Synthetic Approaches to Diterpene Alkaloids[1]

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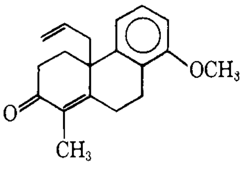
Abstract: Procedures are described for the synthesis of tetracyclic intermediates incorporating the bridged nitrogen-containing ring common to many of the diterpene alkaloids.

In connection with an interest in general methods for the total synthesis of diterpene alkaloids,[2] we wish to record at this time some experimental observations that have been made in this laboratory over a period of the last several years.

When ketone **1**[2] is treated with 1 equiv of peracid the keto epoxide **2** is obtained as the only characterizable product. The yield is only about 30%, and an extended study of this reaction, involving the use of various peracids and reaction conditions, failed to lead to any substantial improvement. It is noteworthy that benzonitrile–hydrogen peroxide[3] is without effect on ketone **1**, which is recovered unchanged when subjected to the action of these reagents.[4]



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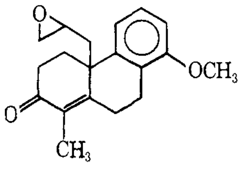

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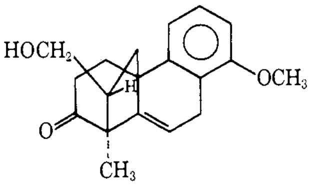
Treatment of compound **2** with potassium *t*-butoxide leads to internal alkylation, with attack at the secondary instead of the primary position in the epoxide, and formation of the bridged product **3**. Catalytic hydrogenation (Pd) then afforded the saturated derivative **4**. The orientation tentatively assigned to the hydroxymethyl group in these substances is based upon the observation that acetylation of **4** furnishes two acetyl derivatives.[5] One of the compounds showed both ketonic and acetate absorption in the infrared and is presumably the normal acetylation product. The other derivative showed only acetate absorption, and formula **5** is suggested as a plausible structure for this compound.



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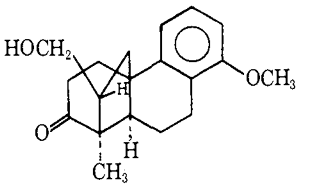
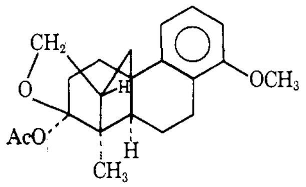


4

Wolff–Kishner reduction of keto alcohol **4** proceeded smoothly to give the expected product **6a**, which was readily converted into the benzoate ester **6b**. Numerous attempts to effect pyrolytic elimination of benzoic acid to the corresponding methylene derivative failed to give the desired product. Although benzoic acid was eliminated, no material showing methylene absorption in the infrared was detected, and it is not unlikely that double-bond migration occurs during pyrolysis.[6] In order to avoid this difficulty, the alcohol **6a** was oxidized to aldehyde **7**, which was converted into ketone **8**[2] *via* ozonolysis of the enol acetate.



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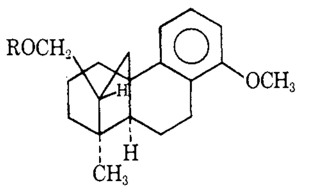
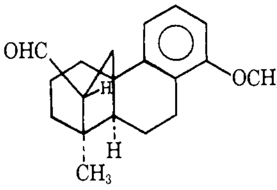


6a, R = H
b, R = Bz



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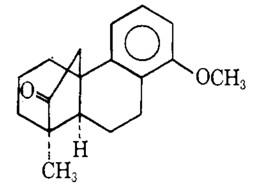
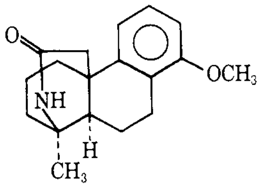


8

For the purpose of expanding the bridged ring with incorporation of nitrogen, Beckmann rearrangement of the oxime of **8** was regarded as the most direct route. The oxime was readily prepared, and rearrangement proceeded smoothly to give a single lactam in good yield. Of the two lactams, **9** and **10**, that may be found by this procedure, only **10** is useful for synthesis of diterpene alkaloids, and it was therefore a matter of considerable importance to establish unequivocally the structure of the rearrangement product. A preliminary assignment could be made on the basis of the nmr spectrum which exhibited a broad, unresolved



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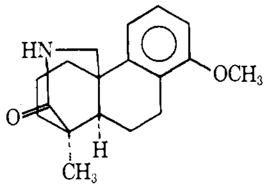

10

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[1] This work was supported by a grant from the Robert A. Welch Foundation.

[2] R. B. Turner, G. D. Diana, G. E. Fodor, K. Gebert, D. L. Simmons, A. S. Rao, O. Roos, and W. Wirth, *J. Amer. Chem. Soc.*, 88, 1786 (1966).

[3] G. B. Payne, *Tetrahedron*, 18, 763 (1962).

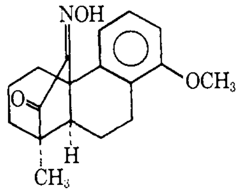
[4] We are indebted to Miss Lynda Weber for this experiment.

[5] These substances were not completely characterized.

[6] *Cf.* B. B. Smith and H. R. Nace, *J. Amer. Chem. Soc.*, 76, 6119 (1954).

2-proton signal at δ 2.48 in the region expected for the α-hydrogens of lactam **9**.

As an alternate approach in which formation of the desired isomer **10** appeared to be assured, ketone **8** was condensed with butyl nitrite (large excess) in the presence of sodium hydride.[7] The reaction mixture was separated into acidic and neutral fractions. Processing of the acid fraction gave not the expected oximino ketone **11**, but instead about 25% of a nitrile acid for which analytical data suggested structure **12a**. The neutral fractions afforded a small amount of a crystalline nitrile which is regarded as the butyl ester **12b**.



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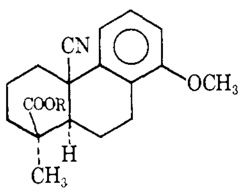
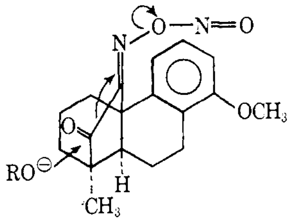


12a, R = H
b, R = C_4H_9
c, R = CH_3

The mechanism whereby these products arise is not entirely clear. It is assumed that condensation of ketone **8** with butyl nitrite leads initially to the anion of oximino ketone **11**. In the presence of sodium hydride butoxide ion would also be formed. Since the anion of **11** is not a likely candidate for base-induced cleavage, we suggest that further reaction of this substance with butyl nitrite might yield a neutral species (**13**) in which attack by butoxide ion would reasonably lead to compound **12b**. The presence of moisture in the reaction mixture, or of sodium hydroxide in the sodium hydride employed, would account for the formation of nitrile acid (**12a**).



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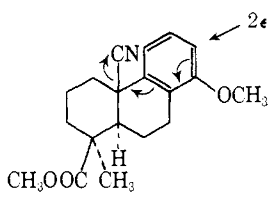
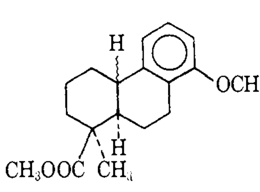
The encouragement provided by these preliminary observations prompted a more detailed investigation of the reaction sequence. Ketone **8** was accordingly condensed with 1.3 equiv of butyl nitrite in *t*-butyl alcohol with potassium *t*-butoxide as the catalyst. The product, which was obtained in 80% yield, proved to be the desired oximino ketone **11**, λ_{max} 247 mμ (ϵ 8390).[8] Treatment of this compound with *p*-toluenesulfonyl chloride afforded an unstable *p*-toluenesulfonoxy derivative which was converted directly into nitrile acid (**12a**) by the action of alkali in aqueous tetrahydrofuran. Reaction of the tosylate with sodium methoxide gave methyl ester **12c** which could also be obtained from the nitrile acid (**12a**) by reaction with diazomethane.

Preliminary attempts directed toward reduction of the nitrile group in **12a** and **12c** were not encouraging. The nitrile group was not attacked under various conditions of palladium-catalyzed hydrogenation, and reduction of **12c** with sodium and liquid ammonia resulted in the formation of a nitrogen-free product, $C_{18}H_{24}O_3$, provisionally formulated as **14**. Direct displacement of the benzylic nitrile function is, of course, an obvious alternative to the mechanism suggested.



12c



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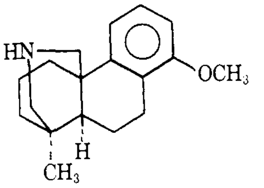
Attention was next directed toward partial reduction of the nitrile acid (**12a**) with lithium aluminum hydride, since initial formation of the carboxylate anion should result in a reduced tendency for this group to accept hydride ion. Reduction was carried out accordingly. There was obtained directly in 70% yield a neutral product which proved to be the desired lactam **10**. The substance differed markedly from the Beckmann rearrangement product **9** and on further reduction with lithium aluminum hydride it furnished an amine (**15**) identical in all respects with an authentic sample kindly furnished for comparison by Professor K. Wiesner.[9] Routine conversions afforded also the phenolic acetamide **16**, which showed all of the properties reported for this substance in the literature.[9]



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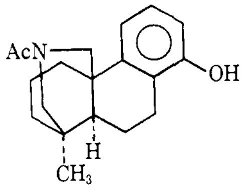

16

We turn now to a description of a few experiments that were carried out in connection with investigation of an alternate route to diterpene alkaloid intermediates.

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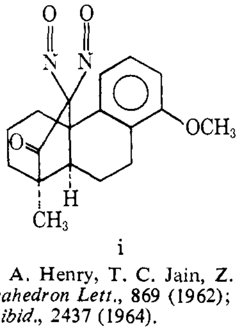
[7] While this manuscript was in preparation, a communication describing a similar sequence of reactions was reported independently by T. Matsumoto, M. Yanagiya, E. Kawakami, T. Okuno, M. Kakizawa, S. Yasuda, Y. Gama, J. Omi, and M. Matsunaga, *Tetrahedron Lett.*, 1127 (1968). Compounds which are common to our work and that of the Japanese investigators are 10 and 11.

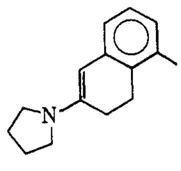
[8] When the condensation of ketone 8 was carried out under the conditions specified here, but in the presence of 3 equiv of butyl nitrite, a different product resulted. Elemental analysis indicated a formula $C_{18}H_{20}N_2O_4$, and hence an additional NO group must have been incorporated. Since the substance showed three aromatic protons in the nmr, an aromatic nitroso derivative is excluded. The ultraviolet spectrum closely resembled that for ketone 8, and the infrared spectrum showed carbonyl absorption at 5.73 μ. We were hence led to consideration of structure i for the new substance. It should be noted, however, that hydrolysis did not yield oximino ketone, α-diketone, nor ketone 8, and treatment of the material with sodium hydride and butyl nitrite as indicated previously did not furnish nitrile acid 12a. The question of the structure of this substance has not been investigated further.



i

[9] J. A. Finley, W. A. Henry, T. C. Jain, Z. Valenta, K. Wiesner, and C. M. Wong, *Tetrahedron Lett.*, 869 (1962); Z. Valenta, K. Wiesner, and C. M. Wong, *ibid.*, 2437 (1964).

The starting material in this sequence was 5-methoxy-2-tetralone which was converted into the corresponding pyrrolidine enamine **17**. Treatment of the latter substance with cyanogen chloride[10] furnished the corresponding cyano ketone.[11] The spectroscopic properties of this substance are in accord with its formulation as the enol tautomer **19a**. Although direct condensation of **19a** with malonic ester failed, presumably owing to the high acidity of the enol, the *p*-toluenesulfonoxy derivative **19b** reacted smoothly with this reagent and furnished compound **20** in good yield.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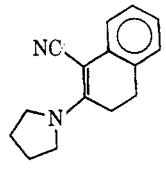
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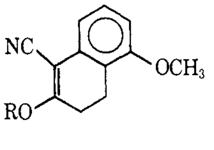
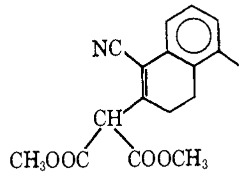

19a, R = H
b, R = Ts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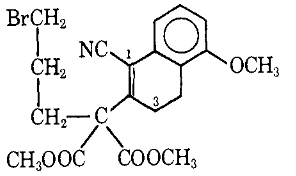
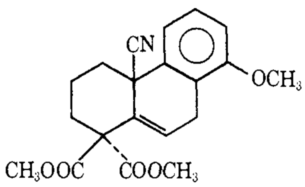

21

Alkylation of the malonate **20** with trimethylene dibromide in the presence of 1.05 equiv of potassium *t*-butoxide yielded a mixture containing some starting material, which could be resolved by chromatography on silica gel. The major product was amorphous, contained one bromine atom, and showed conjugated nitrile absorption in the infrared. We propose formula **21** as the structure of this intermediate. Internal alkylation in **21** promoted by sodium hydride afforded a crystalline product (**22**) in an over-all yield from compound **20** of approximately 50%. The substance exhibits unconjugated nitrile absorption in the infrared and shows one vinyl proton in the nmr. Attack at C-3 in the second stage of alkylation is, therefore, precluded.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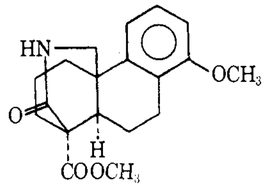
23

Although investigation of this series of reactions beyond the stage of compound **22** has not been undertaken, some preliminary information on catalytic hydrogenation of the unsaturated nitrile **22** is available. Reduction of the substance over palladized charcoal at 50–60° proceeded slowly and furnished a mixture which was chromatographed on alumina. In addition to some recovered starting material there were obtained a substance that appears to be the dihydro derivative of **22** and a lactam ester **23**. The reaction has not been examined further, and the ultimate yield of lactam is therefore uncertain.

Experimental Section

Preparation of Epoxide 2. A solution of 5.0 g of 2,3,4,9,10,12-hexahydro-1-methyl-8-methoxy-12-allyl-2-oxophenanthrene (**1**)[2] in 100 ml of chloroform was treated by slow addition with 42 ml of a benzene solution of perbenzoic acid (0.064 g/ml). The reaction mixture was stored at 5° for 48 hr, at the end of which time the solution was washed successively with dilute sodium hydroxide, water, and saturated sodium chloride solution. After drying over anhydrous magnesium sulfate, the solvent was removed, and the residue was chromatographed on alumina; yield 1.54 g of compound **2**, mp 121–125° (from ether–petroleum ether (bp 30–60°)), $\lambda_{\max}^{\mathrm{CS_2}}$ 5.99 μ (no methylene absorption), $\lambda_{\max}^{\mathrm{MeOH}}$ 228 mμ (ϵ 19,500).

Anal. Calcd for $C_{19}H_{22}O_3$: C, 76.48; H, 7.43. Found: C, 76.74; H, 7.28.

Preparation of Compound 3. A 500-mg sample of epoxide **2** was dissolved in 500 ml of dry benzene. The system was flushed with nitrogen, and 9 ml of *t*-butyl alcohol containing 90 mg of dissolved potassium was added with stirring. The solution was heated to 60–70° for 1 hr, whereupon the reaction was quenched by addition of 100 ml of 2 *N* sulfuric acid. The aqueous phase was extracted twice with methylene chloride, and the combined organic fractions were washed with water and saturated sodium chloride, dried over anhydrous magnesium sulfate, and evaporated. Chromatography of the amorphous residue on alumina furnished 115 mg of **3** which was recrystallized from methylene chloride–petroleum ether; mp 178–179° $\lambda_{\max}^{\mathrm{CS_2}}$ 2.78 and 5.84 μ.

Anal. Calcd for $C_{19}H_{22}O_3$: C, 76.48; H, 7.43. Found: C, 76.48; H, 7.32.

In view of failure of attempts to improve the yield in the epoxidation reaction, similar attempts to seek improvement in the cyclization step have not been undertaken.

Catalytic Hydrogenation of Compound 3. Palladium-on-charcoal, 480 mg, was added to a solution of 400 mg of cyclization product **3** in 15 ml of glacial acetic acid. The mixture was stirred in an atmosphere of hydrogen, and when hydrogen uptake had ceased, the catalyst was removed by filtration. Dilution with water and extraction with ether, followed by the usual washing and drying operations yielded material which was crystallized from acetone–petroleum ether; yield 388 mg, mp 168–169°, $\lambda_{\max}^{\mathrm{CS_2}}$ 2.78 and 5.84 μ.

Anal. Calcd for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05. Found: C, 75.70; H, 8.08.

Wolff–Kishner Reduction of Compound 4. A mixture of 200 mg of hydrogenation product **4** in 15 ml of ethanol, 4 g of potassium hydroxide in 4 ml of water, 25 ml of diethylene glycol, and 4 ml of hydrazine hydrate was heated under reflux for 2 hr in a slow stream of nitrogen. The reflux condenser was then removed and heating was continued at 200° for an additional 2.5 hr. The reaction mixture was then cooled and was poured into ice and 1 *N* hydrochloric acid. Extraction with methylene chloride was followed by standard washing and drying operations. Chromatography of the crude product furnished 100 mg of **6a** together with 70 mg of the corresponding phenol which could be remethylated. The analytical sample, prepared by recrystallization from ether–petroleum ether, melted at 152.5–153.5°; $\lambda_{\max}^{\mathrm{CS_2}}$ 2.79 μ.

Anal. Calcd for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.59; H, 8.91.

Preparation of Benzoate 6b. A 50-mg sample of alcohol **6a** was dissolved in 1 ml of pyridine. Benzoyl chloride (0.2 ml) was added, and the solution was allowed to stand at room temperature for 9 hr. Ice water was then added, and the product was taken into ether. The ether phase was washed successively with water, dilute hydrochloric acid, water, dilute sodium hydroxide, water, and saturated sodium chloride solution. After drying over anhydrous magnesium sulfate, the solvent was removed, and the residue was chromatographed on alumina. The product (**6b**), 56 mg, melted at 150–153°. Several recrystallizations from ether–petroleum ether gave the analytical sample, mp 152–153°; $\lambda_{\max}^{\mathrm{CS_2}}$ 5.85 μ.

Anal. Calcd for $C_{26}H_{30}O_3$: C, 79.97; H, 7.74. Found: C, 79.85; H, 7.79.

Chromium Trioxide–Pyridine Oxidation of Alcohol 6a. A 60-mg sample of alcohol **6a** in 1 ml of pyridine was added to a slurry of 60 mg of chromium trioxide in 0.5 ml of pyridine.[12] After 12 hr at room temperature, the reaction mixture was diluted with water and extracted with ether and methylene chloride. The combined organic fractions were washed with dilute hydrochloric acid, water,

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(10) M. E. Kuehne, *J. Amer. Chem. Soc.*, 81, 5400 (1959).

(11) P. Grafen and R. B. Turner, *Tetrahedron Lett.*, 3935 (1964); *cf.* S. W. Pelletier and P. C. Parthasarathy, *ibid.*, 103 (1964).

(12) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Amer. Chem. Soc.*, 75, 422 (1953).

dilute sodium hydroxide, and saturated sodium chloride solution. Drying over anhydrous magnesium sulfate and removal of the solvent furnished crude material which was chromatographed on alumina. There was obtained 31 mg of aldehyde **7**, mp 105–115°, which was recrystallized from methylene chloride–petroleum ether; mp 115–116°, $\lambda_{\max}^{CH_2Cl_2}$ 3.70 and 5.85 μ.

Anal. Calcd for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 80.55; H, 8.50.

Preparation of Ketone 8. A mixture of 50 mg of potassium acetate and 31 mg of aldehyde **7** in 1 ml of acetic anhydride was heated to 135° for 6 hr. Dilution with water and extraction with ether–methylene chloride, followed by the usual washing and drying operations yielded 46 mg of oily material, $\lambda_{\max}^{CH_2Cl_2}$ 5.78 μ which was employed directly in the next step.

A solution of the crude enol acetate in 2 ml of chloroform and 0.5 ml of methanol was cooled to −10°. Ozone was passed through the solution for 30 sec (0.197 mmol of ozone). After standing at −10° for 20 min, the solution was treated with 1 ml of acetic acid and 100 mg of zinc dust. The mixture was then stirred at 0° for 20 min at the end of which time a negative starch–iodide test was obtained. The product, 39 mg of oil, was isolated by routine manipulation, and afforded, after chromatography, 21 mg of crystalline ketone **8**, mp 144–146°. Recrystallization from methylene chloride–petroleum ether gave a sample, mp 151.5–152.5°, which did not depress the melting point of an authentic specimen.[2] The infrared spectra of the two samples were likewise identical.

The **oxime** prepared as a derivative melted at 215°, $\lambda_{\max}^{CS_2}$ 2.81 μ.

Anal. Calcd for $C_{18}H_{23}O_2N$: C, 75.76; H, 8.12; N, 4.91. Found: C, 75.81; H, 8.02; N, 4.98.

Beckmann Rearrangement of the Oxime of Ketone 8. A solution of 90 mg of oxime obtained in the preceding experiment in 1 ml of pyridine was heated under reflux (nitrogen atmosphere) for 1 hr with 1 ml of phosphorus oxychloride. The product was isolated by standard methods and, after recrystallization from methylene chloride–methanol, afforded 56 mg of pure lactam **9**, mp 276–277°, $\lambda_{\max}^{CH_2Cl_2}$ 2.98 and 6.04 μ. The nmr spectrum showed a broad, unresolved 2-proton signal at δ 2.48 and a methyl singlet at δ 1.32.

Anal. Calcd for $C_{18}H_{23}O_2N$: C, 75.76; H, 8.12; N, 4.91. Found: C, 75.50; H, 8.12; N, 4.89.

Reaction of Ketone 8 with Butyl Nitrite. a. Sodium Hydride and Excess Butyl Nitrite. A solution of 100 mg of ketone **8** in 5 ml of dry benzene was heated under reflux for 1 hr (nitrogen atmosphere) with 150 mg of sodium hydride. Freshly distilled butyl nitrite, 1.5 ml, was then added. The mixture was stirred at room temperature for 3 hr, at the end of which time a further 2 ml of butyl nitrite and 100 mg of sodium hydride were added. After 12 hr the reaction was quenched by the addition of water, and the product was taken into ether.

The ether phase was extracted with dilute sodium hydroxide solution, and was finally washed with water and saturated sodium chloride solution. After drying over anhydrous magnesium sulfate, the solvent was evaporated. The residue, 40 mg, on chromatography furnished 8 mg of crystalline material, mp 108–109°, $\lambda_{\max}^{CH_2Cl_2}$ 4.50 and 5.80 μ, to which structure **12b** is tentatively assigned.

Acidification of the alkaline extracts followed by standard work-up afforded, after recrystallization from ethanol, 25 mg of crystals, mp 300–305°, $\lambda_{\max}^{KBr}$ 4.50 and 5.90 μ (broad), that proved identical with a sample of nitrile acid (**12a**) obtained as described below.

b. Potassium *t*-Butoxide and 1.3 Equiv of Butyl Nitrite. A solution of 500 mg of ketone **8** in 25 ml of *t*-butyl alcohol containing 1 g of dissolved potassium was treated under a nitrogen atmosphere with 210 mg of freshly distilled butyl nitrite. After the reaction had proceeded for 3 hr a further 30 mg of butyl nitrite was added, and the reaction mixture was allowed to stand for an additional 12 hr. The solution was then poured into ice water and was extracted with chloroform and ether. The acidic product was isolated by base extraction, and after crystallization from methylene chloride–petroleum ether, afforded a pure sample of **oximino ketone 11**, mp 183–186°; $\lambda_{\max}^{CH_2Cl_2}$ 2.90, 3.05, 5.80, and 5.93 μ; $\lambda_{\max}^{MeOH}$ 247 mμ (ϵ 8390).

Anal. Calcd for $C_{18}H_{21}O_3N$: C, 72.22; H, 7.07; N, 4.68. Found: C, 72.06; H, 7.01; N, 4.63.

c. Potassium *t*-Butoxide and 3-Equiv of Butyl Nitrite. Repetition of the above experiment but with addition of 550 mg of butyl nitrite afforded a deep yellow compound, mp 153° dec; $\lambda_{\max}^{CH_2Cl_2}$ 5.72 and 6.13 μ. The structure of this substance is in doubt.

Anal. Calcd for $C_{18}H_{20}O_4N_2$: C, 65.84; H, 6.14; N, 8.53. Found: C, 65.75; H, 6.24; N, 8.43.

Preparation of Nitrile Acid (12a). A solution of 400 mg of oximino ketone **11** in a 4 ml of dry pyridine was treated at 0° with 400 mg of *p*-toluenesulfonyl chloride. The mixture was allowed to stand at 8° for 3 days and was then diluted with water and extracted with ether. Routine washing and drying of the ether solution followed by evaporation of the solvent gave 407 mg of crude tosylate, which was heated under reflux with 200 ml of tetrahydrofuran and 50 ml of 1 *N* sodium hydroxide. The bulk of the solvent was removed under reduced pressure, and the remaining aqueous alkaline solution was thoroughly extracted with ether. The product was finally isolated by acidification and extraction with ether–methylene chloride. Recrystallization of the crude material from ethanol furnished 361 mg of nitrile acid (**12a**), mp 303–306°; $\lambda_{\max}^{KBr}$ 4.50 and 5.90 μ (broad).

Anal. Calcd for $C_{18}H_{21}O_3N$: C, 72.22; H, 7.07; N, 4.68. Found: C, 72.19; H, 6.95; N, 4.73.

Esterification of the acid with diazomethane gave the corresponding methyl ester **12c**, mp 211.5–212.5°; $\lambda_{\max}^{CH_2Cl_2}$ 4.50 and 5.80 μ.

Anal. Calcd for $C_{19}H_{23}O_3N$: C, 72.82; H, 7.40; N, 4.47. Found: C, 72.92; H, 6.87; N, 4.76.

Reduction of Nitrile Acid (12a) with Sodium in Liquid Ammonia. A solution of 100 mg of nitrile acid (**12a**) in 100 ml of liquid ammonia was treated with 200 mg of sodium metal added in small pieces over a period of 0.5 hr. At the end of this time the ammonia was allowed to evaporate, water was added, and the basic aqueous phase was washed with ether. Acidification and ether extraction furnished 67 mg of product, mp 215–215.5°; $\lambda_{\max}^{KBr}$ 5.90 μ.

Anal. Calcd for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08. Found: C, 74.54; H, 8.12.

Preparation of Lactam 10. Nitrile acid (**12a**), 100 mg, was suspended in 200 ml of dry ether. Excess lithium aluminum hydride was added, and the mixture was stirred vigorously for 4 hr. The excess lithium aluminum hydride was decomposed by careful addition of water. The ether layer was then decanted, and the residual inorganic material was thoroughly washed with ether and chloroform. The combined organic fractions were washed, dried, and evaporated, and yielded 64 mg of lactam **10**, mp 302–304°, $\lambda_{\max}^{CH_2Cl_2}$ 3.00 and 6.03 μ. The nmr spectrum showed a broad unresolved, 2-proton signal at δ 1.26.

Anal. Calcd for $C_{18}H_{23}O_2N$: C, 75.76; H, 8.12; N, 4.91. Found: C, 75.66; H, 8.10; N, 4.79.

Preparation of Amine 15. A 65-mg sample of lactam **10** was dissolved in 25 ml of tetrahydrofuran. A large excess of lithium aluminum hydride was added, and the mixture was heated under reflux in a nitrogen atmosphere for 3 days. The excess reagent was then destroyed by addition of water, benzene was added, and the organic phase was separated by decantation. The product was extracted from the organic solution with dilute hydrochloric acid, which was then made basic and extracted with benzene. The resulting benzene solution of the product was finally washed with water, dried, and evaporated; yield 45 mg, mp 104–108°. Recrystallization from benzene–heptane gave a pure sample mp 108–109°. A mixture melting point with authentic material[9] showed no depression and the infrared spectra of the two specimens were identical.

Preparation of the Pyrrolidine Enamine of 5-Methoxy-2-tetralone (17). A solution of 17.6 g of 5-methoxy-2-tetralone and 11.8 ml of pyrrolidine in 50 ml of benzene was heated to reflux temperature under a constant water separator. After collection of water had ceased, the solvent was evaporated, and the residual material was crystallized from petroleum ether; yield 20.2 g, mp 79°, $\lambda_{\max}^{EtOH}$ 245 (12,750) and 322 mμ (ϵ 18,100).

Anal. Calcd for $C_{15}H_{19}ON$: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.42; H, 8.40; N, 6.18.

Preparation of Cyano Enamine 18. An 8.5-g sample of enamine **17** was dissolved in 20 ml of purified dioxane containing 5.6 ml of triethylamine. A solution of 4.33 g of cyanogen chloride in 15 ml of dioxane was then added with ice cooling, and the reaction mixture was allowed to stand at 0° for 3 hr and at room temperature for 7 hr. Dilution with ether was followed by thorough washing with water, dilute sodium bicarbonate solution, and saturated sodium chloride. The solution was finally dried and evaporated. Recrystallization of the crude product from benzene–heptane yielded 5.6 g of product **18**, mp 116–116.5°; $\lambda_{\max}^{EtOH}$ 245 (14,100) and 327 mμ (18,600).

Anal. Calcd for $C_{16}H_{18}ON_2$: C, 75.56; H, 7.13; N, 11.01. Found: C, 75.38; H, 7.10; N, 10.86.

Hydrolysis of Cyano Enamine 18. A 2.8-g sample of cyano enamine **18** was heated under reflux with 60 ml of 3% hydrochloric acid for 3 hr. The product (**19a**) separated as a crystalline solid and was isolated by filtration. The material obtained in this way was washed with water, dried, and recrystallized from ethanol–hexane; yield 2.1 g, mp 181.5–182.5°, $\nu_{\max}^{\text{Nujol}}$ 3135, 2218, 1644, 1606, and 1582 cm^{-1}; $\lambda_{\max}^{\text{EtOH}}$ 220 (16,640) and 291 mμ (ε 8120).

Anal. Calcd for $C_{12}H_{11}O_2N$: C, 71.63; H, 5.51; N, 6.96. Found: C, 71.62; H, 5.64; N, 6.91.

Preparation of *p*-Toluenesulfonate (19b). The product of the preceding experiment (**19a**), 2.15 g, was dissolved in benzene, and 6.8 ml of pyridine and 2.84 g of *p*-toluenesulfonyl chloride were added. After standing at room temperature for 3 hr, the reaction mixture was poured into ice and concentrated hydrochloric acid. The product was taken into methylene chloride, and after the usual washing and drying operations, the solvent was evaporated. Crystallization of the crude product from methylene chloride–heptane afforded 3.3 g of material melting at 146.5–147.5°; $\nu_{\max}^{\text{Nujol}}$ 2220, 1640, 1595, and 1575 cm^{-1}; $\lambda_{\max}^{\text{EtOH}}$ 215 (20,800), 285 (10,000), and 290 mμ (ε 10,400).

Anal. Calcd for $C_{19}H_{17}O_4NS$: C, 64.21; H, 4.82; N, 3.94; S, 9.02. Found: C, 64.33; H, 4.92; N, 3.55; S, 8.79.

Preparation of Cyano Malonate (20). A mineral oil dispersion of sodium hydride, 445 mg, containing 50% of the hydride, was washed with benzene and suspended in 45 ml of dry dioxane. Dimethyl malonate, 7.1 ml, was added with stirring. A dioxane solution of 3.17 g of tosylate **19b** was then introduced by dropwise addition, and the reaction mixture was stirred at room temperature for 2 days and at 80° for 2 hr. The product was isolated in the usual way by water dilution and ether extraction; yield 2.5 g, mp 103–106° (from hexane); $\nu_{\max}^{\text{film}}$ 2210, 1733, 1620, and 1580 cm^{-1}; $\lambda_{\max}^{\text{EtOH}}$ 213 (15,300) and 285 mμ (ε 10,400).

Anal. Calcd for $C_{17}H_{17}O_5N$: C, 64.75; H, 5.43; N, 4.44. Found: C, 64.98; H, 5.50; N, 4.20.

Alkylation of Compound 20 with Trimethylene Dibromide. Cyano malonate (**20**), 1.16 g, was dissolved in 8.5 ml of dimethylformamide containing 1.05 equiv of potassium *t*-butoxide. The reaction vessel was flushed with nitrogen, and a threefold excess of trimethylene dibromide was added. The mixture was allowed to stand at room temperature for 4 days, at the end of which time another molar equivalent of trimethylene dibromide was added. The reaction was completed by heating to 60° for 8 hr and was then diluted with water and extracted with ether. After washing and drying, the solvent was removed, and the residual oil was chromatographed on silica gel. In addition to starting material there was obtained an amorphous product, $\nu_{\max}^{\text{film}}$ 2210, 1740, 1618, and 1580 cm^{-1}.

Anal. Calcd for $C_{20}H_{22}ONBr$: Br, 18.3. Found: Br, 18.0.

The crude mixture obtained from 1.24 g of **20** was taken without chromatography and heated for several hours under vacuum to remove trimethylene dibromide. The material was then dissolved in 20 ml of benzene and 20 ml of dimethyl sulfoxide. To this solution there was added a twofold excess of benzene-washed sodium hydride–mineral oil dispersion, and the reaction mixture was stirred until hydrogen evolution ceased (24–48 hr). Standard work-up, followed by chromatography on silica gel afforded 770 mg of product (**22**), which melted at 130.5–131° after recrystallization from ether–petroleum ether; $\nu_{\max}^{\text{film}}$ 2200, 1732, and 1600 cm^{-1}; $\lambda_{\max}^{\text{EtOH}}$ 273.5 (2340) and 281 mμ (ε 2450).

Anal. Calcd for $C_{20}H_{21}O_5N$: C, 67.59; H, 5.96; N, 3.94. Found: C, 67.49; H, 6.02; N, 3.97.

Catalytic Hydrogenation of Compound 22. A 300-mg sample of nitrile diester **22** in 50 ml of methanol was shaken with 30 mg of 10% palladized charcoal at 50–60° in a hydrogen atmosphere. When the uptake of hydrogen ceased, the solution was filtered, and the filtrate was evaporated to dryness. Chromatography of the residue on alumina afforded starting material **22**, a second substance which appeared to be dihydro **22**, and lactam ester **23**, mp 241.5–243.5°; $\lambda_{\max}^{CH_2Cl_2}$ 2.95, 5.78, and 6.0 μ.

Anal. Calcd for $C_{19}H_{23}O_4N$: C, 69.28; H, 7.04; N, 4.25. Found: C, 69.35; H, 6.76; N, 3.99.

The Solvolysis of Bridgehead-Substituted *exo*-2-Norbornyl Bromides[1]

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Abstract: The solvolysis of six bridgehead-substituted *exo*-2-norbornyl bromides in 80% aqueous ethanol is described: namely, the 1-carbomethoxy (**2**), 1-acetoxy (**3**), 1-benzamido (**4**), 1-amino (**5**), and 1-carboxylate (**6**), together with the parent bromide (**1**) itself. The solvolytic reactivity at 25° of the bromides **2**–**6** relative to that of **1** varies by 10^5-fold, the values being for **2**, 4.9×10^{-4}; for **3**, 2.4×10^{-3}; for **4**, 1.1; for **5**, 46; and for **6**, 4.0. Arguments are presented that these bromides represent a spectrum of solvolysis behavior. The rates illustrate a competition between inductive retardation and anchimeric acceleration by the bridgehead function, the latter effect growing in importance from **2** through **5**, with **6** being a somewhat special case apart. In no case does 1,6 σ-electron delocalization seem far advanced in the slow step of the solvolysis, thus affording a rationale for the greater deactivation by −I groups (**2** and **3**) than activation by +R groups (**4** and **5**). Even though unbridged ions intervene in some of these solvolyses, the solvolysis products are always *exo* substituted. Thus from **2** resulted the *exo*-ethoxy and *exo*-hydroxy analogs **9** and **10**, respectively. Some of the bromides underwent total rearrangement to norcamphor (**13**) *via* stabilized ions engendered by a Wagner–Meerwein rearrangement. The timing of this rearrangement varied from *after* the slow step (in **3**) to *simultaneously* with it (in **4** and **5**) The bromo acid anion **6** led to extensively rearranged products, again *exo* in nature, in this case the 2-ethoxy and 2-hydroxy esters **14** and **15**, respectively.

The solvolytic reactivites of many types of substituted norbornanes have been extensively investigated.[2] Bridgehead-substituted *exo*-2-norbornyl derivatives, however, are one of the less pursued classes. Only two groups, that of Schleyer[3] and that of Brown,[4]

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(1) Taken from portions of the dissertation of W. J. W., June 1967. Part of this material was presented at the Great Lakes Regional Meeting of the American Chemical Society, Milwaukee, Wis., June 1968, Abstracts of Papers, p 37.

(2) The solvolysis of no other system has been so extensively discussed and the references are myriad. However, for some reviews largely devoted to the norbornyl derivatives, *cf.*, J. A. Berson in "Molecular Rearrangements," Vol. 1, P. de Mayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, Chapter 3; B. Capon, *Quart. Rev.* (London), **18**, 45 (1964); P. D. Bartlett, "Nonclassical Ions," W. A. Benjamin, Inc., New York, N. Y., 1965; G. D. Sargent, *Quart Rev.* (London), **20**, 301 (1966); G. E. Gream, *Rev. Pure Appl. Chem.*, **16**, 25 (1966); H. C. Brown, *Chem. Brit.*, 199 (1966); and H. C. Brown, *Chem. Eng. News*, **45**, No. 7, 87 (Feb 13, 1967).