21367-60-2; **15**, 21367-61-3; **16**, 21367-62-4; **17**, 21367-63-5; **18**, 21367-64-6; **19**, 21367-65-7; **20**, 21367-66-8; **21**, 21449-60-5; **22**, 21367-67-9; **23**, 21367-68-0; 1-(diethylacetyl)-4-4-diethylpyrazolidine-3,5-dione, 21367-56-6.

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Notes

The Condensation of Succinic Anhydride with Benzylidinemethylamine. A Stereoselective Synthesis of *trans*- and *cis*-1-Methyl-4-carboxy-5-phenyl-2-pyrrolidinone

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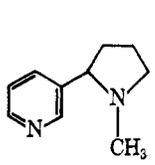
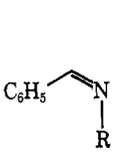
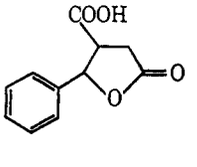
Our interest in examining structural parameters associated with the peripheral and central activities of the tobacco alkaloid nicotine (**1**) has led to a consideration of potentially versatile synthetic routes to substituted 2-arylpyrrolidines. As part of this program, we wish to report our studies on the condensation of benzylidinemethylamine (**2**) with succinic anhydride. By analogy with the Perkin condensation[1] of benzaldehyde and succinic anhydride to form the phenylparaconic acid (**3**), this reaction would be expected to yield the carboxypyrrolidinone system (**4**) and thus provide a facile entry to uniquely substituted nicotine analogs.



1



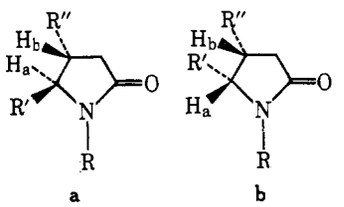
2, R = CH_3
12, R = C_6H_5



3

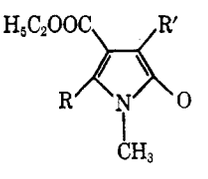
The spectral data of the crude isolate obtained from this reaction corresponded to the lactam system, **4**. Fractional crystallization separated the reaction product into two $C_{12}H_{13}NO_3$ acids, A (major) and B (minor). The nmr spectra of the two isomers can be readily interpreted in terms of the *trans*- and *cis*-carboxypyrrolidinones, **4a** and **4b**, respectively. A doublet centered near 5.0 ppm in both spectra is attributed to proton H_a based on its coupling with H_b and by analogy with the corresponding assignments reported for related 5-substituted-2-pyrrolidinones.[2] From the estimated dihedral angles, H_{a-b} (120°, *trans* isomer, and 0°, *cis* isomer), and the Karplus relationship,[3] the coupling constants, J_{a-b} (5 Hz, isomer A, and 9 Hz, isomer B) support the assignments of compound A as the *trans* isomer, **4a**, and compound B as the *cis* isomer, **4b**. Similar stereochemical conclusions were recently reported for the related 4-aryl-5-ethoxycarbonyl-2-pyrrolidinone system, **5**.[2b,c] Protons $H_{b,c,d}$ of **4a** form a complex multiplet centered near 3.4 ppm while the corresponding signals for **4b** are separated into three quartets; the lowest field quartet (3.85 ppm) can be assigned to H_b since irradiation of the low field doublet (due to H_a) caused the quartet to collapse to a triplet (J = 9 Hz).

Confirmation of the above structure assignments was obtained by an independent synthesis of the *cis* acid. The condensation[4] of diethyl oxalacetate with benzaldehyde and methylamine gave the pyrrolinone, **6**. Attempted borohydride and catalytic reductions of **6**

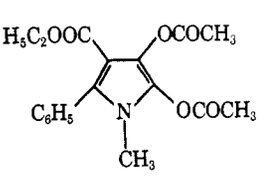


a **b**

4, R = CH_3; R′ = C_6H_5; R″ = COOH
5, R = H; R′ = $COOC_2H_5$; R″ = Aryl
8, R = CH_3; R′ = H; R″ = $COOC_2H_5$
11, R = CH_3; R′ = C_6H_5; R″ = $COOC_2H_5$
14, R = R′ = C_6H_5; R″ = COOH



6, R = C_6H_5; R′ = OH
7, R = H; R′ = $OCOCH_3$
9, R = C_6H_5; R′ = $OCOCH_3$



10

(1) M. Anteunis, *Bull. Soc. Chem. Belges.*, **69**, 356 (1960).

(2) (a) A. M. Duffield, H. Budzikiewicz, and Carl Djerassi, *J. Amer. Chem. Soc.*, **87**, 2026 (1965); (b) F. Zymalkowski and P. Pachaly, *Chem. Ber.*, **100**, 1137 (1967); (c) P. Pachaly, *ibid.*, **101**, 2176 (1968).

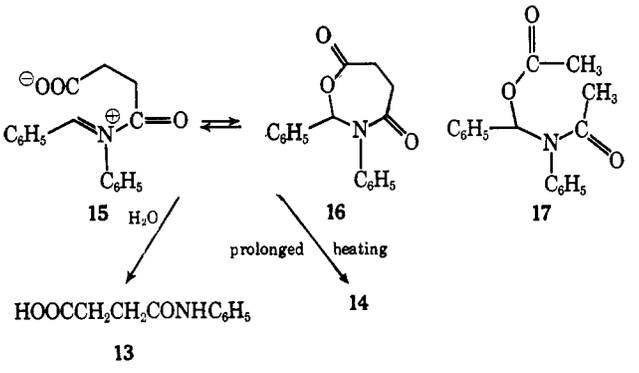
(3) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).

(4) J. R. Merchant and V. Srinivasan, *Rec. Trav. Chim. Pays-Bas*, **81**, 144 (1962).

afforded only unreacted starting material. The related enol acetate, **7**, has been reported to undergo catalytic reduction to the pyrrolidinone, **8**.[5] Therefore, overnight acetylation of **6** in acetic anhydride and pyridine was attempted. The product obtained was not the expected enol acetate, **9**, but rather a compound analyzing for a diacetate. The nmr spectrum revealed signals for two singlet methyl groups in addition to that of the N-methyl group. The only structure consistent with the above data is the pentasubstituted pyrrole, **10**, which presumably was formed by acetylation of the desired enol acetate. When the acetylation period was limited to 20 min, **9** was isolated in high yield and could be successfully reduced to one of the two possible isomeric esters, **11**. The nmr signals for the methyl and methylene protons of the ester function occurred at unusually high fields, 0.90 ppm and 3.68 ppm, respectively, indicating the *cis* configuration, **11b**, for the reduction product since, according to molecular models, these protons should be shielded by the aromatic cloud. As predicted also from molecular models, the corresponding signals of the *trans* ester, **11a**, prepared from **4a**, occurred at normal fields, 1.28 ppm for the methyl triplet and 4.22 ppm for the methylene quartet. Saponification of the ester isolated from the above reduction yielded an acid identical in all respects with the *cis* acid, **4b**, obtained from the succinic anhydride–benzylidinemethylamine condensation.

A review of the literature revealed that the condensation of succinic anhydride with benzylidineaniline (**12**) is reported to yield N-phenylsuccinamic acid (**13**).[6] However, when subjected to the reaction conditions employed in our study, a mixture of the isomeric pyrrolidinones, **14**, was obtained from which the *trans* isomer, **14a**, was isolated in pure form. The structure of **14a** followed directly from its nmr spectrum which showed a doublet at 4.58 ppm characteristic of the C_5 methine proton.

These different experimental results can be rationalized by assuming a common intermediate, the charged species **15**, which would be stabilized by cyclization to the lactone, **16**. Such an intermediate might survive



mild conditions and subsequently undergo hydrolysis to the succinamic acid and benzaldehyde. However, when subjected to the prolonged heating used in our studies, this same intermediate could undergo rearrangement to form the pyrrolidinones. In support of this proposal is the report that benzylidineaniline (**12**) and acetic anhydride form the acetoxy derivative, **17**, which is analogous to the proposed cyclic intermediate, **16**.[7] Additionally, charged structures similar to **15** have been proposed for reaction products if imines and maleic anhydride.[8] Such a reaction pathway differs markedly from the mechanism commonly accepted for the Perkin condensation.[9] Further studies on this reaction are currently in progress.

Experimental Section[10]

***trans*- and *cis*-1-Methyl-4-carboxy-5-phenyl-2-pyrrolidinones (4a and 4b).**—Benzylidinemethylamine[11] (11.9 g, 100 mmol), bp 102° (30 mm), nmr δ 3.45 ppm d (J = 1.5 Hz, NCH_3), 8.37 q (J = 1.5, $NCHC_6H_5$), and succinic anhydride (11.0 g, 100 mmol) were heated at reflux in 200 ml of anhydrous benzene for 36 hr. The slightly yellow reaction mixture was extracted with aqueous bicarbonate; the combined extracts were washed with benzene and hexane and then filtered. Upon acidification with phosphoric acid to pH 2 an oil separated which crystallized slowly on standing at 5° to give 16.3 g (71.2%) of crude product melting at 108–185°. Concentration of the aqueous layer to $^1/_2$ its original volume yielded an additional 2.4 g. The over-all yield of the mixture of acids was 18.7 g (82.5%).

Crystallization of the crude acid (10.0 g) from acetone gave 1.6 g of the *cis* acid, **4b**, which after recrystallization from acetone was analytically pure: mp 244–245°; ir (Nujol) 3300–2500 cm^{-1} (OH), 1740 (carboxyl C=O), 1660 (lactam C=O); nmr (deuteriopyridine) δ 2.72 ppm q (J = 9 Hz, C_3H), 2.72 s (NCH_3), 3.43 q (J = 9, C_3H), 3.85 q (J = 9, H_b), 4.97 d (J = 9, H_a), 7.30 m (C_6H_5).

Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.75; H, 5.98; N, 6.39; NE, 219. Found: C, 65.64; H, 5.90; N, 6.45; NE, 217.

The above mother liquors were concentrated to dryness and the residue crystallized twice from water to yield 5.2 g *trans* acid, **4a**: mp 127–128°; ir (Nujol) 3300–2500 cm^{-1} (OH), 1750 (carboxyl C=O), 1680 (lactam C=O); nmr (deuteriopyridine) δ 2.67 ppm s (NCH_3), 3.35 m (CH_2 + H_b), 5.09 d (J = 5, H_a), 7.38 m (C_6H_5).

Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.75; H, 5.93; N, 6.39; NE, 219. Found: C, 65.51; H, 5.93; N, 6.31; NE, 218.

***trans*-1-Methyl-4-ethoxycarbonyl-5-phenyl-2-pyrrolidinone (11a).**—The *trans* acid (1.0 g, 4.56 mmol), absolute ethanol (50 ml), concentrated sulfuric acid (1.0 g), and molecular sieves (2.5 g) were stirred overnight at room temperature. The filtered reaction mixture in chloroform was washed with saturated aqueous bicarbonate and water; the chloroform was dried ($MgSO_4$) and concentrated. The residue was distilled to yield 0.9 g (80%) *trans* ester, **11a**, as a colorless oil: bp 120° (1.5 mm, short path); ir 1750 cm^{-1} (ester C=O), 1700 (lactam C=O); nmr δ 1.28 ppm t (J = 7 Hz, CH_2CH_3), 2.70 s (NCH_3), 2.93 m (CH_2 + H_b), 4.22 q (J = 7, OCH_2CH_3), 4.81 d (J = 5, H_a), 7.39 m (C_6H_5).

Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 67.99; H, 6.82; N, 5.67.

5-Phenyl-4-ethoxycarbonyl-3-hydroxy-3-pyrrolin-2-one (6).—A mixture of benzaldehyde (10.6 g, 100 mmol), 40% aqueous methylamine (7.75 g, 100 mmol), and the sodium salt of diethyl

(5) P. L. Southwick, E. P. Previc, J. Casanova, Jr., and E. H. Carlson, *J. Org. Chem.*, **21**, 1087 (1956).

(6) A. Ludwig and R. I. Georgescu, *Bul. Chim. Soc. Romane Chim.*, **39**, 41 (1937–1938).

(7) (a) H. R. Snyder, D. B. Bright, and J. C. Lorenz, *J. Amer. Chem. Soc.*, **73**, 1836 (1951); (b) A. Burgstahler, *ibid.*, 3021.

(8) J. van Alphen, *Rec. Trav. Chim. Pays-Bas*, **61**, 895 (1942).

(9) Y. Ogata and M. Tsuchida, *J. Org. Chem.*, **24**, 78 (1959).

(10) All reactions were performed under a nitrogen atmosphere and solvents were concentrated on a rotary evaporator under vacuum. Melting points were taken on a Thomas–Hoover apparatus and are uncorrected. Except where noted, infrared spectra were measured in chloroform solution with a Perkin-Elmer Model 337 spectrophotometer and ultraviolet spectra in 95% ethanol with a Cary Model 11 spectrophotometer. Nmr spectra were recorded in the Model A-60A Varian Associates spectrometer using deuteriochloroform as solvent and tetramethylsilane as an internal standard (TMS = 0.0 ppm). Microanalyses were performed by the Microanalytical Laboratory, University of California, Berkeley.

(11) C. K. Ingold and C. W. Shoppe, *J. Chem. Soc.* 1199 (1929).

oxalacetate (21.0 g, 100 mmol) in 100 ml of ethanol was heated at reflux with stirring until solution was complete (about 30 min). The reaction mixture was then added to 1l. of water and the pH adjusted to 2 with dilute phosphoric acid to precipitate 20.0 g (76.7%) of crude product melting at 162–165°. Two recrystallizations from ethanol provided the pure pyrroline, **6**: mp 164–165°; ir 3430 cm^{-1} (OH), 1710 (lactam C=O), 1680 (ester C=O); uv 272 mμ shoulder (ε 10,900), 242 (ε 25,100); (10^{-3} *N* ethanolic NaOH) 307 mμ (ε 23,900), 229 (ε 20,900); nmr δ 1.11 ppm t (*J* = 7 Hz, CH_2CH_3), 2.82 s (NCH_3), 4.17 q (*J* = 7, OCH_2CH_3), 5.06 s ($NCHC_6H_5$), 7.32 m (C_6H_5), 8.50 b (OH, exchanges with D_2O).

Anal. Calcd for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79; N, 5.36. Found: C, 64.53; H, 5.64; N, 5.59.

1-Methyl-2,3-diacetoxy-4-ethoxycarbonyl-5-phenylpyrrole (10).—The hydroxypyrrolinone, **6** (13.1 g, 50 mmol), was stirred overnight at room temperature in 40 ml of acetic anhydride containing anhydrous pyridine (4.0 g, 50 mmol). The reaction mixture was concentrated and the residue dissolved in chloroform which was then washed twice with water. After drying ($MgSO_4$) and removing the solvent, a solid was obtained which was crystallized from benzene to give 12.0 g (70%) of the pyrrole, **10**: mp 122–124°; ir 1780 cm^{-1} (acetoxy C=O), 1710 (ester C=O), uv 273 mμ (ε 7000), 220 mμ shoulder (ε 16,400); nmr δ 1.00 ppm t (*J* = 6 Hz, CH_2CH_3), 2.40 s and 2.42 s ($COCH_3$), 3.97 q (*J* = 7, OCH_2CH_3), 7.30 s (C_6H_5).

Anal. Calcd for $C_{18}H_{19}NO_6$: C, 62.60; H, 5.55; N, 4.06. Found: C, 61.84, 62.89; H, 5.56, 5.91; N, 4.12.

1-Methyl-3-acetoxy-4-ethoxycarbonyl-5-phenyl-3-pyrrolin-2-one (9).—Following the above procedure, only limiting the acetylation period to 20 min, the hydroxypyrrolinone, **6** (13.1 g, 50 mmol), was monoacetylated. The solid obtained after removing the chloroform was washed with ether to yield 14.7 g (97.5%) of crude enol acetate, **9**. Sublimation at 90° (0.05 mm) provided an analytical sample: mp 101–102°; ir 1790 cm^{-1} (acetoxy C=O), 1710 (ester C=O), 1670 (lactam C=O); uv, end absorption; nmr δ 1.10 ppm t (*J* = 7 Hz, CH_2CH_3), 2.32 s ($COCH_3$), 2.73 s (NCH_3), 4.08 m (OCH_2CH_3), 5.13 s ($NCHC_6H_5$), 7.30 m (C_6H_5).

Anal. Calcd for $C_{16}H_{17}NO_5$: C, 63.36; H, 5.65; N, 4.62. Found: C, 63.15; H, 5.99; N, 4.87.

***cis*-1-Methyl-4-ethoxycarbonyl-5-phenyl-2-pyrrolidone (11b).**—Enol acetate **9** (7.5 g, 25 mmol) in 50 ml of glacial acetic acid was hydrogenated at atmospheric pressure over 50 mg of PtO_2 for 15 hr. An additional 50 mg of catalyst was added and hydrogenation continued for 10 hr. The total hydrogen uptake was 40 mmol. Filtration and removal of the solvent gave, after washing with ether, 4.0 g (65%) of crude ester **11b**. Sublimation at 80° (0.05 mm) provided the analytical sample: mp 80–81°; ir 1750 cm^{-1} (ester C=O), 1700 (lactam C=O); nmr δ 0.90 ppm t (*J* = 7 Hz, CH_2CH_3), 2.52 q (*J* = 9, C_3H), 3.11 q (*J* = 9, C_3H), 3.68 m (H_b + OCH_2CH_3), 4.81 d (*J* = 9, H_a), 7.20 m (C_6H_5).

Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 68.02; H, 6.78; N, 5.64.

The above ester (2.0 g, 8.1 mmol) was heated at reflux in 25 ml of 5 *N* HCl containing 10 ml of dioxane. Removal of the solvent and crystallization of the residue from acetone gave 1.6 g (90%) of a solid identical in all respects with the *cis* acid **4b**.

***trans*-1,5-Diphenyl-4-carboxy-2-pyrrolidinone (14a).**—Following the procedure describing the preparation of **4**, benzylidineaniline (18.1 g, 100 mmol) and succinic anhydride (11.0 g, 100 mmol) were heated at reflux in 200 ml of benzene for 36 hr. Cooling and scratching induced crystallization and yielded 20.0 g (71.5%) of crude product melting at 120–158°. Three crystallizations from acetone gave the pure *trans* acid **14a**: mp 179–180° with softening at 166°; ir (Nujol) 2800–2500 cm^{-1} (OH), 1740 (carboxyl C=O), 1670 (lactam C=O); nmr δ 3.07 ppm m (CH_2 + H_b), 5.55 d (*J* = 4 Hz, H_a), 7.25 m (2 C_6H_5).

Anal. Calcd for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37; N, 4.98. Found: C, 72.63; H, 5.02; N, 4.91.

Registry No.—Succinic anhydride, 108-30-5; **2**, 622-29-7; **4a**, 20-178-20-5; **4b**, 20-178-21-6; **6**, 20-178-22-7; **9**, 20-178-23-8; **10**, 20-178-24-9; **11a**, 20-178-25-0; **11b**, 20-178-26-1; **14a**, 20-178-27-2.

N-Acylenamines from Oxazolines. A New Route to 2-Acetamidoglycals

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When acetylated with isopropenyl acetate in the presence of a trace of *p*-toluenesulfonic acid, the two epimeric aldoses, 2-acetamido-2-deoxy-D-glucose and 2-acetamido-2-deoxy-D-mannose, show sharply divergent behavior. The former gives a mixture of the anomeric 1,3,4,6-tetra-*O*-acetyl-2-(*N*-acetylacetamido)-2-deoxy-D-glucopyranoses, together with 2-acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-α-D-glucopyranose.[2] The latter, on the other hand, gives at least five products[3,4] and among these is 3,4,6-tri-*O*-acetyl-2-(*N*-acetylacetamido)-1,2-dideoxy-D-*arabino*-hex-1-enopyranose, obtained in 14% yield; partial deacetylation of this di-*N*-acylenamine gives 2-acetamido-D-glucal (**4**, 2-acetamido-1,2-dideoxy-D-*arabino*-hex-1-enopyranose), the first amino sugar related glycal to be encountered. It was unfortunate that a substance of such potential interest should be available in such low yield from a comparatively expensive aldose, and we now wish to report an alternative and novel synthesis of **4** which makes this unsaturated amino sugar much more readily accessible.

Ozazolines that are derived from 2-acylamino-2-deoxyaldoses, and in which C-1 and C-2 of the sugar moiety are part of the oxazoline ring, have been made by a variety of methods[5–9] and an investigation in this laboratory has recently shown that acetylated oxazolines (such as **1** and **3**) may be prepared quite conveniently by treatment of 2-acylamino-2-deoxyaldoses with a mixture of acetic anhydride and anhydrous zinc chloride.[10] We have now found that the acetylated oxazoline, **1**,[9,11] from 2-acetamido-2-deoxy-D-glucose, readily isomerizes when heated at 100° in tetramethylurea solution containing a trace of *p*-toluenesulfonic acid. Thin layer chromatography of the amorphous product revealed a compound which was unsaturated; on de-*O*-acetylation with sodium methoxide, it gave a crystalline product which proved to be 2-acetamido-D-glucal (**4**). That the immediate product of the isomerization, **2**, had not crystallized was not surprising, since an earlier attempt[3] to obtain this substance in crystalline form had failed. (See Scheme I.)

The acetylated oxazoline derived from 2-acetamido-2-deoxy-D-mannose (**3**)[9,10] also gave **2** and, after de-*O*-

(1) Staff Fellow, National Institutes of Health, 1967–1969.
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