The 6α-methyl-11β,17α-dihydroxy-21-acetoxy-1,4-pregnadiene-3,20-dione[1] was dehydrated by thionyl chloride in pyridine to 6α-methyl-17α-hydroxy-21-acetoxy-1,4,9(11)-pregnatriene-3,20-dione (I), m.p. 192–194°; $[\alpha]_D$ + 18° (acetone); $\lambda_{max}^{95\% \text{ alc.}}$ 239 mμ, $a_M$ = 15,450. *Anal.* Found: C, 72.03; H, 7.57. This was converted by known methods[2] to a crude 9,11-bromohydrin and then to the 6α-methyl-9β,11β-oxido-17α-hydroxy-21-acetoxy-1,4-pregnadiene-3,20-dione (II), m.p. 260–265°; $[\alpha]_D$ + 60° (pyridine); $\lambda_{max}^{95\% \text{ alc.}}$ 249 mμ, $a_M$ = 16,150. *Anal.* Found: C, 69.48; H, 7.21. Reaction of II with hydrofluoric acid gave 6α-methyl-9α-fluoro-11β,17α-dihydroxy-21-acetoxy-1,4-pregnadiene-3,20-dione (III), m.p. 237–239°; $[\alpha]_D$ + 87° (acetone); $\lambda_{max}^{95\% \text{ alc.}}$ 239 mμ, $a_M$ = 15,250. *Anal.* Found: C, 65.94; H, 6.95; F, 4.72. Hydrolysis of III with potassium bicarbonate in methanol produced 6α-methyl-9α-fluoro-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione (IV), m.p. 243–250 (dec.); $[\alpha]_D$ + 93° (dioxane); $\lambda_{max}^{95\% \text{ alc.}}$ 238 mμ, $a_M$ = 15,150. *Anal.* Found: C, 67.48; H, 7.61; F, 5.02. Conversion of IV to the corresponding 21-fluoro analog[3] gave 6α-methyl-9α,21-difluoro-11β,17α-dihydroxy-1,4-pregnadiene-3,20-dione (V), m.p. 262–274 (dec.); $[\alpha]_D$ + 71° (acetone); $\lambda_{max}^{95\% \text{ alc.}}$ 239 mμ, $a_M$ = 15,000. *Anal.* Found: C, 66.87; H, 7.69; F, 9.80.

In a like manner 6α-methyl-11β,17α-dihydroxy-21-acetoxy-4-pregnene-3,20-dione[1] was converted to a similar series of compounds: 6α-methyl-17α-hydroxy-21-acetoxy-4,9-(11)-pregnadiene-3,20-dione (VI), m.p. 175–176°; $[\alpha]_D$ + 91° (Chf.); $\lambda_{max}^{95\% \text{ alc.}}$ 239.5 mμ, $a_M$ = 16,400. *Anal.* Found: C, 71.75; H, 7.71; 6α-methyl-9α-bromo-11β,17α-dihydroxy-21-acetoxy-4-pregnene-3,20-dione (VII), m.p. 153–155° (dec.); $[\alpha]_D$ + 148° (Chf.); $\lambda_{max}^{95\% \text{ alc.}}$ 239.5 mμ, $a_M$ = 14.225. *Anal.* Found: Br, 16.0; 6α-methyl-9β,11β-oxido-17α-hydroxy-21-acetoxy-4-pregnene-3,20-dione (VIII), m.p. 180–182°; $[\alpha]_D$ + 65° (Chf.); $\lambda_{max}^{95\% \text{ alc.}}$ 242 mμ, $a_M$ = 14, 625. *Anal.* Found: C, 69.41; H, 7.93; 6α-methyl-9α-fluoro-11β,17α-dihydroxy-21-acetoxy-4-pregnene-3,20-dione (IX), m.p. 219–220°; $[\alpha]_D$ + 113° (acetone); $\lambda_{max}^{95\% \text{ alc.}}$ 239 mμ, $a_M$ = 15,775. *Anal.* Found: C, 65.69; H, 7.49; F, 4.29; 6α-methyl-9α-fluoro-11β,17α,21-trihydroxy-4-pregnene-3,20-dione (X), m.p. 228–230°; $[\alpha]_D$ + 112° (acetone); $\lambda_{max}^{95\% \text{ alc.}}$ 239 mμ, $a_M$ = 16,400. *Anal.* Found: C, 67.20; H, 8.01; F, 5.47; and 6α-methyl-9α,21-difluoro-11β,17α-dihydroxy-4-pregnene-3,20-dione (XI), m.p. 210–212°; $[\alpha]_D$ + 89° (acetone); $\lambda_{max}^{95\% \text{ alc.}}$ 239 mμ, $a_M$ = 14,225. *Anal.* Found: C, 66.35; H, 8.07; F, 9.24.

In addition, using the method of reference 3, 6α-methyl-11β,17α,21-trihydroxy-4-pregnene-3,20-dione[1] was converted to 6α-methyl-11β,17α-dihydroxy-21-fluoro-4-pregnene-3,20-dione (XII), m.p. 220–223°. *Anal.* Found: C, 70.14; H, 7.95; F, 6.76. Likewise, 6α-methyl-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione[1] gave 6α-methyl-11β,17α-dihydroxy-21-fluoro-1,4-pregnadiene-3,20-dione (XIII), m.p. 216–222°. *Anal.* Found: F, 3.63.

Compounds III, IV, V, IX, X, XI, XII and XIII all show considerably greater glucocorticoid and anti-inflammatory activity[4] than does hydrocortisone in animal assays. Compound III, 6α-methyl-9α-fluoro-11β,17α-dihydroxy-21-acetoxy-1,4-pregnadiene-3,20-dione, was more active in the anti-inflammatory assay than any of the previously reported analogs of hydrocortisone of which we are aware. Its enhancement of the glucocorticoid activity was particularly noteworthy, being 120 times as active as hydrocortisone when administered parenterally, and 190 times hydrocortisone by oral administration. None of the above compounds exhibited appreciable sodium retaining properties.[5]

(2) J. Fried and E. F. Sabo, THIS JOURNAL, **75**, 2273 (1953).

(3) By a modification of the method of P. Tannhauser, R. J. Pratt and E. V. Jensen, *ibid.*, **78**, 2658 (1956).

(4) Assays were performed by members of the Department of Endocrinology of The Upjohn Company and will be reported in detail elsewhere. The glucocorticoid assays were by the method of R. O. Stafford, L. E. Barnes, B. J. Bowman and M. M. Meinzinger, *Proc. Soc. Exp. Biol. Med.*, **89**, 371 (1955); the anti-inflammatory assays by a modified granuloma pouch technique (A. Robert and J. E. Nezamis, *Acta Endocrinologica*, in press).

(5) This may be contrasted with the activity of 2-methyl-9α-fluorohydrocortisone reported by W. W. Byrnes, L. E. Barnes, B. J. Bowman, W. E. Dulin, E. H. Morley and R. O. Stafford, *Proc. Soc. Exp. Biol. Med.*, **91**, 67 (1956), where the mineralocorticoid properties were shown to be enhanced to a much greater extent than the glucocorticoid.

G. B. SPERO
RESEARCH LABORATORIES J. L. THOMPSON
THE UPJOHN COMPANY F. H. LINCOLN
KALAMAZOO, MICHIGAN W. P. SCHNEIDER
J. A. HOGG

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## A NEW ANALGETIC

*Sir:*

To date the preparation of effective synthetic analgetics has been confined to a great extent to pyrazolone derivatives, *e.g.*, aminopyrin (1-phenyl-2,3-dimethyl-4-dimethylamino-5-pyrazolone)[1] and phenylbutazone (1,2-diphenyl-4-butyl-3,5-pyrazolidinedione),[2] and to morphine-like analogs, such as meperidine (ethyl 1-methyl-4-phenylisonipecotate)[3] and levorphan (3-hydroxy-N-methylmorphinan).[4] Each of these and related type compounds have suffered from certain disadvantages, such as addiction and dependence (morphine and analogs), as well as toxic effects on the hematopoetic system (pyrazolone derivatives). More recently it has been reported[5] that replacement of the 1-methyl group of meperidine with the phenyl ethyl or para-amino phenyl ethyl moiety leads to a less toxic morphine-like compound.

At this time we wish to present a preliminary report on the preparation of a compound which we have found to possess good analgetic activity in experimental animals. The constitutional aspects of this new preparation are far removed from the usual features attending previously outlined anal-

(1) A. Stolz, U. S. Patent 579,412 (1897).

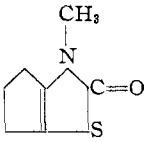
(2) J. R. Geigy, A.-G., Swiss Patent 269,980 (1950).

(3) O. Eisleb, U. S. Patent 2,167,351 (1939).

(4) O. Schnider and A. Grussner, *Helv. Chim. Acta*, **32**, 821 (1949).

(5) T. D. Perrine and N. B. Eddy, *J. Org. Chem.*, **21**, 125 (1956); J. Weijlard, *et al.*, THIS JOURNAL, **78**, 2342 (1956).

getics. This new substance is 2,3,5,6-tetrahydro-3-methyl-4(H)-cyclopentathiazolo-2-one (I).[6]



I

When $\alpha$-chlorocyclopentanone is allowed to react with ethyl xanthamidate in boiling 1-propanol, there was obtained the crystalline compound, 2,3,5,6 - tetrahydro - 4(H) - cyclopentathiazolo - 2-one. Purification by recrystallization from water or water–ethyl alcohol (9:1) mixture gave product of m.p. 144–145°; *Anal.* Calcd. for $C_6H_7NOS$: C, 51.06; H, 5.02; N, 9.93; S, 22.60. Found: C, 51.02; H, 4.96; N, 9.96; S, 22.90. Ultraviolet absorption measurements at *p*H 7 gave $\lambda_{max}^{C_2H_5OH}$ 252 m$\mu$, $\epsilon$ 4430; $\lambda_{min}^{C_2H_5OH}$ 229 m$\mu$, $\epsilon$ 2500. Methylation of this thiazolone with methyl iodide in a basic medium gave rise to I which, after purification by crystallization from water, melted at 70–71°. *Anal.* Calcd. for $C_7H_9NOS$: N, 9.04; S, 20.68. Found: N, 8.90; S, 21.00. Absorption data in the ultraviolet are $\lambda_{max}^{C_2H_5OH}$ 253 m$\mu$, $\epsilon$ 4170; $\lambda_{min}^{C_2H_5OH}$ 231 m$\mu$, $\epsilon$ 2720.

The pharmacodynamic evaluation of this compound revealed a rather surprising activity in reducing experimental pain. The Wolf–Hardy principle for testing analgesia was employed in experimental animals according to a method described by Gross.[7] A beam of heat was directed against the tips of the tails of white mice and the reaction time measured from the onset of pain stimulus to the tail flick. Analgetic effects were expressed in terms of prolonged reaction time to the pain stimulus. With this method the above-mentioned compound produced a marked prolongation of the reaction time in the range of one-tenth to one-fifth of the LD50. It was characterized by a rapid onset of action and a maintenance of the analgetic effect for several hours following parenteral administration. Compared to aminopyrine the material was more potent, somewhat less toxic and devoid of antipyretic activity.

(6) According to *Chemical Abstracts*, an alternate name for I is N-methylcyclopentano-[d]4-thiazolin-2-one.

(7) F. Gross, *Helv. Physiol. Acta*, C31 (1947), *v5*.

RESEARCH DEPARTMENT GEORGE DESTEVENS
CIBA PHARMACEUTICAL PRODUCTS, INC. HEINO A. LUTS
SUMMIT, NEW JERSEY JURG A. SCHNEIDER

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## THE PURE OZONE TO OXYGEN FLAME[1]

*Sir:*

We live in a world of molecular oxygen and an overwhelming number of studies on combustion are devoted to oxidation with molecular oxygen. On the other hand, the active modification of the element, or ozone, has not been studied in the pure form.

Ozone has been known since 1785, when van Marum observed its formation in the electric spark discharge in oxygen. The highly sensitive nature of pure ozone and the extreme facility with which it explodes or detonates, has so far prevented combustion studies with pure ozone.

Before studies of the behavior of pure ozone with various fuel gases could be started profitably it was first necessary to achieve the combustion or decomposition flame of pure ozone to oxygen. It could be expected, since the exothermic heat (at constant pressure of 1 atm. and 291°K.) of the reaction $O_3 \rightarrow 1.5\ O_2$ equals $-$ 33,923 $\pm$ 180 cal./mole, that appreciable flame temperatures should be attained and that a stable ozone–oxygen flame should exist. Flame temperature calculations can be made with great accuracy since the enthalpy and the dissociation constants for the $O_2 \rightleftarrows 2O$ reaction are well known; these temperatures are, at initial conditions of 298°K. and 1.0 atm. pressure, for 100, 66.7, 40.0 and 18.2 mole % $O_3$ in $O_2$, respectively, 2677°, 2277°, 1687° and 1027°K.

By using pure ozone, containing less than a few parts per million of organic impurities, as described originally by C. E. Thorp,[2] we have been able to burn ozone–oxygen mixtures to oxygen in the entire range from 17–100 mole % $O_3$. The all-Pyrex glass apparatus was extremely simple; it consisted of a narrow glass gasholder, from which any desired mixture of $O_3$–$O_2$ or pure $O_3$ could be delivered at any predetermined rate, by simple displacement with water. From the gasholder the gas mixture went to a Pyrex glass, quartz, or aluminum tip. Stopcocks greased with $C_nF_{2n+2}$ or Kel-F, were used. The burning velocities were determined by the standard schlieren method. In the range of 17 to about 50 mole % $O_3$, the flame cannot be observed visually, but can be seen very easily on the screen of the schlieren apparatus. The flame is visible above this range. Pure 100% ozone burns with a faint, non-luminous flame, blue in color, with a typical pink cast. The experimental burning velocities, at 298°K. and 1.0 atm. pressure, are shown in Fig. 1.

The ozone flame is of particular theoretical interest since it is the simplest flame imaginable. Outside of the "fuel" $O_3$ and the "product of combustion" $O_2$, the only possible intermediates are oxygen atoms.

In recent years Drs. J. O. Hirschfelder,[3] Theodore von Kármán[4] and R. Sandri,[5] and their associates, have developed the theory of laminar flame propagation. Dr. von Kármán presented his results recently[6] and they are in essential agreement with Fig. 1. The more extensive data of Dr. Sandri[7] are given in Table I and are compared with our experimental results in Fig. 1. As can be seen,

(1) This research was supported by the United States Air Force through the Air Force Office of Scientific Research of the Air Research and Development Command under Contract No. 18(600)-1475.

(2) C. E. Thorp, U. S. Patent 2,700,648, Jan. 25, 1955; see also "Bibliography of Ozone Technology," Vol. II: "Physical and Pharmacological Properties," 1955, Armour Research Foundation of Illinois Institute of Technology, Chicago, Ill.

(3) J. O. Hirschfelder, C. F. Curtiss and D. E. Campbell, *J. Phys. Chem.*, **57**, 403 (1953); Proc. IVth International Symposium on Combustion, 1953, p. 197.

(4) T. von Kármán and S. S. Penner, "Selected Combustion Problems," (AGARD): Combustion Colloquium, Cambridge University, England, pp. 5–41 (1953), and *C. A.*, **48**, 10409e (1954).

(5) R. Sandri, *Canadian J. Chem.*, **34**, 313, 324, 331 (1956).

(6) T. von Kármán, Proc. VIth International Symposium on Combustion, held at Yale University, Aug. 19–24, 1956.

(7) An extension of Sandri's theory to ozone-rich mixtures will be published soon in *Canadian J. Chem.* (1957).