zinc dust in dilute alcohol[12] at room temperature furnished a mixture of III and 17α-hydroxycorticosterone acetate, m.p. 217–20°; $[\alpha]^{23}D$ +156° (*c*, 0.36 in $CHCl_3$); $\lambda_{max.}^{alc.}$ 241 mμ (ϵ = 16,700); (*Anal.* Calcd. for $C_{23}H_{32}O_6$: C, 68.29; H, 7.97. Found: C, 68.47; H, 8.14), identified further by infrared comparison with an authentic sample.

Similarly, 11-epicorticosterone[1,2,13] on monoacetylation, followed by tosylation and elimination of toluenesulfonic acid with sodium acetate in acetic acid yielded the known $\Delta^{4,9(11)}$-pregnadiene-21-ol-3,20-dione 21-acetate,[14] m.p. 160–160.5°; $[\alpha]^{23}D$ +128° (*c*, 0.76 in acetone), +150° (*c*, 0.80 in $CHCl_3$); which on treatment with N-bromoacetamide afforded 9α-bromocorticosterone acetate, m.p. 152–53° (dec.); $[\alpha]^{23}D$ +178° (*c*, 0.94 in $CHCl_3$); (*Anal.* Calcd. for $C_{23}H_{31}O_5Br$: C, 59.10; H, 6.68; Br, 17.10. Found: C, 59.15; H, 6.70; Br, 17.03).

An attractive feature of this synthetic route is that it permits the introduction of radioactive halogen or tritium into the stable 9-position in the final step.

(12) The use of other reagents commonly employed for reductive dehalogenations such as Raney nickel with or without hydrogen, chromous chloride, zinc in acetic acid and others, led to III, V and/or their 4,5-dihydro products. Of particular interest is the reaction of IV with potassium iodide in acetone, which at the boiling point yielded III and V, while at room temperature it afforded in almost quantitative yield $\Delta^{4,6,8(9)}$-pregnatriene-17α,21-diol-3,20-dione acetate, m.p. 188–191°; $[\alpha]^{23}D$ +531° (*c*, 1.02 in $CHCl_3$); $\lambda_{max.}^{alc.}$ 244 mμ (ϵ = 14,300), 285–300 mμ (ϵ = 3,100), 385 mμ (ϵ = 6,700), *cf.* R. Yashin, G. Rosenkranz and C. Djerassi, THIS JOURNAL, **73**, 4654 (1951).

(13) S. H. Eppstein, P. D. Meister, D. H. Peterson, H. C. Murray, H. M. Leigh, D. A. Lyttle, L. M. Reineke and A. Weintraub, *ibid.*, **75**, 408 (1953).

(14) C. W. Shoppee and T. Reichstein, *Helv. Chim. Acta*, **26**, 1316 (1943).

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DECATETRAENEDIOIC ACID, A FUMAGILLIN DEGRADATION PRODUCT

Sir:

The antibiotic fumagillin[1,2,3] has been shown to be an acid with an empirical formula of $C_{26-27}H_{34-36}O_7$. We have found that fumagillin can be hydrolyzed under mild alkaline conditions liberating a highly unsaturated acid $C_{10}H_{10}O_4$ with the properties of 2,4,6,8-decatetraenedioic acid.[4]

This appears to be the first isolation of this acid from a natural source. The ultraviolet absorption spectrum shows peaks at 336 mμ and 351 mμ similar to fumagillin. On hydrogenation, fumagillin absorbs about 5 moles of hydrogen. Hydrolysis of hydrogenated fumagillin yields sebacic acid. These facts lead us to the conclusion that fumagillin is a mono-ester of decatetraenedioic acid: $[C_{16-17}H_{25-27}O_3]$—O—CO—$(CH{=}CH)_4$COOH.

Isolation of Decatetraenedioic Acid from Fumagillin.—One gram of fumagillin was suspended in 50 ml. of alcohol, and 12 ml. of *N* NaOH added. The fumagillin dissolved, and the solution became red. The solution was boiled under reflux for 15 minutes, diluted with 35 ml. of water to redissolve a precipitate, boiled for ten minutes more, filtered, cooled and acidified. The precipitate (305 mg.) was dissolved in 3.5 ml. of *N* NaOH, treated with Darco G-60, filtered and acidified: yield, 288 mg. of a yellow powder, insoluble in chloroform, alcohol, or water, m. p. 295–297° dec.

Anal. Calcd. for $C_{10}H_{10}O_4$: C, 61.85; H, 5.19. Found: C, 61.68; H, 5.27.

The infrared spectrum showed bands at 3.65, 3.76 and 3.90 (carboxylic OH), 5.93 (carbonyl), and 6.13 and 6.32 microns (C=C) in Nujol mulls.

The methyl ester[4] was prepared through the acid chloride, m. p. 214–217°; $E_{1\ cm.}^{1\%}$ 3180 at 335 mμ and $E_{1\ cm.}^{1\%}$ 2950 at 351 mμ in alcohol containing 2% chloroform.

Anal. Calcd. for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 65.10, 64.88; H, 6.60, 6.43.

This ester was compared directly with a synthetic sample kindly supplied by Prof. R. Kuhn. The two were shown to be identical by mixed melting point, infrared (Nujol mull) and ultraviolet spectra.

Isolation of Sebacic Acid from Hydrogenated Fumagillin.—Fumagillin (10.1 g.) was hydrogenated with Adams catalyst in alcohol at room temperature and three atmospheres pressure. After 15 minutes over 5 molar equivalents of hydrogen had been consumed. The solution was filtered and concentrated with addition of water to remove alcohol. A solution of 1.67 g. (2 molar equivalents) of sodium hydroxide in 250 ml. was added and the solution heated for one hour on a steam-bath. The cooled solution was extracted with ether, evaporated to 50 ml. and acidified. A white solid (3.32 g.) precipitated, m. p. 132–133°, showing no depression with authentic sebacic acid.

The authors wish to thank E. F. Shelberg and associates for microanalyses, and W. H. Washburn for infrared spectra.

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A NEW CLASS OF ANTITUBERCULAR COMPOUNDS

Sir:

During the screening of a large number of substances chosen from a wide range of chemical types, the discovery was made by Dr. R. L. Mayer and co-workers of the Division of Microbiology that 4,4′-diethoxythiocarbanilide (2) had high antituberculous activity in mice infected with the H37RV strain.[1] The synthesis and testing of over 300 thiocarbanilides and related substances revealed the rather specific structural features necessary for activity.

Shortening the 4-substituent to methoxy (1) (see

(1) T. E. Eble and F. R. Hanson, *Antibiotics & Chemotherapy*, **1**, 54 (1951).

(2) I. N. Asheshov, F. Strelitz and E. A. Hall, *ibid.*, **2**, 361 (1952).

(3) Our titration and elementary analyses agree best for $C_{26}H_{34}O_7$, as do the data of Eble and Hanson; Asheshov, *et al.*, however, prefer $C_{30}H_{40}O_8$.

(4) R. Kuhn and C. Grundmann, *Ber.*, **69**, 1757 (1936).

(1) R. L. Mayer, P. C. Eisman and E. A. Konopka, *Proc. Soc. Exp. Biol.*, in press.

TABLE I

No.	R	R′	Extension of T50 value[a]	Concn. (%) in diet	M.p., °C.	Formula	N, % Calcd.	N, % Found
1	CH_3O	CH_3O	0.5	0.5	188–189[3]			
2	C_2H_5O	C_2H_5O	>15	.1	170–171[3]			
			11	.05				
3	C_4H_9O	C_4H_9O	>15	.025	166–167	$C_{21}H_{28}N_2O_2S$	7.52	7.74
4	C_2H_5O	$C_6H_{13}O$	>15	.5	153–154	$C_{21}H_{28}N_2O_2S$	7.52	7.62
5	$C_8H_{17}O$	$C_8H_{17}O$	+1.0	.5	154–156	$C_{29}H_{44}N_2O_2S$	5.78	6.04
6	C_4H_9	C_4H_9	>15	.025	149–150	$C_{21}H_{28}N_2S$	8.23	8.41
7	$(CH_3)_3C$	$(CH_3)_3C$	0.0	.5	192–193[4]			
8	C_4H_9O	Cl	>15	.5	166–168	$C_{16}H_{19}ClN_2OS$	8.37	8.19
9	C_4H_9O	$(CH_3)_2N$	>15	.025	119–121	$C_{19}H_{25}N_3OS$	12.24	12.20
10	Cl	Cl	+0.7	.1	166–168[5]			
11	$(CH_3)_2N$	$(CH_3)_2N$	−0.5	.1	185–186[5]			
12	C_4H_9O	H	0.0	.5	136–137	$C_{17}H_{20}N_2OS$	9.33	9.50
13	2,4′-Diethoxythiocarbanilide		+2.0	.5	143–145	$C_{17}H_{20}N_2O_2S$	8.86	8.94
14	3,4′-Diethoxythiocarbanilide		−2.5	.1	110–112	$C_{17}H_{20}N_2O_2S$	8.86	8.90
15	4,4′-Diethoxy-3,3′-dimethylthiocarbanilide		−1.0	.5	161–162	$C_{19}H_{24}N_2O_2S$	8.13	8.15
16	4,4′-Diethoxy-N-methylthiocarbanilide		−2.7	.3	58–59	$C_{18}H_{22}N_2O_2S$	8.48	8.60
17	4,4′-Diethoxycarbanilide		+0.5	.3	225–226[6]			
18	1,3-Bis-(*p*-phenetyl)-guanidine		−1.3	.05	121–122[6]			
19	1-(4-Ethoxycyclohexyl)-3-(*p*-phenetyl)-2-thiourea		+1.3	.5	109–119[b]	$C_{17}H_{26}N_2O_2S$	8.69	8.69

[a] This value represents the extension of life in days of treated animals over that of controls. 50% of the control animals are dead by the 20th day. An extension of life of greater than five days is considered to indicate significant antitubercular activity. The test is carried out as described by Donovick, *et al.*[2] [b] Mixture of stereoisomers.

Table I) destroys activity, while lengthening the chain results in a fourfold increase to a maximum of activity in the neighborhood of three to four carbon atoms (3). Increase beyond this causes activity to decline (4) and disappear (5). Replacement of alkoxy by an alkyl of equivalent length (6) results in similar activity. Branching of the alkyl chain at the carbon adjoining the ring (7) causes complete loss of activity. One of the 4-alkoxy groups may be replaced by halogen (8) or dialkyl amino (9) and still retain some activity. Replacement of both of them (10) (11) causes total loss of activity. Removal of one of the 4-alkoxyl groups (12) also results in loss of activity.

That 4-substitution on both benzene rings is necessary for activity is shown by the inertness of the 2- (13) and 3- (14) position isomers. A second substituent (methyl (15), halogen, amino) in the ring destroys activity as does substitution of methyl on the ureido nitrogen (16). The thiocarbanilide moiety is shown to be essential by the inactivity of the corresponding carbanilide (17), guanidine (18), guanylthiourea, dithiobiuret, and the cyclohexyl substituted thiourea (19).

The favorable results obtained by our associates of the Division of Microbiology[1] with the more active thiocarbanilides in delayed and limited therapeutic trials in both mice and guinea pigs together with their low toxicity (M.T.D. 5% in diet) and absence of development of resistant strains suggest that they be given serious consideration in the treatment of tuberculosis.

Synthesis of the thiocarbanilides involved reaction of an amine with carbon disulfide using potassium ethyl xanthate as catalyst,[7] with thiophosgene or with an isothiocyanate.[8]

(2) R. Donovick, C. McKee, W. P. Jambor and G. Rake, *Am. Rev. Tuber.*, **60**, 90 (1949).
(3) J. v. Braun and E. Beschke, *Ber.*, **39**, 4377 (1906).
(4) A. Pahl, *ibid.*, **17**, 1235 (1884).
(5) A. Baur, *ibid.*, **12**, 534 (1879).
(6) J. Riedel, German Patent 66, 550, *Frdl.* **3**, 914.
(7) L. Guglianelli, A. Novelli, C. Ring and C. Anaslosi, *Anal. Asoc. Quim. Argent.*, **15**, 337 (1927).
(8) G. Dyson and H. J. George, *J. Chem. Soc.*, **125**, 1702 (1924).

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TOTAL SYNTHESIS OF EPIANDROSTERONE

Sir:

The brilliant researches of Sir Robert Robinson and collaborators on steroid synthesis have recently culminated in a "formal" total synthesis of epiandrosterone, VII, involving "relays" through intermediates which were supplied (for the further steps) by degradation of the natural steroids.[1] We are reporting herein a different approach which has been completed without relays, thus yielding totally synthetic epiandrosterone.

5-Methoxy-2-tetralone, readily produced from the sodium–alcohol reduction of 2,5-dimethoxy-

(1) H. M. E. Cardwell, J. W. Cornforth, S. R. Duff, H. Holtermann and R. Robinson, *J. Chem. Soc.*, 361 (1953).