on the sulfonate. Similarly, if the distance is twice that in the starting ester, ρ would be reduced by a factor of $1 - (^1/_2)^2$ or $^3/_4$. These two are reasonable limits for an unassisted ionization, but for major solvent participation, where the positive charge is located largely on the solvent, an extra bond distance is again interposed. The reduction factor now might be $1 - (^1/_2)^3 = ^7/_8$. This factor might also be an upper limit for the ρ for the Menschutkin reaction.

These crude estimates cannot now be refined to a level worthy of the name calculation without better ideas about "attenuation" and about transition-state dimensions. Qualitatively the effect must be there and thus a solvolysis ρ cannot be as large as that for the formation of independent isolated ions. Thus the use of ρ compared to that for equilibrium dissociation to estimate the charge development must give too low an answer, and our earlier prediction is in error. We cannot say whether the charge development in the solvolysis is greater than that in the substitutions on methyl arenesulfonates although other evidence strongly suggests that it is.

Experimental Section

Preparation of Esters and Other Materials. The para-substituted benzenesulfonate esters were prepared by using a modification of the method of Schleyer as cited in ref 10 that gave purer products. Freshly purified pyridine (50–75 mL) and dry isopropyl alcohol (3 mL) were cooled to 0 °C and the para-substituted benzenesulfonyl chloride (90 mol % based on alcohol) was added slowly with stirring. When solution was achieved, the well-stoppered flask was placed in a freezer at −10 °C until precipitation of pyridine hydrochloride appeared complete (1 to 2 days). The mixture was poured onto excess concentrated HCl plus 200 g of ice with good stirring. The nitro-, chloro-, and methyl-substituted benzenesulfonates all crystallized after several minutes of stirring and were collected, washed with ice water, and dried in vacuo. The unsubstituted benzenesulfonate remained an oil. It was taken up in ether, the ether layer washed with water, dried over K_2CO_3, and filtered, and the ether was evaporated. Residual solvent was pumped away at $<10^{-2}$ mmHg. The solid esters were all crystallized from petroleum ether. All four esters were >99% pure by HPLC and had melting points of 52–53 °C (*p*-nitro), 36.5–38 °C (*p*-chloro), and 20 °C (*p*-methyl). The *p*-chloro ester does not appear to have been reported in the literature before. NMR ($CDCl_3$) δ 7.75 (m, 2 H), 7.40 (m, 2 H), 4.64 (septet, J = 7 Hz, 1 H), 1.20 (d, J = 7 Hz, 6 H). Anal.[11] Calcd for $C_9H_{11}O_3SCl$: C, 46.06; H, 4.72; S, 13.66; Cl, 15.11. Found: C, 46.52; H, 4.58; S, 14.19; Cl, 15.43. 1,8-Bis(dimethylamino)-naphthalene (Proton Sponge, Aldrich) was sublimed before use. Sulfolane was purified as in earlier work.[12]

Kinetics. The Proton Sponge and 20 to 30 mg of biphenyl (as an internal standard) were weighed into a dry 25-mL volumetric flask and about 20 mL of sulfolane was added. The flask was swirled until solution appeared complete. The ester was then weighed in and the flask filled to the mark with the solfolane and shaken for 10 min. Aliquots of the solution were pipetted into 1-mL ampules and the ampules sealed with a torch. The ampules were placed in a water bath at 65 °C (Neslab Model RTE-8, rated at ±0.02 °C). An ampule was removed periodically, opened, and the extent of reaction measured by direct injection into the HPLC. The latter consisted of a Kontron 414LC pump, Valco C6W valve, 25-cm Custom LC C18 ODS column, and either a Kratos Spectroflow 757 or Hitachi 655A-22 variable wavelength detector. The eluant was 2:1 acetonitrile/water, flowing at 1.5 mL/min. The wavelength monitored depended on the ester (nitro 253 nm, chloro 268 nm, methyl 262 nm, and hydro 267 nm) and was chosen for maximum ester response. All injections were in triplicate. Injection volumes were 4 to 5 μL except for the *p*-nitro ester. Its more intensely absorbing solution was first diluted 20:1 with acetonitrile and then 10-μL injection volumes were used. Peak areas were determined with a HP3390A integrator and first-order rate constants calculated by an unweighted, linear least-squares fit for a plot of the logarithm of the ratio of unreacted ester to biphenyl internal standard vs time.

Registry No. $PhSO_3Pr$-*i*, 6214-18-2; *p*-$MeC_6H_4SO_3Pr$-*i*, 2307-69-9; *p*-$ClC_6H_4SO_3Pr$-*i*, 69564-62-1; *p*-$O_2NC_6H_4SO_3Pr$-*i*, 1830-67-7.

(10) L. F. Fieser, M. Fieser, *Reagents for Organic Synthesis*; John Wiley & Sons: New York, 1967; Vol. I, p 1180.
(11) Analysis performed by Galbraith Laboratories, Knoxville, TN.
(12) Lewis, E. S.; Vanderpool, S. H. *J. Am. Chem. Soc.* **1977**, *99*, 1946.

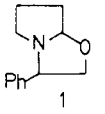
Robinson–Schopf Condensations with Succinaldehyde

John M. McIntosh

Department of Chemistry, University of Windsor, Windsor, Ontario, Canada N9B 3P4

Received June 9, 1987

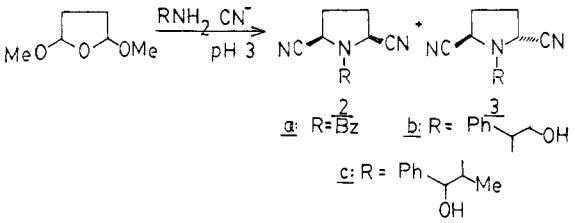
In connection with other work, a general route to chiral (nonracemic) α-substituted pyrrolidines was required. Among other avenues being explored, the Robinson–Schopf[1] condensation using (*R*)-phenylglycinol, succinaldehyde, and cyanide ion was attempted as a route to **1**.



1

This reaction has been very successfully applied, using glutaraldehyde, to the preparation of the corresponding piperidine systems.[2] However, a recent report[3] which suggests that it is unsuccessful using succinaldehyde and other work relating to the condensation of succinaldehyde with primary amines[4] prompts us to report our attempts to effect this and closely related reactions.

Condensation of succinaldehyde, formed in situ from 2,5-dimethoxytetrahydrofuran, benzylamine, and KCN in aqueous citric acid gave two products which were separated by chromatography. These were identified as the cis (**2a**) and trans (**3a**) diastereomers of *N*-benzylpyrrolidine-2,5-



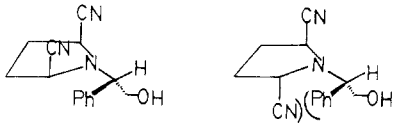
dicarbonitrile. The 300-MHz proton spectrum of **2a** showed the benzylic protons as a clean singlet whereas in **3a** they appeared as an AB quartet.[4] Similar analysis of the cis and trans isomers of *N*-benzyl-2,6-dicyanopiperidine has been published.[5]

Substitution of (*R*)-phenylglycinol for benzylamine led to the formation of two products. Crystallization of the chromatographically more mobile material (**2b**) gave a substance whose carbon NMR spectrum showed only one cyano carbon and two absorptions for the four ring carbons. The proton NMR spectrum showed a narrow

(1) Langdale-Smith, R. A. *J. Org. Chem.* **1971**, *36*, 226.
(2) Guerrier, L.; Royer, J.; Grierson, D. S.; Husson, H.-P. *J. Am. Chem. Soc.* **1983**, *105*, 7754. Grierson, D. S.; Royer, J.; Guerrier, L.; Husson, H.-P. *J. Org. Chem.* **1986**, *51*, 4475.
(3) Quang, P. Q.; Arseniyaadis, S.; Husson, H.-P. *Tetrahedron Lett.* **1987**, *28*, 547.
(4) Takahashi, K.; Saitoh, H.; Ogura, K.; Tida, H. *Heterocycles* **1986**, *24*, 2905.
(5) Bonin, M.; Chiaroni, A.; Riche, C.; Beloeil, J.-C.; Grierson, D. S.; Husson, H.-P. *J. Org. Chem.* **1987**, *52*, 382.

0022-3263/88/1953-0447$01.50/0

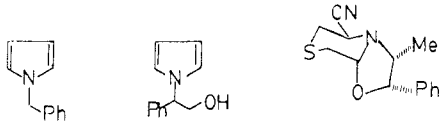
Chart I



four-proton multiplet (δ 3.95) for the hydroxymethylene and amino nitrile protons. In contrast, the spectrum of the less mobile material (**3b**) showed two cyano and four ring carbons and the proton spectrum showed the amino nitrile protons as two widely spaced absorptions (δ 4.51 and 3.79). The symmetry properties of the cis and trans isomers make possible the formation of two diastereomers of the trans isomer, but only one of the cis. The presence of the chiral center on the nitrogen substituent should render the remaining carbons nonequivalent in all three cases. However, in the cis isomer, the N-substituent can avoid interactions with the cyano groups (Chart I) and rapid conformational changes can average the signals leading to a simplified spectrum. The same rotational motion is much more hindered in the trans isomer (Chart I). On this basis **2b** and **3b** are assigned the cis and trans configurations, respectively. The melting points of the two isomers also agree with the previous observation[4] that the cis isomers are higher melting materials. If the assignment is correct, the carbon spectrum of **3b** suggests that only one of the two possible diastereomers is being formed. The observation[4] that relatively facile thermal interconversion between the kinetic (cis) and thermodynamic (trans) products of reactions of this type may account for the discrepancy in the relative amounts of the two isomers in the three series examined.

When norephedrine was used in the reaction, only one compound (**3c**) was isolated. Its chromatographic mobility corresponded closely to that of **3b** and it exhibited doubling of the ring and cyano carbons and widely separated amino nitrile protons. These similarities lead to the assignment of the trans configuration to this material. Again it appears that only one diastereomer of **3c** is being formed. The strain incorporated in the fused five-membered rings of compounds of type **1** must account for their failure to form.

Early fractions from the chromatography of the **a** and **b** series showed traces of material which suggested the presence of **4** and **5**. Condensation of succinaldehyde with benzylamine or phenylglycinol at pH 6 (standard Paal–Knorr conditions[6]) led to high yields of **4** and **5**, respectively.



4 **5** **6**

Finally, condensation of the bis diethylacetal of 3-thiaglutaraldehyde and norephedrine at pH 3 led to a low yield of **6**. The NMR spectra of **5** show it to be diastereomerically pure. The incorporation of the sulfur atom in the piperidine ring opens new possibilities in its synthetic applications and some of these are currently under investigation.

Experimental Section

NMR spectra were run in $CDCl_3$ solutions at 300 MHz (proton) and 75 MHz (carbon) on a Bruker AC-300 instrument. Proton chemical shifts are reported relative to internal TMS and carbon shifts relative to the center peak of $CDCl_3$ (δ = 77.0). Proton assignments were aided by decoupling experiments and carbon assignments were determined with the use of the DEPT pulse sequence.

General Condensation Procedure. To 90 mL of a 0.1 M aqueous citric acid solution was added 1.1 g (8.3 mmol) of 2,5-dimethoxytetrahydrofuran, 4.5 mmol of the requisite amine, and 0.4 g (6.15 mmol) of KCN. The solution was stirred at ambient temperature for 48–72 h. Any solid was removed by filtration, the filtrate was treated with excess solid $NaHCO_3$, and the basified solution was extracted with CH_2Cl_2. The dried extracts were evaporated, combined with the filtration residue and chromatographed (Si gel, ether/hexane).

If hydrolysis of 2,5-dimethoxytetrahydrofuran was performed in 0.2 M H_2SO_4, the pH of the solution adjusted to ca. 6, and 1 equiv of amine added, the pyrrole derivatives **3** and **4** were formed very rapidly. Addition of 1.5 equiv of KCN did not change this result.

2a: mp 71 °C; yield 58%; R_f (Et_2O) 0.38; ^1H NMR 7.36 (m, 5 H), 4.06 (s, 2 H) ($PhCH_2$), 3.93 (d, 2 H, J = 4.1 Hz) (NCHCN), 2.31 (m, 4 H) (ring CH_2); ^{13}C NMR 135.2, 128.9, 128.7, 128.31, 116.9, 53.4 (CH_2N), 51.1 (CHCN), 28.6. Anal. Calcd for $C_{13}H_{13}N_3$: C, 73.91; H, 6.20. Found: C, 74.02; H, 6.12.

3a: oil, yield 13%; R_f (Et_2O) 0.51; ^1H NMR 7.36 (m, 5 H), 4.28 (d, 1 H, J = 12.9) (low-field half of AB quartet, $PhCH_2$), 3.70 (d, 2 H, J = 3.2 Hz) (NCHCN), 3.65 (d, 1 H, J = 12.9 Hz) (high-field half of AB quartet, $PhCH_2$), 2.39–2.34 (m, 2 H), 2.28–2.23 (m, 2 H); ^{13}C NMR 135.6, 128.9, 128.7, 128.2, 117.4, 54.5 (CH_2N), 51.7 (CHCN), 28.3. Anal. Calcd for $C_{13}H_{13}N_3$: C, 73.91; H, 6.20. Found: C, 74.21; H, 6.03.

2b: mp 111–112 °C; yield 18%; R_f (Et_2O) 0.52; ^1H NMR 7.39 (m, 5 H), 4.17 (m, 1 H), 3.94 (m, 4 H), 2.61–2.35 (m, 2 H), 2.35–2.25 (m, 2 H), 1.94 (br s, 1 H) (OH); ^{13}C NMR 138.1, 129.1, 128.7, 128.0, 119.1, 67.8 (CH_2OH), 66.1 (PhCH), 51.6 (CHCN), 29.5. Anal. Calcd for $C_{14}H_{15}N_3O$: C, 69.69; H, 6.27. Found: C, 69.21; H, 6.19.

3b: oil; yield 65%; R_f (Et_2O) 0.30; ^1H NMR 7.35 (m, 5 H), 4.51 (dd, 1 H, J = 3.5, 6.8 Hz) (NCHCN), 4.17 (dd, 1 H, J = 5.1, 4.5 Hz) (PhCHN), 3.94 (m, 2 H), 3.79 (t, 1 H, J = 5.6 Hz) (NCHCN), 2.37–2.28 (m, 2 H), 2.28–2.19 (m, 2 H), 2.05 (br s, 1 H) (OH); ^{13}C NMR 137.3, 128.7, 128.2, 127.9, 117.5, 117.0, 65.5 (CH_2OH), 64.6 (PhCH), 50.7 (CHCN), 50.2 (CHCN), 28.9, 27.3. Anal. Calcd for $C_{14}H_{15}N_3O$: C, 69.69; H, 6.27. Found: C, 69.21; H, 6.15.

3c: mp 119–119.5 °C; yield 60% R_f (Et_2O) 0.26; ^1H NMR 7.35 (m, 5 H), 5.12 (d, 1 H, J = 2.3 Hz), 4.36 (dd, 1 H, J = 3.4, 6.7 Hz), 4.11 (dd, 1 H, J = 4.1, 7.2 Hz), 3.36 (dq, 1 H, J = 2.5, 6.9), 2.50–2.26 (m, 4 H), 1.00 (d, 3 H, J = 6.9); ^{13}C NMR 140.7, 128.4, 127.6, 125.8, 118.2, 117.7, 73.5 (PhCH), 59.2 (CH_3CHN), 50.7 (CHCN), 49.1 (CHCN), 29.2, 28.8, 10.4. Anal. Calcd for $C_{15}H_{17}N_3O$: C, 71.13; H, 5.97. Found: C, 70.99; H, 5.63.

5: oil; ^1H NMR 7.29 (m, 4 H) (Ar + OH), 7.12 (d, 2 H, J = 6.6 Hz) (Ar), 6.79 (d, 2 H, J = 1.4 Hz), 6.21 (d, 2 H, J = 1.4 Hz), 5.21 (dd, 1 H, J = 5.4, 7.9 Hz), 4.16 (m, 2 H); ^{13}C NMR 138.4, 128.7, 128.0, 126.5, 119.9, 108.6, 65.1, 64.8. Anal. Calcd for $C_{12}H_{13}NO$: C, 76.98; H, 7.00. Found: C, 76.99; H, 6.66.

6: mp 154–156 °C; yield 36%; ^1H NMR 7.60 (m, 5 H), 5.07 (d, 1 H, J = 7.8 Hz) (H8), 4.39 (t, 1 H, J = 6.0 Hz) (H2), 4.35 (t, 1 H, J = 3 Hz) (H6), 3.29 (dq, 1 H, J = 1.5, 7.0 Hz) (H7), 3.14 (dd, 1 H, J = 3.3, 13.8 Hz) ($H5_{ax}$), 2.90 (d, 2 H, J = 6.6 Hz) (H3), 2.78 (dd, 1 H, J = 2.4, 13.8 Hz) ($H5_{eq}$), 0.70 (d, 3 H, J = 7.0 Hz); ^{13}C NMR 138.7, 128.3, 128.2, 127.9, 114.6, 87.9, 80.8, 58.6, 50.4, 31.5, 30.2, 13.5. Anal. Calcd for $C_{14}H_{16}N_2OS$: C, 64.58; H, 6.19. Found: C, 64.02; H, 6.22.

Acknowledgment. The financial assistance of the Natural Sciences and Engineering Research Council of Canada in the form of operating grants and funds for the purchase of the NMR spectrometer made this work possible and is gratefully acknowledged.

Registry No. **2a**, 72219-11-5; **2b**, 111998-65-3; **3a**, 72219-10-4; **3b**, 111998-66-4; **3c**, 111998-67-5; **4**, 2051-97-0; **5**, 111998-68-6; **6**, 111998-69-7; succinaldehyde, 638-37-9; 2,5-dimethoxytetrahydrofuran, 696-59-3; benzylamine, 100-46-9; (*R*)-phenylglycinol, 56613-80-0; norephedrine, 700-65-2; 3-thiaglutaraldehyde bis(diethyl acetal), 45204-84-0.

(6) Young, D. M.; Allen, C. H. F. *Organic Syntheses*, Wiley: New York, 1943; Collect. Vol. II, p 219.