New Compounds

t-Butyl Ester of 7-Aminocephalosporanic Acid

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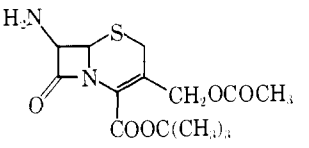
For synthetic work in the cephalosporin series of antibiotics it may sometimes be convenient to mask the 4-carboxyl function with a group which can subsequently be removed without destroying the β lactam or other sensitive sites in the molecule. The susceptibility of the cephalosporins to hydrogenation[1] makes the benzyl ester group appear unsuitable for this purpose.[2] However, their stability acid[3] suggests that the *t*-butyl ester group may be useful, and the preparation and properties of *t*-butyl 7-aminocephalosporanate (I) are now reported.



I

Experimental Section[4]

***t*-Butyl 7-Aminocephalosporanate.**—Dry dioxane was freed from peroxides by passage through a column of neutral activated alumina. To 100 ml of this solvent were added, in turn, with ice cooling, 10 ml of concentrated H_2SO_4, 10.9 g (0.04 mole) of 7-aminocephalosporanic acid,[5] and 50 ml of liquid isobutylene.[6] The mixture was sealed in a pressure bottle, stirred at 28–30° for 2 hr, and then poured into an excess of ice-cold aqueous $NaHCO_3$. Extraction with two portions of ethyl acetate and evaporation of the extracts gave a light brown oil which rapidly crystallized. Trituration with cyclohexene gave 6.80 g (52%) of the crude ester, mp 110–112° dec. Pure material was obtained by recrystallization from methanol–2-propanol as colorless plates: mp 114–115° dec; λ_{max}^{EtOH} 266 mμ (ϵ 6970) and 246 sh (5885); λ_{max}^{Nujol} 2.94 and 3.00 (NH_2), 5.7 (broad) and 5.84 (lactam and ester C=O), and 6.13 μ (C=C); pmr signals (*ca.* 5% in $CDCl_3$, TMS internal standard) at δ 1.53 (*t*-butyl CH_3), 1.8 (broad, NH_2), 2.10 (acetyl CH_3), 3.45 and 3.51 (main peaks of 2-CH_2 quartet), and 4.68–5.24 (multiplet, exocyclic CH_2, 6- and 7-CH).[7]

Anal. Calcd for $C_{14}H_{20}N_2O_5S$: C, 51.20; H, 6.14; N, 8.53. Found: C, 51.29; H, 6.37; N, 8.49.

Titration with $HClO_4$ in acetic acid gave an equivalent weight of 327.5 (calcd 328.4).

Removal of *t*-Butyl Group.—The *t*-butyl ester (0.50 g, 1.52 mmoles) was dissolved in 10 ml of ice-cold trifluoroacetic acid,[8] and the solution was kept at room temperature for 30 min.[9] Evaporation of the trifluoroacetic acid left a gum, which was dissolved in water and brought to pH 4 to precipitate 0.38 g of 7-aminocephalosporanic acid (91% pure by ultraviolet assay; yield 83.5%). It was characterized by paper electrophoresis at pH 2.2 and by its infrared spectrum.

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(1) (a) R. J. Stedman, K. Swered, and J. R. E. Hoover, *J. Med. Chem.*, **7**, 117 (1964), and references cited therein; (b) S. A. Harris, U. S. Patent 3,193,550 (1965).

(2) The hydrogenolysis of cephalosporin benzyl esters is nonetheless mentioned in the patent literature, *e.g.*, Ciba Ltd., Belgian Patent 645,157 (1964), but it is not clear whether this process has any practical utility.

(3) G. G. F. Newton and E. P. Abraham, *Biochem. J.*, **62**, 651 (1956).

(4) Corrected capillary melting points are reported. Infrared, ultraviolet, and pmr spectra were determined with a Perkin-Elmer Infracord, a Cary Model 14 recording spectrophotometer, and a Varian Model A-60 spectrometer, respectively. Evaporations (reduced pressure) and recrystallizations were carried out without heating.

(5) R. B. Morin, B. G. Jackson, E. H. Flynn, and R. W. Roeske, *J. Am. Chem. Soc.*, **84**, 3400 (1962).

(6) General procedure of R. Roeske, *J. Org. Chem.*, **28**, 1251 (1963).

(7) These assignments are in agreement with the detailed study of cephalosporin pmr spectra reported by G. F. H. Green, J. E. Page, and S. E. Staniforth, *J. Chem. Soc.*, 1595 (1965).

(8) H. Kappeler and R. Schwyzer, *Helv. Chim. Acta*, **44**, 1136 (1961).

(9) The time could probably be decreased considerably. Cephalosporin C was substantially unchanged after standing in trifluoroacetic acid for this period, as shown by the ultraviolet spectrum and paper electrophoresis. It was destroyed by more prolonged exposure (half-life about 2 hr).

Some Ureas and Urethans Derived from *p*-Aminophenol[1]

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The antitumor activity of bis(*p*-aminophenylcarbonate)[2] has prompted the synthesis of the two possible rearrangement products, the urethan V and the urea II, to determine if the activity of the carbonate could be attributed to its rearrangement *in vivo*. Treatment of *p*-benzyloxyaniline with phosgene in the presence of 2 molar equiv of triethylamine formed a blocked derivative I of the urea II; use of 1 equiv of triethylamine afforded the isocyanate III, which with *p*-nitrophenol afforded the urethan precursor IV to V. The nitrophenylurethan IV showed the high reactivity to bases noted[3] for other nitrophenylurethans, and it reacted with *n*-butyl amine to form the urea VI. Unlike the carbonate, none of these compounds showed antitumor activity.

Experimental Section[4]

4,4′-Bis(benzyloxy)carbanilide (I).—A solution of 20 g (0.10 mole) of 4-benzyloxyaniline (Aldrich Chemical Co., mp 52–56°) and 28 ml (20 g, 0.20 mole) of triethylamine in 400 ml of toluene was stirred at 45° while a stream of phosgene was bubbled in. Precipitation began almost immediately and after 10 min prevented further stirring, whereupon introduction of phosgene was discontinued. The mixture was maintained at 45° for 10 more min, cooled to 5°, and filtered. The filter cake, a mixture of triethylamine hydrochloride and product, was washed with benzene and triturated with water to remove the soluble amine salt. The product, which remained, was recrystallized from hot dimethylformamide–water (250:15 ml) to yield 18.3 g (86%), mp

(1) This work was carried out under the auspices of the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, Public Health Service, Contract No. Ph-43-64-500. The opinions expressed in this paper are those of the authors and not necessarily those of the Cancer Chemotherapy National Service Center.

(2) Personal communication from Dr. Harry B. Wood, Jr., of the Cancer Chemotherapy National Service Center.

(3) K. D. Kopple, *J. Am. Chem. Soc.*, **79**, 6442 (1957); T. Mukaiyama, T. Akiba, and T. Asahi, *Bull. Chem. Soc. Japan*, **33**, 1137 (1960); *J. Pharm. Sci.*, **52**, 852 (1963).

(4) Melting points were observed on a Fisher-Johns hot stage and are corrected. All the compounds described occurred in several crystal forms, as distinguished in the infrared by minor variations in wavelength, intensity, or resolution of bands; the infrared data recorded summarize only the important features of the spectra.