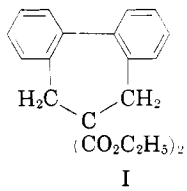
Communications TO THE EDITOR

Optical Activity in a Biphenyl Which has only A 2,2′-Three-carbon-atom Bridge

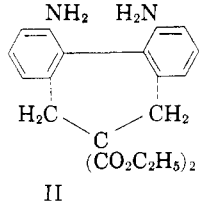
Sir:

While substituted biphenyls having 2,2′-three-atom bridges *as well as* large 6,6′-substituents have been resolved,[1] attempts to resolve 2,2′-bridged biphenyls devoid of 6,6′-substituents have been unsuccessful.[1,2,3]

We wish to report the preparation of optically active 6,6-dicarbethoxydibenzo[*a*,*c*]-1,3-cycloheptadiene, I, and the observation that this optically active substance has the 249 mμ band in its ultraviolet absorption spectrum as has biphenyl.



I



II

This band is generally assigned to inter-ring conjugation and, heretofore, interpreted as necessitating coplanarity of the two aromatic rings.[4] The extension of this interpretation to the spectrum of I would preclude enantiomorphism even though Fisher-Taylor-Hirschfelder models indicate a nonplanar configuration for the molecule.

Optically active (+) 6,6′-dinitrodiphenic acid[5] was converted *via* conventional reactions into (−) 1,11-diamino-6,6-dicarbethoxydibenzo[*a*,*c*]-1,3-cycloheptadiene (II), m.p. 111–113°; $[\alpha]^{32.5}$ −25.4° (*l* = 1, *c*, 1.062 g. in 95% ethanol). *Anal.* Calc'd for $C_{21}H_{24}N_2O_4$: C, 68.45; H, 6.57; N, 7.60. Found: C, 68.33; H, 6.42; N, 7.60. Then 2 g. of diamine II with 1.3 g. of powdered cuprous oxide was added to 67 ml. of 50% aqueous hypophosphorous acid and cooled to −15°. With vigorous stirring, a solution of 1.1 g. of sodium nitrite dissolved in 5 ml. of water was slowly added and the temperature was maintained at −15°. After two hours the reaction mixture was warmed to about 5° and extracted with cyclohexane. After washing with dil. sodium hydroxide, the dried solution was chromatographed on an alumina column and developed with cyclohexane containing 2% ethanol. The colorless eluate was evaporated under a vacuum to leave 0.8 g. of colorless I, m.p. 64–66°. *Anal.* Calc'd for $C_{21}H_{22}O_4$: C, 74.53; H, 6.57. Found: C, 74.51; H, 6.57. This, on being dissolved in cyclohexane gave an active solution; $\alpha_D^{32.5}$ +0.18°, $[\alpha]_D^{32.5}$ +2.25°, which became inactive after about five hours at this temperature. The ultraviolet and infrared absorption spectra of I obtained from the optically active cyclohexane solution were identical with those obtained from authentic racemic I (m.p. 64–66°) prepared from diphenic acid.

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Received August 1, 1956

(1) G. H. Beaven, D. H. Hall, M. S. Lesslie, and E. E. Turner, *J. Chem. Soc.*, 854 (1952).
(2) F. Bell, *J. Chem. Soc.*, 1527 (1952).
(3) G. H. Beaven, G. R. Bird, D. M. Hall, E. A. Johnson, J. E. Ladbury, M. S. Lesslie, and E. E. Turner, *J. Chem. Soc.*, 2708 (1955).
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8-Isotestosterone

Sir:

We have recently described[1] the synthesis of 8-isoprogesterone, a stereoisomer of the natural hormone which still retained appreciable biological activity. Inversion of configuration at C-8 carries with it a major conformational change since either ring B or ring C must now assume a boat conformation and it has also been found that striking rotatory dispersion changes[2] are associated with this stereochemical alteration. In view of the great current interest in androgen analogs[3] we would like to report the synthesis of 8-isotestosterone (VI) and its preliminary biological examination.

The eleven-step synthesis of Δ[16]-8α-allopregnen-3β-ol-20-one acetate (I) from diosgenin has already been recorded.[1] Beckmann rearrangement[4] of its oxime with *p*-acetamidobenzenesulfonyl chloride in pyridine solution followed by hydrolysis yielded 8α-androstan-3β-ol-17-one (II), m.p. 151–153°,

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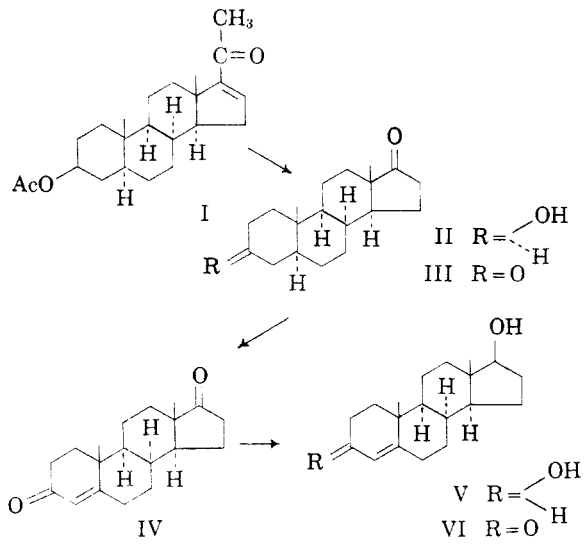

$[\alpha]_D$ + 220° (all rotations in chloroform), $\lambda_{max}^{CHCl_3}$ 5.75 μ; *Anal.* Calc'd for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41. Found: C, 78.59; H, 10.38. Oxidation of II with chromium trioxide in acetic acid and recrystallization from isopropyl ether afforded 8α-androstane-3,17-dione (III), m.p. 168–170°, $[\alpha]_D$ +202°, $\lambda_{max}^{CHCl_3}$ 5.75 and 5.86 μ; *Anal.* Calc'd for $C_{19}H_{28}O_2$: C, 79.12; H, 9.79. Found: C, 79.23; H, 9.93. The introduction of the required 4,5-double bond was carried out without isolation of intermediates by dibromination to the 2,4-dibromo derivative, refluxing with sodium iodide in acetone solution, and deiodinating with chromous chloride,[5] whereupon Δ^4-8α-androstene-3,17-dione (IV) could be isolated (m.p. 193–197°, λ_{max}^{EtOH} 243 mμ, log ϵ 4.17, $\lambda_{max}^{CHCl_3}$ 5.75, 6.0, and 6.12 μ, typical rotatory dispersion[2] of 8α-Δ^4-3-keto steroid; *Anal.* Calc'd for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.58; H, 9.20). Preferential reduction of the 17-ketone group of IV by means of sodium borohydride[6] failed and resort was, therefore, taken to the alternate scheme[7] of lithium aluminum hydride reduction to the crude diol V and selective oxidation of the allylic alcohol function with manganese dioxide. The resulting 8-isotestosterone (VI) (m.p. 182–184°,[4] $[\alpha]_D$ +134° (*c*, 0.035 in dioxane), λ_{max}^{EtOH} 242 mμ, log ϵ 4.18, $\lambda_{max}^{CHCl_3}$ 2.95, 5.98, and 6.10 μ; *Anal.* Calc'd for $C_{19}H_{28}O_2$: C, 79.12; H, 9.79. Found: C, 78.91; H, 10.03) was assayed by the chick comb test using 53 chicks on four different dose levels with testosterone as control. Under these conditions, 8-isotestosterone exhibited 40% of the androgenic activity of testosterone thus demonstrating that in the estrogenic,[8] progestational,[1] and androgenic hormone series, inversion of configuration at the rather inaccessible C-8 center is still compatible with relatively high biological activity.

We are indebted to the American Cancer Society for an Institutional Research Grant and through the Committee on Growth of the National Research Council for a research grant in support of this work.

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Received August 24, 1956

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(8) An isomer of estrone, derived from equilin and regarded as 8-isoestrone (A. Serini and W. Logemann, *Ber.*, **71**, 186 (1938); see also W. G. Dauben and L. Ahramjian, *J. Am. Chem. Soc.*, **78**, 633 (1956)) has been reported to exhibit about one-third the estrogenic potency of estrone in rats.

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