermal contraction studies were carried out in the following manner. Strips of the protein film of known lengths were immersed for 2 min. in water at temperatures varying by 10 deg. C. from 30° C. to 100° C. The strips were then dried and the final length noted. Contraction began at 50° C. and at 90° C. 20 per cent contraction had occurred.

The α–β transformation was studied by preparing samples according to Rudall's method for 'epidermin'[4]. Protein strips were oriented by 200 per cent extension, maintained for 1 hr., followed by relaxation to constant length. The strips were then immersed in saturated ammonium sulphate at 90° C. for 2 min., removed and extended 90 per cent. They were then fixed in 10 per cent formalin for 48 hr. and finally washed.

The X-ray patterns (Fig. 1,*c*) of these samples are the same in parallel and perpendicular mount. They consist of two sharp interferences, an outer ring of spacing 4·65 A., and an inner one of 5·2 A. The