magnetic resonance spectra were recorded with a JEOL 60 in $CDCl_3$. Melting points were determined with a Kofler apparatus and are not corrected.

2-Iodothiophene (2) and NH_4F in DMSO.—2-Iodothiophene (**2**, 6.49 g, 30.9 mmol), ammonium fluoride (0.31 g, 8.5 mmol), and DMSO (6 ml) were stirred in a round-bottom flask with reflux condenser and calcium chloride valve at 170–175° (oil bath) during 6 hr. The reaction course was followed by glc and a continuous buildup of 2,5-diiodothiophene was observed during this time. The dark reaction mixture was taken up with boiling ether, filtered with Celite, washed with water, dried with sodium sulfate, and analyzed. Glc analysis of the mixture revealed unreacted **2** without contamination by the 3 isomer and a new major peak preceeded by a small peak and followed by other smaller impurities at much higher retention times. The first new peak had a retention time ratio of 0.80 (see Table I) and was identified on this basis, by enhancing technique, and by its mass spectrum as belonging to 5-iodothiophenealdehyde (**5**). The glc-determined yield of **5** was 1.5%. The largest new peak was analogously identified as 2,5-diiodothiophene (**4**, 25%, retention time ratio 1.00). While no detectable peaks had molecular ions which fitted the polyiodothiophene molecular composition, two small but still appreciable peaks had identical mass spectra with prominent ions at m/e values of 432 (M^+), 305 (−I, base peak), 178 (−2I, base peak in the less retained isomer), 134 (−CI_2S), 96 (C_5H_4S), and 82 (C_4H_2S). Distillation of the mixture allowed recovery of pure 2-iodothiophene, uncontaminated by the 3 isomer as shown by its ir.[10] The residue from this distillation was chromatographed on a 1.8 × 21 cm silica gel column using *n*-hexane as eluent; a white solid was obtained, which was recrystallized from ethanol, mp 36–37°, mmp with 2,5-diiodothiophene (**4**) 38.5–39.5°. This compound, which corresponds to the product with retention time ratio 1.00, had an ir spectrum identical with that of authentic **4**. The pmr spectrum showed a single peak as expected at τ 3.12 ppm. The reaction mixture showed no peak for either isomeric diiodothiophenes or fluorothiophenes, but small amounts of thiophene and dimethyl sulfide were detected by glc and confirmed by mass spectrometry. No attempts to optimize the yield of **4** were made, but lower and higher temperatures were found to give too slow a reaction and extensive tarring, respectively.

2-Iodothiophene in DMSO.—**2** (7.45 g, 35.4 mmol) and DMSO (5.50 g, 70.5 mmol) were heated in the dark at 190–195° during 18 hr to yield 18% (glc) of 2,5-diiodothiophene (**4**), whose identification was carried out as described in the fluoride experiment. Thiophene and dimethyl sulfide were present in the reaction mixture as well as the two isomers **6** and the aldehyde **5** in tiny amounts. Isomeric diiodothiophenes were absent.

Irradiation of 2-Iodothiophene (2).—**2** was irradiated during 18 hr without solvent at room temperature with a 254-nm mercury lamp. No **4** was formed.

"Parallel" Reactivity Tests of 2-Iodothiophene.—**2** (30 mmol) was heated in DMSO (75 mmol) with and without ammonium fluoride (11 mmol) at 165–170° during 6 hr to yield, respectively, 5 and 0.5% **4**. In either case only traces of free iodine were present.

Thermal Stability of 2-Iodothiophene (2).—**2** was heated without solvent during 15 hr at 190° (gentle reflux). No new compound could be detected by glc analysis.

2-Iodothiophene (2) and *N*,*N*-Dimethylaniline.—**2** (4.08 g, 19.4 mmol) and *N*,*N*-dimethylaniline (3.47 g, 28.8 mmol) were heated from 100 to 180° during 1.5 hr without any color change. Glc analysis showed no changes in the composition of the mixture. After 20 min at 180° the mixture turned dark blue, but glc analysis ruled out the formation of **4** and of *N*-(2-thenyl)-*N*-methylaniline (**9**). Heating the above mixture at 160° during 1 hr caused complete solidification; ether extraction did not yield any **4**; and digestion with aqueous sodium bicarbonate at 100° and extraction with ether gave a mixture which did not contain either **4** or **9**.

2,5-Diiodothiophene (4).—This compound was prepared in 17% yield from thiophene (0.121 mol), iodine (0.243 mol), and mercuric oxide (0.184 mol) in benzene according to a procedure described in the literature for 2-iodothiophene.[11] The product was recrystallized from ethanol: mp 39–40° (lit.[12] 40°); pmr ($CDCl_3$) singlet at τ 3.12 ppm; ir (KBr) 2825 (w), 2300 (w), 1380 (w), 1198 (w), 947 (m), 918 (w), 783 (s), and 727 cm^{-1} (w). The mass spectrum was essentially identical with that reported in the literature.[13] Distillation of the reaction mixture gave 24% of pure 2-iodothiophene (**2**).

5-Iodo-2-thiophenaldehyde (5).—This compound was prepared (18%) by treatment of **2** with *n*-butyllithium at −70°, followed by reaction with dry dimethylformamide in ether–hexane according to a described procedure:[14] mp 52° (lit.[15] 51–52°); ir (KBr) 1528 (s), 1503 (w), 1404 (s), 1370 (m), 1288 (m), 1223 (s), 1190 (w), 1043 (s), 950 (m), 807 (s), 743 (s), 675 (w), and 664 cm^{-1} (s); pmr ($CDCl_3$) singlets at δ 7.40 and 9.76 ppm; mass spectrum (75 eV, solid inlet 50°, chamber 150°) m/e 238 (M^+, base peak), 237 (2-I-thenoyl), 210 (C_4H_4SI), 209 (C_4H_3SI), 128 (HI), 127 (I), 111 (−I), 110 (−HI), 82 (−I, −CHO), 57, 45, 39.

Registry No.—DMSO, 67-68-5; **2**, 3437-95-4; **4**, 625-88-7; **5**, 5370-19-4.

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N-Phenyl-1-thio-1,2-azetidinedicarboximide, the Phenylthiohydantoin of Azetidine-2-carboxylic Acid[1]

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L-Azetidine-2-carboxylic acid (**1**), a naturally occurring antimetabolite of proline[2] that has been isolated from the Liliaceae,[3] is unstable in mineral acids and the four-membered azetidine ring undergoes degradative ring-opening reactions.[4] Derivatives of **1** prepared in acidic media are thus suspect unless the integrity of the azetidine moiety can be shown to be intact. In our studies on the behavior of ring homologs of α-imino acids related to proline and their 2,4-dinitrophenyl-, 6-dimethylaminonaphthalene-1-sulfonyl-, and 3-phenyl-2-thiohydantoin (PTH) derivatives in various chromatographic systems,[5] it was necessary to prepare such derivatives of **1** including the PTH derivative **7a**, since **1** is the first member of this homologous series.

The procedure of Edman[6] as modified by Sjöquist[7] for the preparation of PTH amino acids, which involves the cyclization of the phenylthiocarbamoyl amino acid in aqueous acetic acid–hydrogen chloride, when applied to **1** did not yield **7a**. Heating **1** in toluene with excess phenyl isothiocyanate[8] likewise gave intractable mixtures when examined by tlc. The feasibility of cycliz-

(1) Supported in part by Grant CA-06432, United States Public Health Service.

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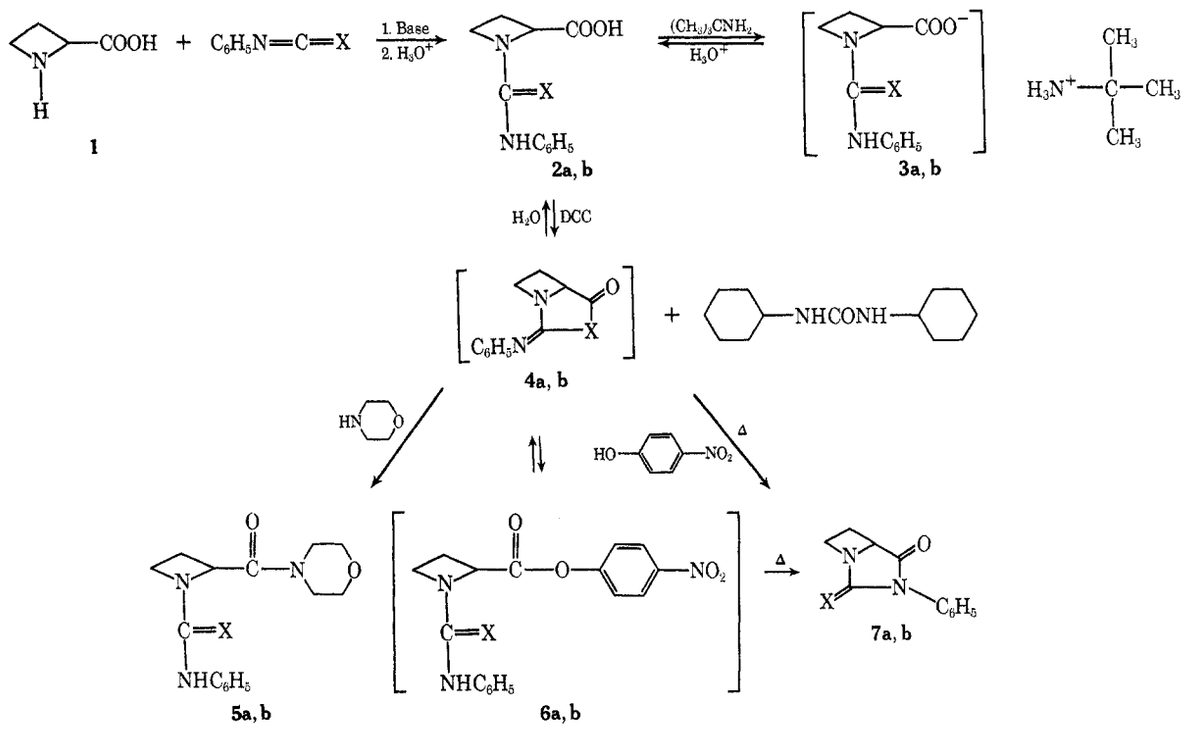

a, series, X = S
b, series, X = O

ing the phenylthiocarbamoyl derivative **2a** under mild conditions to the 2-phenyliminothiazolidin-5-one **4a**, followed by *thermally* rearranging[9] the latter to **7a** in anhydrous aprotic solvents, was then investigated.

Reaction of **2a** with dicyclohexylcarbodiimide (DCC) in dry acetonitrile at room temperature gave an immediate reaction as evidenced by the precipitation within 30 min of dicyclohexylurea in 80% yield. The formation of the expected 2-phenylimino-5-thiazolidinone **4a**, a compound tautomeric with the 2-anilino-5-thiazolinones proposed by Edman[9] as the intermediate in the acid-catalyzed cleavage of phenylthiocarbamoyl peptides, was adduced by the appearance of a broad peak at 235 nm (shoulder, 275 nm) in the uv spectrum (Figure 1). The reactivity of **4a**, cogently demonstrated by its acylation of morpholine at room temperature (**4a** → **5a**), precluded its isolation.

Heating the solution of **4a** under reflux gave rise to gradual formation of **7a** with an absorption maximum at 277 nm (Figure 1). The appearance of isosbestic points at 253 and 295 nm was indicative of the presence of only two ultraviolet-absorbing compounds in the reaction mixture, *viz.*, **4a** and **7a**. After 4 hr, the latter was isolated. This thermal rearrangement of **4a** was highly unpredictable, leading frequently to racemized **7a** (see Experimental Section), and another route to **7a** was investigated. The *p*-nitrophenyl ester of the phenylthiocarbamoyl imino acid, *viz.*, **6a**, prepared *in situ* from **4a**, more readily rearranged to **7a**. In fact, **6a** proved to be a superior intermediate; not only was the reaction time reduced considerably, but **7a** was obtained with retained optical activity.[10]

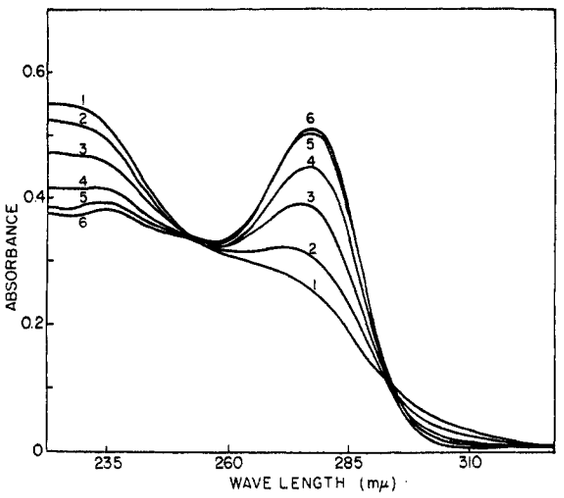

Figure 1.—The conversion of **4a** to **7a**. Aliquots of the reaction mixture were diluted with acetonitrile and scanned (1) immediately after removal of dicyclohexylurea, (2) after heating under reflux for 5 min, (3) for 15 min, (4) for 30 min, (5) for 60 min, and (6) for 120 min.

In order to correlate the major infrared bands of **7a** with that of the higher ring homologs already described[8,11] and to identify its fragmentation ions on electron impact, the corresponding oxygen analog **7a** was prepared for comparison. In this sequence (**b** series), **4b** was so reactive that it rapidly absorbed traces of moisture and hydrolyzed back to **2b** on prolonged heating, and **7b** could not be prepared except through the *p*-nitrophenyl ester **6b**.

The fragmentation pattern exhibited by **7a** on electron impact was quite analogous to the mass spectrum of PTH proline.[12] The peak at *m/e* 55, which can be

(9) P. Edman, *Acta Chem. Scand.*, **10**, 761 (1956).

(10) Since the reaction proceeds smoothly whether the *p*-nitrophenol is added after the imino thiazolidinedione is formed, or before the addition of DCC itself, the intermediate here must be the *p*-nitrophenyl ester **6a**, and the accelerated reaction is not due merely to catalysis by *p*-nitrophenol. In the latter mode of addition, the formation of **4a** is likely bypassed to give **6a** directly.

(11) L. K. Ramachandran, A. Epp, and W. B. McConnell, *Anal. Chem.*, **27**, 1734 (1955).

(12) B. W. Melvas, *Acta Chem. Scand.*, **23**, 1679 (1969).

ascribed to the four-membered 1-azetine radical ion, (**8**) appears to be characteristic for this compound in the same manner as the 1-pyrroline radical ion (**9**, *m/e* 69) is for PTH proline.[12] The oxygen analog **7b** fragments to give the phenyl isocyanate radical ion, $C_6H_5NCO\cdot^+$ (*m/e* 119, $\%\Sigma_{40}$ 25.3), as base peak; and again, the diagnostic **8** appeared as a fairly intense peak at *m/e* 55.

8

9

The 2,4-dinitrophenyl- and the 6-dimethylaminonaphthalene-1-sulfonyl derivatives of **1** have also been prepared and are reported here. These, as well as **7a**, are useful derivatives for the chromatographic and/or mass spectrographic identification of azetidine-2-carboxylic acid (**1**) in biological systems.[4,8]

Experimental Section

Melting points were taken on a Mettler FP-2 apparatus and are corrected; optical rotations were determined in a Perkin-Elmer Model 141 polarimeter. Spectrophotometers used were: uv, Beckman DK-2A; ir, Beckman IR-10; nmr, Varian A-60A; mass spectra, Hitachi Perkin-Elmer RMU-6. Microanalyses were performed by Schwartzkopf Microanalytical Laboratory, Woodside, N. Y., and Galbraith Laboratories, Knoxville, Tenn.

tert-**Butylammonium 1-(Phenylthiocarbamoyl)-L-azetidine-2-carboxylate (3a).**—1[13] (303 mg, 3.0 mmol), 30 ml of CH_3CN, 10 ml of dry pyridine, and 0.42 g (3.1 mmol) of C_6H_5NCS were heated under reflux for 4 hr and then concentrated to a syrup under reduced pressure. The residue was diluted with 5% $NaHCO_3$ solution, then extracted three times with ether. The bicarbonate extract was acidified to pH 2 with 6 *N* HCl and extracted repeatedly with *ca.* 100-ml portions of EtOAc, and the combined EtOAc extracts were washed (H_2O), dried (Na_2SO_4), and evaporated to dryness. The residue was recrystallized from MeOH containing 2 ml of *tert*-butylamine by addition of ether, 844 mg and 24 mg (crop 2), yield 93%. The analytical sample was recryst from MeOH–ether, mp (broad) 170–182°, $[\alpha]^{27}D$ −367° (*c* 1.47, 95% EtOH).

Anal. Calcd for $C_{15}N_{23}N_3O_2S$: C, 58.2; H, 7.49; N, 13.58; S, 10.36. Found: C, 58.06; H, 7.58; N, 13.44; S, 10.17.

N-**Phenyl-1-thio-1,2-azetidinedicarboximide (7a). By Thermal Rearrangement of 4a.**—Free **2a** was obtained from **3a** (155 mg, 0.50 mmol) by extracting a pH 2 solution of the latter with EtOAc. The extract was dried (Na_2SO_4) and evaporated to dryness below 30°, and the residue was further dried *in vacuo* (128 mg) and dissolved in 10 ml of spectrophotometric grade CH_3CN; to this was added 103 mg (0.50 mmol) of dicyclohexylcarbodiimide (DCC). After 30 min the precipitate of dicyclohexylurea (89 mg, 80%, mp 231–232°) was removed by filtration and rinsed with CH_3CN, and the combined filtrate (29.7 ml) was heated under reflux in a volumetric t-tube. Aliquots (100 μl) were taken after 0, 5, 15, 30, 60, and 120 min of reflux, diluted to 50 ml with CH_3CN, and the uv spectra recorded (Figure 1). After 2 hr of additional reflux, the reaction solution was evaporated to dryness ad the product was purified by preparative tlc on 1 mm thick silica gel PF_{254} (dried at 110° for 4 hr just before use) using $CHCl_3$ as solvent (four passes), and recrystallized from CH_2Cl_2–petroleum ether (bp 30–60°): yield 55 mg; mp 128–130°; $[\alpha]^{26}D$ −65.1° (*c* 0.335, CH_3CN); uv max (EtOH) 235, 279 nm (log ε 3.96, 4.14); ir (KBr) 1755, 1740 (C=O), 1375 (CH_2), 1325 cm^{-1} (C=S); ir (CH_2Cl_2) 1760 (C=O), 1375 (CH_2), 1330 cm^{-1} (C=S); nmr ($CDCl_3$) δ 2.83 (m, 2, H-3), 4.31 (m, 2, H-4), 4.90 (t, 1, $J_{2,3}$ = 8 Hz, H-2); mass spectrum (70 eV, 100°) *m/e* (rel intensity) 218 (M^+, 56.7), 189 (5.1), 162 (11.5), 149 (17.5), 137 (6.1), 135 (100), 132 (15.5), 104 (14.1), 91 (10.0), 77 (65.5), 72 (16.1), 67.5 (4.3), 55 (26.3), 51 (37.8). Crop 2 contained 17 mg, mp 125–126° (66% yield).

Anal. Calcd for $C_{11}H_{10}N_2OS$: C, 60.53; H, 4.62; N, 12.83; S, 14.69. Found: C, 60.54; H, 4.63; H, 13.00; S, 14.73.

(13) Purchased from Calbiochem Corp., Los Angeles, Calif. The optical rotation of this sample lot was reported to be $[\alpha]^{23}D$ −123° (*c* 3.5, H_2O).

This thermal rearrangement was unpredictable, especially when the solvents were EtOAc, dioxane, or a less pure grade of CH_3CN, and reaction times up to 72 hr were necessary for completion. Prolonged reaction times and multiple chromatographic manipulations caused racemization, which was reflected in the *rise* in melting point of the product: thus, for mp 131–134°, $[\alpha]^{28}D$ −59.5°; mp 134–138°, $[\alpha]^{28}D$ −46.8°; mp 160–166°, $[\alpha]^{28}D$ −15.8°; mp 163–166°, $[\alpha]^{28}D$ −11.0°; mp 166–167°, $[\alpha]^{28}D$ 0. The racemic product was analyzed, uv max (EtOH) 235, 279 nm (log ε 3.97, 4.14).

Anal. Calcd for $C_{11}H_{10}N_2OS$: C, 60.53; H, 4.62; N, 12.83; S, 14.69. Found: C, 60.53; H, 4.68; N, 12.88; S, 14.70.

7a *via p*-**Nitrophenyl Ester 6a.**—**2a** was coupled with DCC as above. After removal of the dicyclohexylurea, 278 mg (2.0 mmol) of *p*-nitrophenol was added, and the reaction mixture was heated under reflux for 2 hr and then diluted with EtOAc. The mixture was extracted repeatedly with 5% Na_2CO_3 solution until no more yellow color was extracted, washed (H_2O), dried (Na_2SO_4), and evaporated to dryness under reduced pressure. The product was purified by preparative tlc as above and recrystallized from CH_2Cl_2–petroleum ether, 61 mg, mp 130–132°, and crop 2, 14 mg, mp 126–127° (69% yield), $[\alpha]^{27}D$ −62.4° (*c* 1.05, CH_3CN).

7a was also obtained in reasonable yield when excess *p*-nitrophenol (1.0 g) was added *before* the DCC and the reaction was allowed to proceed at room temperature overnight. After work-up essentially as above, 44 mg was obtained, mp 128–130°, $[\alpha]^{28}D$ −66.5° (*c* 0.783, CH_3CN), and 15 mg, mp 126–127°, $[\alpha]^{28}D$ −67.2° (*c* 0.603, CH_3CN). The ir, uv, nmr, and mass spectra of the **7a** prepared *via* the *p*-nitrophenyl ester here were identical with the spectra of the optically active **7a** prepared above by the thermal rearrangement of **4a**.

Anal. Calcd for $C_{11}H_{10}N_2OS$: C, 60.53; H, 4.62; N, 12.83; S, 14.69. Found: C, 60.43; H, 4.73; N, 13.11; S, 14.82.

1-(Phenylthiocarbamoyl)-L-azetidine-2-carbomorpholide (5a).—**2a** was coupled with DCC as above. After removal of the dicyclohexylurea, 0.50 g of morpholine was added to the intermediate **4b**. Tlc ($CHCl_3$–88% HCOOH, 100:5; silica gel F_{254}) of an aliquot of the reaction mixture 40 min after addition of morpholine indicated that a new product, R_f 0.31, had formed. After overnight reaction at room temperature, the mixture was diluted with water and extracted four times with $CHCl_3$, and the combined $CHCl_3$ extract was washed (H_2O), dried (Na_2SO_4), and evaporated to dryness. Recrystallization of the residue from CH_2Cl_2–petroleum ether gave 128 mg (84%) of **5a**, colorless needles, mp 194–197° dec. After two more recrystallizations, the product melted at 195–198° dec; $[\alpha]^{28}D$ −284° (*c* 1.09, CH_3CN); ir (KBr) 3305 (NH), 1650 (amide C=O), 1550 (NCS I), 1400 cm^{-1} (NCS II).

Anal. Calcd for $C_{15}H_{19}N_3O_2S$: C, 58.99; H, 6.27; N, 13.76; S, 10.50. Found: C, 58.76; H, 6.33; N, 13.66; S, 10.60.

1-(Phenylcarbamoyl)-L-azetidine-2-carboxylic Acid (2b).—To a solution of 808 mg (8.0 mmol) of **1** in 60 ml of H_2O containing 3.39 g of KOH was added at room temperature a fivefold excess of phenyl isocyanate in three equal portions over 1.5 hr. After 4 hr of stirring at room temperature, the reaction mixture was worked up as for **3a** above and the product was recrystallized from acetone–hexane: 1.48 g (84%); mp (after recrystallization again from acetone–hexane), 147–151°; $[\alpha]^{27}D$ −163° (*c* 1.55, 95% EtOH); ir (KBr) 3400 (NH), 1745, 1725 (COOH), 1620 (amide I), 1535 cm^{-1} (amide II).

Anal. Calcd for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72. Found: C, 59.85; H, 5.60; N, 12.91.

L-*N*-**Phenyl-1,2-azetidinedicarboximide (7b).**—To a solution of 440 mg (2.0 mmol) of **2b** in 40 ml of CH_3CN (spectrophotometric grade) was added 412 mg (2.0 mmol) of DCC, whereupon dicyclohexylurea precipitated almost immediately. *p*-Nitrophenol (1.0 g) was then added and the reaction mixture was heated under reflux for 24 hr. Crude **7b** was obtained by work-up similar to the procedure for **7a** and was recrystallized from CH_2Cl_2–petroleum ether: yield 82 mg; mp 117–118°; $[\alpha]^{29}D$ −20.3° (*c* 0.777, CH_3CN); ir (KBr) 1785, 1710 (C=O's), 1380 cm^{-1} (CH_2); ir (CH_2Cl_2) 1790, 1725 (C=O's), 1380 cm^{-1} (CH_2); nmr ($CDCl_3$) δ 2.78 (m, 2, H-3), 4.01 (m, 2, H-4), 4.73 (t, 1, $J_{2,3}$ = 8 Hz, H-2); mass spectrum (70 eV, 100°) *m/e* (rel intensity) 202 (M^+, 33.1), 174 (19.0), 146 (4.8), 119 (100), 104 (12.9), 91 (25.6), 77 (15.0), 64 (16.2), 55 (18.0). Crop 2 contained 41 mg: mp 115–117°; $[\alpha]^{29}D$ −19.7° (*c* 0.910, CH_3CN); total yield 30% (best yield was 49%).

Anal. Calcd for $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.98; N, 13.85. Found: C, 65.40; H, 4.91; N, 13.77.

1-(Phenylcarbamoyl)-L-azetidine-2-carbomorpholide (5b).—The intermediate **4b** was prepared from 220 mg (1.0 mmol) of **2b** and 206 mg (1.0 mmol) of DCC in 25 ml of CH_3CN as above. Morpholine (0.50 g) was added after 3 min. The reaction time and work-up followed the procedure for **5a**. The product was purified by preparative tlc on 1 mm silica gel PF_{254} using $CHCl_3$–HOAc (95:5) (5–7 passes) and recrystallized from CH_2Cl_2–petroleum ether, 73 mg (25% yield), mp 186–187°. After recrystallization twice from CH_2Cl_2–petroleum ether, the product had mp 188–189°; $[\alpha]^{28}D$ −201° (*c* 1.11, CH_3CN); ir (KBr) 3260 (NH), 1665, 1640 (amide C=O's), 1535 cm^{-1} (amide II).

5b was obtained in 53% yield when 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride[14] was substituted for DCC in this reaction. The crude product was recrystallized directly without prior purification by tlc after removal of the water-soluble urea: mp 186–188°, $[\alpha]^{28}D$ −197° (*c* 1.05, CH_3CN).

Anal. Calcd for $C_{15}H_{19}N_3O_3$: C, 62.27; H, 6.62; N, 14.52. Found: C, 62.19; H, 6.91; N, 14.61.

1-(2,4-Dinitrophenyl)-L-azetidine-2-carboxylic Acid.—This DNP derivative of **1** was prepared in 80% yield according to the dinitrophenylation procedure of Rao and Sober,[15] and recrystallized from H_2O-saturated CH_2Cl_2–hexane, mp 119–120°.

Anal. Calcd for $C_{10}H_9N_3O_6$: C, 44.95; H, 3.40; N, 15.73. Found: C, 44.87; H, 3.26; N, 15.57.

1-(5-Dimethylaminonaphthalene-1-sulfonyl)-L-azetidine-2-carboxylic Acid, Cyclohexylammonium and Piperidinium Salts.—The dansyl derivative of **1** was prepared in the same manner as for the higher ring homologs[8] except that the free imino acid instead of the methyl ester was used. Recrystallization of the dansyl derivative from EtOH containing excess cyclohexylamine afforded the cyclohexylammonium salt in 80% yield, mp (broad) 170–181° after recrystallization from EtOH. Tlc[5] indicated that this product was homogeneous.

Anal. Calcd for $C_{22}H_{31}N_3O_4S$: C, 60.95; H, 7.21; N, 9.69. Found: C, 61.08; H, 7.02; N, 9.71.

The piperidinium salt was prepared in 89% yield by substituting piperidine for cyclohexylamine in the above procedure, and recrystallized from CH_2Cl_2–petroleum ether, mp 117–123°.

Anal. Calcd for $C_{21}H_{29}N_3O_4S$: C, 60.12; H, 6.97; N, 10.02. Found: C, 59.94; H, 7.17; N, 9.79.

Registry No.—**2b**, 32970-20-0; **3a**, 32970-21-1; **5a**, 32970-22-2; **5b**, 32970-23-3; **7a**, 32970-24-4; **7b**, 32970-25-5; 1-(2,4-dinitrophenyl)-L-azetidine-2-carboxylic acid, 32970-26-6; 1-(5-dimethylaminonaphthalene-1-sulfonyl)-L-azetidine-2-carboxylic acid, 32970-27-7 (cyclohexylammonium salt), 32970-28-8 (piperidinium salt).

Acknowledgment.—We are indebted to Mrs. O. Hamerston for the ir spectra, Miss F. N. Shirota for the nmr spectra, and Mr. J. McMahon for the mass spectra.

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Beckmann Rearrangements of Tetrahydro-α-santonin Oximes

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The Beckmann rearrangement[1,2] of cis- and trans-fused tetrahydro-α-santonin oximes has been carried out. Cis- and trans-fused tetrahydro-α-santonins (I) were prepared by the reported method,[3] and converted to their oximes (II) by the usual method.

The Beckmann rearrangement of *cis*-tetrahydro-α-santonin oxime (IIa) with *p*-toluenesulfonyl chloride at 50° afforded only 4-aza-*A*-homo-*cis*-tetrahydro-α-santonin (IIIa). No other isomeric products were found by tlc or by ir spectral examination of the mother liquor after separation of IIIa. This indicates that the cis-fused tetrahydro-α-santonin oxime (IIa) has the *E* configuration (anti form) (Chart I).

The oxime from *trans*-4β-tetrahydro-α-santonin oxime (IIb), mp 199–202°, showed two spots on tlc at R_f 0.36 and 0.26 (1:4 ratio). The oxime from *trans*-4α-tetrahydro-α-santonin oxime (IIc), mp 221–225°, showed two spots with the same R_f value of 0.36 and 0.26 but in a different ratio (5:1). Mixture melting point determination of these trans oximes (IIb and IIc) showed a depression. Therefore, the trans-fused tetrahydro-α-santonin oximes (IIb and IIc) are two different syn–anti mixtures, with IIb having the 4β configuration (H-4, δ 3.60 ppm) and IIc having the 4α configuration (H-4, δ 2.46 ppm).[4] This was further confirmed by the observed ratio of Beckmann rearrangement products. Although IIb and IIc did not react under the conditions described for IIIa, they did react with thionyl chloride in dioxane at 70° (Chart II).

The product of the Beckmann rearrangement of *trans*-4β-oxime (IIb) showed two spots on tlc (R_f 0.43 and 0.24, chloroform–methanol). The product from IIb was chromatographed on silica gel and yielded a 4-aza lactam (IIIb, R_f 0.43) and a 3-aza lactam (IIIc, R_f 0.24) in a ratio of 2:3. On the other hand, the Beckmann rearrangement product of *trans*-4α-oxime (IIc) gave a mixture of 4-aza lactam (IIIb) and 3-aza lactam (IIIc) in the ratio of 2:1.

The Schmidt reaction of *cis*-tetrahydro-α-santonin (Ia) produced 4-aza-*A*-homo-*cis*-tetrahydro-α-santonin (IIIa) in good yield, while *trans*-4α-tetrahydro-α-santonin (Ic) gave 4-aza-*A*-homo-*trans*-tetrahydro-α-santonin (IIIb) in 40% yield. These lactams were identical with those obtained from the Beckmann rearrangement.

The stereochemistry of the Beckmann rearrangement products (IIIa, b, and c) was confirmed by analysis of their nmr spectra. In the case of 4-aza-*A*-homo-*cis*-tetrahydro-α-santonin (IIIa), a doublet at δ 5.99 ppm (J = 4.5 Hz) could be assigned to the amide hydrogen. The angle between the amide hydrogen and H-5 should be approximately 53° (a)[5] from the Karplus equation.[6] When the amide hydrogen was irradiated, the multiplet (1 H) at 3.76 ppm changed to a double quartet ($J_{5,14}$ = 6.7 and $J_{5,6}$ = 9.0 Hz), and could therefore be attributed to the H-5. Irradiation of the H-7 at 4.36 ppm (1 H, dd, $J_{7,6}$ = 4.3 and $J_{7,8}$ = 11.0

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(5) In this case, a value of the vicinal coupling constant was obtained by parameters in the equations

$$J = 6.6\cos^2\phi + 2.6\sin^2\phi \quad (0° \leq \phi \leq 90°)$$
$$J = 11.6\cos^2\phi + 2.6\sin^2\phi \quad (90° \leq \phi \leq 180°)$$

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