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′-dimethyl-thiocarbanilide		−1.0	.5	161–162	$C_{19}H_{24}N_2O_2S$	8.13	8.15
16	4,4′-Diethoxy-N-methyl-thiocarbanilide		−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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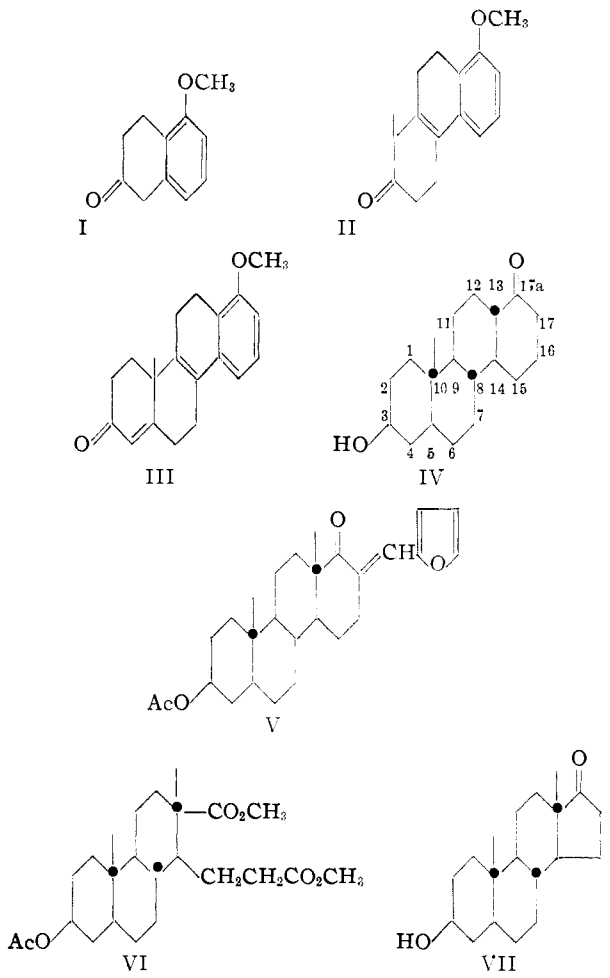
TOTAL SYNTHESIS OF EPIANDROSTERONE

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).



naphthalene,[2] was treated in the presence of sodium methoxide with 1-diethylamino-3-pentanone methiodide[3] followed—without isolation of the intermediary tricyclic compound II (m.p. 96.5–97°; C, 78.94; H, 7.55)—by methyl vinyl ketone[4] to produce the methoxyketomethyloctahydrochrysene III (m.p. 174.2–175°; C, 81.48; H, 7.61), which is thus very readily available in quantity. Reduction of 20 g. of III with lithium and alcohol in ammonia[5] followed by acid hydrolysis gave upon chromatography 5 g. of unsaturated ketonic material consisting of *dl*-D-homo-18-nor-13,14-dehydroepiandrosterone (IV with C=C at 13, 14) (m.p. 163.5–164°; λ_{max}^{EtOH} 248.5 mμ, log ε 4.12; C, 78.75; H, 9.78), and the 16,17-dehydroisomer (IV with C=C at 16,17) (m.p. 138–139°; λ_{max}^{EtOH} 226 mμ, log ε 3.89; C, 79.33; H, 10.27). Hydrogenation of the former, the preponderant isomer, over palladium catalyst gave, after isomerization with alkali, exclusively *dl*-D-homo-18-nor-epiandrosterone, IV (m.p. 159–161°; C, 78.50; H, 10.43). This same substance was produced directly on hydrogenation of the 16,17-dehydro ketone; hence the mixture of unsaturated ketones could be employed for production of pure IV. Only traces of other ketonic materials were formed in the lithium treatment; thus the two combined reduction steps, during which no less than six new asymmetric centers are introduced, nevertheless constitute stereospecific production of IV from III.

Condensation of IV with furfural, methylation,[6] and acetylation yielded an easily separable mixture of *dl*-17-furfurylidene-D-homoepiandrosterone acetate V (m.p. 192–192.5°; C, 76.19; H, 8.53), and the preponderant oily 13-iso ("lumi") compound (3-hydroxy compound, m.p. 88–90°; C, 78.26; H, 9.16). The infrared spectrum of the former was identical with that of V prepared from authentic D-homoepiandrosterone.[7]

Ozonolysis of *dl*-V followed by esterification with diazomethane afforded *dl*-dimethyl 3-β-acetoxyetioallohomobilianate VI (m.p. 136–137°; C, 68.12; H, 9.29) having an infrared spectrum identical with that of VI prepared by degradation of authentic epiandrosterone. Dieckmann cyclization of *dl*-VI with potassium *t*-butoxide, followed by acid hydrolysis, gave *dl*-epiandrosterone (m.p., 161–162°; C, 78.42; H, 10.49) having an infrared spectrum indistinguishable from that of authentic *d*-epiandrosterone. Resolution studies are in progress.

Similarly *dl*-13-iso-V yielded *dl*-13-iso-VI (m.p. 116.5–117.5°; C, 68.36; H, 9.29), which was converted to *dl*-lumiepiandrosterone (m.p. 157–158°; C, 78.32; H, 10.09), having an infrared spectrum identical with that of authentic lumiepiandrosterone.[8]

Studies to be reported in detail later have shown that intermediates can be obtained readily with the 11-oxygen function, and we are currently studying the application of our general scheme to the synthesis of the 11-oxygenated adrenal hormones as well as to other 11-desoxy hormones.

(2) J. W. Cornforth and R. Robinson, *J. Chem. Soc.*, 1855 (1949).

(3) *Cf.* J. W. Cornforth and R. Robinson, ref. 2.

(4) *Cf.* The Wilds method—A. L. Wilds, J. W. Ralls, W. C. Wildman and K. E. McCaleb, THIS JOURNAL, **72**, 5794 (1950)—for directing the orientation of ring addition in the Robinson-Mannich base type of reaction through the agency of a vinylogously active methyne hydrogen.

(5) These conditions differ from those generally preferred by A. J. Birch, *Quart. Rev.*, **4**, 69 (1950), in that lithium was employed according to A. L. Wilds and N. A. Nelson (in press) and a large excess of alcohol was used.

(6) The procedure of W. S. Johnson, THIS JOURNAL, **65**, 1317 (1943), was used, the 3-hydroxyl being protected from methylation as the tetrahydropyranyl ether; see C. W. Greenhalgh, H. B. Henbest and E. R. H. Jones, *J. Chem. Soc.*, 1190 (1951).

(7) Obtained from epiandrosterone by the procedure of D. A. Prins and C. W. Shoppee, *J. Chem. Soc.*, 494 (1946).

(8) J. R. Billeter and K. Miescher, *Helv. Chim. Acta*, **34**, 2053 (1951).

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"THERMODYNAMIC PROPERTIES OF GASEOUS DIFLUORODICHLOROMETHANE (FREON-12)": A CORRECTION

Sir:

It has been called to my attention that Fig. 3 in the paper of this title[1] gives a misleading impression of the accuracy of the data of Buffington and

(1) J. F. Masi, THIS JOURNAL, **74**, 4738 (1952).