3-Isopropyl-1,3-diazabicyclo[3.3.1]nonan-2-one, a Simple **Bicyclic Urea with a Bridgehead Nitrogen Atom**

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Stabilization of a bicyclic compound containing the CO-N (bridgehead) unit, which formally violates Bredt's rule, was achieved by introduction of a second electron-donating atom (N) to give the N-CO-N (bridgehead) structure and by working with a conformationally strainless bicyclic ring system. 3-Isopropyl-1,3-diazabicyclo-[3.3.1]nonan-2-one (9), the first simple urea with a bridgehead N atom, was synthesized in two ways. Reaction of 3-(N-isopropylaminomethyl] piperidine with 1 equiv of phosgene in methylene chloride at 0° gave the desired urea directly. Alternatively, excess phosgene in ether at -75° gave biscarbamyl chloride 10, which with silver carbonate in refluxing acetonitrile gave 9. Once formed, 9 was stable to hydrolysis and ring-opening polymerization and is strainless by these criteria.

Lukes¹ proposed that bicyclic lactams such as 2quinuclidone (1) should be incapable of existence



because resonance form 1b would be prohibited (Bredt's rule). However, ingenuity in synthesis has prevailed, and Pracejus^{2,3} has prepared 2,2-dimethyl- and 2,2,6trimethyl-2-quinuclidones. These lactams show unusual properties: their carbonyl infrared absorptions are found at anomalously high frequencies, they hydrolyze readily in water, and they appear to polymerize.3

To stabilize molecules containing N-C=O links at the bridgehead, introduction of a strongly electrondonating atom such as nitrogen adjacent to the carbonyl group would meet the demand of C=O for electrons via form 2c.



To our knowledge, no simple bridgehead urea has yet been reported. That the problem of synthesis of such compounds may not be trivial is shown by the work of Misito and Chiavarelli.⁴ Although they readily obtained compounds 3a and 3b from the parent diamine,



(2) H. Pracejus, Chem. Ber., 92, 988 (1959).

(3) H. Pracejus, ibid., 98, 2897 (1965)

(4) D. Misito and S. Chiavarelli, Gazz. Chim. Ital., 96, 1696 (1966); Chem. Abstr., 66, 85777 (1966).



these investigators showed that the corresponding urea (3, Z = CO) was not formed under similar conditions.

To avoid conformational strains such as those also present in 1, we selected the strainless two-chair bicyclo [3.3.1] nonane structure shown in 2a-c. Form 2b may make a small contribution in this system, inasmuch as the homomorphic olefin 4 has been prepared as an unstable compound.^{5,6} One attempt to synthesize lactam 5, on the other hand, gave only polymer.7





3-Aminomethylpyridine was converted using acetone to 3-isopropylidenaminomethylpyridine (6), which on successive hydrogenations gave 3-(isopropylaminomethyl)piperidine (8). Reaction with di-m-tolyl car-



bonate failed to give the desired bicyclic urea 9; so attention was given to the very reactive acyl chloride phos-

- (5) J. A. Marshall and H. Faubl, J. Amer. Chem. Soc., 92, 948 (1970).
- (6) J. R. Wiseman, *ibid.*, **92**, 956 (1970).
 (7) H. K. Hall, Jr., *ibid.*, **82**, 1209 (1960).

gene. Reaction with phosgene in ether in the presence of various bases (triethylamine, cyclohexyldiethylamine, barium oxide, calcium carbonate), gave a mixture consisting largely of the N,N'-biscarbamoyl chloride 10 and a little urea 9. Refluxing 10 with silver carbonate in acetonitrile converted it to 9.



An alternate route was found by using dichloromethane at 0° as the reaction solvent.⁸ Reaction of **8** with 1 equiv of phosgene, followed by addition of 2.2 equiv of triethylamine, was carried out. The reaction mixture remained homogenous and $\sim 50\%$ yields of cyclic urea 9 were obtained. At -40° a mixture with biscarbamoyl chloride 10 was obtained.

The urea 9, bp 150° (0.2 mm), melted at 47–48°, had the proper elemental analysis, and was pure according to gas chromatography. The precision mass spectrum supported the assigned structure, giving a parent peak corresponding to $C_{10}H_{18}ON_2$. The nmr spectrum, other than that of the *N*-isopropyl group, was somewhat featureless, but was consistent with structure 9.

Compound 9 was stable to boiling water for 20 hr but hydrolyzed slowly in hot sodium hydroxide solution. It showed no signs of polymerization after heating for extended periods with *p*-toluenesulfonic acid, phosphoric acid, or potassium *tert*-butoxide, and only starting material was recovered. Finally, the ir spectrum of urea 9 showed a carbonyl group at the normal frequency for a tetraalkylurea, 1650 cm⁻¹. All three criteria show that the molecule is not strained.

We have been able to synthesize the first bicyclic urea with a bridgehead nitrogen atom, owing to the fact that the demand of the carbonyl group for electrons has been satisfied by the other nitrogen atom and because conformational strain is absent from the 3-substituted bicyclo [3.3.1]nonane system. In fact, compound 9 represents the other extreme of stability from quinuclidone 1. We anticipate that, by variation of electron-donating atom and of ring size, a variety of bicyclic nitrogen compounds of intermediate reactivity can be prepared. The synthesis methods developed in this investigation should apply to bridgehead urethanes, sulfonamides, and phosphonamides as well as to ureas, which, because of the widespread occurrence of such linkages in pharmaceutically active compounds, should be of interest in medicinal chemistry. Moreover, ring-opening polymerization of the more strained members should lead to novel polymers of possible bio-

(8) J. P. Li and J. H. Biel, J. Org. Chem., 35, 4100 (1970).

medical utility. The synthesis of other bridgehead nitrogen compounds is currently underway in these laboratories.

Experimental Section

Infrared spectra were taken on a PE 337 spectrometer. Gas chromatograms were taken on a 150 cm, 63 mm stainless steel column containing 30% SE-30 on 100/120 mesh Varaport 30. Melting points and boiling points are uncorrected.

3-Isopropylidenaminomethylpyridine (6).—3-Aminomethylpyridine (106.5 g, 0.99 mol, Research Organic and Inorganic Chemicals Co.), acetone (182 ml, 3 mol), and benzene (300 ml) were heated to reflux in a 1-l. round-bottom flask provided with Dean-Stark trap and water condenser. The reaction was discontinued when the rate of water collection became slow. Benzene and excess acetone were removed by distillation at atmospheric pressure using a heating mantle. The residual oil was distilled. Compound 6, bp 68–80° (0.3 mm), 109.2 g, was obtained as a colorless liquid. It showed two peaks by vpc (ratio of peaks in order of increasing retention time, 1:1). The infrared spectrum of 6 showed a strong band at 1670 cm⁻¹ (C=N). It appears that 6 may have been formed in a mixture with its tautomer 6a.

CH=NCH(CH₃)₂ 6a

3-Isopropylaminomethylpyridine (7).—The above sample of 6 was taken up in ethyl acetate (350 ml) and placed under hydrogen (ca. 40 psi) at 20° using platinum oxide (500 mg) as catalyst. When hydrogen uptake became slow, the catalyst was separated by filtration and the filtrate was concentrated, leaving a yellow oil, 130 g. Vpc analysis showed two peaks in the ratio 15:85 (order of increasing retention time). The oil was distilled to give 95.4 g, bp 72–80° (1.6 mm). An infrared spectrum of 7 showed the absence of a band at 1670 cm⁻¹ attributable to C=N, while absorption at >3000 cm⁻¹ indicates the presence of the pyridine ring. Thus the hydrogenation of the C=N link seems to have been almost complete.

3-(Isopropylaminomethyl)piperidine (8).-The above product, 7, 95.4 g, was taken up in water (200 ml) and the solution was acidified with concentrated hydrochloric acid (110 ml). The solution was placed under hydrogen (2000 psi) at 75° using ruthenium oxide as catalyst (ca. 1 g) and maintained under these conditions until gas absorption became slow. The catalyst was filtered. Excess water was removed by means of a rotary The viscous residue was cooled in an ice bath and a evaporator. concentrated aqueous solution of 40% sodium hydroxide was The resulting aqueous slush was exadded slowly with swirling. tracted with two portions of ether. The combined extract was dried over anhydrous sodium sulfate. Ether was removed by means of a rotary evaporator and the resulting oil was distilled, bp 56-61° (0.3-0.2 mm), yield 56 g (57%). In this experiment 8 was at least 93% pure by vpc, and in other runs approached 100%. An nmr spectrum of the material showed no signals attributable to aromatic hydrogens.

Anal. Calcd for $C_9H_{20}N_2$: C, 69.17; H, 12.90; N, 17.93. Found: C, 69.11; H, 12.90; N, 18.06.

Reaction of 3-(Isopropylaminomethyl)piperidine (8) with Excess Phosgene in Ether at -75° to Give the Biscarbamoyl Chloride 10.—A 1–l., three-necked Morton flask was fitted with a jacketed pressure-equalizing dropping funnel, cold-finger condenser, and three-way stopcock. The flask was provided with a magnetic stirrer. The apparatus was dried using a Bunsen flame and cooled under a stream of nitrogen. To the flask was added anhydrous ether (500 ml). Phosgene (4.20 ml, 0.0583 mol) was admitted by distillation from a calibrated trap in which it had been liquefied. The dropping funnel was charged with a solution of 3-(isopropylaminomethyl)piperidine (8, 3.0 g, 0.0192 mol) in 50 ml of ether. The reaction mixture was cooled to -75° using a Dry Ice-isopropyl alcohol bath. The solution in the addition funnel was cooled and the diamine solution was added by drops with efficient stirring. After addition was complete, the reaction mixture was allowed to warm to room temperature and stirring was continued for 4 hr. The solid was separated by filtration and the filtrate was concentrated using a

rotary evaporator, giving 10 as a colorless oil, 1.0 g. A strong infrared absorption band appeared at 1740 cm⁻¹ (COCl), but none between 3600-3050 cm⁻¹ (absence of NH). A weaker band at 1650 cm⁻¹ (urea) was also present. That the above material was mainly the biscarbamoyl chloride 10 was supported by gravimetric analysis. A sample of this material (234 mg) was dissolved in acetone (2 ml) and treated with a solution of silver nitrate (307 mg) in water (10 ml). Mixing was accompanied by a fairly vigorous evolution of gas and rapid precipitation. After brief standing, the silver chloride was separated by filtration, washed with water, and dried to give 202 mg (theoretical mass 237 mg).

Reaction of Biscarbamoyl Chloride 10 with Silver Carbonate to Give Urea 9.—A sample which was largely biscarbamoyl chloride 10, 844 mg, was dissolved in anhydrous acetonitrile (13 ml, from phosphorus pentoxide) in a 25-ml round-bottom flask provided with a magnetic stirring bar. Silver carbonate (1.65 g) was added to the solution and the mixture was stirred while being heated at reflux for 18 hr. The mixture was allowed to cool, filter, and evaporate. The crude dark oil (450 mg) was purified by molecular distillation, bp 220° (0.2–0.3 mm), to give 9 as a colorless oil (100–150 mg). The nmr spectrum and vpc retention time of this material were essentially identical with those of 9 prepared by the alternate route (below).

Reaction of 3-(N-Isopropylaminomethyl) piperidine (8) with Phosgene in Methylene Chloride at 0° to give 3-Isopropyl-1,3diazabicyclo[3.3.1]nonan-2-one (9).—A 1-l. three-necked Morton flask was fitted with a mechanical stirrer, cold-finger, condenser, and three-way stopcock. The exit from the condenser was pro-tected with a Drierite tube. The apparatus was dried with a Bunsen flame and cooled under a stream of nitrogen. To the flask was added dry methylene chloride (450 ml from 4-A molecular sieves) and 3-(N-isopropylaminomethyl)piperidine (8) (100% by vpc), yield 3.0 g, 0.0192 mol. Phosgene (1.36 ml, 0.0192 mol) was condensed in a graduated trap cooled in a Dry Ice-isopropyl alcohol bath. The reaction flask was cooled in an ice bath and the cold finger was charged with Dry Ice and isopropyl alcohol. The phosgene was transferred to the reaction flask by distillation at room temperature (10 min) using efficient stirring. Stirring was continued for 5 min after addition was complete and the reaction solution (colorless to slightly yellow) was allowed to come to room temperature.

The three-way stopcock was replaced with a pressure-equalizing addition funnel containing a solution of anhydrous triethylamine (5.2 ml) from barium oxide in 25 ml of methylene chloride. The solution was added by drops with stirring over 10 min at room temperature, and the final, almost colorless, solution was left at room temperature for 16 hr. It was washed with 3 ml of concentrated hydrochloric acid in 100 ml of water, with 3 g of sodium bicarbonate in 50 ml of water, and with 100 ml of water. After drying over anhydrous sodium sulfate, the solution was concentrated. The colorless residue, 3.35 g, was purified by molecular distillation, bp 150° (0.25 mm), bath 200°, to give 9 as a colorless oil, 1.02 g (28%). Vpc showed only a single peak (>98%) past solvent, retention time 4.5 min at 185° using a flow rate of 60 ml of He per minute.

Seeding the distillate with crystals obtained by preparative gas chromatography induced crystallization.

An nmr spectrum of the distillate (CCl₄) showed a pentuplet (septuplet?) at δ 4.3, a series of multiplets at 4.2–0.9, and a

doublet at 1.18. The mass spectrum (sample by preparative gas chromatography) showed the parent ion at m/e 182.1433, corresponding to $C_{10}H_{18}ON_2$. The analytical sample of 9 was recrystallized twice from ethyl acetate at -45° and resublimed under N₂, mp 48.2-49.2°. Anal. Calcd for $C_{10}H_{18}N_2O$: C, 65.90; H, 9.95; N, 15.37. Found: C, 65.68; H, 9.84; N, 15.23.

When the reaction was performed under identical conditions, but at -40° , the product contained approximately equal amounts of 9 and 10. The latter could be destroyed by excess AgNO₃ in acetone-water, and urea 9 could be recovered in 29% yield.

Stability of 3-Isopropyl-1,3-diazabicyclo[3.3.1]nonan-2-one to Water, Acid, and Base.—The title material was soluble in water. A solution was monitored by gas chromatography in order to detect changes due to possible hydrolysis. No change was observed, however, after 24 hr at room temperature. Another sample (71 mg) as a solution in water (2.0 ml) was heated under reflux for 20 hr. Chromatograms following standard injections showed no change over this period. The material was completely stable toward water.

Sodium Hydroxide Solution.—A solution of 30 mg of 9 and 57 mg of sodium hydroxide in 0.5 ml of water and 0.36 g of tetrahydrofuran was refluxed. After 2 hr about 80% of 9 had disappeared (by vpc) and after 6 hr almost none remained. No other peaks were detected. Slow hydrolysis occurs under these conditions.

Potassium tert-Butoxide.—A sample of 9 (30 mg) was mixed with a small quantity of potassium tert-butoxide (~ 0.1 mg). The mixture was allowed to stand at room temperature for 22.5 hr under nitrogen. There was no change in the composition of the material as determined by infrared analyses. The mixture was heated at 120–125° (under nitrogen) for 22 hr. The infrared spectrum recorded after this time was essentially identical with that of starting material.

p-Toluenesulfonic Acid Monohydrate.—Another sample of 9 (92 mg) was placed in contact with a few small crystals of p-toluenesulfonic acid monohydrate (under nitrogen). The infrared spectrum recorded after standing for 10 hr at room temperature showed no change from starting material. The mixture was heated at 105–120° for 24 hr. An infrared spectrum recorded after this time was essentially identical with one of starting material.

85% Phosphoric Acid.—A mixture of 9 (96 mg) and 85% phosphoric acid (2.5 mg) was heated for 17 hr at 200° in a Wood's metal bath (sealed tube under vacuum). At the end of this time, the tube was opened and a sample was examined by infrared. The spectrum was essentially identical with one of starting material.

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