[CONTRIBUTION FROM THE ORGANIC CHEMISTRY DEPARTMENT, RESEARCH DIVISION, ABBOTT LABORATORIES]

Synthesis of Some Imidazo[4,5-*d*]pyridazines and Imidazo[4,5-*d*]triazolo[4,3-*b*]pyridazines

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4-Amino- and 7-amino-1-β-D-ribofuranosylimidazo[4,5-*d*]pyridazine (VIa and b) have been prepared as possible adenosine antimetabolites. Treatment of 1-benzyl-4,7-dichloroimidazo[4,5-*d*]pyridazine (VII) with ethanolic hydrazine hydrate resulted in conversion to the corresponding 4-hydrazino compound (VIII). The latter material could be readily cyclized to 6-benzyl-5-chloroimidazo[4,5-*d*]triazolo[4,3-*b*]pyridazine (IX). The halogen atom in IX has proven to be quite reactive, and was replaced with a variety of nucleophilic agents. Reduction of IX with sodium in liquid ammonia gave 5-amino-imidazo[4,5-*d*]triazolo[4,3-*b*]pyridazine (X), while a similar reduction of VIII gave 4-hydrazinoimidazo[4,5-*d*]pyridazine (XII).

Recently, we reported on the synthesis of several compounds containing the imidazo[4,5-d]pyridazine ring system as potential antagonists of purine metabolism.[1] We have now extended this work to include 4 (and 7)-amino-1-β-D-ribofuranosylimidazo[4,5-*d*]pyridazine (VIa, b) isomeric with the naturally occurring nucleoside, adenosine. Also, the compound, 1-benzyl-7-chloro-4-hydrazinoimidazo[4,5-*d*]pyridazine (VIII), has offered a ready access to compounds containing the previously unknown imidazo[4,5-*d*]triazolo[4,3-*b*]pyridazine ring system, *e.g.* X.

Treatment of 4-aminoimidazo[4,5-*d*]pyridazine hydrochloride (I) with benzoyl chloride in refluxing pyridine gave an excellent yield of the 4-benzamido compound (II), which was converted to the chloromercuri derivative (III) using the so-called Fox modification[2] to avoid traces of mercuric oxide in the product. Condensation of the chloromercuri derivative (III) with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl chloride (IV), using the excellent general method of Kissman, Pidacks, and Baker,[3] gave a mixture of crude blocked nucleosides (Va, b). Catalytic debenzoylation in refluxing methanolic sodium methoxide gave a mixture of nucleosides (VIa, b), which were isolated at this stage as a mixture of their picrate salts. The free nucleosides were regenerated with IRA-400 (carbonate form),[4] and the resulting mixture separated by fractional crystallization from water.

The two compounds thus obtained, 4-amino-1-β-D-ribofuranosylimidazo[4,5-*d*]pyridazine (VIa) and the isomeric 7-amino compound (VIb), were assigned structures on the basis of a comparison of their ultraviolet absorption spectra[5] with those of 4-amino-1-methyl- and 7-amino-1-methylimidazo[4,5-*d*]pyridazine[1] (Table I). It seems highly probable that both VIa and b possess a C_1-C_2-*trans*-configuration, in view of the rule postulated by Baker *et al.*[6] on the stereochemistry of nucleoside formation.

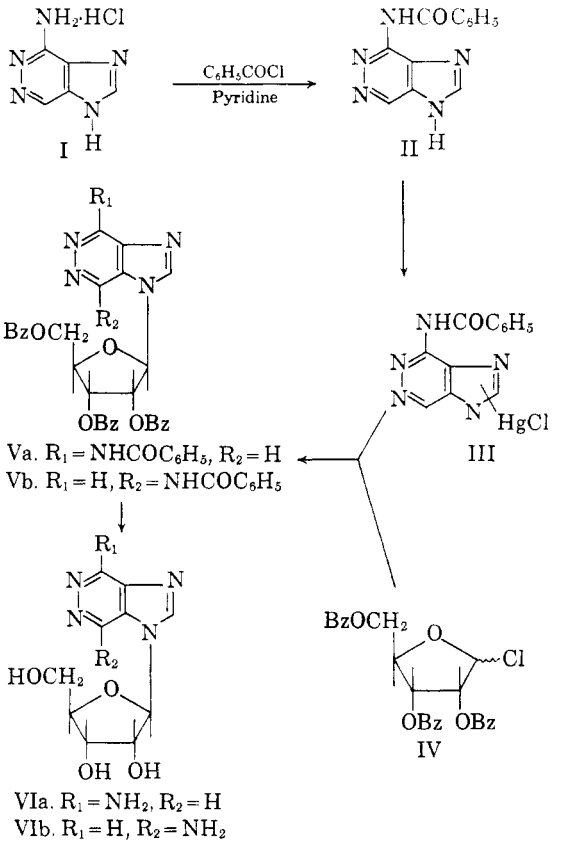


TABLE I

COMPARISON OF ULTRAVIOLET ABSORPTION MAXIMA

Imidazo[4,5-*d*]pyridazine	λ_{max}, mμ 0.10*N* HCl	λ_{max}, mμ 0.10*N* NaOH
4-Amino-1-β-D-ribofuranosyl-	258	254
4-Amino-1-methyl[a]	258	255
7-Amino-1-β-D-ribofuranosyl-	308	310
7-Amino-1-methyl[a]	263	261

[a] See ref. 1.

(1) J. A. Carbon, *J. Am. Chem. Soc.*, **80**, 6083 (1958).

(2) B. R. Baker, K. Hewson, H. J. Thomas, and J. A. Johnson, Jr., *J. Org. Chem.*, **22**, 954 (1957).

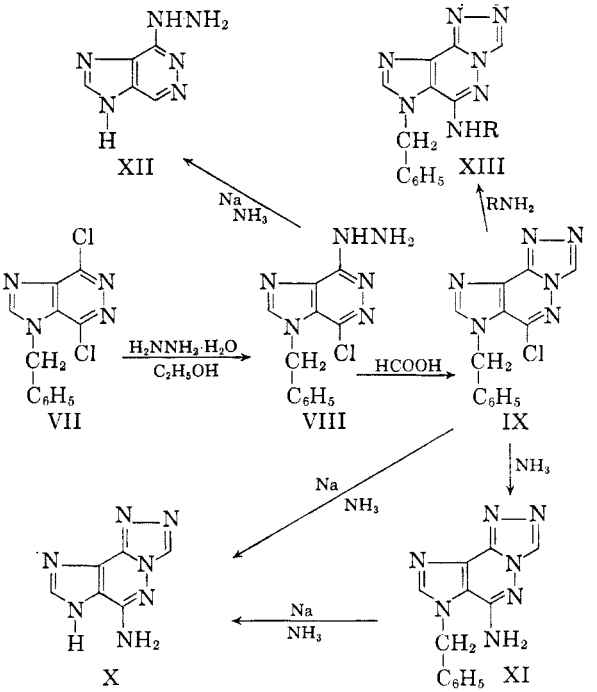
(3) H. M. Kissman, C. Pidacks, and B. R. Baker, *J. Am. Chem. Soc.*, **77**, 18 (1954).

(4) B. R. Baker and K. Hewson, *J. Org. Chem.*, **22**, 959 (1957).

The conversion of 1-benzyl-4,7-dichlorimidazo[4,5-*d*]pyridazine[1] (VII) to 1-benzyl-7-chloro-4-hydrazinoimidazo[4,5-*d*]pyridazine (VIII)[7] was readily accomplished by treatment with hydrazine hydrate in refluxing ethanol. The latter compound (VIII) could be ring-closed with boiling formic acid to give 6-benzyl-5-chloroimidazo[4,5-*d*]triazolo(4,3-*b*]pyridazine (IX). This type of ring closure has been previously observed with other hydrazino-substituted pyridazines[8] and phthalazines.[9]

Our previous work[1] has shown that 1-benzyl-7-chloro-4-substituted-imidazo[4,5-*d*]pyridazines may be successfully reduced with sodium in liquid ammonia to give the corresponding 4-substituted compound in which the 1-benzyl and 7-chloro groupings have been removed. An attempt to apply this reaction to IX to form the unsubstituted imidazo[4,5-*d*]triazolo[4,3-6]pyridazine ring system resulted instead in replacement of the halogen atom at the 5-position by ammonia and normal cleavage of the benzyl grouping to form 5-aminoimidazo[4,5-*d*]triazolo[4,3-*b*]pyridazine (X). The structure of the latter compound (X) was proved by treatment of IX with ethanolic ammonia to form 5-amino-6-benzylimidazo[4,5-*d*]triazolo-[4,3-6]pyridazine (XI), followed by sodium in liquid ammonia reduction of XI to give a material identical in all respects with X.

The sodium in liquid ammonia reduction of VIII proceeded normally, however, to give a good yield of 4-hydrazinoimidazo[4,5-*d*]pyridazine (XII). This apparently increased reactivity of the halogen atom in the imidazo[4,5-*d*]triazolo[4,3-*b*]-pyridazine (IX) over that shown by the imidazo-[4,5-*d*]pyridazine (VIII) was borne out by other experiments. For example, treatment of IX with ethanolic ammonia, benzyl amine, or hydrazine hydrate at 80–100° resulted in the facile formation of the corresponding 5-amino (XI), 5-benzylamino (XIII, R = $CH_2C_6H_5$), or 5-hydrazino (XIII, R = NH_2) compound. However, when similar reactions were attempted on compound VIII, the starting material was invariably recovered unchanged. These results are not surprising, considering the loss of aromaticity of the pyridazine ring in IX as compared with the completely aromatic ring system in VIII.



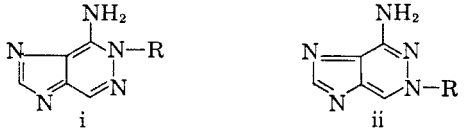
The compounds reported in this paper are being screened for antitumor activity at the Sloan-Kettering Institute for Cancer Research. The results of these tests will be reported elsewhere.

EXPERIMENTAL[10]

4-Benzamidoimidazo[4,5-d]pyridazine (II). 4-Aminoimidazo[4,5-*d*]pyridazine hydrochloride[1] (I) (17.2 g., 0.10 mole) was suspended in 100 ml. of dry pyridine and 30 g. (0.22 mole) of benzoyl chloride carefully added with stirring. The mixture was refluxed for 30 min., excess pyridine removed *in vacuo*, and the residual semisolid mass boiled with 200 ml. of ethanol for 10–15 min. The white product was filtered with suction and recrystallized from *N,N*-dimethylformamide-water to obtain 22.3 g. (93.3%) of colorless needles, m.p. 298–299° dec.

Anal. Calcd. for $C_{12}H_9N_5O$: C, 60.24; H, 3.79; N, 29.28. Found: C, 60.24; H, 3.91; N, 29.17.

(5) The comparatively high absorption maximum of VIb (308 mμ) as compared with that of 7-amino-1-methylimidazo[4,5-*d*]pyridazine (263 mμ) can possibly be attributed to the interactions between the amino group and the closely adjacent and rather bulky sugar residue. For example, 6-dimethylamino-9-ethylpurine has an absorption maximum at 277 mμ, while with the corresponding 7-ethyl compound, the maximum falls at 295 mμ [B. R. Baker *et al.*, *J. Org. Chem.*, **19**, 638 (1954)]. Another possibility would be that ribosidation had occurred on one of the pyridazine nitrogens to give a structure such as i or ii. Although we



R = β-D-ribofuranosyl

cannot exclude these structures for VIb, they appear to be rather unlikely, particularly since ribosidation of a vast number of purines has failed to give any products alkylated on a pyrimidine nitrogen.

(6) B. R. Baker, J. P. Joseph, R. E. Schaub, and J. H. Williams, *J. Org. Chem.*, **19**, 1786 (1954).

(7) Although two isomers are theoretically possible from this reaction, depending upon which chlorine atom is replaced, we consistently obtained only one product. The structure was assigned as shown (VIII) mainly on the basis of steric considerations, as replacement at the 7-position is probably hindered by the close proximity of the 1-benzyl group.

(8) J. Druey and B. H. Ringier, *Helv. Chim. Acta*, **34**, 195 (1951).

(9) N. Takahayashi, *J. Pharm. Soc. Japan, Pure Chem. Sect.*, **75**, 1242 (1955); **76**, 765, 1296 (1956).

(10) All melting points are uncorrected and were taken on a Fisher-Johns melting point apparatus.

Chloromercuri-4-benzamidoimidazo[4,5-d]pyridazine (III). To 500 ml. of 50% aqueous ethanol containing 23.08 g. (0.085 mole) of mercuric chloride was added 20.3 g. (0.085 mole) of 4-benzamidoimidazo[4,5-*d*]pyridazine (II); then, with vigorous mechanical stirring, 49 ml. of 10% aqueous sodium hydroxide was slowly dropped in at a rate such that the yellow mercuric oxide color disappeared before the next drop was added. Stirring was continued an additional 30 min., 20 g. of Celite[11] was added, and the mixture filtered with suction. The product was washed with water, then with ethanol, and dried *in vacuo* at 50°. The white powder thus obtained weighed 57 g. (including 20 g. of Celite[11]), 92% of theory.

*4-Amino-1-β-*D*-ribofuranosylimidazo[4,5-d]pyridazine* (VIa) *and 7-amino-1-β-*D*-ribofuranosylimidazo[4,5-d]pyridazine* (VIb). A stirred mixture of 37 g. (0.078 mole) of chloromercuri-4-benzamidoimidazo[4,5-*d*]pyridazine (III), 20 g. of Celite,[11] and 1200 ml. of xylene was distilled until all moisture was removed. A solution of 37.5 g. (0.078 mole) of 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl chloride[3,12] in 200 ml. dry xylene was added and the mixture was stirred and refluxed for 2 hr., then filtered with suction while still hot. The filter cake was washed well with 300 ml. of hot chloroform. The xylene filtrate was evaporated to dryness *in vacuo* and the residue was dissolved in 200 ml. of chloroform. The combined chloroform extracts were washed with 500 ml. of 30% aqueous potassium iodide, then with 500 ml. of water, dried over anhydrous magnesium sulfate, clarified with decolorizing carbon, and finally evaporated to dryness *in vacuo* to leave 50.2 g. of crude blocked nucleosides (V) as a brown syrup.

The 50.2 g. of crude blocked nucleosides from above was mixed with 500 ml. of methanol, 50 ml. of 1*N* methanolic sodium methoxide added, and the resulting mixture was refluxed for 30 min., a clear solution being formed at the boiling point. The solution was cooled, neutralized with 2.5 ml. of glacial acetic acid, evaporated to dryness *in vacuo*, and the residue partitioned between 200 ml. of water and 200 ml. of chloroform. The separated aqueous layer was washed with an additional 100 ml. of chloroform and then evaporated to dryness *in vacuo* below 50°. A solution of the resulting sirup in 100 ml. of methanol was treated with 300 ml. of 10% methanolic picric acid, kept overnight in the cold, and the resulting yellow precipitate filtered with suction and washed with two 100-ml. portions of water.

The crude picrate from above was suspended in 2000 ml. of water and treated with 200 g. of IRA-400 (carbonate form) at 60° with mechanical stirring until the picrate had all disappeared and the solution was colorless. After filtering with suction and washing the resin with water, the combined filtrates were evaporated to dryness *in vacuo* below 50°, and the residual colorless solid was separated into two ribosides by fractional crystallization from water.

The least water-soluble of the two compounds, *7-amino-1-β-*D*-ribofuranosylimidazo[4,5-d]pyridazine* (VIb), was obtained as colorless needles from water, m.p. 218–220° dec.; yield, 1.93 g. (9.9%); $[\alpha]_D^{26}$ −22° (0.50% in water). This material traveled as a single spot (R_f 0.39) on paper using water-saturated butanol as solvent.[13]

Anal. Calcd. for $C_{10}H_{13}N_5O_4$: C, 44.95; H, 4.91; N, 26.21; O, 23.93. Found: C, 44.88; H, 5.04; N, 26.18; O, 23.66.

The more water soluble of the two ribosides, *4-amino-1-β-*D*-ribofuranosylimidazo[4,5-d]pyridazine* (VIa), consisted of colorless tiny needles when recrystallized from ethanol, or precipitated from a little water by the addition of acetone, m.p. 229–230° dec.; yield, 0.57 g. (2.9%); $[\alpha]_D^{26}$ −48° (0.50% in water). Paper chromatography using water-saturated butanol revealed only a single spot of R_f 0.22.[13]

Anal. Calcd. for $C_{10}H_{13}N_5O_4$: C, 44.95; H, 4.91; N, 26.21; O, 23.93. Found: C, 44.96; H, 5.12; N, 26.16; O, 23.66.

1-Benzyl-7-chloro-4-hydrazinoimidazo[4,5-d]pyridazine (VIII). 1-Benzyl-4,7-dichloroimidazo[4,5-*d*]pyridazine (VII)[1] (27.9 g., 0.10 mole) was suspended in 200 ml. of ethanol, 12.5 g. (0.25 mole) of hydrazine hydrate added, and the mixture refluxed for 5 hr. After cooling, the product was filtered with suction and recrystallized from *N,N*-dimethylformamide-water (1:1) with Norit to give 17.3 g. (62.9%) of colorless needles, m.p. 191.5–192.0° dec.

Anal. Calcd. for $C_{12}H_{11}ClN_6$: C, 52.47; H, 4.04; N, 30.59. Found: C, 52.49; H, 4.12; N, 30.65.

6-Benzyl-5-chloroimidazo[4,5-d]triazolo[4,3-b]pyridazine (IX). Thirty-three grams (0.12 mole) of 1-benzyl-7-chloro-4-hydrazinoimidazo[4,5-*d*]pyridazine (VIII) was refluxed with 150 ml. of 98% formic acid for 1 hr., the excess formic acid removed *in vacuo*, and the residual yellow syrup stirred with 250 ml. of water until solidified. The product was filtered with suction, washed with water, and recrystallized from *N,N*-dimethylformamide-water (2:3) to obtain colorless prismatic needles, m.p. 208–209°; yield 29 g. (85%).

Anal. Calcd. for $C_{13}H_9ClN_6$: C, 54.84; H, 3.19; Cl, 12.45; N, 29.52. Found: C, 55.05; H, 3.46; Cl, 12.58; N, 29.87.

5-Amino-6-benzylimidazo[4,5-d]triazolo[4,3-b]pyridazine (XI).[14] Eighteen grams (0.063 mole) of 6-benzyl-5-chloroimidazo[4,5-*d*]triazolo[4,3-*b*]pyridazine (IX) was treated with 50 ml. of ethanol containing 15 ml. of liquid ammonia in a sealed autoclave at 100° for 4 hr. The product was isolated by suction filtration, washed with water, and recrystallized from *N,N*-dimethylformamide-water to obtain 12.5 g. (74.6%) of pale yellowish prisms, m.p. 279–282°.

Anal. Calcd. for $C_{13}H_{11}N_7$: C, 58.86; H, 4.18; N, 36.96. Found: C, 58.38; H, 4.07; N, 36.85.

5-Aminoimidazo[4,5-d]triazolo[4,3-b]pyridazine (X). A. To 22 g. (0.077 mole) of 6-benzyl-5-chloroimidazo[4,5-*d*]-triazolo[4,3-*b*]pyridazine (IX) in 500 ml. of liquid ammonia was carefully added, with vigorous mechanical stirring, 7.6 g. (0.33 g. atom) of metallic sodium. The sodium was added in small pieces over a 1-hr. period. The deep blue solution was neutralized by the careful addition of 18.7 g. (0.35 mole) of ammonium chloride and finally allowed to evaporate to dryness. The residual yellow-orange solid was washed with ether, dissolved in 200 ml. of warm dilute ammonium hydroxide, decolorized with Norit, and precipitated by neutralization with hydrochloric acid to give 4.1 g. (33%) of a cream-colored powder, m.p. >350°. As this material was insoluble in all of the common solvents, it was purified for analysis by dissolving in aqueous ammonia, filtering, and reprecipitating with acetic acid, m.p. >350°.

Anal. Calcd. for $C_6H_5N_7$: C, 41.13; H, 2.88; N, 55.99. Found: C, 41.12; H, 3.04; N, 55.39.

B. A similar reduction of 5-amino-6-benzylimidazo[4,5-*d*]-triazolo[4,3-*b*]pyridazine (XI) (8.4 g., 0.0317 mole) in 300 ml. of liquid ammonia with 1.59 g. (0.069 g. atom) of sodium, followed by neutralization with 3.85 g. (0.072 mole) of ammonium chloride gave 5.0 g. (90.2%) of the same product (X), m.p. >350°.

Anal. Calcd. for $C_6H_5N_7$: C, 41.13; H, 2.88; N, 55.99. Found: C, 41.11; H, 3.18; N, 55.95.

The infrared spectra of the products from A and B were identical in all respects.

4-Hydrazinoimidazo[4,5-d]pyridazine (XII). 1-Benzyl-7-chloro-4-hydrazinoimidazo[4,5-*d*]pyridazine (VIII) (17.1 g., 0.062 mole) was mixed with 500 ml. of liquid ammonia, and 6.2 g. (0.27 g. atom) of small pieces of sodium metal were added over a 1-hr. period. The reaction mixture was stirred vigorously throughout this addition. After stirring for an additional half-hour, the solution was carefully neutralized with 16 g. (0.30 mole) of ammonium chloride and

(11) Johns-Manville Co.

(12) R. K. Ness, H. W. Diehl, and H. G. Fletcher, Jr., *J. Am. Chem. Soc.*, **76**, 763 (1954).

(13) Paper chromatograms were run by the ascending technique using strips of Whatman No. 1 paper. The spots were visualized by means of an ultraviolet lamp.

(14) This preparation was carried out by M. Freifelder and G. R. Stone of our Laboratories.

finally allowed to evaporate to dryness. The residual brown solid was washed with ether, suspended in 200 ml. of warm water, enough conc. hydrochloric acid added to dissolve the product, decolorized with Norit, and the filtrate adjusted to *p*H 8 with 10% sodium hydroxide. The white product was filtered with suction, washed well with water, and dried *in vacuo* at 50°, yield 7.0 g. (75%), m.p. >350°. Further purification was achieved by precipitation of the product by neutralization of a solution in aqueous hydrochloric acid.

Anal. Calcd. for $C_5H_6N_6$: C, 40.00; H, 4.03; N, 55.97. Found: C, 40.13; H, 3.92; N, 56.29.

The *monohydrochloride* was prepared by dissolving the free base in aqueous hydrochloric acid, evaporating to dryness *in vacuo*, and recrystallizing the residual colorless solid from aqueous ethanol to obtain colorless leaflets, m.p. >350°.

Anal. Calcd. for $C_5H_7ClN_6$: C, 32.18; H, 3.78; Cl, 18.99; N, 45.05. Found: C, 32.62; H, 4.03; Cl, 18.92; N, 45.59.

6-Benzyl-5-benzylaminoimidazo[4,5-d]triazolo[4,3-b]pyridazine (XIII, R = $CH_2C_6H_5$). One gram (0.0035 mole) of 6-benzyl-5-chloroimidazo[4,5-d]triazolo[4,3-*b*]pyridazine (IX) was mixed with 15 ml. of ethanol and 2 ml. of benzylamine and refluxed for 3 hr. The clear solution was cooled, and the almost colorless product which separated was isolated by suction filtration. Recrystallization from *N,N*-dimethylformamide-water or methyl cellosolve-water gave colorless prisms, m.p. 238–239°, yield 0.80 g. (64.5%).

Anal. Calcd. for $C_{20}H_{17}N_7$: C, 67.59; H, 4.82; N, 27.59. Found: C, 67.66; H, 5.04; N, 27.33.

6-Benzyl-5-hydrazinoimidazo[4,5-d]triazolo[4,3-b]pyridazine (XIII, R = NH_2). One gram (0.0035 mole) of 6-benzyl-5-chloroimidazo[4,5-*d*]triazolo[4,3-*b*]pyridazine (IX), 25 ml. of ethanol, and 0.50 g. (0.010 mole) of hydrazine hydrate was mixed and refluxed for 2.5 hr. The precipitate of yellow needles which separated on cooling was filtered with suction and recrystallized from *N,N*-dimethylformamide containing a little ethanol to obtain yellow needles, m.p. 268–269° dec., yield 0.60 g. (61%). This material was extremely insoluble in the common organic solvents with the exception of hot *N,N*-dimethylformamide or hot nitrobenzene. It could be dissolved in aqueous hydrochloric acid but was apparently destroyed, as neutralization only precipitated an oil which could not be crystallized.

Anal. Calcd. for $C_{13}H_{12}N_8$: C, 55.70; H, 4.32; N, 39.98. Found: C, 56.02; H, 4.53; N, 40.07.

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NORTH CHICAGO, ILL.

[CONTRIBUTION FROM THE DIVISION OF CHEMICAL RESEARCH OF G. D. SEARLE AND CO.]

dl-18-nor-D-Homosteroids

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Several 17a-ethynyl and alkyl derivatives of *dl*-18-nor-D-homosteroids were prepared. None of the 17a-alkyl compounds was significantly active as an anabolic agent.

The enhanced anabolic activity of the 17-alkyl-19-nortestosterones compared with the analogous compounds in the natural series is well known.[2] W. S. Johnson and co-workers[3] have prepared and described the properties of several 18-nor-D-homosteroids bearing a carbonyl or hydroxyl group in the 17a-position. As a result of a cooperative effort with Professor Johnson, we became interested in 17a-alkyl-18-nor-D-homotestosterones and several closely related compounds.

Following the directions of Johnson *et al.*,[3c] 1-methoxy-8-keto-10a-methyl-5,6,8,9,10,10a,11,12-octahydrochrysene (I) was converted to the 3-ketal and reduced stepwise to produce *dl*-3-ethylenedioxy-18-nor-D-homoandrost-5-en-17a-one (II) along with a lesser amount of the C:D-*cis* isomer(III) which has not been previously reported. The latter was readily isomerized to the *trans* isomer (II) by treatment with base. In our hands the overall yield of pure II from the aromatic ketal was about 5% compared with 17% reported. In view of the critical nature of the Birch reduction, such variations in yields are not unexpected. Our yield of about 25% in the two step reduction of I to the saturated ketone (IV) compares more favorably with that obtained by Johnson's group.

Treatment of the saturated ketone (IV) with ethylmagnesium bromide afforded a good yield of a single product (VIII) which has been designated as a 17a α alcohol. This configuration assignment is based upon the work of Ruzicka and co-workers,[4] who have shown that the addition of methylmagnesium bromide to D-homoandrosterone gave the 17aβ-methyl isomer exclusively. Examination of molecular models (II and IV) indicates that the absence of an angular methyl group at C-13 favors frontside approach by a bulky molecule such as a

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(2) (a) C. Djerassi, L. Miramontes, G. Rosenkrantz, and F. Sondheimer, *J. Am. Chem. Soc.*, **76**, 4092 (1954). (b) F. B. Colton, L. N. Nysted, B. Riegel, and A. L. Raymond, *J. Am. Chem. Soc.*, **79**, 1123 (1957).

(3) (a) W. S. Johnson, B. Bannister, R. Pappo, and J. E. Pike, *J. Am. Chem. Soc.*, **77**, 817 (1955). (b) W. S. Johnson, B. Bannister and R. Pappo, *J. Am. Chem. Soc.*, **78**, 6331 (1956). (c) W. S. Johnson, B. Bannister, R. Pappo, and J. E. Pike, *J. Am. Chem. Soc.*, **78**, 6354 (1956).

(4) L. Ruzicka, N. Wahba, P. Th. Herzig, and H. Heusser, *Ber.*, **85**, 491 (1952).