

activity of the asymmetric centers or has conferred new activity on additional chromophoric groups.

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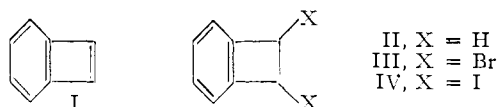
RECEIVED DECEMBER 16, 1955

### BENZOCYCLOBUTENE AND BENZOCYCLOBUTADIENE DIMER<sup>1</sup>

Sir:

Several fully aromatic hydrocarbons are known which may be considered to be dibenzo derivatives of the unknown cyclobutadiene.<sup>2,3,4a,b</sup> The simpler benzocyclobutadiene (I) has not been described, although molecular orbital calculations for the system have been made.<sup>5</sup> The closely related benzocyclobutene (II), the lower homolog of indane, also has not been described; doubts have been expressed concerning the stability of such a system<sup>6</sup> in which the considerable strain upon the ring is not compensated by any added resonance energy. We now wish to report the synthesis of the stable benzocyclobutene (II) and the generation of the unstable benzocyclobutadiene (I), isolated only as a dimer.

Treatment of  $\alpha,\alpha,\alpha',\alpha'$ -tetrabromo-*o*-xylene with excess sodium iodide in refluxing ethanol for two days has been reported<sup>7</sup> to give 1,2-dibromobenzocyclobutene (III). This reaction has been repeated and pure III isolated as colorless crystals, m.p. 52.4–52.8°. *Anal.* Calcd. for  $C_8H_6Br_2$ : C, 36.68; H, 2.31; Br, 61.02; mol. wt., 262. Found: C, 36.72; H, 2.35; Br, 60.83; mol. wt. (isothermal distillation), 258, 259. Dibromide III was unchanged by refluxing bromine after two days, and unaffected by maleic anhydride after fifteen hours at 90°. Nitric acid oxidized III to phthalic acid and bromine at 150° slowly converted III to  $\alpha,\alpha,\alpha',\alpha'$ -tetrabromo-*o*-xylene.



Refluxing a solution of III and excess sodium iodide in ethanol for eight days gave 1,2-diiodobenzocyclobutene (IV); m.p. 62.7–62.9°. *Anal.* Calcd. for  $C_8H_4I_2$ : C, 26.99; H, 1.70; I, 71.31; mol. wt., 356. Found: C, 26.84; H, 1.93; I, 71.05; mol. wt. (isothermal distillation), 350. Oxidation of IV with nitric acid gave phthalic acid. Hydrogenolysis of IV at room temperature in ethanol in the presence of palladium charcoal and sodium ethoxide gave, after distillation through a Nester spinning band column, pure II, b.p. 150.0° (748 mm.). *Anal.* Calcd. for  $C_8H_8$ : C, 92.26;

(1) A part of this material was presented before the Division of Organic Chemistry at the 128th meeting of the American Chemical Society, Minneapolis, Minnesota, September, 1955.

(2) W. C. Lothrop, *THIS JOURNAL*, **63**, 1187 (1941).

(3) R. F. Curtis and G. Viswanath, *Chem. and Ind.*, 1174 (1954).

(4) (a) M. P. Cava and J. F. Stucker, *ibid.*, 446 (1955); (b) *THIS JOURNAL*, **77**, 6022 (1955).

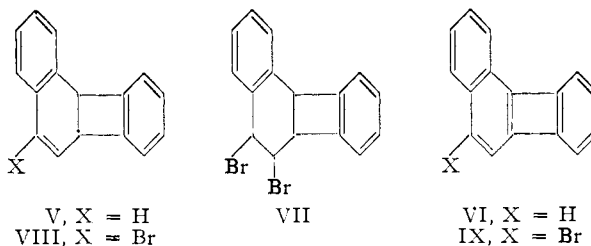
(5) J. D. Roberts, A. Streitweiser, Jr., and Clare M. Regan, *ibid.*, **74**, 4579 (1952).

(6) W. Baker, *J. Chem. Soc.*, 258 (1945).

(7) H. Finkelstein, Dissertation, Strassbourg, 1910.

H, 7.74. Found: C, 92.33, 92.47; H, 7.74, 7.72;  $\lambda_{\max}^{EtOH}$  260 m $\mu$  ( $\log \epsilon = 3.09$ ), 265.5 m $\mu$  ( $\log \epsilon = 3.28$ ), 271.5 m $\mu$  ( $\log \epsilon = 3.27$ );  $d_{25}^{425} = 0.957$ ;  $n_D^{25} 1.5409$ . The mass spectrum of II exhibited a parent peak at 104 m/e.; the infrared spectrum contained a band at 10.05  $\mu$  characteristic of a cycloalkane ring.<sup>8</sup>

Dehalogenation of either III or IV with zinc in ethanol (containing hydroquinone) gave, in 70–80% yield, not the expected I, but a crystalline dimer (V), m.p. 74.5°. *Anal.* Calcd. for  $C_{16}H_{12}$ : C, 94.07; H, 5.92; mol. wt., 204. Found: C, 93.89; H, 5.93; mol. wt. (isothermal distillation), 200. Dimer V was aromatized by N-bromosuccinimide in benzene to 1,2-benzobiphenylene (VI), identical with an authentic sample.<sup>4b</sup> Only one mole of bromine added to V to give a dibromide (VII), m.p. 111.5–112.2°. *Anal.* Calcd. for  $C_{16}H_{12}Br_2$ : C, 52.78; H, 3.32; Br, 43.90. Found: C, 52.91; H, 3.46; Br, 43.70. Reaction of VII with potassium *t*-butoxide in *t*-butyl alcohol gave the monobromide (VIII), m.p. 124.3–124.6°. *Anal.* Calcd. for  $C_{16}H_{11}Br$ : C, 67.86; H, 3.92; Br, 28.22. Found: C, 67.59; H, 4.02; Br, 28.01. Aromatization of VIII by N-bromosuccinimide in benzene gave 3-bromo-1,2-benzobiphenylene (IX), m.p. 125–



126°, identical in all respects with a sample synthesized from simple naphthalene precursors.<sup>9</sup> These reactions establish the structure of V, including the position of the double bond.

The formation of dimer V appears to occur via a Diels–Alder condensation between two molecules of I, followed by spontaneous aromatization of the initially formed product to V.

(8) L. W. Marrison, *J. Chem. Soc.*, 1614 (1951).

(9) M. P. Cava and J. F. Stucker, to be published shortly.

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RECEIVED DECEMBER 20, 1955

### SYNTHESIS OF POTENT ORAL ANABOLIC-ANDROGENIC STEROIDS

Sir:

In the course of studies on the synthesis of 11-oxygenated C-19 steroids<sup>1</sup> we have prepared a number of analogs (III, XI and XII) of this category which have been shown to possess oral anabolic and androgenic potency considerably higher than any other hitherto reported (see Table I).

The preparation of these compounds was in part accomplished by extension of the utility of 3-enamines formed selectively from polycarbonyl

(1) M. E. Herr and F. W. Heyl, *THIS JOURNAL*, **75**, 5927 (1953).

3-keto- $\Delta^4$ -steroids,<sup>1,2</sup> in particular their reaction with Grignard reagents.

11 $\beta$ -Hydroxy-4-androstene-3,17-dione (I)<sup>1,3</sup> was converted to 3-(N-pyrrolidiny)-11 $\beta$ -hydroxy-3,5-androstadien-17-one (II) in essentially quantitative yield by the reaction of pyrrolidine with I as previously described,<sup>2</sup> m.p. 190° (dec.),  $[\alpha]_D -81^\circ$  (CHCl<sub>3</sub>); *Anal.* Calcd. for C<sub>23</sub>H<sub>33</sub>NO<sub>2</sub>: C, 77.69; H, 9.36; N, 3.94. Found: C, 78.09; H, 9.55; N, 4.03. The reaction of II with a large excess of methylmagnesium bromide, followed by alkaline hydrolysis gave in 56% yield, 11 $\beta$ ,17 $\beta$ -dihydroxy-17-methyl-4-androsten-3-one (III), m.p. 205–209°,  $[\alpha]_D +125^\circ$  (CHCl<sub>3</sub>),  $\lambda_{\text{max}}^{\text{alc.}}$  243 ( $\epsilon$  15,575); *Anal.* Calcd. for C<sub>20</sub>H<sub>30</sub>O<sub>3</sub>: C, 75.44; H, 9.49. Found: C, 75.61; H, 9.27. Compound III was also prepared from 17 $\beta$ -hydroxy-17-methyl-4-androstene-3,11-dione (IV).<sup>4</sup> Reaction of IV with pyrrolidine gave 3-(N-pyrrolidiny)-17 $\beta$ -hydroxy-17-methyl-3,5-androstadien-11-one (V), m.p. 175–185° (dec.),  $[\alpha]_D -90^\circ$  (CHCl<sub>3</sub>); *Anal.* Calcd. for C<sub>24</sub>H<sub>36</sub>NO<sub>2</sub>: C, 78.01; H, 9.52; N, 3.79. Found: C, 77.87; H, 9.51; N, 3.83. Reduction of V with lithium aluminum hydride and hydrolysis gave III, identical by melting point and infrared comparison with the product prepared as described above.

17 $\beta$ -Hydroxy-17-methyl-4,9(11)-androstadiene-3-one (VI), m.p. 170–172°,  $[\alpha]_D +57^\circ$  (CHCl<sub>3</sub>); *Anal.* Calcd. for C<sub>20</sub>H<sub>28</sub>O<sub>2</sub>: C, 79.96; H, 9.39. Found: C, 79.59; H, 9.08, was prepared from 11 $\alpha$ ,17 $\beta$ -dihydroxy-17-methyl-4-androsten-3-one<sup>4</sup> by the action of base<sup>5</sup> on its 11-tosyl derivative (VII), m.p. 141–144° (dec.),  $[\alpha]_D +41^\circ$  (CHCl<sub>3</sub>); *Anal.* Calcd. for C<sub>27</sub>H<sub>38</sub>O<sub>5</sub>S: C, 68.61; H, 7.68; S, 6.78. Found: C, 68.86; H, 7.86; S, 6.89, as well as by the action of a large excess of methylmagnesium bromide on 3-(N-pyrrolidiny)-3,5,9(11)-androstatrien-17-one (VIII)<sup>6</sup> with subsequent alkaline hydrolysis.

Compound VI was converted to 11 $\beta$ ,17 $\beta$ -dihydroxy-9 $\alpha$ -fluoro-17-methyl-4-androsten-3-one (XI) by a sequence of reactions essentially the same as that described by Fried and Sabo<sup>7</sup> for the preparation of 9 $\alpha$ -fluorohydrocortisone from 17 $\alpha$ ,21-dihydroxy-4,9(11)-pregnadiene-3,20-dione 21-acetate. The reaction of VI with N-bromoacetamide in aqueous acid and acetone at 15° produced 9 $\alpha$ -bromo-11 $\beta$ ,17 $\beta$ -dihydroxy-17-methyl-4-androsten-3-one (IX), m.p. 150–154° (dec.),  $[\alpha]_D +112^\circ$  (CHCl<sub>3</sub>); *Anal.* Calcd. for C<sub>20</sub>H<sub>29</sub>BrO<sub>3</sub>: Br, 20.11. Found: Br, 18.75. Compound IX in methanol, upon titration with 1 equivalent of 0.1N sodium hydroxide afforded 17 $\beta$ -hydroxy-9 $\beta$ ,11 $\beta$ -epoxy-17-methyl-4-androsten-3-one (X), m.p. 183–185°,  $[\alpha]_D -40^\circ$  (CHCl<sub>3</sub>); *Anal.* Calcd. for C<sub>20</sub>H<sub>28</sub>O<sub>3</sub>: C, 75.92; H, 8.92. Found: C, 75.60; H, 8.96. The epoxide (X) in methylene chloride was treated with 48% hydrofluoric acid to give XI,

m.p. 270° (dec.),  $[\alpha]_D +109^\circ$  (EtOH),  $\lambda_{\text{max}}^{\text{alc.}}$  240 m $\mu$  ( $\epsilon$  16,700); *Anal.* Calcd. for C<sub>20</sub>H<sub>29</sub>FO<sub>3</sub>: C, 71.40; H, 8.69; F, 5.65. Found: C, 71.71; H, 8.66; F, 5.75. Oxidation of XI with chromium trioxide in acetic acid yielded 17 $\beta$ -hydroxy-9 $\alpha$ -fluoro-17-methyl-4-androstene-3,11-dione (XII), m.p. 213–220° (dec.),  $[\alpha]_D +144^\circ$  (CHCl<sub>3</sub>); *Anal.* Calcd. for C<sub>20</sub>H<sub>27</sub>FO<sub>3</sub>: C, 71.83; H, 8.14; F, 5.68. Found: C, 72.13; H, 8.30; F, 5.83.

TABLE I  
ORAL ANABOLIC-ANDROGENIC ACTIVITY

Compound	Anabolic	Androgenic
17-Methyltestosterone	1.0	1.0
11 $\beta$ ,17 $\beta$ -Dihydroxy-17-methyl-4-androsten-3-one (III)	2.9	0.9
11 $\beta$ ,17 $\beta$ -Dihydroxy-9 $\alpha$ -fluoro-17-methyl-4-androsten-3-one (XI)	20.0	9.5
17 $\beta$ -Hydroxy-9 $\alpha$ -fluoro-17-methyl-4-androstene-3,11-dione (XII)	22.0	8.5

We are indebted to S. C. Lyster, G. H. Lund and R. O. Stafford<sup>8</sup> of the Department of Endocrinology, The Upjohn Research Division, for the data in Table I, which records the oral anabolic and androgenic potency<sup>9</sup> of several of these substances in terms of 17-methyltestosterone as a standard.

The authors are indebted to J. L. Johnson, Mrs. G. S. Fonken and J. E. Stafford for spectral data, and to W. A. Struck and associates for microanalyses.

(8) S. C. Lyster, G. H. Lund and R. O. Stafford, *Endocrinology*, in press.

(9) Measured by weight increase in levator ani muscle and seminal vesicles in castrate immature rats.

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RECEIVED DECEMBER 14, 1955

#### A TOTAL SYNTHESIS OF 11-OXYGENATED STEROIDS<sup>1</sup>

Sir:

Three total synthetic routes to 11-oxygenated steroids have been described<sup>2,3,4</sup> but it still seemed to us that there was a need for a short yet flexible synthesis capable of leading to substances of type I where R<sub>1</sub>, R<sub>2</sub> and R<sub>3</sub> may be any desired groups. The precursor of I that we chose to synthesize is II, and this communication reports the total synthesis of II, R<sub>1</sub> = R<sub>2</sub> = CH<sub>3</sub>, R<sub>3</sub> = H.

6-Methoxy- $\alpha$ -tetralone<sup>5</sup> was converted *via* the hydroxymethylene ketone to the 2-methyl deriva-

(1) This work was supported, in part, by a research grant (G-3974) from the National Institutes of Health.

(2) (a) R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler, and W. M. McLamore, *THIS JOURNAL*, **74**, 4223 (1952); (b) L. B. Barkley, M. W. Farrar, W. S. Knowles, H. Raffelson, and Q. E. Thompson, *ibid.*, **76**, 5014 (1954).

(3) L. H. Sarett, G. E. Arth, R. M. Lukes, R. E. Beyler, G. I. Poos, W. F. Johns and J. M. Constantin, *ibid.*, **74**, 4974 (1952), and subsequent papers.

(4) W. S. Johnson, R. Pappo and A. D. Kemp, *ibid.*, **76**, 3353 (1954).

(5) G. Stork, *ibid.*, **69**, 576 (1947).

(2) F. W. Heyl and M. E. Herr, *THIS JOURNAL*, **75**, 1918 (1953).

(3) C. J. W. Brook and J. K. Norymberski, *Biochem. J.*, **55**, 374 (1953), have described a preparative method for obtaining this compound from cortisol by sodium bismuthate oxidation.

(4) S. H. Eppstein, P. D. Meister, H. Marian Leigh, D. H. Peterson, H. C. Murray, L. M. Reineke and A. Weintraub, *THIS JOURNAL*, **76**, 3174 (1954).

(5) S. Bernstein, R. H. Lenhard and J. H. Williams, *J. Org. Chem.*, **19**, 41 (1954).

(6) F. W. Heyl and M. E. Herr, *THIS JOURNAL*, **77**, 488 (1955).

(7) J. Fried and E. F. Sabo, *ibid.*, **75**, 2273 (1953); **76**, 1455 (1954).