New Compounds

t-Butyl Ester of 7-Aminocephalosporanic Acid

R. John Stedman

Research and Development Division, Smith Kline and French Laboratories, Philadelphia, Pennsylvania 19101

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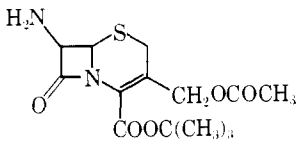
For synthetic work in the cephalosporin series of antibiotics it may sometimes be convenient to mask the 4-carboxyl function with a group which can subsequently be removed without destroying the β lactam or other sensitive sites in the molecule. The susceptibility of the cephalosporins to hydrogenation[1] 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. Stanitforth, *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]

Carol W. Mosher, Edward M. Acton, and Leon Goodman

Life Sciences Research, Stanford Research Institute, Menlo Park, California 94025

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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.

249–250°. Further recrystallization afforded an analytical sample: mp 251–252.5°; λ_{max}^{Nujol} (μ) 3.00 or 3.05 (NH), 6.03 or 6.09 (C=O, urea), 8.05 and 9.8 (O-phenyl), 12.2 (*p*-C_6H_4), 13.4 and 14.4 (C_6H_5); λ_{max}^{EtOH} 260 mμ (ϵ 6800).

Anal. Calcd for $C_{27}H_{24}N_2O_3$: C, 76.4; H, 5.70; N, 6.60. Found: C, 76.5; H, 6.01; N, 6.44.

Hydrogenolysis at 1 atm with 5% palladium–carbon catalyst in dimethylformamide afforded 88% of **4,4′-dihydroxycarbanilide** (II), mp 269–275° dec (lit.[5,6] 240° dec, 280° dec, prepared less conveniently by other methods).

The toluene mother liquor from the initial filtration (above) contained crude ***p*-benzyloxyphenyl isocyanate**[7] (III); this could be prepared in 39% yield, mp 51–55° (recrystallized from petroleum ether, bp 30–60°), if only 1 molar equiv of triethylamine was used in the above reaction.

O-(*p*-Nitrophenyl)-N-(*p*-benzyloxyphenyl)urethan (IV).—A solution of 9.9 g (0.044 mole) of *p*-benzyloxyphenyl isocyanate (III) and 6.25 g (0.045 mole) of *p*-nitrophenol in 200 ml of benzene was treated with 10 drops of triethylamine, refluxed for 10 min, and stored overnight at 25°. The mixture was chilled and 13.3 g of a solid, mp 140–158°, was collected on a filter and washed with ether. Recrystallized from $CHCl_3$–petroleum ether (170: 15 ml) afforded 11.7 g (73%) in 2 crops: mp 159–162°; λ_{max}^{EtOH} 238 mμ (ϵ 22,400), 310 (broad, 10,000); infrared data, λ_{max}^{Nujol} (μ) 3.00 or 3.05 (NH), 5.75 or 5.82 (C=O, urethan), *ca.* 6.5 and 7.4 (NO_2), 8.0–8.3 (O-phenyl plus urethan), 12.2 (*p*-C_6H_4), 13.4–13.6 and 14.4 (C_6H_5). The compound was homogeneous on chromatography in butanol–acetic acid–water (5:2:3) on Whatman No.1 paper, R_f 0.92, detected under ultraviolet light.

Anal. Calcd for $C_{20}H_{16}N_2O_5$: C, 65.9; H, 4.43; N, 7.69. Found: C, 65.5; H, 4.28; N, 7.80.

This urethan in the presence of bases was easily dissociated to *p*-nitrophenol and, presumably, the isocyanate III. Upon solution of the urethan in dimethyl sulfoxide, formation of some urea I was noted, presumably *via* the intermediate isocyanate.

O-(*p*-Aminophenyl)-N-(*p*-hydroxyphenyl)urethan (V).—A suspension of 7.63 g (0.021 mole) of the urethan IV and 0.8 g of palladium black (100%) in 75 ml of glacial acetic acid at 45° was hydrogenated at 1 atm for 24 hr. The turbid white supernatant was decanted from the catalyst, the catalyst was washed with acetic acid, and the liquids were concentrated *in vacuo* to form 5.23 g of residual solid. Recrystallization from 200 ml of ethanol afforded 3.6 g (70%), chromatographically homogeneous with R_f 0.84; λ_{max}^{EtOH} 245 mμ (ϵ 29,300), 288 (3540); λ_{max}^{Nujol} (μ) 3.0 (NH), 5.80 (C=O, urethan), 8.3 (broad, O-phenyl plus urethan), 12.1 (*p*-C_6H_4). Bands of weak–medium intensity were also present in the infrared at 13.6 and 14.4 μ, but it could be established (*e.g.*, from paper chromatography) that these were not due to unremoved O-benzyl; in various samples the NH or the C=O bands were resolved into 2 peaks or a broad band appeared at 11 μ. The compound decomposed gradually on heating from 200–260°.

Anal. Calcd for $C_{13}H_{12}N_2O_3$: C, 63.9; H, 4.95; N, 11.5. Found: C, 63.7; H, 4.92; N, 11.4.

1-[*p*-(Benzyloxyl)phenyl]-3-butylurea (VI).—A solution of 0.50 g (1.4 mmoles) of the urethan IV in 25 ml of chloroform was treated with 0.25 ml (2.5 mmoles) of *n*-butylamine. After 5 min the resultant yellow solution was concentrated *in vacuo* to form a solid residue (0.70 g), which was triturated with water and then extracted, in $CHCl_3$ solution, with water to remove yellow color. The solid, recovered from the chloroform layer, was recrystallized from aqueous methanol to form 0.36 g (88% yield); mp 140–141°; λ_{max}^{Nujol} (μ) 3.02 (NH), 6.10 (C=O, urea), 8.0–8.1 (O-phenyl), 12.1 (*p*-C_6H_4), 13.5–13.6 and 14.4 (C_6H_5); λ_{max}^{EtOH} 245 mμ (ϵ 24,100), 293 (1960). The compound was identical with a sample prepared from equimolar quantities of benzyloxyaniline and *n*-butyl isocyanate in benzene–CH_2Cl_2 solution and recrystallized (78% yield), mp 142–143°.

Anal. Calcd for $C_{18}H_{22}N_2O_2$: C, 72.4; H, 7.43; N, 9.39. Found: C, 72.5; H, 7.53; N, 9.28.

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(6) G. V. Jadhav, *J. Indian Chem. Soc.*, **10**, 391 (1933).

(7) J. Sova, A. Sekera, and C. Vrba, *Chem. Listy*, **51**, 2339 (1957); *Chem. Abstr.*, **52**, 6248*h* (1958); no melting point was recorded.

The Six Trimethoxyphenylisopropylamines (Trimethoxyamphetamines)

ALEXANDER T. SHULGIN

1483 Shulgin Road, Lafayette, California

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In view of the well-known *vic*-trimethoxy arrangement found in reserpine, colchicine, podophyllotoxin, and mescaline, many other trimethoxy compounds have been prepared and tested, especially in the psychotomimetic area.[1] Of the six possible position isomers of trimethoxyamphetamine, syntheses of the 3,4,5,[2] 2,4,5,[3] and 2,4,6[4] isomers have been published. The synthetic route to a fourth, the 2,3,4 isomer, has been outlined but with no experimental detail.[1d]

The particulars of this latter preparation and of the syntheses of the two remaining isomers (2,3,5 and 2,3,6) are reported here. Table I compiles the properties of these six possible trimethoxyamphetamines, of the corresponding nitropropene precursors, and of the related benzaldehydes along with their characterizing malononitrile and dinitrophenylhydrazone derivatives. The psychotomimetic efficacies of the first three isomers listed have been compared.[1d] The evaluation of the remaining three isomers is not yet complete.

Experimental Section

The three phenylisopropylamines described are all prepared from the corresponding nitropropenes by a modification of the procedure described by Ramirez and Burger,[5] for which a single illustration will suffice. Different routes have been employed to each of the nitropropenes, and each is described: procedure A, the appropriate benzaldehyde is treated with nitroethane, yielding the nitropropene; procedure B, the allyl ether of an appropriate phenol is allowed to undergo the Claisen rearrangement, and a phenylpropene is prepared by methylation of the intermediate allyl phenol, followed by base-catalyzed isomerization; the propene is then nitrated with tetranitromethane to yield the nitropropene; procedure C, the appropriate aromatic ether is lithiated with butyllithium; reaction with propionaldehyde followed by dehydration provides the phenylpropene which is nitrated as above.

All compounds listed in Table I carried acceptable microanalyses. Melting points were determined on a Kofler Heizbank and are corrected.

Procedure A. 1-(2,3,4-Trimethoxyphenyl)-2-nitropropene.—To a solution of 2,3,4-trimethoxybenzaldehyde (12.4 g, prepared as described by Papadakis and Boand[6]) in glacial acetic acid (45 g), there was added ammonium acetate (4.1 g) and nitroethane (7.0 ml). The mixture was held at reflux for 1.5 hr and cooled, and water was added to induce crystallization. The sticky product was removed by filtration, washed with 50% acetic acid, and recrystallized from boiling methanol. The yield was 6.5 g of fine yellow needles, The two parallel syntheses were similar, employing 3,4,5-trimethoxybenzaldehyde obtained from Aldrich Chemical Co. and 2,4,6-trimethoxybenzaldehyde prepared as described by Benington, *et al.*[4]

2,3,4-Trimethoxyamphetamine.—The above nitropropene was reduced by the Soxhlet technique described by Ramirez and Burger.[5] Rather than using the picrate as a means of isolation, the crude acidic reaction mixture was treated with potassium sodium tartrate (10 g/g of nitropropene employed) and 25% NaOH solution was then added to raise the pH above 9. The mixture was then extracted with CH_2Cl_2. The oil remaining upon evaporation was dissolved in anhydrous ether, and this

(1) (a) D. I. Peretz, J. R. Smythies, and W. C. Gibson, *J. Mental Sci.*, **101**, 317 (1955); (b) A. T. Shulgin, S. Bunnell, and T. Sargent, *Nature*, **189**, 1011 (1961); (c) A. T. Shulgin, *Experientia*, **19**, 127 (1963); (d) *ibid.*, **20**, 366 (1964).

(2) P. Hey, *Quart. J. Pharm. Pharmacol.*, **20**, 129 (1947).

(3) V. Bruckner, *J. Prakt. Chem.*, **138**, 268 (1933).

(4) F. Benington, R. D. Morin, and L. C. Clark, Jr., *J. Org. Chem.*, **19**, 11 (1954).

(5) F. A. Ramirez and A. Burger, *J. Am. Chem. Soc.*, **72**, 2782 (1950).

(6) P. E. Papadakis and W. Boand, *J. Org. Chem.*, **26**, 2075 (1961).