Molecular Rearrangements in the Course of Ritter Reactions

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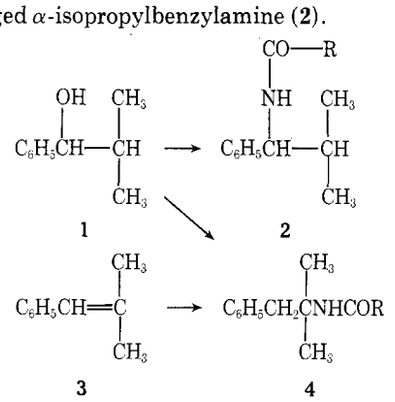
It is well known that the Ritter reaction occurs *via* ionic intermediates and that molecular rearrangements take place if the initial carbonium ion intermediate can isomerize to a more stable one.[2] Thus Boltze and Mühlenbein[3] reported that α-isopropylbenzyl alcohol (**1**) reacts with hydrogen cyanide or with nitriles under acidic conditions to yield amides of α,α-dimethylphenethylamine (**4**). On the other hand, this seems to contradict the report by Christol, *et al.*,[4] that Ritter reactions of **1** form amides of the unrearranged α-isopropylbenzylamine (**2**).



a, R = CH_3
b, R = C_6H_5

A check of the reaction conditions which were used by these two groups showed that a reasonable cause for this discrepancy could have been the different order of addition of reagents used, since this in turn could have easily changed the type of mechanistic factor which controlled the reactions. Thus, Boltze and Mühlenbein first mixed the carbinol and the acids, and only later added the nitrile, whereas Christol and coworkers first mixed the carbinol with the nitrile, and added the sulfuric acid last. In the first case, the initially formed carbonium ion may therefore have had ample time to rearrange into a more stable structure before the nitrile was added (*e.g.*, thermodynamic control of reaction), while in the second case the nitrile could trap the carbonium ions as they were being formed (*e.g.*, kinetic control). This would also explain Christol's additional observation that, while the Ritter reaction of **1** yielded **2**, the same reaction with the styrene derivative **3** only yielded **4**.

To check our rationalization, we only changed the order of addition of reagents when **1** was allowed to react with nitriles in a mixture of sulfuric and acetic acid under otherwise identical conditions. As was expected, **2** was obtained when sulfuric acid was the last reagent which was added, while **4** was obtained when the nitrile was added last.[5]

Experimental Section

Melting points were determined in capillaries and are uncorrected; nmr spectra were recorded on a Varian Associates A-60 spectrometer with TMS as internal standard.

α-Isopropylbenzyl Alcohol (1). To a refluxing suspension of 13 g (0.34 mol) of lithium aluminium hydride in 300 ml of tetrahydrofuran was added 100 g (0.675 mol) of isobutyrophenone (Aldrich) in 200 ml of tetrahydrofuran. After 2 hr of additional refluxing, the reaction mixture was cooled to room temperature and treated with 15 ml of water, 15 ml of 15% aqueous sodium hydroxide, and 39 ml of water. The suspension was filtered, the filter residue was washed thoroughly with 200 ml of tetrahydrofuran, and the solvent of the combined filtrates was evaporated under reduced pressure to yield 84.9 g of crude **1**, which was purified by fractionation over a Vigreux column and gave 73.9 g (0.526 mol, 78% of theory) of **1**, bp 77–78° (0.3 mm).

***N*-(α,α-Dimethylphenethyl)acetamide (4a).** To a solution of 6.0 g (0.04 mol) of compound **1** in 6.0 ml of glacial acetic acid and 3.3 ml of 95% sulfuric acid was added dropwise 1.9 g (0.046 mol) of acetonitrile at 70°, and the mixture was kept for an additional 1 hr at this same temperature. Then it was added to enough crushed ice to keep the resulting solution at room temperature, treated with 14 ml of 25% aqueous sodium hydroxide, returned just to acidic by addition of 15% aqueous sulfuric acid, and extracted in two steps with 150 ml of methylene chloride. The combined extracts were washed with 3 × 50 ml of water and dried over sodium sulfate and the solvent was evaporated under reduced pressure to yield 7.1 g of an oil, which crystallized in cyclohexane to give 2.7 g (0.014 mol, 35% of theory) of **4a**: mp 89–90° (lit.[3] mp 91–92°); nmr ($CDCl_3$) 2 CH_3 at 1.29 (s), CH_3 at 1.85 (s), CH_2 at 3.02 (s), C_6H_5 at 7.19 ppm (complex).

***N*-(α,α-Dimethylphenethyl)benzamide (4b).** By the method described for the preparation of **4a**, but using 3.3 g (0.032 mol) of benzonitrile instead of the acetonitrile, the crude product was 6.4 g of crystalline material which was purified by recrystallization in 95% ethanol: mp 109–110°; nmr ($CDCl_3$) 2 CH_3 at 1.43 (s), CH_2 at 3.14 (s), 10 aromatic at 7.1–7.8 ppm (complex).

Anal. Calcd for $C_{17}H_{19}NO$: C, 80.60; H, 7.56; N, 5.53. Found: C, 80.95; H, 7.33; N, 5.57.

***N*-(α-Isopropylbenzyl)acetamide (2a).** To a solution of 6.0 g (0.04 mol) of **1** and 1.9 g (0.046 mol) of acetonitrile in 6.0 ml of glacial acetic acid was added 3.3 ml of 95% sulfuric acid at 70°. After the previously described work-up, which yielded 6.6 g of crude product, a recrystallization in 2-propanol gave 2.6 g (0.0135 mol, 34% of theory) of **2a**: mp 114–116°; nmr ($CDCl_3$) CH_3 at 0.78 (d), CH_3 at 0.95 (d), CH_3 at 1.9 (s), CH at 1.9 (heptet), CH at 4.7 (broad triplet), C_6H_5 at 7.2 ppm (s).

Anal. Calcd for $C_{12}H_{17}NO$: C, 75.40; H, 8.96; N, 7.32. Found: C, 75.60; H, 8.56; N, 7.37.

***N*-(α-Isopropylbenzyl)benzamide (2b).** By the method described for the preparation of **2a**, but using 3.3 g (0.032 mol) of benzonitrile instead of acetonitrile, the crude product was 6.2 g of crystalline material, which was purified by recrystallization in ethanol: mp 139–140° (lit.[4] mp 141°); nmr ($CDCl_3$) CH_3 at 0.87 (d), CH_3 at 1.02 (d), CH at 2.23 (heptet), CH at 5.01 (broad triplet), 10 aromatic at 7.4–7.9 ppm (complex).

Acknowledgment. We wish to acknowledge the helpful discussions with Dr. J. L. Marsh and with Mr. L. Dorfman, whose staff we thank for microanalyses and spectra.

Registry No.—**1**, 611-69-8; **2a**, 33617-85-5; **2b**, 51310-27-1; **4a**, 5531-33-9; **4b**, 51310-28-2; isobutyrophenone, 611-70-1.

References and Notes

(1) To whom inquiries should be directed to Dyestuffs & Chemicals Division, CIBA-GEIGY Corp., P.O. Box 11422, Greensboro, N. C. 27409.
(2) For a recent review of this reaction see L. I. Krimen and D. J. Cota, *Org. React.*, **17**, 213 (1969).
(3) K.-H. Boltze and H. Muhlenbein, German Patent 1,144,713 (Oct 14, 1960).
(4) H. Christol, A. Laurent, and M. Mouseron, *Bull. Soc. Chim. Fr.*, 2313 (1961).
(5) The structure of the products was assigned unequivocally from their nmr spectra, since the chirality of the benzylic carbon of **2** gives diastereotopic character to its two methyl groups.

N-Acyllactam Rearrangements. The Fate of the Carboxyl Carbon and the Synthesis of 2-*tert*-Butyl-1-pyrroline

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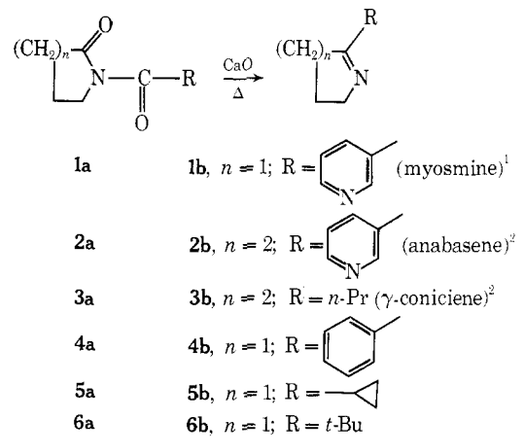
The rearrangement of *N*-acyllactams to 2-substituted cyclic imines has recently been investigated in our labora-

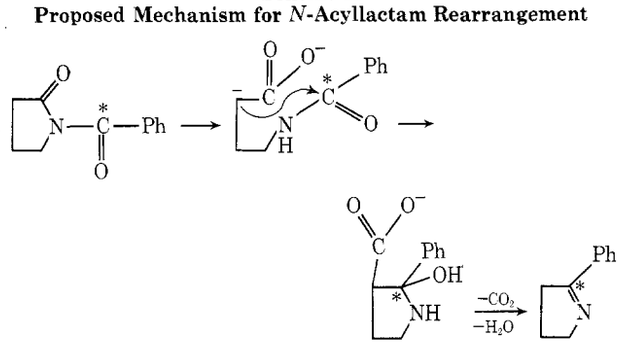
tory,[1,2] and has resulted in a simple entry into pyrroline and piperideine alkaloids, 1–3 (Scheme I). As a result of some exploratory research into the possible role of **1a** as an intermediate in nicotine biosynthesis,[3] we had occasion to consider the fate of the carboxyl carbon of the *N*-acyl moiety.

Scheme I
Synthesis of 2-Substituted Pyrrolines and Piperideine



To examine this point, and utilizing our experience with a readily available model, ^{14}C-carboxyl labeled benzoyl chloride was treated with 2-pyrrolidone to yield **4a** (specific activity 246 dpm/mmol). Dry distillation of an equal weight portion of **4a** and calcium oxide resulted in formation of **4b** (specific activity 233 dpm/mmol). Within the experimental error of our counting, one could suggest that all of the carbonyl carbon of the *N*-acyl group was maintained in the product. A partial mechanism consistent with this observation is delineated in Scheme II. Based on a consideration of this type, one might predict that the reaction would *not* be sensitive to the inherent electronic and steric effects of the R group. Two further entries suggest this to be true, **5** and **6** (Scheme I).

Scheme II
Proposed Mechanism for *N*-Acyllactam Rearrangement



N-Cyclopropanoyl-2-pyrrolidone (**5a**) was readily converted to 2-cyclopropyl-1-pyrroline (**5b**) without secondary reorganization of the cyclopropyl moiety. The propensity of this strained ring to suffer skeletal reorganization under many different reaction conditions is well documented.[4] For our last test of the nonparticipation of R during the reaction, we wished to examine a molecule which would be difficult to prepare by other methods. Since our previous synthetic efforts had shown us that the sequence worked equally well in the five- and six-ring series, our most important consideration focused on the nature of the R group. A literature search revealed a synthesis of 2-*tert*-butyl-1-piperideine starting from 2-*tert*-butyl-1-pyridine.[5] Since no corresponding pyrroline had ever been reported, and an obvious method was not apparent to incorporate the *tert*-butyl group into a pyrroline, this seemed a reasonable test molecule for our synthetic efforts. Dry distillation of *N*-pivaloyl-2-pyrrolidone (**6a**) in the presence of calcium oxide gave **6b**.

The ease of preparing *N*-acyllactams, coupled with the specificity of the rearrangement regardless of ring size and constitution of R, suggest this to be a general and useful methodology for 2-substituted cyclic imines.

Experimental Section

Nmr spectra were recorded on a Varian A-60 instrument, using TMS as an internal standard and deuteriochloroform as solvent. Boiling and melting points are uncorrected. Carbon-14 analyses were performed by liquid scintillation counting, using the channels ratio technique to determine efficiencies.

Synthesis of 2-Phenyl-1-pyrroline (4b). Benzoyl chloride (140 g), ^{14}C label at the carbonyl carbon, was converted to *N*-benzoyl-2-pyrrolidone by the method previously reported.[1] The product was repeatedly crystallized from hot ethanol (mp 91°) to constant specific activity of 246 dpm/mmol. This product was mixed with an equal weight of calcium oxide and the resulting mixture was heated with a free flame to give crude 2-phenyl-1-pyrroline.[1] A sample was purified by preparative glc [10 ft × 0.25 in. column, 10% Carbowax 20M on Chromosorb W, impregnated with 6% (w/w) sodium hydroxide]. A sample counted 233 dpm/mmol.

Synthesis of *N*-Cyclopropanoyl-2-pyrrolidone (5a). A solution of cyclopropanoyl chloride (5 g, 0.048 mol) and pyridine (10 g) was allowed to stir while 8.25 g of 2-pyrrolidone was slowly added. After stirring at room temperature for 8 hr, the reaction mixture was taken up in methylene chloride and washed with dilute hydrochloric acid until the washings were acidic. The methylene chloride solution was washed with saturated sodium bicarbonate, and the resulting neutralized solution was dried over anhydrous sodium sulfate and reduced in volume. The crude product was crystallized from chloroform–hexane to yield 6.9 g (94%) of **5a:** mp 62–63°; nmr δ 2.61 (t, 2), 1.97 (m, 2), 3.75 (t, 2), 3.17 (m, 1), 0.97 (m, 4).

Anal. Calcd for $C_8H_{11}NO_2$: C, 62.7; H, 7.2; N, 9.1. Found: C, 62.3; H, 7.1; N, 9.3.

Synthesis of 2-Cyclopropyl-1-pyrroline (5b). Calcium oxide (1.5 g) was intimately mixed with an equal weight of **5a** and the mixture was subjected to dry distillation with a free flame. Redistillation of the crude product yielded 0.78 g (73%) of **5b:** bp 45° (10 mm); picrate derivative mp 150–151°; nmr δ 3.75 (m, 2), 0.81 (d, 4), 1.5–2.6 (unresolved multiplet, 5).

Anal. (picrate) Calcd for $C_{13}H_{14}N_4O_7$: N, 16.5. Found: N, 16.5.

Preparation of 2-*tert*-Butyl-1-pyrroline (6b). A solution of 2-pyrrolidone (17 g) and pyridine (7.9 g) in 100 ml of benzene was stirred at room temperature while pivaloyl chloride (12 g) in 25 ml of benzene was slowly added. The reaction mixture was diluted with *ca.* 100 ml of methylene chloride and washed with dilute hydrochloric acid until the washings were acidic. The methylene chloride layer was separated and washed with saturated bicarbonate. This solution was dried over anhydrous sodium carbonate, filtered, and reduced in volume. Distillation (62–65°, 0.2 mm) gave 13.7 g (81% yield) of the desired *N*-acyllactam, which was taken immediately to the next step. An equal-weight mixture (6.72 g) of the above product and calcium oxide was heated with an open flame to yield the crude pyrroline. Distillation gave 2.0 g (40%) of **6b:** bp 110° (1.5 mm); nmr δ 1.15 (s, 9), 1.85 (m, 2), 2.5 (t, 2), 3.75 (t, 2).

Anal. Calcd for $C_8H_{15}N$: C, 76.8; H, 12.0; N, 11.2. Found: C, 76.8; H, 12.1; N, 10.9.

Acknowledgment. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research.

Registry No.—4a, 2399-66-8; **4b,** 700-91-4; **5a,** 51269-66-0; **5b,** 51269-67-1; **5b** picrate, 51269-68-2; **6a,** 51269-69-3; **6b,** 51269-70-6; cyclopropanoyl chloride, 4023-34-1; 2-pyrrolidone, 616-45-5; pivaloyl chloride, 3282-30-2.

References and Notes

(1) B. P. Mundy, B. R. Larsen, L. F. McKenzie, and G. Braden, *J. Org. Chem.*, **37**, 1635 (1972).
(2) B. P. Mundy and B. R. Larsen, *Syn. Commun.*, **2**, 197 (1972).
(3) Three *N. tabaccum* plants were administered [^{14}C]-γ-aminobutyric acid. After a metabolic period of 24 hr was allowed, the plants were frozen in liquid nitrogen and homogenized in chloroform. Nonlabeled

1a was added to the homogenate with the expectation that any naturally occurring 1a would mix with this and be reisolated. Careful purification of 1a after reisolation demonstrated *no* activity to be present. This work was presented at the Montana Academy of Sciences, Dillon, Mont., 1973.

(4) See L. N. Ferguson in "Highlights of Alicyclic Chemistry," Franklin Publishing Corp., Palisade, N. J., 1973, for a well-documented review on cyclopropane chemistry.
(5) M. F. Brundon and B. E. Reynolds, *J. Chem. Soc.*, 2445 (1964).

Facile Addition of Bromine to a Reissert Compound

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Contribution No. 366 from CIBA Research Centre, Goregaon, Bombay 63, India

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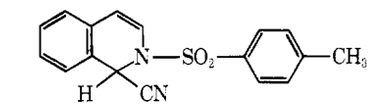
The chemistry of Reissert compounds has been reviewed in detail.[1] Dihydro Reissert compounds have been described by Shamma, *et al.*;[2] their nmr data have been studied by Bramley and Johnson.[3] This note describes the facile addition of bromine to Reissert compound **1** and the tentative stereochemistry of the vicinal dibromide **2** and its derivatives.

The bromination of isoquinoline is reported to give 4-bromoisoquinoline under drastic conditions.[4] A mechanism involving the addition of bromine followed by the elimination of hydrogen bromide has been postulated.[5] The dibromide has eluded isolation and characterisation. 1-Cyano-2-*p*-toluenesulfonyl-1,2-dihydroisoquinoline (**1**) was prepared according to the method described by Wefer, *et al.*[6] The bromination of **1** took place readily to give 1-cyano-3,4-*cis*-dibromo-2-*p*-toluenesulfonyl-1,2,3,4-tetrahydroisoquinoline (**2**), which could be isolated and characterized. The analytical values and the spectral data were in agreement with structure **2**. Refluxing **2** with ethanol and 2-propanol gave **5** and **6**, respectively. Treatment of **2** with aqueous sodium bicarbonate gave 4-bromo-1-cyano-3-hydroxy-1,2,3,4-tetrahydroisoquinoline (**7**). The above α-amino alcohol **7** would be expected to exist in equilibrium with the open-chain structure **8** in solution. However, poor solubility of the compound in solvents such as $CHCl_3$ and CCl_4 precluded such a study. The ir spectrum of **7** in Nujol showed bands at 3350 and 1700 cm^{-1}, showing evidence for the δ-amino aldehyde structure **8**. In the nmr spectrum of the compound in CD_3SOCD_3 the signal corresponding to the aldehydic proton was not discernible, showing the absence of any significant amount of **8** in solution.

That the addition of bromine to **1** may take place in the cis fashion is shown by the magnitude of the coupling constant of C_3 and C_4 protons in **2** (J = 2.5 Hz). The above coupling constant is consistent also with a configuration in which the bromine atoms are trans and diaxial. However, it is highly unlikely that the bromine atoms would be axial. The magnitude of the coupling constants of C_3 and C_4 protons in **5**, **6**, and **7** remains of the same order as in **2**, indicating a cis orientation of the hydrogen atoms. The facile formation of the above compounds can be visualised as the addition of elements of ethanol, 2-propanol, or water to the iminium species **3** or the enamine **4**.

Treating **2** with 1 mol of morpholine in dioxane gave 4-bromo-1-cyano-2-*p*-toluenesulfonyl-1,2-dihydroisoquinoline (**4**), in which the C_1 proton occurs as a doublet (J = 0.5 Hz). This is in agreement with the observations of Chhabra, *et al.*,[7] on the long-range spin coupling in isoquinoline Reissert compounds. In the presence of morpholine, a facile trans-diaxial elimination of the elements of hydrogen bromide can be postulated for the formation of **4** from **2**. However, the pathway involving the formation of iminium species **3** and loss of proton to give **4** cannot be ruled out under the above conditions. Confirmation of the product as **4** was obtained by establishing its identity with the product obtained by Reissert reaction on 4-bromoisoquinoline. Refluxing **2** with 3 mol of morpholine in dioxane caused elimination of *p*-toluenesulfonic acid along with hydrogen bromide to give 4-bromoisoquinaldonitrile (**9**). The latter compound has also been obtained by Wefer, *et al.*,[6] by use of sodium hydride in xylene.



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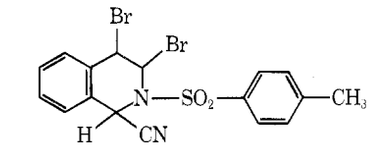

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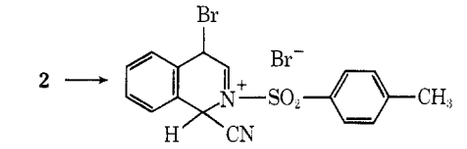
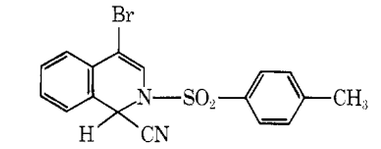
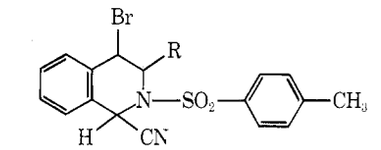


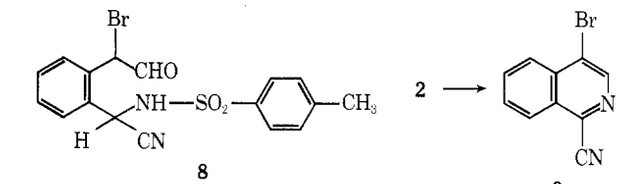
3



4



5, R = OC_2H_5
6, R = $OCH(CH_3)_2$
7, R = OH



8 **9**

Experimental Section

Melting points are uncorrected. The ir spectra were examined as Nujol mulls on a Perkin-Elmer Model 421 spectrophotometer. The uv spectra in 95% ethanol were recorded on a Beckman Model DK-2A spectrophotometer and the nmr spectra were recorded on a Varian Associates A-60 spectrometer with TMS as internal standard.

1-Cyano-2-*p*-toluenesulfonyl-1,2-dihydroisoquinoline (1). The above compound was prepared in 52% yield according to the procedure of Wefer, *et al.*:[6] mp 101°: ir 1620 and 1170 cm^{-1}; uv max 227 nm (log ϵ 4.26) and 285 (3.93); nmr ($CDCl_3$) δ 2.31 (s, 3 H, ArCH_3), 6.11 (d, 1 H, J = 6 Hz, C_4 H), 6.18 (d, 1 H, J = 0.6 Hz, C_1 H), 6.80 (d, 1 H, J = 6 Hz, C_3 H), 6.95–7.90 (m, 8 H, aromatic).

3,4-*cis*-Dibromo-1-cyano-2-*p*-toluenesulfonyl-1,2,3,4-tetrahydroisoquinoline (2). To a solution of 12.41 g (0.04 mol) of **1** in 150 ml of chloroform was added gradually 7.04 g (0.044 mol) of bromine in 40 ml of chloroform at room temperature and the solution was stirred for 4 hr. Evaporation of the solvent gave a residue, which crystallized on trituration with ether. It was recrystallized