REGRESSION OF LYMPHOSARCOMA TRANSPLANTS IN MICE

Sir:

Chemotherapy with cortisone acetate (CORTONE MERCK) as an adjunct to a riboflavin deficient diet brings about regression of well-established (13 day) transplants of lymphosarcoma 6C3HED in mice of the C_3H strain. Compound A acetate also shows significant activity.

Heilman and Kendall[1] observed an arrest in the growth of lymphosarcoma transplants following therapy with Compound E; however, the neoplasms usually recurred in a few days or weeks following withdrawal of the drug and the animals succumbed despite the resumption of treatment.

Regression of lymphosarcoma transplants occurred in mice subjected to riboflavin deficiency and such animals were refractory to subsequent inoculations with the tumor.[2]

Combination therapy consisting of administering cortisone acetate to mice with a restricted intake of riboflavin might be expected to enhance regression. Accordingly, mice[3] with well-established (13 day post-transplant) lymphosarcomas (10,000 cell subcutaneous inoculation) were transferred from a stock to a riboflavin deficient ration and treatment with 500γ or 1 mg. of cortisone acetate daily was instituted (50 mice were employed on each level). A reduction in the size of the tumors was noted by the second day and tumor tissue was non-palpable after four days of treatment. An early arrest (but not regression) of tumor growth was observed in 10 mice given 250γ of cortisone acetate daily. Measurable sites were still present in controls (a total of 108 mice) maintained on the riboflavin deficient diet but without additional therapy. Regression was also noted in four days when 1 mg. of cortisone acetate was administered daily to mice (10 in each group) maintained on a purified diet supplemented with 4, 6 or 8γ of riboflavin daily. Many animals succumbed from incidental causes such as Tyzzer's disease or Salmonella infection. Death may have been ascribable in some cases to a toxemia produced by the rapid resorption of necrotic tissue. The few surviving animals were refractory to a second transplant of the tumor. Although the growth of transplants in 40 mice receiving a natural food ration and 1 mg. of cortisone acetate daily was definitely suppressed, the effect was only transitory and the animals succumbed from their tumors.

Compound A acetate[4] was somewhat less effective than cortisone acetate as a carcinolytic agent. Two levels were employed, namely, 1 mg. (20 mice) and 4 mg. (10 mice). Dihydrocortisone acetate, pregnenolone, 21-acetoxy-pregnenolene, DCA, progesterone, 11-keto-progesterone, Compound S acetate, adrenosterone, and 3,11,20-triketo-4,21-diacetoxy-17-hydroxy-pregnane were inactive when administered to 10 mice in each group at a level of 1 mg. daily for six days.

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(1) Heilman and Kendall, *Endocrinology*, **34**, 416 (1944).

(2) Stoerk and Emerson, *Proc. Soc. Exp. Biol. and Med.*, **70**, 703 (1949).

(3) The C_3H mice employed in these tests were 3–5 months of age. The sexes were equally divided in each group.

(4) Dr. George W. Wolley, Head of the Division of Steroid Biology of the Sloan-Kettering Institute, has found that Compound A acetate showed activity when administered at a level of 4 mg. daily in lymphatic leukemia P1534, lymphosarcoma 6C3HED and in normal mice (*Proc. Soc. Exp. Biol. and Med.*, **74**, 286 (1950)).

THE SYNTHESIS OF RACEMIC β-Δ^6-DIHYDRODESOXYCODEINE METHYL ETHER

Sir:

Hydrogenation over copper–chromium oxide of 3,4-dimethoxy-9,10-dioxo-13-cyanomethyl-5,8,-9,10,13,14-hexahydrophenanthrene (I)[1] yields the ketolactam II[2] (m. p. 263–264.5°, found, C, 68.62; H, 5.77; ultraviolet λ_{max} 281 mμ, log ϵ 4.16, *IR* λ_{max} 3.00, 5.88, 5.97 μ) which on Wolff–Kishner reduction and remethylation yields the lactam III (m. p. 210–212.5°, found, C, 72.44; H, 7.09; OCH_3, 20.31; ultraviolet λ_{max} 282, log ϵ 3.17). Reduction of III with lithium aluminum hydride followed by methylation with formaldehyde–formic acid yields the racemic base IV, (oil, found, C, 76.66; H, 8.44) purified through its picrate (m. p. 198.5–200°, found, C, 56.55; H, 5.76).

We have prepared both epimers at C_{14} of Δ^6-dihydrodesoxycodeine (IVa, IVb) for comparison with this material. β-Dihydrothebainone[3] on hydrogenation yields the corresponding alcohol (m. p. 165.5–166°, $\alpha^{30}D$ −23° (*c* 0.920, alc.) found, C, 71.34; H, 8.36; methiodide m. p. 264–265°, found, C, 51.15; H, 6.51) which on methylation yields the methyl ether (m. p. 152.5–153.5°, $\alpha^{30}D$ −9° (*c* 0.643, alc.) found, C, 71.93; H, 8.77; OCH_3, 19.44; methiodide m. p. 243–245°, found, C, 52.30; H, 6.57; picrate, m. p. 190–191°, found, C, 55.27; H, 5.85). On conversion to the tosylate and detosylation with boiling collidine[4] this ether affords β-Δ^6-dihydrodesoxycodeine methyl ether[5] (IVa) (oil, found, C, 76.23; H, 8.27) purified through its picrate, m. p. 210–212° (found, C, 56.51; H, 5.72).

Dihydrothebainol[6] by a similar series of transformations (methyl ether, oil, $\alpha^{27}D$ −28° (*c* 1.519, alc.) found, C, 71.42; H, 8.73; OCH_3, 18.88; methiodide m. p. 279–281°, found, C, 52.35; H, 6.48; hydrobromide (through which the base was purified) m. p. 254.5–255°, $\alpha^{28}D$

(1) M. Gates, THIS JOURNAL, **72**, 228 (1950).

(2) Compare *ibid.*, **72**, 1141 (1950).

(3) L. F. Small and G. L. Browning, Jr., *J. Org. Chem.*, **3**, 618 (1939).

(4) J. von Euw and T. Reichstein, *Helv. Chim. Acta*, **29**, 654 (1946).

(5) The prefix β refers to a configuration at C_{14} epimeric with that of morphine; *cf.* Small and Browning, ref. 3.

(6) A. Skita, F. F. Nord, J. Reichert and P. Stukart, *Ber.*, **54**, 1562 (1921).