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3-Amino-4-phenylpyrazole as an Intermediate

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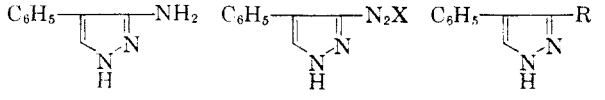
The displacement of the amine group in 3-amino-4-phenylpyrazole (I) by other groups,



I

II a. R = H
b. R = Br
c. R = NO_2
d. R = N=N—S—C_2H_5
e. R = S—C_2H_5

through the intermediate diazonium salt, has been found to be a useful preparative scheme for 3-substituted pyrazoles. The amine was diazotized in aqueous mineral acid by reaction with sodium nitrite, and the intermediate diazonium salt was converted into 4-phenylpyrazole (IIa, 93% yield) by reaction with hypophosphorous acid, and into 3-bromo-4-phenylpyrazole (IIb, 85.6% yield) by reaction with cuprous bromide: Pyrolysis of the corresponding diazofluoroborate in the presence of sodium nitrite and copper bronze afforded 3-nitro-4-phenylpyrazole in 22.4% yield.

Reaction of diazotized 3-amino-4-phenylpyrazole with ethyl mercaptan proceeded abnormally,[3] giving the diazonium sulfide (IId, 72.5% yield) instead of the expected 3-ethylmercapto-4-phenylpyrazole (IIe). The diazonium sulfide (IId) was relatively stable and was recrystallized from hot ethanol; however, prolonged boiling in methanol resulted in its reduction to 4-phenylpyrazole (52% yield). The diazonium sulfide gave colored products by reaction with phenol, β-naphthol, and dimethylaniline.

It is of interest to note that 3-amino-4-phenylpyrazole (I) can be diazotized in aqueous solution. This behavior is in contrast to the special conditions[4] required for the diazotization of 2-aminopyridine, which also contains the amidine function (—N=C—NH_2).

It has been known for some time that 3- and 5-aminopyrazoles form diazonium salts; however, most of the cases studied have involved derivatives bearing a substituent on the pyrazole nitrogen atom, and relatively little attention has been directed to replacement reactions.[5a] 4-Aminopyrazoles from typical diazonium salts which undergo the usual coupling[5a,6] and replacement[3] reactions.

Electrophilic substitution of the pyrazole ring in other than the 4-position is rare.[5b] If a phenyl group is at C_4, nitration will occur in the benzene ring.[7] The availability of certain 3-aminopyrazoles[8] and their subsequent conversion to 3-substituted pyrazole by the procedure described appears to be an attractive synthetic procedure in this series.

EXPERIMENTAL

4-Phenylpyrazole from I. 3-Amino-4-phenylpyrazole[8] (2.3 g., 0.0414 ml.) was added to boiling concd. hydrochloric acid (4.5 ml.) and, when solution was complete, an additional portion of concd. hydrochloric acid (5 ml.) was added. The mixture was cooled (0–5°) and sodium nitrite (1.5 g.) in water (3.5 ml.) was added dropwise over a 5-min. period. The resulting solution was stirred and hypophosphorous acid (15 ml., 50% aqueous) was added dropwise (5 min.) while the temperature was maintained at 0°. The resulting solution was stirred for an additional 10 min. at 0°, and then placed in a refrigerator (24 hr.). Crude IIa (1.78 g., 93% yield, m.p. 225–227°) was collected and recrystallized from methanol-water. Pure IIa melted at 227–228° and did not depress the melting point of an authentic sample (m.p. 228°).[9]

3-Bromo-4-phenylpyrazole from I. 3-Amino-4-phenylpyrazole 1.5 g., 0.0095 ml.) was dissolved in hot hydrobromic acid (10%, 5 ml.) and an excess of sodium nitrite (2.5 g.) in water (5 ml.) was added. Excess urea (~2 g.) was added to destroy excess sodium nitrite; the solution was filtered, and concd. hydrobromic acid (48%, 5 ml.) and cuprous bromide (~0.5 g.) were added. The solution was boiled to complete the reaction and then allowed to stand in an ice bath. The product weighed 2.0 g. (94.8% yield, m.p. 142–144°) and melted at 146–146.5 (1.8 g., 85.6% yield) after recrystallization from methanol. This product caused no depression in melting point when mixed with authentic IIb.[8]

3-Nitro-4-phenylpyrazole from I. 3-Amino-4-phenylpyrazole (1.8 g., 0.0113 ml.) was dissolved in fluoboric acid solution (10 ml.) in a 250-ml. beaker. The mixture was kept

(1) Now Mrs. Thomas Rouse.
(2) From the M.S. Thesis of Iive Mae Aldre, University of Minnesota, 1958.
(3) *Cf.* O. Stadler, *Ber.*, **17**, 2078 (1884).
(4) *Heterocyclic Compounds*, R. C. Elderfield, ed., Vol. I, Ch. 8, Harry S. Mosher, p. 444, John Wiley & Sons, New York, 1950.
(5) (a) *Cf. Heterocyclic Compounds*, R. C. Elderfield, ed., Vol. V, Ch. 2, Thomas L. Jacobs, p. 141. John Wiley and Sons, New York, 1957; (b) Ref. 5a, p. 99.
(6) L. Knorr, *Ber.*, **37**, 3520 (1904); A. Bertho and H. Nüssel, *Ann.*, **457**, 278 (1927); A. Michaelis and A. Schäfer, *Ann.*, **407**, 229 (1915); G. T. Morgan and I. Ackerman, *Ann.*, **123**, 1308 (1923).
(7) E. Alexander, *Principles of Ionic Reaction*, John Wiley and Sons, New York, 1950, p. 104.
(8) *Cf.* W. E. Parham and J. L. Bleasdale, *J. Am. Chem. Soc.*, **73**, 4664 (1951).
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in an ice-salt bath and the solution was stirred efficiently. A cold (0°) solution of sodium nitrite (1 g.) in water (3 ml.) was added dropwise. The resulting mixture was maintained at 0°, and stirring was continued for an additional 5 min. The solid diazonium fluoborate was filtered by suction on a sintered glass filter, washed several times with cold fluoboric acid and then with water. It was very soluble in 95% ethanol.

Then sodium nitrite (20 g.) was dissolved in water (40 ml.) and copper filings (4 g.) were added. The mixture was stirred efficiently and a suspension of the fluoborate salt in water (10 ml.) was added very slowly. Frothing occurred and a few drops of ether was added from time to time to break the foam. The reaction was complete when all of the salt was added.

The crude product was filtered by suction and washed a few times with water and dilute (10%) sodium hydroxide. The product, 3-nitro-4-phenylpyrazole, weighed 0.48 g. (0.0025 mole; 22.4% yield; m.p. 205–208°). Recrystallization of this material from chloroform gave pale yellow needles melting at 209–210°. This product caused no depression in melting point when mixed with authentic IIc.[8]

Reaction of 4-phenylpyrazole-3-diazonium chloride with ethyl mercaptan. The diazotization of I (1.8 g., 0.011 ml. was carried out as described above for the preparation of 4-phenylpyrazole. The resulting mixture was maintained at 0° and ethyl mercaptan (7.2 g., 0.0113 ml.) was added dropwise with swirling. A few drops of ethyl mercaptan was added in excess. The reaction mixture containing a yellow solid was maintained at ice-salt temperature for 24 hr. The solid was then collected, washed with water, and dried by vacuum. Crude IId (1.9 g., 72.5%, m.p. 98–100°) was recrystallized from aqueous methanol which afforded pure IId as long yellow needles (m.p. 101–101.5°).

Anal. Calcd. for $C_{11}H_{12}N_4S$: C, 56.89; H, 5.17; N, 24.13. Found: C, 56.47; H, 5.25, N, 24.05.

The reaction of IId *with methanol.* A solution of IId (0.56 g., 0.0024 ml.) in methanol (50 ml.) was heated at the reflux temperature for 7.5 hr. The methanol was removed, and the pale yellow solid (0.18 g., 52% yield, m.p. 222–225°) was collected and recrystallized from chloroform. The pure product (m.p. 227–228°) was identified as 4-phenylpyrazole (m.p. and mixed m.p. 227–228°).

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Practical Synthesis of 5α-Androstan-17β-ol[1]

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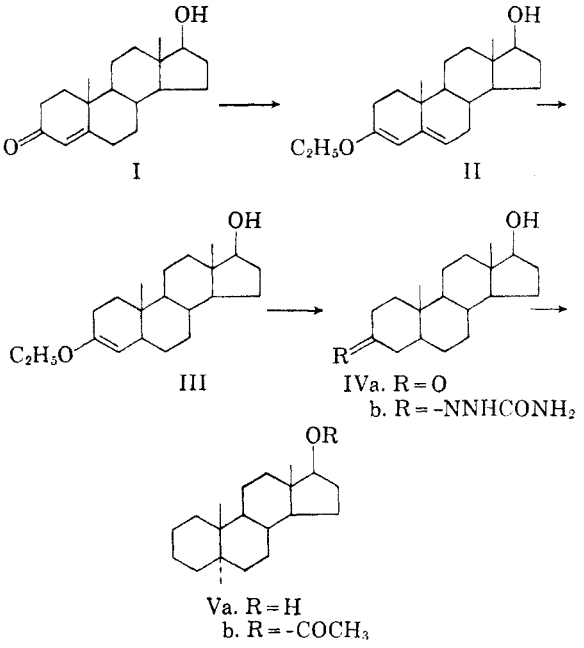
Under a contract with the Cancer Chemotherapy National Service Center, this laboratory was asked to prepare a number of steroids not available commercially. One such compound was 5α-androstan-17β-ol (Va). This latter compound has been prepared by a number of investigators from testosterone (I)[2]; however, none of the published methods appeared attractive for the preparation of V on a large scale.

In this paper a procedure is described for the preparation of V which is amenable to large scale operation. The reaction sequence is as follows:



Testosterone (I) was smoothly converted to 3-ethoxy-3,5-androstadien-17β-ol (II) by reaction with triethyl orthoformate in ethanolic hydrogen chloride. Reduction of the 5,6-double bond of II to give the enol ether (III) was effected catalytically with 5% palladium on charcoal in ethanol. The enol (III) was reversed to the 3-keto compound with acid and the 17β-hydroxyandrostan-3-one (IVa) was converted *in situ* to the sparingly soluble 3-semicarbazone (IVb).[3] The overall yield for the three steps was 64%. Since the completion of this work, the direct reduction of I to IVa in high yield has been reported using lithium in liquid ammonia.[4] This reduces the present scheme to a three-step synthesis. The semicarbazone (IVb) was reduced in 93% yield by the method of Wolff-Kishner as modified by Huang-Minlon.[5] Excess hydrazine hydrate was employed in the reduction to prevent the formation of the epimeric 3-ol compounds.[6]

The product obtained was identical with material obtained from IVa by the procedure of Kagi and Miescher.[2a]

EXPERIMENTAL

3-Ethoxy-3,5-Androstadien-17β-ol (II). Testosterone (100 g., 0.347 mole), 864 ml. of dry benzene, 86.4 ml. of ethyl

(1) This work was done under Contract #SA-43-ph-1948 with the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health.

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(3) A. Butenandt, K. Tscherning, and G. Hanisch, *Ber.* **68**, 2097 (1935).

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(6) J. D. Dutcher and O. Wintersteiner, *J. Am. Chem. Soc.*, **61**, 1992 (1939).