2-Amino- and Substituted Aminomethyl-1,2,3,10b-tetrahydrafluoranthen-3-ones

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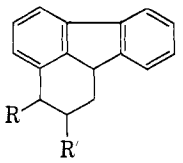
Received December 2, 1963

The report of the tranquilizing effect of 2-piperidinomethyl-1-tetralone hydrochloride[3] suggested the synthesis of the corresponding derivative and related compounds of 1,2,3,10b-tetrahydrofluoranthen-3-one.



I, R = =O; R′ = $CH_2NR_2 \cdot HCl$
II, R = =O; R′ = =NOH
III, R = =O; R′ = $NH_2 \cdot HCl$

The 2-piperidinomethyl-, 2-morpholinomethyl-, 2-dimethylaminomethyl, and 2-diethylaminomethyl-1,2,-3,10b-tetrahydrofluoranthen-3-one hydrochlorides (I) were prepared by a Mannich reaction between 1,2,3,10b-tetrahydrofluoranthen-3-one, paraformaldehyde, and the corresponding amine hydrochloride. The yield is very sensitive to the conditions used. The reaction with diethylamine hydrochloride was the only one to yield two products. Similar infrared spectra for these two compounds would suggest that they are racemic mixtures. The usual by-products formed in a Mannich reaction were isolated and their structures are being studied further.

2-Amino-1,2,3,10b-tetrahydrofluoranthen-3-one hydrochloride (II) was prepared by the catalytic reduction of 2-oximino-1,2,3,10b-tetrahydrofluoranthen-3-one (III) in the presence of hydrogen chloride. The oximino compound (III) was prepared by treating 1,2,3,-10b-tetrahydrofluoranthen-3-one with butyl nitrite and hydrochloric acid. This reaction proceeded normally in contrast to that reported[4] for 4-phenyltetralone in which 4-phenyl-2-nitroso-1-naphthol was formed. The product (III) was different from 2-nitrosofluoranthen-3-ol which was synthesized from fluoranthen-3-ol.

2-Piperidinomethyl-1,2,3,10b-tetrahydrofluoranthen-3-one (I) showed no reserpine-like activity. When given by stomach tube to CF1 white mice at doses of 75 and 300 mg./kg., this compound did not lower the catechol amine content of the adrenal glands as measured by the solvent extraction method of Shore and Olin.[5] Moreover, no drooping of the eyelids, or ptosis, was seen in these mice, whereas animals treated with catechol amine releasing agents such as reserpine or guanethidine showed unmistakable signs of ptosis. Based on these negative results, the remaining compounds were not tested.

Experimental[6]

1,2,3,10b-Tetrahydrofluoranthen-3-one.—This ketone was prepared in a 70% yield from β-9-fluorenylpropionic acid by a modification of the method of Kloetzel and Chubb.[7] Phosphorus pentachloride was used to make the acid chloride, and 1,1,2,2-tetrachloroethane was used as the solvent for the Friedel-Crafts reaction.

2-Piperidinomethyl-1,2,3,10b-tetrahydrofluoranthen-3-one Hydrochloride.—1,2,3,10b-Tetrahydrofluoranthen-3-one (11 g.), piperidine hydrochloride (9.12 g.), and paraformaldehyde (2.24 g.) in isoamyl alcohol (50 ml.) were refluxed under nitrogen for 30 min., poured into 400 ml. of ethyl acetate, and cooled. The amine hydrochlorides formed were dissolved in hot absolute ethanol (50 ml.) and treated with a 5-fold volume of acetone. Cooling gave unchanged piperidine hydrochloride which was filtered. The filtrate was combined with the first ethyl acetate–isoamyl alcohol filtrate and the solvent was removed and gave a yellow-orange oil. Triturating with ethyl acetate gave a solid amine hydrochloride (12.0 g.) which, after recrystallizing once from a mixture of absolute ethanol and acetone and a second time from ethyl acetate and ethanol, gave a sample which decomposed at 162° and finally melted at 215–230°.

The ethyl acetate filtrate gave nitrogen-free by-products of the Mannich reaction which are being studied further.

The remaining 2-aminomethyl-1,2,3,10b-tetrahydrofluoranthen-3-ones were made by a similar method, differing only in that the reaction mixture for the diethylamino and dimethylamino derivatives were poured into dry ether. The amine hydrochlorides were then recrystallized from absolute ethanol. The morpholino derivative was poured into water, made basic, and after removal of the morpholine was reprecipitated from ether with hydrogen chloride. The yields, melting points, and analyses are given in Table I.

2-Oximino-1,2,3,10b-tetrahydrofluoranthen-3-one (II).—1,2,3,10b-Tetrahydrofluoranthen-3-one (11.0 g.) suspended in anhydrous ether (100 ml.) was treated with a slow stream of hydrogen chloride and with *n*-butyl nitrite (5.15 g.). The addition of butyl nitrite required 1 hr. Hydrogen chloride was passed through for an additional 30 min. and the stirring was continued for 2 hr. The solid orange-brown product (11.9 g.) obtained underwent decomposition in the range 162–177°.

TABLE I
2-AMINOMETHYL-1,2,3,10b-TETRAHYDROFLUORANTHEN-3-ONES

Amino	Yield, %	M.p., °C., dec.	Empirical formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
Piperidino	67	162[a]	$C_{22}H_{24}ClNO$	74.66	74.13	6.83	6.71	3.95	4.13
Morpholino	16	162–164[a,b]	$C_{21}H_{22}ClNO_2$	70.88	70.71	6.23	6.14	3.94	3.90
Dimethylamino	38	184–84.5[a]	$C_{19}H_{20}ClNO$	72.71	72.68	6.10	6.44	4.47	4.41
Diethylamino	11	161[a]	$C_{21}H_{24}ClNO$	73.77	73.86	7.07	6.96	4.09	4.39
	0.7	141–41.5[a,c]	$C_{21}H_{24}ClNO$	73.77	73.87	7.07	7.09	4.09	4.00

[a] The resulting decomposition products melted in the range of 210–230°. [b] Recrystallized from absolute ethanol. [c] Separated from the alcohol filtrate from the recrystallization of the 161° melting compound. This product was recrystallized from a mixture of ethyl acetate and absolute ethanol.

(1) Abstracted in part from the Ph.D. thesis of I. H. Petersen, Aug., 1960.

(2) Union Carbide Corporation Fellow, 1958–1959.

(3) J. Knoll, *Arch. Exptl. Pathol. Pharmakol.*, **236**, 92 (1959); *Chem. Abstr.*, **53**, 11655 (1959).

(4) S. Wawzonek and J. Kozikowski, *J. Am. Chem. Soc.*, **76**, 1641 (1951).

(5) P. A. Shore and J. S. Olin, *J. Pharmacol. Exptl. Therap.*, **122**, 295 (1958).

(6) Melting points are corrected.

(7) M. C. Kloetzel and F. L. Chubb, *J. Am. Chem. Soc.*, **72**, 150 (1950).

Recrystallization from *n*-propyl alcohol did not change the decomposition range.

Anal. Calcd. for $C_{16}H_{11}NO_2$: C, 77.09; H, 4.44; N, 5.62. Found: C, 77.36; H, 4.51; N, 5.89.

2-Nitrosofluoranthen-3-ol.—Fluoranthen-3-ol[8] (2.0 g.) in absolute ethanol (50 ml.) at 0° was treated with concentrated hydrochloric acid (1 ml.) and *n*-butyl nitrite (0.5 g.) in ethanol (35 ml.). The mixture was stirred at 0° for 1 hr. and heated at 100° for 1.5 hr. The resulting brown precipitate after fractional crystallization from absolute ethanol and successive crystallizations from absolute ethanol and from benzene gave yellow-orange needles melting at 216° dec.; yield 0.135 g.

Anal. Calcd. for $C_{16}H_9NO_2$: C, 77.72; H, 3.67; N, 5.67. Found: C, 78.29; H, 3.83; N, 5.11.

2-Amino-1,2,3,10b-tetrahydrofluoranthen-3-one Hydrochloride (III).—2-Oximino-1,2,3,10b-tetrahydrofluoranthen-3-one (3.0 g.) was hydrogenated at 3.16 kg./cm.^{2} in absolute ethanol (100 ml.) containing 3 moles of HCl and 10% Pd-C (0.3 g.) for 1.5 hr. The resulting mixture was filtered and the amine hydrochloride was dissolved in hot water degassed previously with nitrogen. Cooling gave yellow crystals which after two further recrystallizations from hot water gave small white platelets melting at 151° dec.; yield 0.85 g.

Anal. Calcd. for $C_{16}H_{13}NO \cdot HCl$: C, 70.71; H, 5.19; N, 5.31. Found: C, 70.24; H, 5.31; N, 5.59.

Acknowledgment.—The authors wish to thank Dr. Richard McLean of Smith, Kline and French Laboratories for the pharmacological results.

(8) J. von Braun and G. Manz, *Ann.*, **488**, 111 (1931).

Pteridinosteroids. II. Synthesis of 17β-Acetoxy-5α-androstano[2,3-*g*]-2′,4′-diaminopteridine[1a,b]

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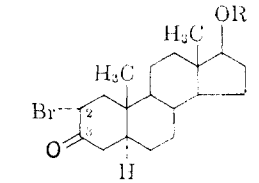
Received February 4, 1964

The synthesis and biological evaluation of pteridinosteroids, a new series of polycyclic compounds, was undertaken in our laboratories in the hope that such compounds may combine the antifolic activity of 2,4-diaminopteridines with lipid solubility and with the favorable cellular transport properties of steroid molecules. The first compound representing this series, a [4,3-*g*]-fused pteridinosteroid, was described recently and was shown to satisfy, qualitatively at least, the above expectations.[2]

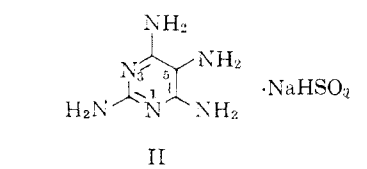
It was hoped that, if the fusion of the pteridine nucleus with respect to the A and B rings is linear, some of the hormonal activities of the steroid may be maintained, modified, or accentuated. (Examples for such effects have been seen in some other steroidally fused heterocycles.[3]) For this reason, the synthesis of a [2,3-*g*]-fused pteridinosteroid was undertaken.

The starting material for this synthesis, 17β-hydroxy-2α-bromo-5α-androstan-3-one (Ia), was prepared by direct bromination of 17β-hydroxy-5α-androstan-3-one (5α-dihydrotestosterone) in glacial acetic acid.[4] Infrared spectrum showed a shift of the carbonyl stretching band from 5.9 to 5.8 μ, indicating equatorial halogen (2α-Br).[5] This compound was acetylated and was carefully purified[6] in the form of the acetate (Ib).

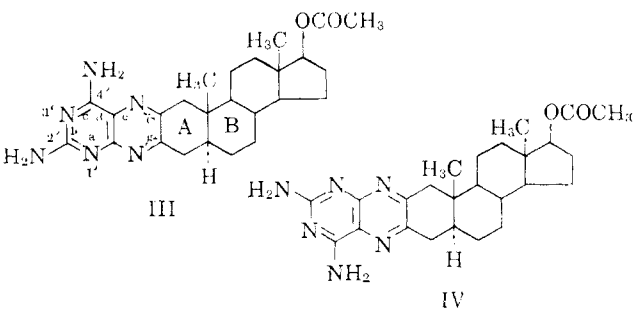
Condensation of Ib with 2,4,5,6-tetraaminopyrimidine bisulfite (II) to form a pteridine ring system, would be expected to require oxidative conditions, since the direct (anaerobic) condensation product would be a nonaromatic dihydropteridine. Therefore, the reaction was tried first in glacial acetic acid solution under a variety of oxidative conditions, including presence of iodine, passing air through the reaction mixture, etc. All of these methods caused the formation of dark-colored by-products which made the purification of the



Ia, R = H
Ib, R = $COCH_3$



II



III

IV

pteridinosteroid extremely difficult. Such by-products might arise from the oxidation and subsequent self-condensation of the tetraaminopyrimidine. This did not occur when the reaction was carried out with air oxidation in pyridine and in the presence of dicyclohexylcarbodiimide, but in this case the yield of the product was very low.

On the other hand, just as in the case of the classical folic acid synthesis,[7] condensation with concomitant oxidation to the pteridine occurred readily if the reactants were simply combined in an aqueous (alcoholic) solution and allowed to react at room temperature with stirring for an extended period of time. A series of experiments was carried out to establish the optimal pH; it was found that condensation at pH 7.5–8.0

(1) (a) This investigation was supported by PHS Research Grant No. CA-06695 and CA-03603, from the National Cancer Institute. (b) A preliminary report of this work was presented before the Division of Medicinal Chemistry, 145th National Meeting of the American Chemical Society, New York, N. Y., Sept., 1963, Abstracts, p. 28-O. (c) To whom inquiries should be directed.

(2) T. J. Bardos, Z. F. Chmielewicz, S. P. Raman, and A. Segaloff, *Steroids*, **2**, 105 (1963).

(3) R. O. Clinton, A. J. Mason, F. W. Stonner, H. C. Newmann, R. G. Christiansen, R. L. Clarke, J. H. Ackerman, D. F. Page, J. W. Dean, W. B. Dickinson, and C. Carabateas, *J. Am. Chem. Soc.*, **83**, 1478 (1961).

(4) A. Butenandt, U. S. Patent 2,311,638 (1943); *Chem. Abstr.*, **37**, 1408 (1943).

(5) R. N. Jones, D. A. Ramsay, F. Herling, and K. Dobriner, *J. Am. Chem. Soc.*, **74**, 2828 (1952).

(6) The presence of trace amounts of impurities caused difficulties in the purification of the pteridinosteroid.

(7) C. W. Waller, B. L. Hutchings, J. H. Mowat, E. L. Stokstad, J. H. Boothe, R. B. Angier, J. Seudy, Y. Subbarow, D. B. Cosulich, M. J. Fahrenbach, M. E. Hultquist, E. Kuh, E. H. Northey, D. R. Seeger, J. P. Sickels, and J. M. Smith, Jr., *J. Am. Chem. Soc.*, **70**, 2828 (1948).