NOTES

Some *p*-Arsenic-substituted Derivatives of Phenylalanine[1]

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Received October 29, 1954

Many ring-substituted β-phenylalanines have been prepared. Some of these[2] have been synthesized in the hope of finding useful therapeutic agents.

This note reports the preparation of some new, arsenic-containing, derivatives of β-phenylalanine in which the phenyl ring carries, in the *para*-position, the arsonic acid (arsono) group ($-AsO_3H_2$), the arsenoso group (–AsO) or the arseno group (—As=As—).

It is felt that these arsenic-substituted phenylalanines may be of potential value as parasiticides. The toxic action of arsenicals is considered to reside in the arsenic portion of the molecule, while the organic portion to which it is attached influences distribution and specificity. It is expected that the polar character of the amino acid side chain will enhance solubility of these compounds in biological fluids, and that the large phenylalanine group, upon which the toxic groupings are substituted, may induce active absorption of the compounds by the infecting organisms, since it is a grouping common to some of the natural amino acids utilized by most organisms. For the same reason, it is probable that ready distribution of these compounds through the tissues will occur, and that excretion of these compounds will be slowed because of active reabsorption in the renal tubules of the animal treated with these substances.

It is considered that the parasiticidal activity of these compounds would not be dependent on competitive inhibition (as phenylalanine analogs)[3] but, rather, that the substituted phenylalanine would serve as a carrier of toxic groupings ("baited hook" effect).

Similar views on alanine derivatives as potential chemotherapeutic agents have been expressed by Elliott, Fuller and Harington.[2]

Experimental

Melting points were obtained with the Fisher–Johns micro-block and are uncorrected. Analyses for nitrogen[4] and arsenic[5] were carried out using published methods.

N-Acetyl-*p*-nitrophenylalanine (I).—This was prepared in 84% yield from *p*-nitrophenylalanine hydrochloride[2] by the method of Chattaway[6]; m.p. 190–192°.

Anal. Calcd. for $C_{11}H_{12}N_2O_5$: N, 11.11. Found: N, 11.29.

N-Benzoyl-*p*-nitrophenylalanine (II).—The method of Steiger[7] provided II in 96% yield, m.p. 200–202°.

Anal. Calcd. for $C_{16}H_{14}N_2O_5$: N, 8.92. Found: N, 8.78.

α-N-Acetyl-*p*-aminophenylalanine Hydrochloride (III).—A solution of 18.6 g. (0.074 mole) of I in dilute sodium hydroxide solution was hydrogenated over Raney nickel[8] for 45 minutes at 45 pounds pressure. Acidification of the filtered solution with hydrochloric acid gave 15.1 g. (79%) of slightly yellow product which was purified by solution in dilute sodium hydroxide, decolorization with charcoal, reprecipitation with hydrochloric acid and recrystallization from alcohol–ether, m.p. 235–240° dec.

Anal. Calcd. for $C_{11}H_{15}ClN_2O_3$: N, 10.83. Found: N, 10.88.

α-N-Benzoyl-*p*-aminophenylalanine Hydrochloride (IV).—Hydrogenation of 26.6 g. of II gave 23.3 g. of IV, m.p. 216–217°; recrystallization from acetone–ether raised the melting point to 218°.

Anal. Calcd. for $C_{16}H_{17}ClN_2O_3$: N, 8.73. Found: N, 8.62.

N-Benzoyl-*p*-arsonophenylalanine (V).—A solution containing 6.4 g. (0.02 mole) of IV in the required amount of dilute hydrochloric acid was cooled to 0–5°, and to this was added, with rapid stirring, 1.32 g. (0.02 mole) of sodium nitrite in 18 ml. of water. The resulting diazonium salt was added slowly to a solution containing 4.6 g. (20% excess) of sodium arsenite and 0.5 g. of cupric sulfate,[9] while the temperature was maintained below 15° and the solution was kept alkaline at all times by addition of sodium carbonate. The temperature of the reaction mixture then was raised slowly to 50°, and dilute hydrochloric acid was added to precipitate V. The yellow precipitate was washed with dilute hydrochloric acid and dried to yield 5.28 g. (67%) of product melting at 245–250°. Purification was effected by solution in dilute sodium hydroxide, treatment with charcoal, precipitation with acid, resolution in 85% alcohol and precipitation with ether to give a grayish-white product melting at 258–260°. Recrystallization from aqueous alcohol gave shiny crystals without raising the melting point.

Anal. Calcd. for $C_{16}H_{16}AsNO_6$: N, 3.56; As, 19.05. Found: N, 3.60; As, 19.25.

***p*-Arsonophenylalanine Hydrochloride** (VI).—Hydrolysis of V with 6 *N* hydrochloric acid yielded 87% of VI. This upon recrystallization from aqueous alcohol melted with considerable decomposition at 265°.

Anal. Calcd. for $C_9H_{13}AsClNO_5$: N, 4.30; As, 22.33. Found: N, 4.40; As, 22.12.

N-Acetyl-*p*-arsonophenylalanine (VII).—A yield of 52% of VII was obtained from III by the procedure used to prepare V. Recrystallization from aqueous alcohol gave a grayish-white solid melting at 242–245°.

Anal. Calcd. for $C_{11}H_{14}AsNO_6$: N, 4.23; As, 22.62. Found: N, 4.18; As, 22.43.

N-Benzoyl-*p*-arsenosophenylalanine (VIII).—The method described by Fox[10] for the reduction of the arsonic acid group to the arsenoso group was used. A suspension of 3.9 g. (0.01 mole) of V in 100 ml. of 2 *N* hydrochloric acid containing 0.2 g. of potassium iodide was stirred while sulfur dioxide was bubbled in for 2 hours at room temperature. The product was filtered off, dissolved in dilute sodium hydroxide, and reprecipitated by the addition of dilute acetic acid. The white solid was collected, washed with dilute hydrochloric acid, and dried to yield 2.68 g. (75%) of white powder, m.p. 270–272°.

Anal. Calcd. for $C_{16}H_{14}AsNO_4$: N, 3.90; As, 20.85. Found: N, 3.96; As, 21.02.

***p*-Arsenosophenylalanine Hydrochloride** (IX).—Hydrolysis of VIII with 6 *N* hydrochloric acid gave IX in 89% yield, m.p. 282–284° dec.

(1) Based on a thesis presented by W. L. Bressler to the Graduate College, University of Oklahoma, for the M.S., January, 1951.

(2) D. F. Elliott, A. T. Fuller and C. R. Harington, *J. Chem. Soc.*, 85 (1948); D. F. Elliott and C. R. Harington, *ibid.*, 1374 (1949); J. H. Burckhalter and V. C. Stephens, This Journal, **73**, 56 (1951).

(3) H. K. Mitchell and C. Niemann, *ibid.*, **69**, 1232 (1947).

(4) A. Friedrich, *Z. physiol. Chem.*, **216**, 68 (1933).

(5) J. B. Niederl and V. Niederl, "Organic Quantitative Microanalysis," John Wiley and Sons, Inc., New York, N. Y., 2nd Ed., 1942, pp. 205–206.

(6) F. D. Chattaway, *J. Chem. Soc.*, 2495 (1931).

(7) R. E. Steiger, *J. Org. Chem.*, **9**, 396 (1944).

(8) R. Mozingo, *Org. Syntheses*, **21**, 15 (1941).

(9) J. F. Norris, *Ind. Eng. Chem.*, **11**, 825 (1919).

(10) H. H. Fox, *J. Org. Chem.*, **12**, 872 (1947).

Anal. Calcd. for $C_9H_{11}AsClNO_3$: N, 4.80; As, 25.69. Found: N, 4.72; As, 25.57.

N-Acetyl-*p*-arsenosophenylalanine (X).—Reduction of 3.3 g. (0.01 mole) of VII with sulfur dioxide gave 2.6 g. (88%) of X melting at 250–252°.

Anal. Calcd. for $C_{11}H_{12}AsNO_4$: N, 4.72; As, 25.21. Found: N, 4.62; As, 25.22.

N-Benzoyl-*p*-arsenophenylalanine (XI).—The corresponding arsonic acid V was reduced with sodium hydrosulfite.[10] A solution of 3.93 g. (0.01 mole) of V in 10 ml. of 2 *N* sodium hydroxide and 100 ml. of water was added to a solution of 50 g. of sodium hydrosulfite and 10 g. of magnesium chloride in 400 ml. of water. The mixture was stirred at 60° for 2 hours. Addition of dilute hydrochloric acid gave a yellow powder which was purified by solution in acetone and reprecipitation with water. For final purification, the material was dissolved in glacial acetic acid and precipitated with a large excess of dilute hydrochloric acid to give 2.15 g. (63%) of XI, m.p. 294–295°.

Anal. Calcd. for $C_{32}H_{28}As_2N_2O_6$: N, 4.08; As, 21.83. Found: N, 4.17; As, 21.65.

***p*-Arsenophenylalanine Hydrochloride (XII).**—Hydrolysis of XI with 6 *N* hydrochloric acid gave XII (79%), melting with decomposition at 282–285°.

Anal. Calcd. for $C_{18}H_{22}As_2Cl_2N_2O_4$: N, 5.08; As, 27.74. Found: N, 4.92; As, 27.98.

N-Acetyl-*p*-arsenophenylalanine (XIII).—The corresponding arsonic acid VII was reduced with sodium hydrosulfite to give 47% of product melting with decomposition at 272–277°.

Anal. Calcd. for $C_{22}H_{24}As_2N_2O_6$: N, 4.99; As, 26.65. Found: N, 4.86; As, 26.42.

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Steroidal Cyclic Ketals. XIII.[1] The Conversion of 11-*epi*-Corticosterone into Corticosterone

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RECEIVED NOVEMBER 10, 1954

In Paper XI[2] of this series, there was described a procedure for the conversion of 11-*epi*-hydrocortisone *via* its bisethylene ketal into hydrocortisone. One of the features of this synthesis was that cortisone (free alcohol) was by-passed. Subsequently, this procedure was extended to the preparation of corticosterone (Va)[3] from the readily available 11-*epi*-corticosterone (I),[4] the details of which will be described here.

11-*epi*-Corticosterone (I) on ketalization (ethylene glycol, benzene and *p*-toluenesulfonic acid monohydrate) was converted in 37% yield into its 3,20-bisethylene ketal (II). Oxidation of the latter with chromic acid–pyridine complex[5] gave in 61% yield the 3,20-bisethylene ketal (III) of 11-dehydrocorticosterone.

Reduction of III with sodium borohydride in a mixture of tetrahydrofuran and aqueous sodium hydroxide gave the bisethylene ketal (IV) of corticosterone. This product was not characterized because on recrystallization gels were obtained. Hydrolysis of the ketal groups with aqueous sulfuric acid in methanol gave corticosterone (Va) in 85% yield. The corticosterone (Va) so formed contained an insignificant trace amount of 11-*epi*-corticosterone (I), as shown by paper chromatographic analysis. Acetylation gave corticosterone 21-acetate (Vb).

From a preparative viewpoint it was found expedient to hydrolyze directly the crude reduction product III without recrystallization. This provided a 77% yield of corticosterone (Va) from II.

Although this four-step synthesis was performed in only a fair over-all yield of 17%, it represents a comparatively facile and convenient method for preparing corticosterone (Va).[6]

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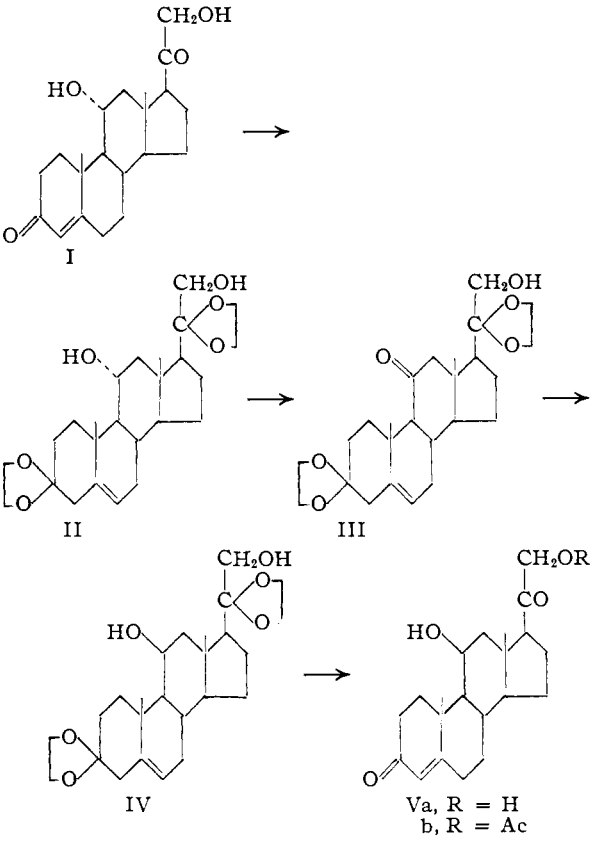

Experimental

Melting Points.—All melting points are uncorrected, and were determined with uncalibrated Anschütz thermometers.

(1) Paper XII, W. S. Allen and S. Bernstein, THIS JOURNAL, **77**, 1028 (1955).

(2) W. S. Allen, S. Bernstein and R. Littell, *ibid.*, **76**, 6116 (1954).

(3) Corticosterone has been synthesized by chemical and biochemical methods: (a) J. von Euw, A. Lardon and T. Reichstein, *Helv. Chim. Acta*, **27**, 1287 (1944); (b) O. Hechter, *et al.*, THIS JOURNAL, **71**, 3261 (1949); (c) N. L. Wendler, Huang-Minlon and M. Tishler, *ibid.*, **73**, 3818 (1951); (d) F. W. Kahnt and A. Wettstein, *Helv. Chim. Acta*, **34**, 1790 (1951).

(4) H. C. Murray and D. H. Peterson, U. S. Patent 2,602,769 (July 8, 1952); J. Fried, *et al.*, THIS JOURNAL, **74**, 3962 (1952); S. H. Eppstein, *et al.*, *ibid.*, **75**, 408 (1953).

(5) G. I. Poos, G. E. Arth, R. E. Beyler and L. H. Sarett, *ibid.*, **75**, 422 (1953).

(6) After completion of this work, there appeared a publication by D. Taub, R. H. Pettebone, N. L. Wendler and M. Tishler, *ibid.*, **76**, 4094 (1954), in which corticosterone was prepared in 20–25% over-all yield from cortisone and hydrocortisone. In this connection, we wish to record here that the intermediate bisethylene ketal (IV) of corticosterone also may be prepared by selective hydrogenation of $\Delta^{5,16}$-pregnadiene-11β,21-diol-3,20-dione 3,20-bisethylene ketal with platinum oxide in absolute alcohol. The preparation of the $\Delta^{5,16}$-diene from either cortisone or 11-*epi*-hydrocortisone has been described already (W. S. Allen and S. Bernstein, *ibid.*, **77**, 1028 (1955); and references cited therein). Of these two pathways to corticosterone we prefer the one *via* 11-*epi*-corticosterone (I).