Reaction of 3-Anilino-2-phenylphthalimidine (21a) with 2a. A mixture of **21a** (0.5 g, 0.0017 mol) and **2a** (0.5 g, 0.004 mol) was heated at 100° for 3 hr. Then the resulting mixture was chilled by ether, and filteration gave 0.6 g (86%) of **10a.**

Reaction of Ethylphthalaldehydate (23) with 4a. A mixture of **23** (5.34 g, 0.03 mol) and **4a** (2.8 g, 0.03 mol) in benzene (50 ml) was refluxed for 6 hr using a Dean-Stark trap. After removal of solvent, the residue was distilled under reduced pressure to afford 6.30 g (83%) of *o*-carbetoxybenzylideneaniline (**24**), bp 159° (2 mm): ir (Neat) 1720 (C=O), 1620 (C=N), 1260 (-CO_2-) cm^{-1}; nmr (CCl_4) δ 1.38 (t, 3, CH_3), 4.33 (q, 2, CH_2), 7.05–8.5 (m, 9, aromatic protons), 9.25 (s, 1, CH=N);* mass spectrum (70 eV) *m/e* 253 (M^+), 224, 208, 280.

Anal. Calcd for $C_{16}H_{15}O_2N$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.94; H, 5.90; N, 5.59.

The residue after distillation was chromatographed on alumina to afford 0.63 g (7%) of **21a,** mp 160–161° (lit.[6] 162°).

Reaction of 24 with 4a. A mixture of **24** (3.0 g, 0.012 mol) and **4a** (1.12 g, 0.012 mol) was heated at 100° for 10 hr. Then the resulting mixture was chromatographed on alumina to afford 2.3 g (64%) of **21a.**

Reaction of 24 with *o*-Toluidine (4b). The reaction between **24** (3.0 g, 0.012 mol) and **4b** (1.29, 0.012 mol) was carried out in a similar manner as described for the reaction of **24** with **4a.** After similar work-up, the yield of 2-phenyl-3-(*o*-toluidino)phthalimidine (**21b**) was 3.75 g (*ca.* 100%), mp 167–168°: ir (Nujol) 3390 (NH), 1700 (C=O) cm^{-1}; nmr ($CDCl_3$) δ 1.90 (s, 3, CH_3), 5.90–7.95 (m, 15).

Anal. Calcd for $C_{21}H_{18}ON_2$: C, 80.23; H, 5.77; N, 8.91. Found: C, 80.14; H, 5.62; N, 8.91.

Base-Catalyzed Methanolysis of 24. A solution of **24** ((3.00 g, 0.0012 mol) in absolute methanol was refluxed for 6 hr in the presence of sodium methoxide (0.3 g). After removal of solvent, the residue was extracted with ethylacetate, washed with water, and dried over sodium sulfate. The ethylacetate layer gave 2.35 g (82%) of **15a.**

Base-Catalyzed Ethanolysis of 24. A solution of **24** (3.0 g, 0.0012 mol) in ethanol was treated in the presence of sodium ethoxide (0.3 g) in a similar manner as the above. After similar work-up, the yield of **15b** was 1.70 g (56%).

Acknowledgment. We wish to thank Dr. K. Fujita and Dr. T. Hirose, JEOL Co, for C-13 nmr spectrum analysis.

Registry No.—**1a,** 16780-82-8; **1b,** 52920-19-1; **2a,** 103-71-9; **2b,** 621-29-4; **2c,** 86-84-0; **2d,** 2243-54-1; **3a,** 36149-34-5; **3b,** 53778-18-0; **3c,** 53779-19-1; **3d,** 53778-20-4; **3e,** 52920-23-7; **4a,** 62-53-3; **4b,** 621-29-4; **8,** 119-67-5; **9a,** 18167-15-2; **10a,** 52920-24-8; **10b,** 52920-27-1; **15a,** 52920-25-9; **15b,** 25770-48-3; **21a,** 19339-69-6; **21b,** 52920-26-0; **23,** 34046-43-0; **24,** 52920-28-2; 2-phenylphthalimidine, 5388-42-1.

Supplementary Material Available. Full carbon-13 nmr data for compounds 2-phenylphthalimidine, 2,3-diphenylphthalimidine, and 2-phenyl-2-(*p*-tolyl)phthalimidine will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the paters in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-74-3924.

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(3) See paragraph at end of paper regarding supplementary material.
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(9) Melting points are uncorrected. The infrared spectra were recorded on a JASCO-IR-E spectrometer. Nmr spectra were taken on JNM-C-60HL and JNM-PS/PFT-100 spectrometers; chemical shifts are expressed in parts per million (δ) down field from TMS as an internal standard. The mass spectra were obtained by HITACHI-RMU-6E spectrometer.
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Acylation of Amino Acid Schiff Bases

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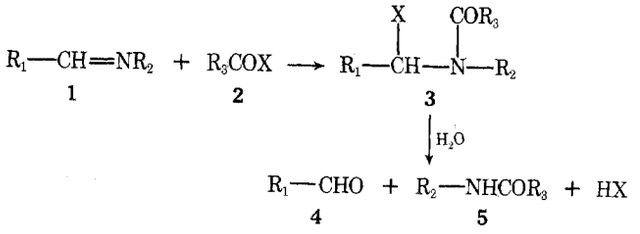
Acylating agents react with amino acid Schiff bases to form intermediates that can be hydrolyzed to acylated amino acids or dipeptides. This procedure offers a new method for preparing semisynthetic penicillins.

Previously, we had found it advantageous to isolate and purify 6-aminopenicillanic acid (6-APA), the basic intermediate for the production of semisynthetic penicillins, as its Schiff base.[1] We now wish to report that it is possible to acylate the Schiff base directly to form the desired penicillin derivative without the necessity of generating the free amino acid for use as the starting material.

It has long been known that the Schiff bases of amines (**1**) could readily be acylated with acid halides (**2**) or anhydrides.[2] The reaction involves an addition across the —CH=N bond to form a stable compound (**3**). Subsequent hydrolysis of the acid halide adduct yields the simple acylation product (**5**) of the original amine.



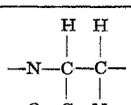
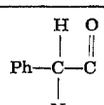
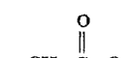
We have directed our studies toward the acylation of the Schiff bases of 6-APA salts and esters. The syntheses of penicillin V (**7a**) and its methyl ester (**7b**) were investi-

Table I
Nmr Data (ppm)[a]

Compd	Solvent	ArCH=N	PhCHCO	OCH_3	NHCH or $NHCH_2$ or $NHCH_3$	CH_2
10	$CDCl_3$	8.22	4.96	3.82	2.82 d (J_{NHCH_3} = 5.0)	
	C_6D_6	7.72	4.88	3.28	2.46 d (J_{NHCH_3} = 5.0)	
	CCl_4	8.11	4.83	3.78	2.80 d (J_{NHCH_3} = 5.0)	
14	$CDCl_3$	8.20	4.93	3.66	4.90 m	3.00
15	DMSO-d_6					
	NH_3^+ = 8.83 b		5.02 b	3.65	4.51 m	2.89
	NH = 9.12 d (J_{NHCH} = 8.0)					

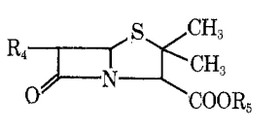
[a] b = broad; d = doublet; m = multiplet.

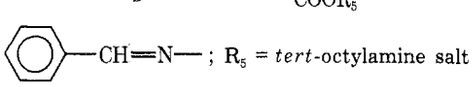
Table II
Nmr Spectrum of Intermediates[a]

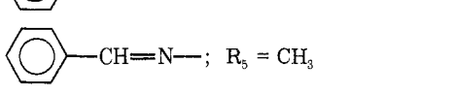
Compd	ArCH=N				CH_3O-	-CH_2	-CH_3
16	8.28	5.54 d (J = 4.0)				1.55	1.40
		5.63 q (J = 9.0, 4.0)	5.02	4.30		1.60	0.98
17	8.22	5.53 d (J = 4.0)				1.55	1.40
		5.63 q (J = 9.0, 4.0)	4.94	4.30	3.84	1.63	1.00

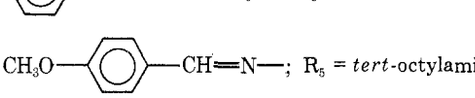
[a] Determined in $CDCl_3$.

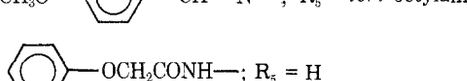
gated, utilizing compounds **6a** and **6b** as substrates for the acylation studies.

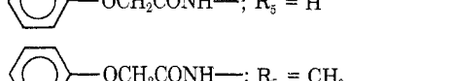


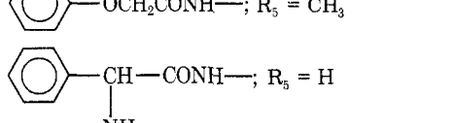
6a, R_4 =  ; R_5 = *tert*-octylamine salt

b, R_4 =  ; R_5 = CH_3

c, R_4 = CH_3O-  ; R_5 = *tert*-octylamine salt

7a, R_4 =  ; R_5 = H

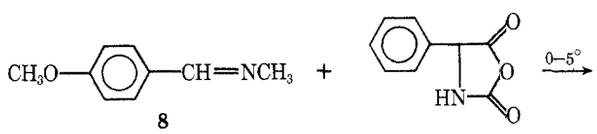
b, R_4 =  ; R_5 = CH_3

c, R_4 =  ; R_5 = H

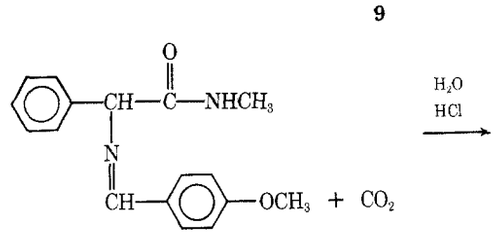
Upon fractional addition of phenoxyacetyl chloride to a cold solution of **6a** in $CDCl_3$, nmr and ir data showed the disappearance of the —CH=N double bond without the formation of an aldehyde. Free 6-APA was not formed in the reaction under anhydrous conditions, but was readily precipitated upon the addition of water to the reaction mixture. After the addition of approximately 1 equiv of acid chloride, the addition of a sodium 2-ethylhexanoate solution in anhydrous methyl isobutyl ketone did not produce the sodium salt of penicillin V. However, after hydrolysis of the intermediate with water, sodium penicillin V crystallized readily.

That the acid chloride did not form a mixed anhydride with the Schiff base carboxyl group that could act as the acylating agent for the 6-APA generated by the addition of water was demonstrated in the following manner: the methyl ester (**6b**) was treated with 1 equiv of phenoxyacetyl chloride in dry $CHCl_3$ at 0° for 35 min; after hydrolysis with dilute acid, an almost quantitative yield of penicillin V methyl ester (**7b**) was obtained. When the reaction was conducted in dry $CDCl_3$ and monitored by nmr, the imine proton absorption at δ 8.55 disappeared, apparently shifted upfield into the complex aromatic region, and no aldehyde proton absorption appeared at a lower field. Other acid chlorides (α-chlorophenacetyl, α-azidophenacetyl) reacted similarly.

However, *ampicillin* (**7c**) *could not be isolated from the* reaction of D-phenylglycyl chloride hydrochloride with the Schiff bases. Therefore, to prepare penicillins of this type by use of this principle, other reactions were considered. *N*-Carboxy-D-phenylglycine anhydride (NCA) has been used to prepare **7c** from 6-APA.[3] This reagent reacted with *p*-*N*-anisylidenemethylamine (**8**) in the following manner.



8 **9**



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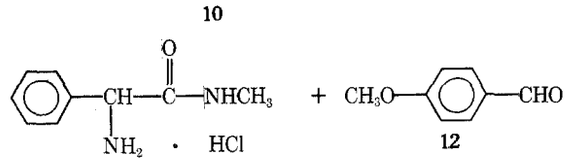
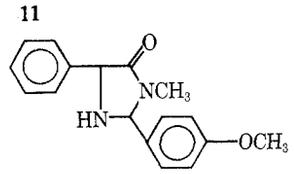


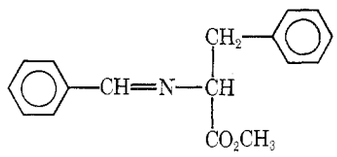
11 **12**



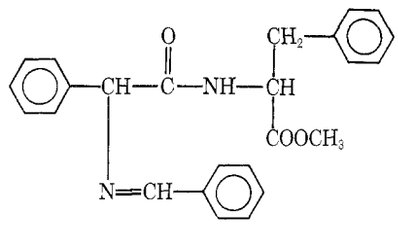
10a

The reaction was usually conducted at about 0–10° in $CDCl_3$ and followed spectrophotometrically in an nmr tube. The nmr data (Table I) (various solvents) indicated the formation of product **10**, and there was no evidence for the existence of the theoretical intermediate **10a**. Products **10** and **11** (*via* hydrolysis of **10**) were isolated and their structures were confirmed by elemental analysis.

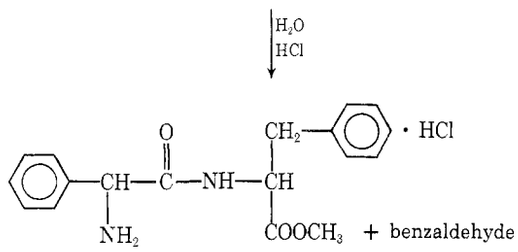
NCA (**9**) reacted with the benzylidene Schiff base of L-phenylalanine methyl ester (**13**) to give the Schiff base of the dipeptide (**14**) in good yield. Hydrolysis of **14** afforded the amino acid derivative (**15**).



13

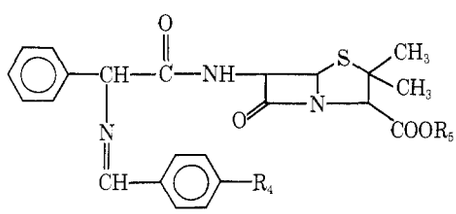


14



15

The benzylidene (**6a**) and anisylidene (**6c**) Schiff base salts of 6-APA were found to react similarly with NCA, giving an intermediate Schiff base that could be hydrolyzed to ampicillin (**7c**). The structures of the intermediates (**16** and **17**) were assigned on the basis of nmr data for the reactants and the intermediates (Table II).



16, $R_4 = H$; R_5 = *tert*-octylamine salt

17, $R_4 = OCH_3$; R_5 = *tert*-octylamine salt

Thus, these procedures offer a general method for preparing semisynthetic penicillins from an intermediate Schiff base of 6-APA.[4] The reaction of NCA with the Schiff bases of amino acids may be useful in decreasing the polymeric reactions that often occur with this type of acylating reagent.[5]

Experimental Section

Melting points were taken on a Fisher-Johns apparatus and are uncorrected. Nmr spectra were obtained by means of a Varian Associates A-60 spectrometer, using tetramethylsilane as the internal standard, and the data were reported as δ units. Mass spectra were determined on a MS-902 spectrometer.

Penicillin V (7a). A stirred slurry of **6a** (2.0 g, 4.6 mmol) in $CDCl_3$ (26 ml) was treated dropwise at 0–3° with a solution of phenoxyacetyl chloride (0.35 ml) in $CDCl_3$ (2 ml) over a period of 5 min. After an additional 7 min of reaction at 1–3°, the solution was sampled for ir and nmr assays (see text). A second portion of phenoxyacetyl chloride (0.35 ml in 2 ml of $CDCl_3$) was added and sampled again after 5 min. The ir curve of this material, when compared with the first spectrum, showed the disappearance of the —CH=N bond at 1640 cm^{-1}; there was no aldehyde present (ir and nmr). When a portion of the reaction solution (5 ml) was treated with 1.0 *N* sodium ethylhexanoate solution in methyl isobutyl ketone (1 ml), no precipitation occurred during a 4-hr period. When the cold reaction solution (10 ml) was agitated with D_2O (5 ml), an nmr spectrum of the organic phase showed an aldehyde peak. THE $CDCl_3$ layer was then mixed with 1.0 *N* sodium ethylhexanoate solution (2 ml) and, after 1.5 hr, sodium penicillin V (500 mg) was collected by filtration. Acidification afforded **7a**, identical with an authentic sample (ir and nmr).

Penicillin V, Methyl Ester (7b). A solution of **6b**[6] (510 mg, 1.5 mmol) in dry $CHCl_3$ (10 ml) was cooled to 0° and treated with phenoxyacetyl chloride (257 mg, 1.5 mmol) with stirring. A sample taken for ir indicated the disappearance of the imine band at 1640 cm^{-1}. After 35 min, the reaction mixture was poured into 0.1 *N* HCl (50 ml) and extracted with EtOAc (75 ml). The organic layer was washed twice with H_2O (50 ml) and with saturated NaCl solution (50 ml), dried ($MgSO_4$), and evaporated to dryness *in vacuo* to give **7b** (528 mg oil, 92% yield, ir identical with that of an authentic sample).

Reaction of *N*-Anisylidene Methylamine (8) with NCA (9). A stirred solution of **8**[7] (3.4 g, 23 mmol) in CH_2Cl_2 (100 ml) was cooled to 1–3° and treated, portionwise, with **9** (4 g, 23 mmol) over a 1-hr period. After 5.5 hr at that temperature, the mixture was treated with benzene (100 ml) and the CH_2Cl_2 was removed *in vacuo*. The benzene solution was lyophilized to give a semicrystalline solid (**10**, 6.9 g) that was washed with hexane and crystallized from ether to afford the analytical sample: mp 93°; mass spectrum M^+ 282 (calcd 282.3).

Anal. Calcd for $C_{17}H_{18}N_2O_2$: C, 72.31; H, 6.44; N, 9.92. Found: C, 72.55; H, 6.54; N, 10.02.

The Schiff base appeared stable to water but, with dilute HCl in acetone, could be hydrolyzed to **11**, mp 239–240°.

Anal. Calcd for $C_9H_{13}ClN_2O$: C, 53.86; H, 6.54; N, 13.96; Cl, 17.66. Found: C, 53.90; H, 6.49; N, 13.77; Cl, 17.96.

***N*-Benzylidene Phenylalanine, Methyl Ester (13).** A stirred solution of L-phenylalanine methyl ester·HCl (8.6 g, 40 mmol) in H_2O (100 ml) was treated with a 40% NaOH solution to adjust the pH to 7.5. The solution was then treated with benzaldehyde (5.2 ml, 51 mmol) and the pH was maintained with NaOH at 6.5–7.0 for 3 hr. The oil that separated initially during the reaction crystallized and was collected by filtration to give **13** (8.8 g). Recrystallization of **13** from hexane gave the analytical sample, mp 52–53°.

Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.31; H, 6.42; N, 5.24. Found: C, 76.54; H, 6.40; N, 5.22.

Schiff bases of amino acids have been difficult to isolate because of the equilibrium formed during their preparation.[8] Direct isolation from H_2O, rather than from organic solvents, is made possible by the insolubility of **13**.

Phenylglycylphenylalanine, Methyl Ester Hydrochloride (15). A stirred solution of **13** (5 g, 18.7 mmol) in CH_2Cl_2 (125 ml) was treated at 0–3° with **9** (3.6 g, 20.3 mmol) over a 20-min period. The mixture was stirred at 1–3° overnight, filtered, and then treated with H_2O (30 ml). The CH_2Cl_2 was removed *in vacuo* and the resulting gummy precipitate crystallized on standing. The solid was collected by filtration and washed with hexane to give **14** (mp 80–82°).

Anal. Calcd for $C_{25}H_{24}N_2O_3$: C, 74.97; H, 6.05; N, 7.00. Found: C, 74.03; H, 5.97; N, 7.29.

Hydrolysis of **14** (1.0 g) was carried out at pH 1.0 in a mixture of CH_2Cl_2 (10 ml) and H_2O (2 ml). The crude salt (**15**, 0.5 g) was collected by filtration and crystallized from *i*-PrOH to give the analytical sample, mp 218°.

Anal. Calcd for $C_{18}H_{21}ClN_2O_3$: C, 61.97; H, 6.08; N, 8.03; Cl, 10.16. Found: C, 61.75; H, 6.11; N, 7.87; Cl, 10.11.

Ampicillin (7c). A stirred slurry of **6c** (5 g, 10.8 mmol) in CH_2Cl_2 (50 ml) was cooled to 1–3° and treated with CF_3CO_2H (0.4 ml, 5.3 mmol), followed by the portionwise addition of **9** (2.1 g, 11.8 mmol) over a 20-min period. After 2 hr at this temperature, the mixture was treated with H_2O (50 ml) and agitated at pH 5.0–5.2 for 3 min. The Schiff base (**16**) could be isolated (3.3 g) from the

aqueous phase by neutralizing the solution with *tert*-octylamine to pH 7.5 and adding benzaldehyde (0.7 ml).

Anal. Calcd for $C_{31}H_{42}N_4O_4S$: S, 5.65; N, 9.9. Found: S, 5.36; N, 9.7.

The Schiff base **16** (3.2 g) was washed with toluene (5 ml) and dissolved in a mixture of H_2O (7 ml) and methyl isobutyl ketone (7 ml), then the pH was adjusted to 1.5 with HCl. The pH was adjusted once more to 4.9 with NaOH, and the precipitate was collected by filtration and air dried to afford **7c** (950 mg, as its trihydrate). The ir and nmr spectra were identical with those of an authentic sample.

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Registry No.—**6a,** 53059-76-0; **6b,** 37628-54-9; **6c,** 53059-78-2; **7a,** 87-08-1; **7b,** 20109-75-5; **7c,** 69-53-4; **8,** 13114-23-3; **9,** 3412-73-5; **10,** 53059-79-3; **11,** 53059-80-6; **13,** 40216-77-1; **14,** 53128-97-5; **15,** 53059-81-7; **16,** 53129-37-6; **17,** 53176-74-2; phenoxyacetyl chloride, 701-99-5; L-phenylalanine methyl ester hydrochloride, 7524-50-7; benzaldehyde, 100-52-7.

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The Stieglitz Rearrangement with Lead Tetraacetate and Triarylmethylamines

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The results of the lead tetraacetate induced Stieglitz rearrangement with various mono-*para*-substituted triarylmethylamines are presented. Migratory aptitudes have been determined. In addition the results of trapping experiments are also given. A concerted mechanism is postulated consistent with all the data.

A common feature of the Curtius–Hofmann–Lossen and the lead tetraacetate-induced rearrangement of carboxylic acid amides is the migration of a group to a potentially electron-deficient nitrogen to yield an isocyanate (eq 1).[1]

$$R{-}\underset{\underset{O}{\|}}{C}{-}\ddot{N}{-}Y \longrightarrow O{=}C{=}\ddot{N}{-}R + :Y \qquad (1)$$

$Y = N_2,\ Cl^-,\ {}^-O_2CR,\ Pb(OAc)_2$

The four rearrangements differ in their departing groups. The similarity to the Stieglitz rearrangement and its variations[2] with N-substituted amines is striking (eq 2). A recent preliminary paper[3] extended the likeness when a lead tetraacetate induced Stieglitz rearrangement was reported on triphenylmethylamine (eq 2, Y = $Pb(OAc)_2$) (eq 3).

$$R_3C{-}\ddot{N}{-}Y \longrightarrow R_2C{=}\ddot{N}{-}R + Y: \qquad (2)$$

$Y = N_2,\ Cl^-,\ O{=}PCl_3$

$$Ph_3CNH_2 \xrightarrow[\Delta]{LTA,\ C_6H_6} PhN{=}CPh_2 + HOAc + Pb(OAc)_2 \qquad (3)$$

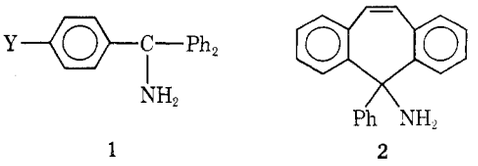
(85–90%)

On the basis of trapping experiments, electronic properties of the migrating group and kinetic isotope effects a concerted mechanism is strongly indicated[4] for the former rearrangements (eq 1). With respect to the Stieglitz rearrangements the situation is less clear. Migratory aptitudes spanning a range of 9 for the *p*-anisyl group to 0.4 for the *p*-nitrophenyl group argued in favor of a concerted pathway for the phosphorus pentachloride induced rearrangement of mono-para-substituted trityl-*N*-hydroxylamines.[5] Solely as a result of the statistical distribution of products obtained from phenyl and *p*-halophenyl migration in the base-induced Stieglitz rearrangement with *p*-halotrityl-*N*-haloamines, and the lack of rearrangement of *N*-methyl-*N*-chlorotritylamine, Stieglitz proposed a nitrene intermediate. Abramovitch[6] offers evidence that the thermolysis of tertiary alkyl azides gives rise to a singlet nitrene and their photochemical decomposition does not involve nitrenes.[7] Both conclusions are in opposition to those of Saunders.[8]

This paper attempts to elucidate the intermediate in the lead tetraacetate induced Stieglitz rearrangement from the results of migratory aptitude studies and trapping experiments.

Results

The mono-para-substituted triphenylmethylamines **1a–c** were prepared from the corresponding alcohols by converting them to the azides followed by lithium aluminum hydride ($LiAlH_4$) reduction. The amines **1d** and **1e** were synthesized by ammonolysis of the corresponding halides. The amine **2** was prepared from the alcohol by conversion to the azide followed by reduction with $LiAlH_4$.



1 **2**

a, Y = H; **b**, Y = Cl; **c**, Y = CH_3; **d**, Y = OCH_3; **e**, Y = NO_2

Treatment of the amines **1a–e** with acetic acid free lead tetraacetate (LTA) in refluxing benzene under nitrogen led to a rapid consumption of LTA (15–20 min as monitored by starch–iodide test paper). The product mixture in each case was obtained in close to quantitative yield (90–95%).