Notes

N-Alkylation of Amides. A Novel Procedure

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Received January 11, 1961

In view of the known acid-catalyzed reaction of aldehydes[1] and acetals[2] with amides to give methylene diamides it seemed reasonable that the reaction could be adapted to a useful reductive amidation procedure. Thus, when acetamide, acetal, or 2,2-dimethoxypropane, and hydrogen were allowed to react at room temperature in acetic acid solution in the presence of a palladium catalyst and sulfuric acid the corresponding *N*-ethyl- and *N*-isopropylacetamides were produced in about 50% yield. Further investigation will undoubtedly increase the scope and usefulness of this reaction.

Experimental

N-Alkylation of Acetamide.—A mixture of 30 g. (0.51 mole) of acetamide, 62 g. (0.525 mole) of 1,1-diethoxyethane, 2 g. of 10% palladium-on-carbon, and 200 ml. of acetic acid containing 6 g. of concd. sulfuric acid was shaken in an atmosphere of hydrogen (40 p.s.i. initial pressure) for 6 hr., at which time absorption was complete. The catalyst was removed by a filtration and 10 g. of anhydrous sodium acetate added to neutralize the sulfuric acid. After removing the precipitated sulfate, the filtrate was fractionated to yield 20 g. (45%) of pure *N*-ethylacetamide, b.p. 97–98° (8 mm.), $n^{30}D$ 1.4313. The infrared spectrum was identical to that of an authentic sample.

N-Isopropylacetamide was similarly obtained from 2,2-dimethoxypropane in 46% yield, b.p. 87–88° (4.5 mm.), $n^{30}D$ 1.4303, and its identity confirmed by comparison of its infrared spectrum with the spectrum of known material. The use of acetone in place of the ketal or ethanol as a solvent produced none of the desired amide.

(1) For leading references see W. A. Noyes and D. B. Forman, *J. Am. Chem. Soc.*, **55**, 3493 (1933) and W. M. Kraft and R. M. Herbst, *J. Org. Chem.*, **10**, 483 (1945).

(2) C. Bischoff, *Ber.*, **7**, 628 (1874); H. E. Johnson and D. G. Crosby, *J. Org. Chem.*, **27**, 2077 (1962).

A New Route to 1-Oxygenated Steroids[1]

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Received January 24, 1962

In connection with work currently under way in our laboratory[4] on the relation of mass spectrometric fragmentation patterns and steroid structure, the need arose for a variety of C-1 oxygenated steroids with the 5α-orientation. Oxygenation at C-1 was the last nuclear location for which synthetic procedures were developed in the steroid field and a survey of the literature demonstrates that none of the methods are completely satisfactory.

The starting material for all of the chemical methods is Δ^1-cholesten-3-one (II).[5] Striebel and Tamm,[6] who were the first to develop a feasible route to cholestan-1-one (VIa), converted IIa into the 1α,2α-oxido 3-ketone (IIIa) and reduced it with lithium aluminum hydride. The resulting mixture of glycols (IVa) was partially acetylated at C-3, oxidized at C-1 and the 3-acetoxy group eliminated with alumina to furnish Δ^2-cholesten-1-one (Va), which could be hydrogenated to cholestan-1-one (VI). The Swiss investigators[6] reported an over-all yield of 47% from IIIa to VIa, but Shoppee and collaborators[7] were unable to duplicate the yields in the separation and partial acetylation of the diol mixture (IVa). Their modification involved oxidation of the diols IVa to the 1,3-diketone, preferential mercaptal formation at C-3, followed by desulfurization, the over-all yield of cholestan-1-one (VIa) from the oxido ketone IIa dropping to 14%. Striebell and Tamm[6] also reported that the diol mixture IVa could be completely acetylated and the 1α,3β-diacetoxy component partially saponified at C-3. The free 3β-hydroxy function was removed through the mesylate and iodide to provide cholestan-1α-ol (IXa) in 30% over-all yield.

An alternate scheme was developed by Henbest and Wilson,[8] who reduced Δ^1-cholesten-3-one (IIa) with lithium aluminum hydride, converted the resulting allylic alcohol to the chloride, removed the chlorine atom with lithium aluminum hydride, epoxidized the resulting Δ^1-cholestene and finally opened the oxide ring with lithium aluminum hydride to give cholestan-1α-ol (IXa), the over-all yield from IIa being less than 10%. A second and

(1) The work at Stanford University was supported by Grant No. CRTY-5061 from the National Cancer Institute of the National Institutes of Health, U. S. Public Health Service.

(2) Recipient of a Fulbright Travel Award from the U. S. Educational Commission in the United Kingdom.

(3) Syntex, S. A., Mexico City, Mexico. The present paper represents Part CLXXXXII in the Syntex series on "Steroids."

(4) See H. Budzikiewicz and C. Djerassi, *J. Am. Chem. Soc.*, **84**, 1430 (1962), and subsequent papers.

(5) A. Butenandt, L. Mamoli, H. Dannenberg, L. W. Masch, and J. Paland, *Ber.*, **72**, 1617 (1939); C. Djerassi and C. R. Scholz, *J. Am. Chem. Soc.*, **69**, 2404 (1947).

(6) P. Striebel and C. Tamm, *Helv. Chim. Acta*, **37**, 1094 (1954).

(7) C. W. Shoppee, S. K. Roy, and B. S. Goodrich, *J. Chem. Soc.*, 1583 (1961).

(8) H. B. Henbest and R. A. L. Wilson, *J. Chem. Soc.*, 3289 (1956).