Preparation of 6-Deuteriopenicillins

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When penicillin (*S*)-*S*-oxide esters are treated with triethylamine and acetonitrile containing D_2O, both epimerization and deuteration at the 6-position occurs. This reaction is found to be a convenient method for the preparation of 6-deuteriopenicillins. 6-Deuteriobenzylpenicillin (*S*)-*S*-oxide benzyl ester (containing more than 95% D in the 6-position) was obtained from the (*S*)-*S*-oxide of penicillin G benzyl ester. Deoxygenation of the sulfoxide followed by catalytic debenzylation gave penicillin G deuterated in the 6-position. A kinetic study of deuterium incorporation and epimerization at C-6 was carried out for the (*S*)-*S*-oxide of penicillin V benzyl ester and for its 6-epimer. Deuteration was found to be faster than epimerization when the sulfoxide with the natural configuration was used as starting material. In the experiment starting with the 6-epimer, epimerization is faster than deuteration. A revised mechanism for the epimerization and deuteration of penicillin *S*-oxide esters is proposed.

Deuteriobenzylpenicillin has been obtained from cultures of *Penicillium chrysogenum* in a medium containing deuterium oxide.[1,2] Benzylpenicillin labeled in the side chain was synthesized by reaction of phenylacetyl-d_7 chloride with 6-aminopenicillanic acid.[3] Deuteration in the β-methyl group was obtained by heating penicillin *S*-oxides in benzene containing deuterium oxide or deuterated *tert*-butyl alcohol.[4-6] This method was also used for the synthesis of tritiated penicillins.[7,8] In the reaction of benzylpenicillin with D-alanine transpeptidase the molecule is cleaved between C-5 and C-6, yielding phenylacetylglycine[9,10] and *N*-formylpenicillamine.[11] For a study of the mechanism of this reaction a penicillin labeled at C-6 would be useful.

6α-Deuteriobenzylpenicillin (**1b**) has been prepared[12] by isomerization of benzyl 6β-[(*p*-nitrobenzylidene)amino]-penicillanate in acetonitrile containing deuterium oxide and triethylamine. Cleavage of the Schiff base, separation of the two isomers, N-phenylacetylation, and debenzylation yielded benzylpenicillin containing more than 70% deuterium in the 6α-position. During a study[13,14] of base-catalyzed epimerization at C-6 of penicillins and their *S*-oxides we observed that the isomer with the natural configuration was still an important fraction of the equilibrium mixture. If incorporation of deuterium could be obtained during this isomerization, a more direct and convenient procedure should be available for the preparation of C-6 labeled penicillins. Accordingly we investigated deuteration during epimerization of penicillin *S*-oxide esters.

Table I. Deuteration and Epimerization[a] of Benzylpenicillin (*S*)-*S*-Oxide Benzyl Ester (4a)

time, h	ratio of 4/5[b]	% D in 4[c]	% recovery (4 + 5)
1	95:5	25	90
6	85:15	80	86
12	70:30	>95	83
24	60:40	>95	77

[a] Reaction conditions: see Experimental Section. [b] Determined by ^{1}H NMR. [c] Determined by ^{1}H NMR after isolation of 4.

N-Deuteriobenzylpenicillin (*S*)-*S*-oxide methyl ester **2a** (48-50% deuterated), obtained by partial exchange of the amide proton against deuterium, was epimerized in methylene chloride in the presence of 0.1 equiv of 1,5-diazabicyclo[4.3.0]non-5-ene (DBN). The equilibrium mixture of **2** and **3** was separated and analyzed for deuterium by ^{1}H NMR. Deuteration in the 6-position was 10% for **2** and 15% for its epimer **3**. It is obvious that 6-deuteriobenzylpenicillins with a high deuterium content cannot be obtained by this procedure, since the D/H ratio in the total proton pool during epimerization is only 0.5:1. An increase of this D/H ratio by addition of deuterium oxide resulted in an extensive decomposition of the penicillin molecule. This can be expected for a reaction mixture containing penicillin *S*-oxides and DBN in the presence of deuterium oxide.

The deuterium-labeling experiments of Firestone and Christensen[12] and also an earlier publication of Sassiver and Shepherd,[15] describing epimerization of cephalosporin sulfoxide esters with triethylamine in dimethyl sulfoxide containing deuterium oxide, led us to the use of a weaker base. Epimerization of benzylpenicillin (*S*)-*S*-oxide benzyl ester (**4a**) in acetonitrile containing triethylamine and deuterium oxide gave a high incorporation of the isotope and a fairly good recovery (58-46%) of **4b** after 12-24 h (see Table I). Reduction of the sulfoxide group of **4b** and hydrogenolysis of the benzyl ester of **6b** gave the potassium salt of **1b** in an overall yield of 25% (calculated on **4a**). The normal/epi ratio of 60:40, obtained after a 24-h epimerization of **4a** under the present conditions, was different from the equilibrium ratio of 40:60 observed during

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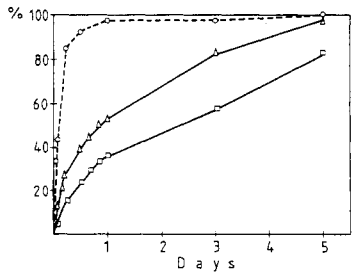


Figure 1. Epimerization and deuteration of (phenoxymethyl)-penicillin (*S*)-*S*-oxide benzyl ester (**7a**): △, percent epimerization (a 7/8 ratio of 40:60 is taken as 100%); ○, percent deuteration of 7; □, percent decomposition of 7 and 8.

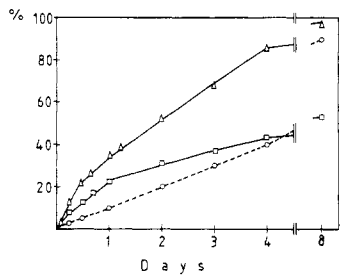


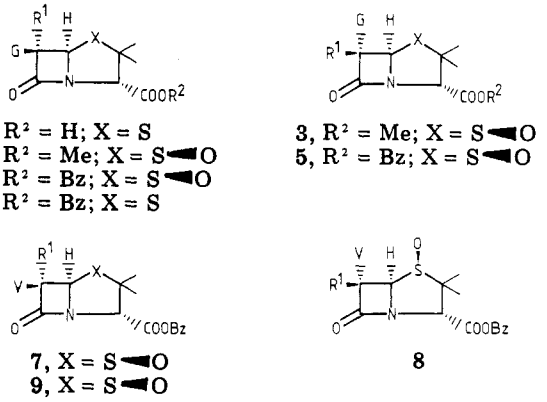
Figure 2. Epimerization and deuteration of 6-epi(phenoxymethyl)penicillin (*S*)-*S*-oxide benzyl ester (**8a**): △, percent epimerization (a 7/8 ratio of 40:60 is taken as 100%); ○, percent deuteration of 8; □, percent decomposition of 7 and 8.

epimerization of **4a** and **7a** in dichloromethane in the prresence of DBN. This means that in the present experiment deuteration at C-6 is complete before epimerization has reached the equilibrium ratio.

Deuteration during epimerization was studied in somewhat more detail for (phenoxymethyl)penicillin (*S*)-*S*-oxide benzyl ester **7a** and for its 6-epimer **8a**. The reaction conditions used during these experiments were identical with those mentioned for **4a**. Epimerization and decomposition of the penicillins were followed during the first 48 h by high-pressure LC. Deuteration at C-6 was determined by ^{1}H NMR spectrometry after separation of the two epimers. Data obtained for **7a** and **8a** are summarized in Figures 1 and 2, which show the progress of epimerization, deuteration, and decomposition. When the percentage of decomposition exceeds 35%, the high-pressure LC method is not reliable anymore because of the interference of some of the degradation products. It can be seen from Figure 1, which refers to the experiment with **7a** as a starting material, that the rate of deuteration at C-6 is faster than that of epimerization. Deuteration of **7** is almost complete after 1 day, while the 40:60 equilibrium ratio (considered as a 100% epimerization) is only observed after 5 days. A similar observation (i.e., deuteration being complete before epimerization has reached the equilibrium ratio) was made by Firestone and Christensen[12] for deuteration and epimerization of benzyl 6β-[(*p*-nitrobenzylidene)amino]penicillinate. It should be noted that the kinetic significance of the percentage epimerization, observed after 2 days or more, is rather questionable, because of extensive loss of **7** and **8** (indicated in Figure 1 as percent decomposition) by conversion into more polar compounds.

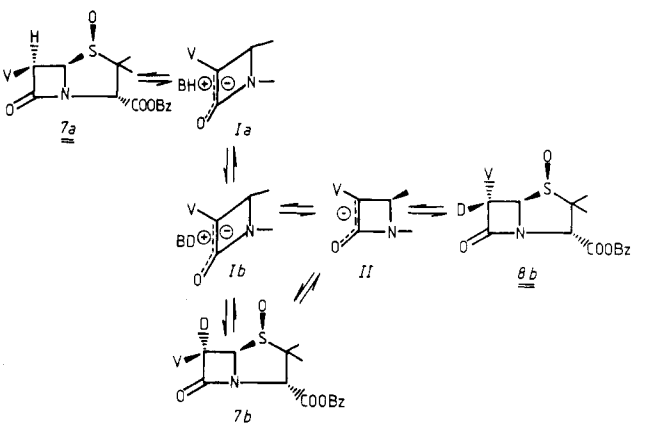
The situation is quite different for the experiment starting with 6-epimer **8a** (Figure 2). In this case deuteration of **8** is slower than epimerization. After 4 days, **8** is 40% deuterated, while the percentage epimerization is 85%. The 7/8 equilibrium ratio of 40:60 is reached only after 8 days. At that time deuteration of **8** is almost complete. Comparison of Figures 1 and 2 shows that the

Chart I[a]

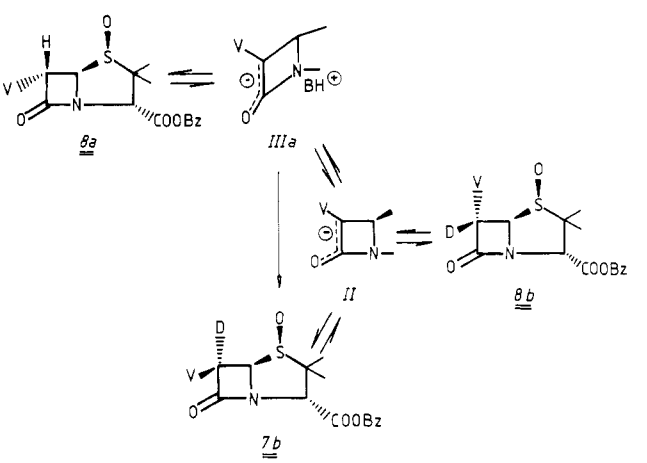


[a] **a**, R¹ = H, **b**, R¹ = D; G = $C_6H_5CH_2CONH$; V = $C_6H_5OCH_2CONH$.

Scheme I



Scheme II



rate of epimerization and also that of decomposition is lower in the experiment where the 6-epimer **8a** is used as a starting material. This was also observed when the isomerizations catalyzed by triethylamine were carried out in acetonitrile without addition of deuterium oxide or water. It should be noted that the epimer formed during these isomerizations, i.e., the 6-epimer **8** on starting from **7**, or the natural sulfoxide **7**, on starting from **8**, is always fully deuterated at C-6.

A possible explanation for these results may be found in a mechanism in which epimerization and deuteration are governed by a series of equilibria between penicillin *S*-oxides, ion pairs, and enolate ions. The proposed mechanisms are shown in Schemes I and II. Exchange of the amide proton against deuterium is not considered

in this discussion. Scheme I shows the equilibria proposed for labeling and epimerization of the natural sulfoxide **7a**. The first step is the formation of an ion pair Ia, in which the counterion BH^+ is located at the exo side of the penicillin molecule. The ion pair is believed to possess a certain stability, and its lifetime may be sufficient to allow a proton–deuterium exchange in the counterion ($BH^+ \rightleftharpoons BD^+$). Thus, the fact that the labeling of **7** proceeds faster than its epimerization may be explained by the equilibrium **7a** ⇌ Ia ⇌ Ib ⇌ **7b**, which operates independently of the epimerization and which is shifted in the direction of Ib and **7b** because of the high D/H ratio in the total proton pool. The ion pair Ib is also in equilibrium with the dissociated enolate ion II in which the stereochemistry at C-6 is lost. The latter leads to the labeled epimer **8b** by deuteration at the endo side. This explains the presence of fully deuterated **8** in the epimerization of the natural sulfoxide **7a**. A similar pathway, as proposed for **7a**, which enables deuteration independently of epimerization, does not seem to be operative when the 6-epimer **8a** is used as a starting material. This may be due to the fact that in the ion-pair IIIa BH^+ is located at the endo side in the vicinity of the sulfoxide. It can be assumed that BH^+ is hydrogen bonded to the sulfoxide and hence not rapidly converted into BD^+. Deuteration of IIIa from the exo side gives **7b**. Another possibility is the formation of a dissociated enolate ion II, which can be deuterated from both endo and exo sides. The finding that the epimerization of **7a** occurs faster than that of **8a** is in agreement with results obtained earlier for hetacillin[16] and phthalimidopenicillinate.[17] These results led to the conclusion that an exo proton is more easily removed than an endo proton by a strong base. It should be noted that these conclusions were based on few experimental data and that the presence of a "hetacillin" or "phthalimido" side chain shifts the isomerization equilibrium almost completely in the direction of the 6-epimer.

Similar epimerization and deuteration experiments were attempted with the (*R*)-*S*-oxide **9a** as a starting material to find out if the orientation of the sulfur–oxygen bond influences the rate of deuteration at the 6-position. However, no conclusive results could be obtained from these experiments because of extensive decomposition of the (*R*)-*S*-oxide during epimerization.

Experimental Section

Melting points are uncorrected; solvents were evaporated under reduced pressure at a bath temperature below 30 °C. Merck precoated silica gel 60 F 254 plates were used for TLC and Merck silica gel (0.04–0.063 mm) for column chromatography. Mass spectra were recorded on a AEI MS12 and ^1H NMR spectra on a Hitachi Perkin-Elmer R-24 apparatus. The liquid chromatograph consisted of an Orlita diaphragm-type metering pump (DMP-AE 10-4), an Orlita PD-4500 pulse damper, a manual Valco sample injection valve, and a Waters Associates Model 440 UV detector with a Kipp BD-40 recorder. Peak areas were measured with a Haff polar planimeter, Type 317. D_2O (99.75% deuterated) was used in all experiments. Penicillin *S*-oxide esters **2a**, **4a**, **5a**, **7a**, and **8a** were prepared as described in ref 13.

Epimerization of *N*-Deuteriobenzylpenicillin (*S*)-*S*-Oxide Methyl Ester (2a) with DBN. Compound **2a** (728 mg, 2 mmol) in anhydrous CH_2Cl_2 (4 mL) containing D_2O (0.2 mL, 22 mmol) was stirred for 24 h at room temperature. The reaction mixture was evaporated, and the residue dissolved in anhydrous benzene (6 mL), evaporated, and dried (in vacuo over P_2O_5), yielding 700 mg of N-deuterated **2a**. The amide function was deuterated about 50% (as calculated from the mass spectrum). N-Deuterated **2a** (546 mg, 1.5 mmol) was epimerized in 3 mL of anhydrous CH_2Cl_2 containing 0.15 mmol of DBN for 20 min at room temperature. After neutralization of the base with H_3PO_4 in D_2O, the organic layer was separated, washed with water, dried (Na_2SO_4), filtered, and evaporated. The residue was crystallized from anhydrous benzene (10 mL), yielding 225 mg (0.62 mmol) of the 6-epimer **3**. Evaporation of the filtrate and crystallization from hot methanol afforded 133 mg (0.37 mmol) of **2**. ^1H NMR showed that **2** was 10% deuterated at C-6 and **3** was 15% deuterated.

Epimerization and Deuteration of Benzylpenicillin (*S*)-*S*-Oxide Benzyl Ester (4a). A solution of **4a**[18] (4.40 g, 10 mmol) in a mixture of CH_3CN (40 mL) and D_2O (4.5 mL, 250 mmol) was treated with Et_3N (1.4 mL, 10 mmol). After 24 h at room temperature (22 °C), the reaction mixture was neutralized with a cooled solution of H_2SO_4 (0.6 mL, 11 mmol) in D_2O (10 mL). The acidic solution was extracted with EtOAc (150 mL). The organic layer was washed at 0 °C with water (2 × 100 mL), dried (Na_2SO_4), filtered, and evaporated. Addition of MeOH (50 mL) to the light yellow oil caused the crystallization of **4b** in two fractions: 2.01 g (46% yield); mp 152 °C dec; R_f (C_6H_6–Me_2CO, 4:1) 0.57; IR (KBr) ν_{max} 3400, 3370, 1685, 1510 (amide), 1782 (β-lactam), 1745, 1208 (ester), 1030 (S=O), 700 (phenyl) cm^{-1}; ^1H NMR ($CDCl_3$, Me_4Si) δ 1.03 (s, CH_3), 1.61 (s, CH_3), 3.52 (s, CH_2CO), 4.61 (s, 3-H), 4.91 (s, 5-H), 5.19 (AB, $CH_2C_6H_5$) 7.10 (s, CONH, partial deuteration), 7.25 (s, C_6H_5), 7.31 (s, C_6H_5). The product also contained deuterium in the amide function as deduced from the mass spectrum.

The filtrate was concentrated to an oil which was chromatographed over silica gel (20 g) with a gradient of CH_2Cl_2 changing to 10% CH_2Cl_2–Me_2CO. Fractions (5 mL) 45–61 gave, after freeze-drying from benzene, amorphous **5b**: 1.42 g (32% yield); mp 122–123 °C dec (with sintering at 68 °C); R_f (C_6H_6–Me_2CO, 4:1) 0.30; IR (KBr) ν_{max} 3290 (br), 1665, 1520 (amide), 1790 (β-lactam), 1750, 1215 (ester), 1040 (S=O), 700 (phenyl) cm^{-1}; ^1H NMR (CCl_4/Me_2SO 3:1; Me_4Si) δ 1.01 (s, CH_3), 1.54 (s, CH_3), 3.48 (s, CH_2CO), 4.35 (s, 3-H), 4.99 (s, 5-H), 5.18 (AB, $CH_2C_6H_5$), 7.15 (s, C_6H_5), 7.28 (s, C_6H_5), 7.90 (s, CONH partial deuteration). The mass spectrum confirmed partial deuteration of the amide function.

Results obtained after 1, 6, and 16 h, as listed in Table I, were obtained from epimerization experiments conducted on 1 mmol of **4a** under identical reaction conditions. The **4**/**5** ratio was determined for the mixture of **4** and **5** by ^1H NMR. Both compounds were separated as described above and analyzed for deuterium in the 6-position by ^1H NMR.

6α-Deuteriobenzylpenicillin Benzyl Ester (6b). A solution of 1.27 g (2.87 mmol) of **4b** (isolated after a 24-h epimerization) in DMF (60 mL) was cooled to −18 °C and treated with PBr_3 (1.1 mL, 11.5 mmol). The reaction mixture was stirred for 15 min at −18 °C and poured into an ice-cold mixture of $NaHCO_3$ (16 g) in H_2O (200 mL). The suspension was extracted with EtOAc (2 × 100 mL), washed with H_2O (2 × 200 mL), and dried (Na_2SO_4). Evaporation of the solvent left an oil (1.27 g), which was freed from residual DMF by chromatography over silica gel (20 g) with CH_2Cl_2–Me_2CO (9:1). Fractions containing **6b** were evaporated, and the residue was freeze-dried from benzene, yielding the title compound (1.12 g, 91%) as an amorphous powder: mp 108–109 °C (sintering at 40 °C); IR (film) ν_{max} 3300, 1665, 1520 (amide), 1785 (β-lactam), 1745, 1205 (ester) 755, 695 (phenyl) cm^{-1}; ^1H NMR (CCl_4, Me_4Si) δ 1.24 (s, CH_3), 1.35 (s, CH_3), 3.43 (s, CH_2CO), 4.28 (s, 3-H), 5.02 (s, $CH_2C_6H_5$), 5.33 (s, 5-H), 6.98 (s, CONH), 7.13 (s, C_6H_5), 7.22 (s, C_6H_5). The product has a deuterium incorporation of 95% as deduced from the ratio of the *m*/*e* 425 and 424 M^+ peaks.

Potassium Salt of 6α-Deuteriobenzylpenicillin (1b). A solution of **6b** (1.275 g, 3 mmol) in a mixture of Me_2CO (120 mL) and H_2O (60 mL) containing $KHCO_3$ (300 mg, 3 mmol) and 10% Pd/C (1.275 g) was subjected to hydrogenolysis at room temperature for 3 h at 3.5 kg/cm^2 of H_2. The catalyst was filtered off and washed with 40 mL of Me_2CO–H_2O (2:1). The filtrate was diluted with H_2O (60 mL), and Me_2CO was removed by concentration at a temperature below 25 °C. The aqueous solution was extracted with EtOAc (120 mL), cooled to 0 °C, covered with

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(18) Compound **4a** has an $[\alpha]^{20}_D$ value of +170° (*c* 0.5, Me_2CO). The value of +204° given in ref 13 is an error.

cold EtOAc (300 mL), and acidified to pH 2.0 with phosphoric acid (20 %). The aqueous layer was extracted again with EtOAc (200 mL). The combined organic layer was washed quickly with water (2 × 100 mL, 0 °C), dried briefly (Na_2SO_4), and filtered. Addition of 3 mL of 1 M potassium 2-ethylhexanoate solution in EtOAc and of anhydrous Me_2CO (50 mL) afforded crystals of **1b** (potassium salt), which were collected and washed with anhydrous Me_2CO (20 mL) to yield 0.687 g (62%) of product: R_f (Me_2CO–HOAc, 19:1) 0.66, (C_6H_6–Me_2CO–HOAc, 75:20:5) 0.63; IR (KBr) ν_{max} 3360, 1670, 1485 (amide), 1780, 1760 (sh, β-lactam) 1615, 1400 (carboxylate), 700 (phenyl) cm^{-1}; ^1H NMR (D_2O, DSSA) δ 1.55 (s, CH_3), 1.58 (s, CH_3), 3.55 (s, CH_2CO), 4.33 (s, 3-H), 4.70 (s, HOD), 5.48 (s, 5-H), 7.25 (s, C_6H_5). Iodometric titration indicated that only 1.7% penicilloic acid was present. Loss on drying (60 °C in vacuo over P_2O_5) was 1.1%.

Epimerization and Deuteration of (Phenoxymethyl)penicillin (*S*)-*S*-Oxide Benzyl Ester (7a) and of Its 6-Epimer (8a). The progress of the epimerization of **7a** and **8a** and the percentage decomposition of these penicillin *S*-oxides were followed by high-pressure LC using a 250 × 4.6 mm LiChrosorb RP-18 (10 μm) column with CH_3OH–H_2O (70:30) as the mobile phase at a flow rate of 2.5 mL/min and UV detection at 254 nm. Molar ratios of **7a** (or **8a**), D_2O, and Et_3N were identical with those described for the isomerization of **4a**. The penicillin *S*-oxide esters **7a** or **8a** (228 mg, 0.5 mmol) were dissolved in a stock solution (2.3 mL), consisting of CH_3CN (50 mL), D_2O (5.63 mL), Et_3N (1.75 mL), and naphthalene (500 mg) as internal standard. The solution was kept at room temperature and at regular intervals 10-μL samples were taken, diluted with MeOH (1 mL), and analyzed by high-pressure LC. The percentage of epimerization was calculated from the **7**/**8** ratio, which was obtained from the peak areas of **7** (k' = 4.8) and **8** (k' = 2.9). A ratio of 40:60 was considered as a 100% epimerization. The percentage degradation of **7** and **8** was calculated from their peak areas and from that of the internal standard (k' = 11). For the determination of the percentage deuteration as a function of the reaction time, 1-mmol samples of **7a** and **8a** were epimerized under the conditions mentioned for **4a**. For reaction times up to 24 h the epimerization mixture was worked up as described for **4a** and both isomers were separated by crystallization from MeOH and C_6H_6. Crystalline **7** and **8** were analyzed for deuterium at C-6 by ^1H NMR spectroscopy. In the case of reaction times exceeding 24 h, chromatography on a silica gel column with C_6H_6–Me_2CO (90:10) was used for separation of **7** and **8**. The percentages of epimerization and degradation were calculated from the amounts of both isomers, isolated after column chromatography.

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Registry No. 1b, 76757-86-3; **2a**, 24652-72-0; **2a** *N*-*d* derivative, 76773-02-9; **3a**, 41536-91-8; **4a**, 54275-92-2; **4b**, 76757-87-4; **5a**, 73036-92-7; **5b**, 76757-88-5; **6b**, 76757-89-6; **7a**, 42879-04-9; **8a**, 42879-05-0.

Syntheses of Amine Derivatives of Phencyclidine

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3-Aminophencyclidine (**5**) was synthesized by reduction of 3-nitrophencyclidine (**3**) using either H_2 with Pd/C or Na_2S in refluxing methanol. Attempts to isolate 4-aminophencyclidine (**2**), which we hoped to synthesize by hydrolysis of carbamate **15** which was isolated after reaction of amide **10** under Hofmann conditions employing bromine in CH_3O^-/CH_3OH at −40 °C, were unsuccessful. 4-Aminomethylphencyclidine (**18**) was synthesized by LAH reduction of nitrile **13** as well as by reductive amination of aldehyde **20**. Nitrile **13** and aldehyde **20** were synthesized from 4-bromophencyclidine (**11**) as was alcohol **26** which served as a precursor to 4-(2-aminoethyl)phencyclidine (**19**). Amine **19** was also synthesized by $NaBH_4$ reduction of β-nitrostyrene **29** which was generated from aldehyde **20** by condensation with nitromethane using 1,5-diazabicycloundecene as the base catalyst followed by LAH reduction of the resulting 4-(2-nitroethyl)phencyclidine (**30**). Mass spectra and ^{13}C NMR spectra have been obtained on most of the phencyclidine derivatives.

As part of a fluorescence immunoassay for phencyclidine (1-(1-phenylcyclohexyl)piperidine (**1**), we required derivatives of **1** which would be sufficiently nucleophilic that they could be covalently coupled to appropriate fluorescent dyes and proteins. Although many phencyclidine analogues have been synthesized,[1] the general procedure used to make most of them precludes incorporation of functional groups, such as primary amines, which contain acidic protons. Recently however 1-[1-(4-aminophenyl)cyclohexyl]piperidine (**4**) was reported[2] to have been prepared by reduction of a nitro phencyclidine, thought to be **2**, which was obtained after nitration of **1** (eq 1). We[3] have repeated this work and find the major product resulting from nitration of **1**, under a variety of conditions, is 3-nitrophencyclidine (**3**) as would be expected from the nitration of a benzylamine.[4] Isomer **2** could be isolated by preparative high-performance LC as a minor product

(1) (a) A. Kalir, H. Edery, Z. Pelah, D. Bolderman, and G. Porath, *J. Med. Chem.*, **12**, 473 (1969), and references cited therein. (b) V. H. Maddox, E. F. Godefroi, and R. F. Parcell, *J. Med. Chem.*, *8*, 230 (1965). For more recent approaches to phencyclidine-type systems see A. Gabrielevitz et al., *Life Sci.*, **26**, 89 (1980).

(2) A. Kalir, S. Maayani, M. Rehavi, R. Elkavets, I. Pri-Bar, O. Buchman, and M. Sokolovsky, *Eur. J. Med. Chem.*, **13**, 17 (1978).

(3) While our work was being completed another group also isolated and characterized **2** and **3**. See P. Geneste, J-M. Kamenka, and A. Mas, *Bull. Soc. Chem. Fr.*, 609 (1978).

(4) H. M. Gilow et al., *J. Org. Chem.*, **36**, 1745 (1971).

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