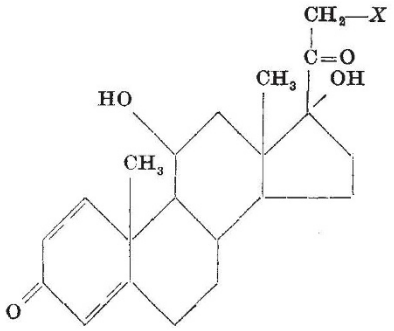
PHARMACOLOGY

Amino-derivatives of 11β,17α,21-Trihydroxy-3,20-Dioxo-1,4-Pregnadiene

THE skeleton of corticosteroids was systematically modified, mainly in order to study the changes in the pharmacological effect of the compounds.

One of the objects of our experiments was the exchange of the C_{21} hydroxyl group of corticosteroids by amino- and substituted amino-groups, respectively.



(*a*) $X = -O-SO_2-C_6H_4-CH_3$; (*b*) $X = -I$; (*c*) $X =$ –1 piperidyl; (*d*) $X =$ 4-morpholyl; (*e*) $X = N(C_2H_5)_2$.

The 21-tosylate (*a*) of 11β,17α,21-trihydroxy-3,20-dioxo-1,4-pregnadiene and the -21-iodine compound (*b*)[1] derived from it served as initial substances in preparing the compounds mentioned.

One mole of the -21-tosylate of 11β,17α,21-trihydroxy-3,20-dioxo-1,4-pregnadiene (*a*) was treated in a tetrahydrofuran solution, in a nitrogen current, with two moles of piperidine at 55° C. for 5 hr. On dropping the reaction mixture into water, 11β,17α,dihydroxy-3-20-dioxo-21(1-piperidyl)-1,4-pregnadiene (*c*) was obtained in 93 per cent yield, in crystalline form; on recrystallizing from a mixture of tetrahydrofuran and petroleum ether, melting point 181° C. (decomposition) was found. Analysis: calculated, C 73·06; H 8·6 per cent; found, C 73·00; H 8·9 per cent.

Compound (*c*) has also been prepared by reacting one mole of the corresponding iodine compound (*b*) with two moles of piperidine under conditions similar to those mentioned. Melting point of product: 181° C. (decomposition). Melting point of the hydrochloride: 236–238° C. (decomposition). Analysis: calculated, C 67·31; H 8·1; Cl 7·6 per cent; found, C 67·07; H 8·1; Cl 7·8 per cent.

In a similar way, 11β,17α,-dihydroxy-3,20-dioxo-21-(4-morpholyl)-1,4-pregnadiene (*d*) was obtained from the tosylate (*a*) and iodine compound (*b*). Melting point 191–193° C. Analysis: calculated, C 69·91; H 8·1 per cent; found, C 69·62; H 8·2 per cent. Melting point of hydrochloride: 235–237° C. (decomposition). Analysis: calculated, C 64·65; H 7·7 per cent; found, C 64·38; H 7·6 per cent.

Similarly to the above-mentioned compounds, 11β,17α,-dihydroxy-3,20-dioxo-21-diethylamino-1,4-pregnadiene (*e*) has been prepared. Melting point of hydrochloride: 227° C. (decomposition). Analysis: calculated, C 66·44; H 8·41; Cl 7·86 per cent; found, C 66·20; H 8·28; Cl 7·61 per cent.

C_{21}-amino -derivatives similar to the corticosteroid derivatives mentioned have also been prepared in an essentially similar way by E. J. Agnello and G. D. Laubach[2].

The compounds prepared by the foregoing technique were subjected to pharmacological tests in the form of bases insoluble in water and of water-soluble hydrochlorides, respectively. Compounds of gluco-corticoid activity are known to possess the general feature of containing oxo-groups on their C_3 and C_{20} atoms, a hydroxyl or oxo-group on their C_{11} atom and a double bond between C_4 and C_5. Also, a common property of these compounds is the hydroxyl function on C_{21}. The α-positioned hydroxyl on C_{17} is absent in the case of corticosterone of similarly gluco-corticoid effect, although only moderately active. Thus, all known efficient substances actually bear an oxygen atom on C_{21}.

The compounds mentioned previously were examined by comparison with the effect of prednisolone. These investigations were carried out by two methods. The accumulation of liver glycogen was investigated on suprarenal gland ectomized rats, extracting the deposited glycogen with trichloracetic acid and determining glycogen by turbidimetry. The anti-phlogistic action of the compounds was examined by the method of rat foot œdema determination evolved by us[3]. Male rats were used in these tests.

The experimental results obtained by both methods disclosed activities of about 80 per cent in respect to prednisolone in the case of the C_{21} piperidine derivative (*c*), of the C_{21} morpholyl derivative (*d*) and of the hydrochlorides of these compounds. Further, it was found that, while on treating rats *per os* with prednisolone the activity of this substance was about 50 per cent of that observed in the case of subcutaneous injections, the water-soluble derivatives were resorbed in 90 per cent.

On the basis of our experiments we can thus state that the C_{21} amino-derivatives of prednisolone possess a gluco-corticoid activity corresponding to that of prednisolone itself. Accordingly, the function of C_{21} does not seem to be an indispensable pre-requisite of gluco-corticoid activity. It appears that its function can be replaced by an amino-group. The water-soluble salts of the compounds prepared in this way are similarly efficient. From the gastro-intestinal tract these latter compounds are more readily resorbed than prednisolone—a substance insoluble in water.

Our experimental results will shortly be published in detail.

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[1] Nussbaum, A. L. (Schering Corp.), U.S. Patent 2814632 (Nov. 20, 1957).
[2] Agnello, E. J., and Laubach, G. D., U.S. Patent 2920999.
[3] Szporny, L., and Fekete, Gy., *Arch. Exp. Path. Pharm.*, **238**, 233 (1960).

Effects of Morphine-like Drugs in Chicks

SEVERAL workers[1–4] have used conscious chicks to study the actions of drugs. Chicks are particularly useful for drugs acting on the central nervous system, as their blood-brain barrier does not form until they are about 3 months old[5,6]. The effects of analgesic drugs on chicks were demonstrated at a meeting of the British Pharmacological Society[7] and are described