Transformations of Penicillin. Part II.[1] *NN'*-Di-isopropylhydrazine, a New Reagent for Protection of Carboxylic Acids

By D. H. R. Barton,* M. Girijavallabhan, and P. G. Sammes, Chemistry Department, Imperial College, London SW7 2AY

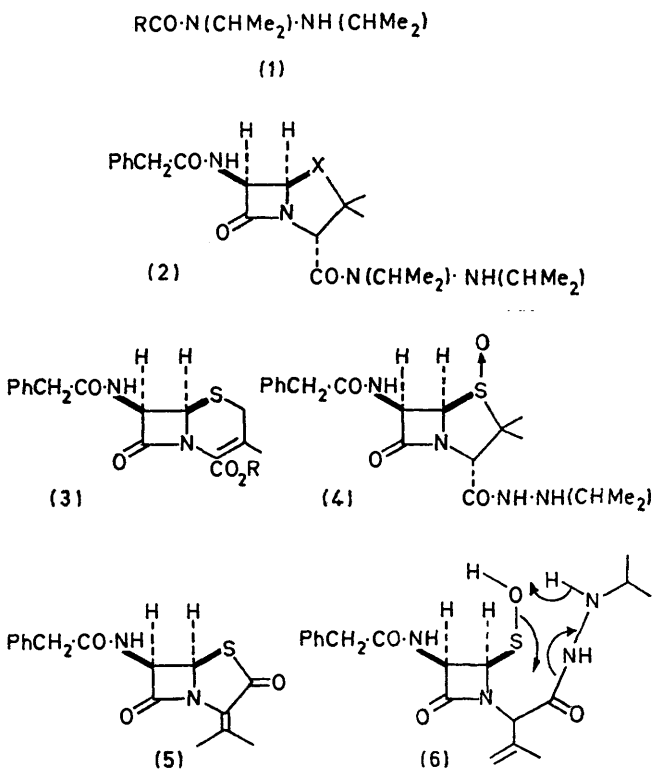
NN'-Di-isopropylhydrazine is a useful reagent for the protection of carboxylic acids. The derived hydrazides can be reconverted by selective oxidation, with, for example, lead tetra-acetate, into the parent acids in very high yield. The protecting group has been used for penicillins. Acid-catalysed rearrangement of the *NN'*-di-isopropylhydrazide from 6β-phenylacetamidopenicillanic acid (*S*)-sulphoxide, followed by oxidative cleavage of the protecting group, afforded the corresponding deacetoxycephalosporanic acid. Thermal rearrangement of the *N*-isopropylhydrazide of 6β-phenylacetamidopenicillanic acid (*S*)-sulphoxide gave a moderate yield of anhydropenicillin.

THE oxidation of substituted hydrazines is the subject of much current interest.[2] In particular, certain acyl-substituted hydrazines have been shown to undergo oxidation with liberation of the acyl group. For example, *N*-acyl-*N'*-phenylhydrazines are smoothly oxidised by manganese dioxide in aqueous acetic acid to liberate the carboxylic acid.[3] Similarly, *N*-benzoyl-*NN'*-diphenylhydrazine may be oxidised with lead tetra-acetate to give a mixture of *cis*- and *trans*-azobenzene and benzoic acetic anhydri

In connection with work on pen[illegible]ved chemistry we desired a carboxylic acid protecting group that would be stable to both acidic and basic conditions and also inert towards acylating agents. *N*-Phenylhydrazides are not completely suitable since further de[illegible]ation to a diacyl hydrazide is possible. Since the[illegible]illidered, di-substituted hydrazine *NN'*-di-isopropylhydrazine is readily available from catalytic reduction of acetone azine,[5] its potential as a protecting group was investigated.

NN'-Di-isopropylhydrazine reacts with carboxylic acid derivatives (either acyl chlorides or *via* the use of mixed anhydrides[6]) to give the corresponding mono-acylhydrazides. No formation of diacyl derivatives could be detected under the normal range of acylation conditions. Thus, benzoyl chloride reacted with *NN'*-di-isopropylhydrazine under Schotten-Baumann conditions to give the monobenzoylhydrazide (1; R = Ph) in high yield. Palmitoyl chloride reacted similarly to give the hydrazide (1; R = n-$C_{15}H_{31}$). In the case of 6β-phenylacetamidopenicillanic acid, prior conversion into its mixed anhydride with ethyl chloroformate, followed by reaction with *NN'*-di-isopropylhydrazine afforded the corresponding hydrazide (2; X = S). The sulphoxide hydrazide (2; X = S→O) was similarly prepared from the sulphoxide acid, again in good yield.

The carboxylic acid function in the foregoing derivatives could be released by selective oxidation under mild conditions. For example, treatment of *N*-benzoyl-*NN'*-di-isopropylhydrazine with lead tetra-acetate and pyridine in dry benzene at room temperature, followed by extraction with aqueous sodium hydrogen carbonate, gave, after reacidification, a quantitative recovery of



benzoic acid. The other hydrazides described behaved similarly.

Although lead tetra-acetate was the preferred oxidant, the hydrazides could also be oxidised, with liberation of the carboxylic acid, by sodium periodate, aqueous *N*-bromosuccinimide, and chromium trioxide in acetic acid. The hydrazide fragment from the oxidation disappears as gaseous materials during work-up,

[1] Part I, D. H. R. Barton, F. Comer, D. G. T. Greig, P. G. Sammes, (Mrs.) C. M. Cooper, G. Hewitt, and W. G. E. Underwood, *J. Chem. Soc.* (*C*), 1971, 3540.

[2] J. B. Aylward, *Quart. Rev.*, 1971, **25**, 407.

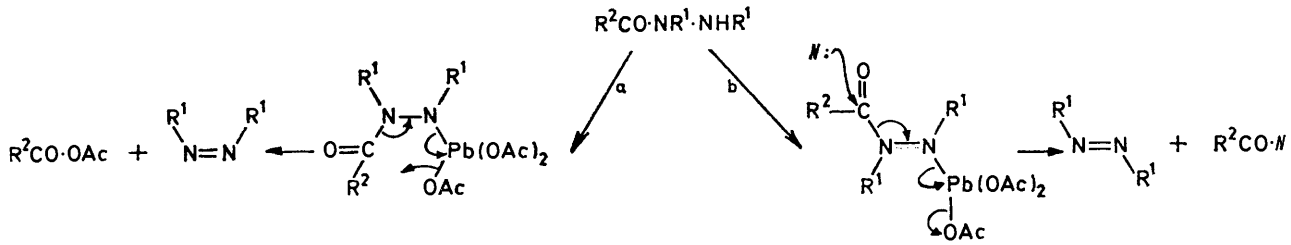
[3] H. B. Milne, J. E. Halver, D. S. Ho, and M. S. Mason, *J. Amer. Chem. Soc.*, 1957, **79**, 637; R. B. Kelly, *J. Org. Chem.*, 1963, **25**, 453; R. B. Kelly, G. R. Umbreit, and W. F. Liggett, *J. Org. Chem.*, 1964. **26**, 1273.

[4] W. A. F. Gladstone, *J. Chem. Soc.* (*C*), 1969, 1571.

[5] H. R. Lochte, J. R. Bailey, and W. A. Noyes, *J. Amer. Chem. Soc.*, 1921, **43**, 2597.

[6] *Cf.* R. B. Morin, B. G. Jackson, R. A. Mueller, E. R. Lavagnino, W. B. Scanlon, and S. L. Andrews, *J. Amer. Chem. Soc.*, 1969, **91**, 1401.

resulting in exceptionally clean products. The lead tetra-acetate oxidation probably proceeds in a manner similar to that recorded for the oxidation of *N*-benzoyl-*NN'*-diphenylhydrazine.[4] In the latter case two mechanisms were proposed. In the absence of external nucleophiles an intramolecular transfer of an acetate group was postulated (Scheme, path a), leading to acetic benzoic anhydride and *cis*-azobenzene, whereas in the presence of external nucleophiles *trans*-azobenzene was formed (path b). In our experiments the presence of pyridine



SCHEME *N* = nucleophile

assisted the reaction, probably because of its ability to act as an external nucleophile. The pyridinium salt thus formed is rapidly hydrolysed during work-up, releasing the carboxylic acid group.

Because of the mild conditions required to cleave the hydrazide, an extension to the protection of alcohols, *via* the oxycarbonylhydrazides is to be expected. The weakly basic nature of the monoacyl-*NN'*-di-isopropylhydrazines may also be of advantage in extraction processes.

Heating the penicillin sulphoxide hydrazide (2; X = S→O) in dioxan containing pyridinium phosphate as catalyst afforded an isomeric mixture of the corresponding deacetoxycephalosporanic acid hydrazides. Oxidation with lead tetra-acetate under the conditions already described afforded the acid (3; R = H) in high yield.[6]

A novel reaction was observed with the penicillin monoisopropylhydrazide (4). This hydrazide was obtained by coupling the corresponding mixed anhydride with monoisopropylhydrazine. That the acylation had occurred on the primary nitrogen atom was deduced by comparison of the chemical shift of the isopropyl methine proton (τ 6·85) with those for the di-isopropyl derivative (τ *ca.* 5·85 and 6·85). Heating this hydrazide (4) under the dehydrating conditions described did not afford the corresponding cephalosporin. Instead the major product was the anhydropenicillin (5), isolated in 49% yield, and identical with an authentic specimen.[7] The anhydropenicillin must be formed *via* an internal redox reaction between the hydrazide function and the sulphenic acid intermediate formed on heating the sulphoxide [see (6)]. Its production is another example of the diverse behaviour of sulphenic acids.[8]

[7] S. Wolfe, J. C. Godfrey, C. T. Holdrege, and Y. G. Perron, *Canad. J. Chem.*, 1968, **46**, 2549; S. Wolfe, R. N. Bassett, S. M. Caldwell, and F. I. Wasson, *J. Amer. Chem. Soc.*, 1969, **91**, 7205.

We have also considered other 1,2-dialkylhydrazines as protecting reagents for penicillins. With 1,2-dimethylhydrazine the penicillin G–ethyl carbonate mixed anhydride gave the corresponding 1,2-dimethylhydrazide. However, its oxidation with lead tetra-acetate gave only a 25% yield of penicillin G.

EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage apparatus. I.r. spectra were determined for Nujol mulls and ^{1}H n.m.r. spectra were recorded with a Varian T60 instrument for solutions in deuteriochloroform containing tetramethylsilane as internal reference. Light petroleum refers to the fraction of boiling range 40—60°. Solutions were dried over anhydrous Na_2SO_4.

N-*Benzoyl*-NN'-*di-isopropylhydrazine* (1; R = Ph).—*NN'*-Di-isopropylhydrazine hydrochloride (1·0 g) in water (5 ml) containing potassium hydroxide (2·5 g) was shaken with a solution of benzoyl chloride (1·5 ml) in light petroleum (20 ml) at room temperature for 15 min. The organic layer was separated, washed with water, and dried. Removal of the solvent under reduced pressure afforded *monobenzoyl*-NN'-*di-isopropylhydrazine* (quantitative recovery). Crystallised once from light petroleum (previously reported as an oil [5]) this gave crystals (2·2 g, 77%) of m.p. 41—42°), $\nu_{max.}$ 3270 and 1640 cm^{-1} (Found: C, 70·7; H, 9·1; N, 12·7. $C_{13}H_{20}N_2O$ requires C, 70·9; H, 9·15; N, 12·7%).

N-*Palmitoyl*-NN'-*di-isopropylhydrazine* (1; R = $C_{15}H_{31}$).—Palmitic acid (1·0 g) was heated with thionyl chloride (2 ml) under reflux for 2 h. On removal of the excess of thionyl chloride, palmitoyl chloride remained. The acid chloride in benzene (25 ml) was shaken with *NN'*-di-isopropylhydrazine hydrochloride (1·8 g) in water (20 ml) containing potassium hydroxide (2·8 g) for 30 min. The organic layer was separated, washed with water, dried, and evaporated to leave the *hydrazide* (1·2 g, 93%), m.p. 38—39° (from light petroleum), $\nu_{max.}$ 3270 and 1650 cm^{-1}, τ 5·85 (1H, m, C*H*Me$_2$) and 6·85 (1H, m, C*H*Me$_2$) (Found: C, 74·6; H, 13·0; N, 7·7. $C_{22}H_{46}N_2O$ requires C, 74·5; H, 13·1; N, 7·9%).

N-6β-*Phenylacetamidopenicillanoyl*-NN'-*di-isopropylhydrazine* (2; X = S).—The *N*-ethylpiperidinium salt of 6β-phenyl midopenicillanic acid (2·25 g) in dry, ethanol-fr loroform (30 ml) was treated with ethyl chloroformate (0·5 ml) at −20° under nitrogen for 20 min. The solution was then washed with ice-cold water (30 ml) and immediately shaken with a solution of di-isopropyl-

[8] D. H. R. Barton, D. G. T. Greig, G. Lucente, P. G. Sammes, M. V. Taylor, (Mrs.) C. M. Cooper, G. Hewitt, and W. G. E. Underwood, *Chem. Comm.*, 1970, 1683.

hydrazine (from 1·12 g of the hydrochloride and 1 equiv. of sodium hydroxide) in water (30 ml). After 15 min at room temperature the organic layer was separated and washed with water (20 ml), 0·5M-tartaric acid (20 ml), and finally water (20 ml). The dried solution was concentrated to afford crystals of the *hydrazide*. Recrystallisation from benzene gave material (1·61 g, 55%) of m.p. 221—223°, $[\alpha]_D^{25}$ +71° (*c* 1·0 in $CHCl_3$), $\nu_{max.}$ ($CHCl_3$) 3300, 1780, and 1680br cm^{-1}, τ 5·85 (1H, m, C*H*Me_2) and 6·85 (1H, m, C*H*Me_2) (Found: C, 60·9; H, 7·4; N, 13·0; S, 7·4. $C_{22}H_{32}N_4O_3S$ requires C, 61·1; H, 7·5; N, 13·0; S, 7·4%).

An improved yield of the hydrazide (75%) was obtained when the freshly distilled *NN'*-di-isopropylhydrazine was added to a solution of the mixed anhydride in dry chloroform.

(1S)-N-6β-*Phenylacetamidopenicillanoyl*-NN'-*di-isopropylhydrazine* S-*Oxide* (2; X = S→O).—Triethylamine (1 g) was added to a stirred solution of (1*S*)-6β-phenylacetamidopenicillanic acid 1-oxide (3·5 g) in dry chloroform (50 ml) containing ethyl chloroformate (1·2 g, 1·1 equiv.) at 0° and under nitrogen. After 2 h the solution was cooled to −20° and freshly distilled di-isopropylhydrazine (1·8 g) was added. After 20 min the solution was washed with water, 0·5M-tartaric acid (20 ml), and finally water (50 ml portions). After drying and removal of solvent the crude product was precipitated from light petroleum. Crystallisation from benzene afforded the *sulphoxide hydrazide* (3·54 g, 77%), m.p. 158—160°, $[\alpha]_D^{25}$ +111° (*c* 1 in $CHCl_3$), $\nu_{max.}$ ($CHCl_3$) 3500, 3380, 1785, and 1685br cm^{-1}, τ 5·9 (1H, m, C*H*Me_2) and 6·8 (1H, m, C*H*Me_2) (Found: C, 58·9; H, 7·0; N, 12·4; S, 7·1. $C_{22}H_{32}N_4O_4S$ requires C, 58·9; H, 7·2; N, 12·5; S, 7·1%).

(1S)-N-6β-*Phenylacetamidopenicillanoyl*-N'-*isopropylhydrazine* S-*Oxide* (4).—The mixed anhydride from the sulphoxide acid (3·5 g) and ethyl chloroformate (1·2 g) in chloroform (50 ml) was treated with isopropylhydrazine (from 1·9 g of the hydrochloride, liberated with sodium hydroxide) in water (20 ml). The mixture was stirred for 5 min at room temperature, then the organic layer was separated, washed with water (2 × 50 ml), dried, and evaporated to leave an oily product. After precipitation from light petroleum and crystallisation from dioxan the *monoisopropylhydrazide* (3·3 g, 75%) had m.p. 86—88° (solvated), $[\alpha]_D^{20}$ +220° (*c* 1·5 in $CHCl_3$), $\nu_{max.}$ ($CHCl_3$) 3500, 3400, 3300, 1800, and 1680br cm^{-1}, τ 6·85 (1H, m, C*H*Me_2) (Found: C, 55·7; H, 7·0; N, 9·5; S, 5·7. $C_{19}H_{26}N_4O_4S,2C_4H_8O_2$ requires C, 55·7; H, 7·2; N, 9·6; S, 5·5%). The n.m.r. spectrum also indicated the presence of 2 mol. equiv. of dioxan of crystallisation.

Oxidations with Lead Tetra-acetate.—The general procedure was as follows. To the hydrazide (2 mmol) at room temperature was added freshly crystallized lead tetra-acetate 1·2 equiv.) and anhydrous pyridine (1·2 equiv.). The solution was stirred for 10 min, then washed with aqueous sodium hydrogen carbonate. The aqueous layer was washed once with dichloromethane, acidified with dilute mineral acid, and extracted with ether. The extract was dried and evaporated to obtain the acid.

Both the benzoyl- (1; R = Ph) and the palmitoyl- (1; R = $C_{15}H_{31}$) hydrazide gave quantitative recoveries of the acid. In the absence of pyridine the palmitoylhydrazide (1; R = $C_{15}H_{31}$) afforded the acid (89%) and acetic palmitoyl anhydride (6%). Attempts to isolate the oxidised hydrazide fragment were abortive.

Similarly, both the penicillin derivative (2; X = S) and its sulphoxide (2; X = S→O) gave near quantitative recoveries of the free acids.

Use of Alternative Oxidants.—(a) *Sodium periodate*. To *N*-benzoyl-*NN'*-di-isopropylhydrazine (1; R = Ph) (0·40 g) in tetrahydrofuran (15 ml) was added sodium periodate (0·42 g) in water (1 ml) followed by 6N-sulphuric acid (1 equiv.). After 5 min at room temperature the organic phase was separated, washed with water, and dried. Evaporation afforded benzoic acid (0·20 g, 89%). Under the same conditions the corresponding palmitoylhydrazide afforded the free acid (87%).

(b) N-*Bromosuccinimide*. To *N*-6β-phenylacetamidopenicillanoyl-*NN'*-di-isopropylhydrazine (0·20 g) in tetrahydrofuran (10 ml) and water (3 ml) were added pyridine (0·06 g) and *N*-bromosuccinimide (0·10 g). After 10 min the acid was extracted in the normal way (0·17 g, 90%).

(c) *Chromium trioxide*. The benzoylhydrazide (0·40 g) was treated with chromium trioxide (0·18 g) in acetic acid (10 ml) for 10 min at room temperature. The mixture was poured into water and extracted with ether. After drying (Na_2SO_4), the solution was evaporated to dryness to yield benzoic acid (0·14 g, 65%).

Rearrangement of the Sulphoxide Acid Di-isopropylhydrazide (2; X = S→O).—Freshly prepared sulphoxide hydrazide (5·0 g) in anhydrous dioxan (80 ml) containing pyridine (80 mg) and orthophosphoric acid (112 mg) was heated under reflux in nitrogen for 18 h. The solvent was removed *in vacuo* and the residue dissolved in benzene (100 ml). The solution was washed with water, dried, and treated with lead tetra-acetate (1·2 equiv.) and pyridine (1·2 equiv.) at room temperature for 10 min. Work-up by the normal method afforded an acid (3·7 g).[9] A sample (0·5 g) was assayed as its derived methyl ester. Purification of the latter by preparative t.l.c. (Merck silica gel G) gave, as the major component, methyl 7β-phenylacetamido-3-methylceph-3-em-4-carboxylate (3; R = Me) (0·26 g, 55%), m.p. 190—192° (lit.,[1] 187—188°), $[\alpha]_D$ +86° (*c* 1·0 in $CHCl_3$), identical in physical properties with an authentic sample.

Rearrangement of the Sulphoxide Acid Monoisopropylhydrazide (4).—The sulphoxide hydrazide (2·5 g) in dry dioxan (85 ml) was heated under reflux in the presence of pyridine (78 mg) and orthophosphoric acid (112 mg) for 16 h. The excess of solvent was removed *in vacuo*. The residue was dissolved in dichloromethane and the mixture washed with water (2 × 50 ml). The organic phase was dried and then evaporated to dryness. The residue was chromatographed through a column of silica gel (Merck) (50 g). Elution with benzene–ethyl acetate (95 : 5) afforded, as the major product, the anhydropenicillin (0·85 g). Crystallisation from carbon tetrachloride afforded needles, m.p. 153—154°, $[\alpha]_D$ +271° (*c* 2·1 in $CHCl_3$) [lit.,[7] 156—158° (decomp.)], $\nu_{max.}$ ($CHCl_3$) 3400, 1790, 1690, 1665, 1640, and 1510 cm^{-1}, identical with an authentic sample (t.l.c. and spectral properties).

N-6β-*Phenylacetamidopenicillanoyl*-NN'-*dimethylhydrazine*.—The *N*-ethylpiperidinium salt of penicillin G (4·47 g) in dry ethanol-free chloroform (25 ml) at −20° was treated, with stirring, with ethyl chloroformate (1 ml) for 15 min. The solution was shaken thoroughly at room temperature with 1,2-dimethylhydrazine dihydrochloride (1·5 g) in water (10 ml) containing sodium hydroxide (850 mg). The chloroform layer was separated, washed with aqueous 0·5M-tartaric acid (20 ml) and water, dried, and evaporated

[9] R. J. Stedman, K. Swered, and J. R. E. Hoover, *J. Medicin. Chem.*, 1964, **7**, 117.

in vacuo. The residue crystallised from benzene to give the NN′-*dimethylhydrazide* (2·6 g), m.p. 100—102°, $[\alpha]_D$ +98° (*c* 1·8 in $CHCl_3$) Found: C, 57·5; H, 6·2; N, 14·85; S, 8·6. $C_{18}H_{24}N_4O_3S$ requires C, 57·4; H, 6·45; N, 14·9; S, 8·5%).

We thank Glaxo Laboratories for financial assistance and for providing us with the experimental procedure for the penicillin oxide rearrangement.

[1/2076 *Received*, 8*th November*, 1971]