

NOVEL ANTI-INFLAMMATORY STEROIDS.  
THE  $\beta$ ,2-d-7-PHENYLTRIAZOLES.

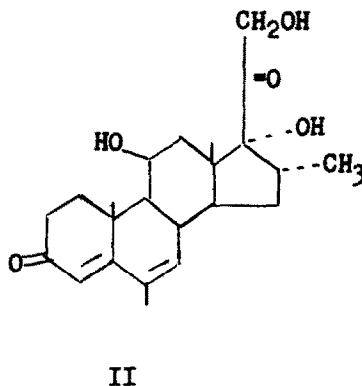
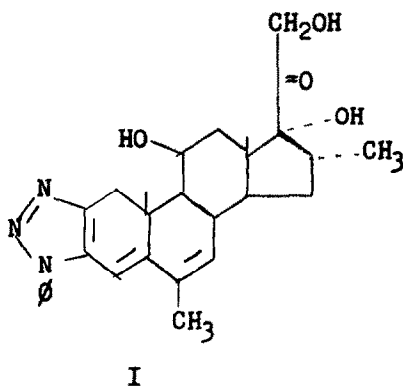
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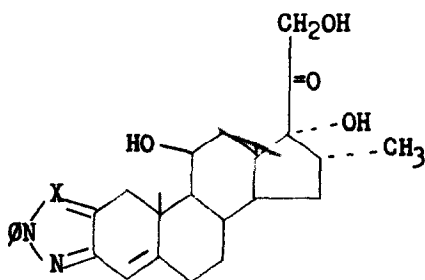
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Recently, Hirschmann *et al.*<sup>1</sup> reported the rather surprising observation that  $\beta$ ,2,c-7-2'-phenylpyrazole derivatives of anti-inflammatory steroids greatly potentiate anti-inflammatory activity.

It has now been found that the  $\beta$ ,2-d-7-3'-phenyltriazole<sup>2</sup> derivative of glucocorticoids also enhances biological activity. This was demonstrated with 6,16 $\alpha$ -dimethyl-3'-phenyl-4,6-pregnadiene-11 $\beta$ ,17 $\alpha$ -21-triol-3,20-dione- $\beta$ ,2-d-7-3'-H-1',2',3'-triazole I which has an activity of 190 times hydrocortisone in the rat systemic granuloma assay<sup>3</sup> compared to 30 times hydrocortisone for the parent 3-ketosteroid II.<sup>4</sup>



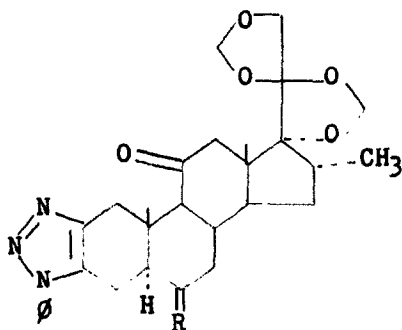


III X = N

IV X = CH

It is interesting to note that the 2'-phenyltriazole III as well as the corresponding phenylpyrazole IV,<sup>1</sup> are essentially inactive in this assay, thereby demonstrating a large degree of structural specificity for the anti-inflammatory activity.

For the synthesis of I, 16 $\alpha$ -methyl-17 $\alpha$ ,20,20,21-bismethylenedioxy-5 $\alpha$ -pregnane-3,6,11-trione<sup>5</sup> was converted to the 3-mono-enamine<sup>7</sup> which on reaction with phenylazide<sup>2,8</sup> in benzene yielded the phenyltriazole V, m.p.  $> 350^\circ$ ;  $\alpha_D^{25} +5^\circ$  (CHCl<sub>3</sub>) ultraviolet  $\lambda_{\text{max}}^{\text{MeOH}}$  228m $\mu$ , E 10,800. Addition of methyl magnesium iodide to V afforded VI, m.p. dec. 350-360 $^\circ$ ;  $\alpha_D^{25} +14^\circ$



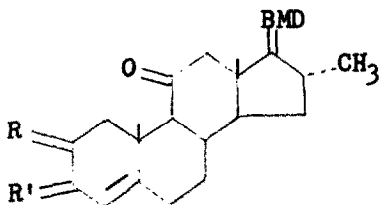
V R = H

VI R =  $\alpha$ -CH<sub>3</sub>,  $\beta$ -OH

(CHCl<sub>3</sub>); ultraviolet  $\lambda_{\text{max}}^{\text{MeOH}}$  229m $\mu$ , E 11,200, which on dehydration with

thionyl chloride in pyridine afforded 6,16 $\alpha$ -dimethyl-3'-phenyl-17 $\alpha$ ,20,20,21-bismethylenedioxy-5-pregnene-11-one- $\sqrt[3]{2,2,7}$ -3'-H-1',2',3'-triazole VII<sup>9</sup>, m.p. 245-254°;  $\alpha_D^{25} +5^\circ$  (CHCl<sub>3</sub>); ultraviolet  $\lambda_{\text{max}}^{\text{MeOH}}$  sh. 224m $\mu$ , E 11,200. Selenium dioxide oxidation of VII afforded a new carbinol VIII, m.p. 280-300°;  $\alpha_D^{25} -25^\circ$  (CHCl<sub>3</sub>); ultraviolet  $\lambda_{\text{max}}^{\text{MeOH}}$  228m $\mu$ , E 10,600. The hydroxyl is assigned to C-4 $\beta$  by analogy with the selenium dioxide oxidation of other  $\Delta^5$ -steroids.<sup>10</sup> Sodium borohydride reduction of VIII at C-11, followed by treatment of the crude product with 60% aqueous formic acid afforded I, m.p. 204-207°;  $\alpha_D^{25} +20^\circ$  (CHCl<sub>3</sub>); ultraviolet  $\lambda_{\text{max}}^{\text{MeOH}}$  263, 318m $\mu$ , E 10,400, 22,500.

Compound III was prepared from 16 $\alpha$ -methyl-17 $\alpha$ ,20,20,21-bismethylenedioxy-4-pregnene-3,11-dione<sup>6</sup> IX, by sodium hydride ethylformate formylation at C-2 to yield X, m.p. dec. 224-232°;  $\alpha_D^{25} +10^\circ$  (CHCl<sub>3</sub>); ultraviolet  $\lambda_{\text{max}}^{\text{MeOH}}$  241, 308m $\mu$ , E 12,200, 4,300, which on treatment with sodium nitrite<sup>11</sup> and acetic acid afforded XI, m.p. dec. 255-257°;  $\alpha_D^{25} +66^\circ$  (CHCl<sub>3</sub>); ultraviolet  $\lambda_{\text{max}}^{\text{MeOH}}$  260m $\mu$ , E 13,700. Conversion to the phenyl hydrazone XII followed by cyclization with phosphorous pentachloride<sup>12</sup> in chloroform afforded 16 $\alpha$ -methyl-2'-phenyl-17 $\alpha$ ,20,20,21-bismethylenedioxy-4-pregnene-11-one- $\sqrt[3]{2,2,7}$ -2'-H-1',2',3'-triazole, m.p. 279-280°;  $\alpha_D^{25} -8^\circ$  (CHCl<sub>3</sub>); ultraviolet  $\lambda_{\text{max}}^{\text{MeOH}}$  304, 310m $\mu$ , E 32,500, 32,000.



IX R = H<sub>2</sub>, R' = O

X R = -CHOH, R' = O

XI R = NOH, R' = O

XII R = NOH, R' = NNH $\phi$

Reduction of XIII at C-11 with sodium borohydride yielded the corresponding 11 $\beta$ -ol, m.p. 212-213°;  $\alpha_D^{25}$  -38° (CHCl<sub>3</sub>); ultraviolet  $\lambda_{\text{max}}^{\text{MeOH}}$  305, 310m $\mu$ , E 32,600, 32,600, which on treatment with 60% aqueous formic acid afforded III, m.p. 235-236°;  $\alpha_{546}^{25}$  +43° (CHCl<sub>3</sub>); ultraviolet  $\lambda_{\text{max}}^{\text{MeOH}}$  304, 310m $\mu$ , E 32,900, 32,400.

## REFERENCES

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5. This compound was first prepared from 16 $\alpha$ -methyl-17 $\alpha$ ,20,20,21-bis-methylenedioxy-3-ethylenedioxy-5,6-oxido-pregnene-11-one<sup>6</sup> by M. Sletzinger and S. Karady; m.p. 245-252°;  $\alpha_D^{25}$  -33° (CHCl<sub>3</sub>). The synthesis of the corresponding 16-desmethyl derivative and a discussion of the stereochemistry at C-5 has been reported, Fried, J. H., Arth, G. E. and Sarett, L. H., J. AM. CHEM. SOC., 81, 1235 (1959).
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9. This structure is supported by the n.m.r. spectrum which shows the absence of olefinic protons. We wish to thank B. Arison and Dr. N. R. Trenner for determining the n.m.r. spectrum.
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