[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING, UNIVERSITY OF CALIFORNIA]

Azabicycloalkanes. II. 1,5-Substituted Morphan[1]

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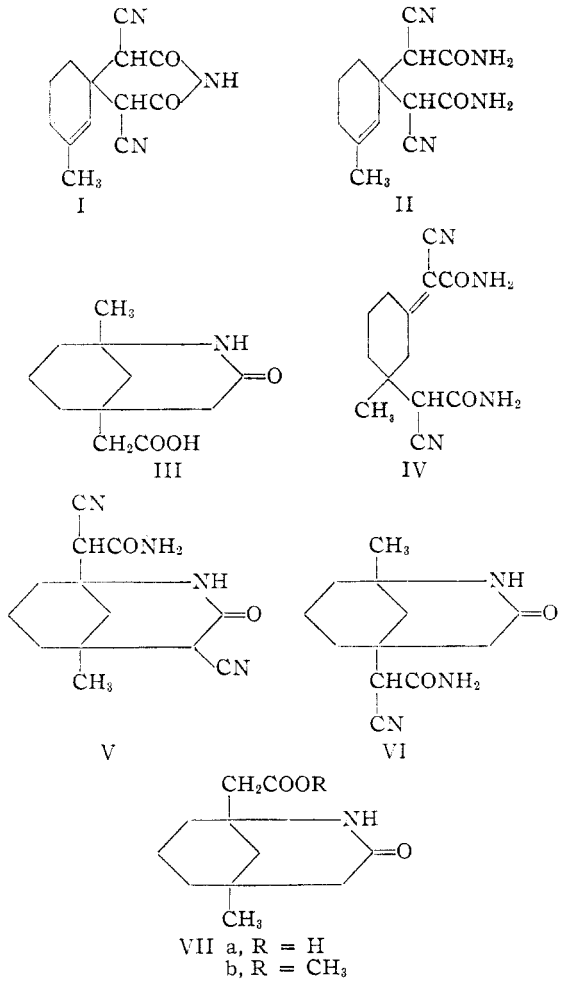
Treatment of 3-methyl-2-cyclohexene-1-one with ethyl cyanoacetate and ammonia in alcohol does not give the expected Guareschi product; instead, there is obtained a bicyclic structure, α,4-dicyano-3-oxo-5-methyl-2-azabicyclo[3.3.1]nonaneacetamide. This amide has been hydrolyzed, decarboxylated and reduced to give 5-methyl-2-azabicyclo[3.3.1]nonaneethanol (5-methylmorphanethanol). The piperidine-catalyzed addition of cyanoacetamide to 3-methyl-2-cyclohexene-1-one in aqueous solution gives 4-cyano-5-methyl-3-oxo-2-azabicyclo[3.3.1]nonanol in 77% yield.

During an investigation of intermediates for the preparation of morphan derivatives containing a quaternary carbon at C-5, a rather unexpected formation of an azabicyclononane system was encountered.

Farmer and Ross[3] have reported that when 3-methyl-2-cyclohexene-1-one is treated with ethyl cyanoacetate and ammonia in alcohol, according to the conditions of the Guareschi reaction,[4] they obtained, in addition to the expected Guareschi imide (I), an amide to which they assigned the diamide structure (II). Since II appeared to be a useful intermediate for the preparation of morphan derivatives the preparation reported by Farmer and Ross was repeated and an alcohol insoluble product was obtained whose melting point and analysis agreed with the product to which they had assigned the diamide structure (II). When this amide was hydrolyzed in either acidic or basic media, and then decarboxylated, a nitrogen-containing acid, $C_{11}H_{17}O_3N$, was obtained. This acid gave no tests for unsaturation with bromine, permanganate, or catalytic hydrogenation and it was not hydrolyzed further under a variety of rather vigorous conditions. At 225° in aqueous alkali, partial hydrolysis occurred with the liberation of at least some of the nitrogen as ammonia. The lack of unsaturation and resistance to hydrolysis suggested that this acid contained a lactam ring and that this lactam had a bridged structure.[5] The only lactam which could arise by cyclization from the diamide structure (II) proposed by Farmer and Ross, would be III. The lactam (III) could have been produced by means of an internal Ritter reaction[6] between a nitrile and the C-3 tertiary carbon, followed by hydrolysis and decarboxylation; however, it would not be possible to obtain the lactam (III) directly from II under alkaline conditions. Thus, the Guareschi product must not have the structure suggested by Farmer and Ross, but must itself be a lactam, or at least possess a structure capable of being converted into a lactam under either acidic or alkaline conditions. Since there is no reasonable path for the conversion of IV into V in an acid medium, the only structures left for consideration are V and VI[7]; however, when the C_{11}-acid was hydrolyzed in 2 *N* sodium hydroxide for 8 hours at 250°,



ammonia was evolved and there was obtained an unsaturated acid, m.p. 104–108°, whose neutral equivalent, elemental analysis and m.p. range indicated that it was probably a mixture of the isomers of 1-methyl-2-cyclohexene-1,3-diacetic acid. The loss of ammonia in this alkaline hydrolysis is evidence for the structure of the lactam-acid (VIIa) since the β-amino acid which would be obtained by opening of the lactam ring would be expected to lose ammonia upon vigorous alkaline hydrolysis. The lactam (III) would have given a stable dibasic amino acid under these conditions.[5]

Further evidence for the structure of the Guareschi product was obtained in tests for unsaturation and in its ultraviolet absorption spectrum. The compound was saturated to permanganate and the absorption spectrum showed only shoulders at about 222, 245 and 280 mμ, with log ε from 3.9 to

(1) Presented in part before the Division of Organic Chemistry, American Chemical Society, Milwaukee, Wis., April 2, 1952.

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(3) E. H. Farmer and J. Ross, *J. Chem. Soc.*, 1570 (1926).

(4) I. Guareschi, *Gazz. chim. ital.*, **48**, II, 97 (1918).

(5) M. W. Cronyn, *J. Org. Chem.*, **14**, 1013 (1949).

(6) J. J. Ritter and P. P. Minieri, THIS JOURNAL, **70**, 4045 (1948).

(7) This would assume the formation of VI by a path which would not involve the intermediate formation of II.

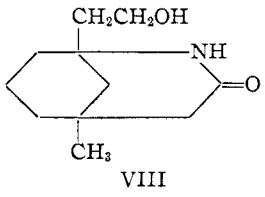
1.4 with no evidence of the characteristic peak at 233 mμ with log ε of 4.04 as shown by ethyl α-cyanocyclohexane-$\Delta^{1,\alpha}$-acetate whose spectrum was used for comparison. Thus, the Guareschi reaction with 3-methyl-2-cyclohexene-1-one must give α,4-dicyano-3-oxo-5-methyl-2-azabicyclo[3.3.1]-nonaneacetamide (V) and the acid obtained by hydrolysis and decarboxylation of V would be 3-oxo-5-methyl-2-azabicyclo[3.3.1]nonaneacetic acid (VIIa).

The lactam (V) probably results from an initial Knoevenagel condensation of 3-methyl-2-cyclohexene-1-one with ethyl cyanoacetate to give ethyl α-cyano-3-methyl-2-cyclohexene-$\Delta^{1,\alpha}$-acetate. This product has been obtained in the piperidine-catalyzed condensation of ethyl cyanoacetate and 3-methyl-2-cyclohexene-1-one.[8] Subsequent Michael addition of cyanoacetamide and aminolysis would give IV; finally, cyclization of IV would give V. A similar addition of an amide to an α,β-unsaturated system giving a seven-membered ring has been observed by Williams.[9]

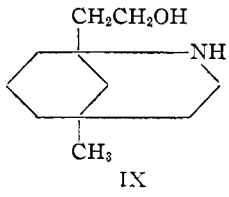
A similar product was obtained when the Guareschi conditions were applied to 3-ethyl-2-cyclohexene-1-one. Since both 2- and 3-substituted 2-cyclohexene-1-ones are readily available this reaction should lend itself to the preparation of a number of morphan derivatives.

The Guareschi product (V) was converted into the corresponding triamide in 63% yield by solution in concentrated sulfuric acid followed by dilution with water.

When the lactam-acid (VIIa) was treated with lithium aluminum hydride there was obtained a mixture of the lactam-alcohol (VIII) in 55% yield and 24% of the amino-alcohol (IX). Long periods of refluxing with excess lithium aluminum hydride did not seem to increase the yield of the amino-alcohol. However, when the lactam-alcohol (VIII) was isolated and then treated with lithium aluminum hydride a 48% yield of the amino-alcohol (IX) was obtained. It would seem that a stable, non-reducible salt of VIII must be produced in the initial reduction. This general type of effect has been observed in the lithium aluminum hydride reduction of other types of functional groups.[10] The methyl ester (VIIb) of the lactam-acid was prepared and reduced over copper chromite catalyst at 210°. The only product isolated was the lactam-alcohol (VIII) which was obtained in 65% yield.



VIII

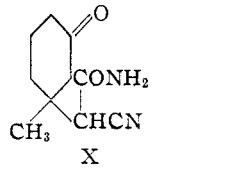


IX

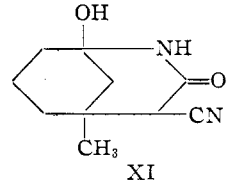
The infrared absorption spectrum[11] of the Guareschi reaction product shows, in addition to the nitrile absorption at 4.61 μ, two bands (5.90 and 6.05–6.15 μ) in the carbonyl region which are characteristic of cyanoacetamides, cyanoacetamide itself having bands at 5.90 and 6.18 μ.[12a] The methyl ester (VIIb) of the lactam-acid shows the characteristic ester absorption at 5.81 μ and a lactam band at 6.05 to 6.10 μ similar to the lactam of *cis*-3-aminocyclohexaneacetic acid which shows a broad band at 6.02–6.10 μ. In the NH and OH region, however, the spectrum of VIIb displayed a rather interesting behavior in that the number of bands varied with the solvent. In chloroform there was one band at 2.96 μ, as the nujol mull two bands appeared at 3.12 and 3.23 μ and in carbon disulfide three bands were present at 2.89, 3.09 and 3.23 μ. The spectrum of the lactam-acid (VIIa) was what would be expected for an acylamino acid, with bands at 5.89 and 6.0–6.25 μ.[12b]

Although the formation of V involved a Michael addition to give a quaternary carbon, V was obtained in good yield since the subsequent cyclization removed the product from the Michael equilibrium. The only previous successful[13] Michael addition with 3-substituted 2-cyclohexene-1-ones occurred in Rabe's preparation of 3-oxo-5-methylbicyclo[3.3.1]nonanol.[14] This fact and the preparation of pyridine derivatives by the addition of cyanoacetamide to α,β-unsaturated ketones[15,16] suggested that the Michael addition of cyanoacetamide to 3-methyl-2-cyclohexene-1-one might be followed by a ring closure to give a bicyclic hydroxy-lactam.

Indeed, when 3-methyl-2-cyclohexene-1-one was treated with cyanoacetamide in the presence of piperidine in water an addition product was obtained in 77% yield which could be either X or XI. The same condensation product was obtained in 24% yield when aqueous potassium hydroxide was used as the catalyst.



X



XI

Neither the ultraviolet nor infrared spectra show any of the characteristics of carbonyl absorption. The infrared absorption bands are those to be expected for a structure such as XI with OH and NH bands at 2.9 and 3.2 μ, the nitrile at 4.63 μ and the lactam at 6.10 μ. The lack of the characteristic double band for a substituted cyanoacetamide in the amide region is also evidence in favor of the hydroxy-lactam structure XI.

The ready formation of this bicyclic hydroxy-lactam under such mild conditions, together with the

(8) E. Knoevenagel and S. Mottek, *Ber.*, **37**, 4464 (1904).

(9) A. Williams, Thesis, University of California, 1951, p. 14.

(10) W. G. Dauben and J. F. Eastham, THIS JOURNAL, **73**, 3260 (1951).

(11) We are indebted to Dr. N. K. Freeman, Department of Medical Physics, University of California, Berkeley, for the infrared spectra referred to in this paper.

(12) H. M. Randall, R. G. Fowler, N. Fuson and J. R. Dangl, "Infrared Determination of Organic Structures," D. Van Nostrand Co., Inc., New York, N. Y., 1949 (a) p. 126; (b) p. 13.

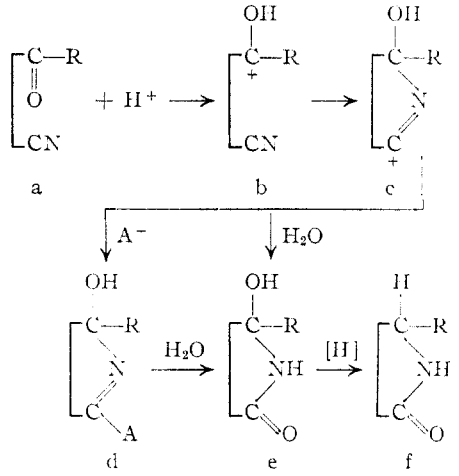
(13) *Cf.* D. Vörlander and J. Gärtner, *Ann.*, **304**, 7 (1898); E. H. Farmer and J. Ross, *J. Chem. Soc.*, **127**, 2358 (1925); 3233 (1926); G. F. Woods, THIS JOURNAL, **69**, 2549 (1947).

(14) P. Rabe, *Ber.*, **37**, 1671 (1904); P. Rabe and K. Appuhn, *ibid.*, **76**, 982 (1943).

(15) E. P. Kohler and B. L. Souther, THIS JOURNAL, **44**, 2903 (1922).

(16) C. Barat, *J. Indian Chem. Soc.*, **7**, 321 (1930); **8**, 699 (1931).

observation[17] that γ-cyanoketones give dihydropyridones with hydrochloric or hydrobromic acids, suggests that the reductive-cyclization in Gates' morphine synthesis[18] may proceed by way of a hydroxy-lactam as an intermediate[19]



The occurrence of intermediates such as c and d is substantiated by Kohler's isolation of 2-bromopyridines when the system was such that dehydration of the d type intermediate could occur to give aromatization of the system; otherwise, hydrolysis to the hydroxy-lactam e was apparently necessary before dehydration could occur. The elimination of water in Gates' bicyclic structure could not occur since it would lead to a violation of Bredt's rule.[20]

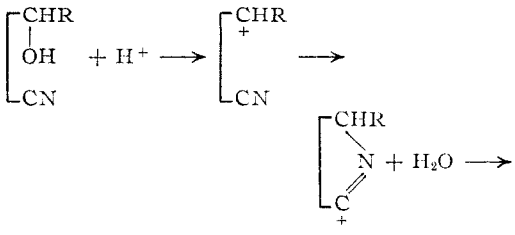
The production of N-substituted amides by the acid-catalyzed addition of a carbonyl to a nitrile is also illustrated by the formaldehyde–nitrile condensations.[21] These carbonyl condensations are analogous to the general three-component ionic reactions involving olefins.[22] In this case the carbonyl group takes the place of the alkene, $A^+ = H^+$, and B = RCN.

Ethyl cyanoacetate and 3-methyl-2-cyclohexene-1-one were condensed in an alcoholic solution of ethylamine to give a low yield of N-ethyl-4-cyano-5-methyl-3-oxo-2-azabicyclo[3.3.1]nonanol. This was a rather interesting result in view of the similarity in conditions between this reaction and the Guareschi reaction with the same ketone.

(17) E. P. Kohler, A. Graustein and D. R. Merrill, THIS JOURNAL, **44**, 2536 (1922).

(18) M. Gates, R. B. Woodward, W. F. Newhall and R. Kuenzl, *ibid.*, **72**, 1141 (1950); J. H. Helberger and A. von Rebay, *Ann.*, **539**, 187 (1939).

(19) M. Gates, private communication, has suggested that this ring closure may have occurred by way of an initial reduction of the carbonyl to the secondary alcohol which could then give the lactam through an acid-catalyzed Ritter reaction[6]



Dr. Horace Brown of Merck and Co., Inc., has found that the reductive-cyclization will not proceed if the copper chromite catalyst is washed free of all traces of acetic acid.

(20) J. Bredt, *Ann.*, **437**, 1 (1924).

(21) D. T. Mory and E. Ringwald, THIS JOURNAL, **69**, 635 (1947).

(22) T. L. Cairns, P. J. Graham, P. L. Barrick and R. S. Schreiber, *J. Org. Chem.*, **17**, 751 (1952).

Experimental[23]

3-Methyl-2-cyclohexene-1-one.—A variation of the procedure of Smith and Roualt[24] which gave considerably improved yields was used. Eight moles (1045 g.) of ethyl acetoacetate and four moles (120 g.) of paraformaldehyde were mixed and 40 ml. of piperidine was added. The solution became warm and the temperature was maintained between 50 and 60° by cooling in an ice–salt-bath. When the reaction was no longer exothermic, the mixture was left standing at room temperature for 30 min. and it was then heated on the steam-bath for 1 hr. The light oil was added to 2 l. of 20% sulfuric acid and the solution was stirred and heated to reflux for 8 hr. After extraction with methylene chloride, drying over anhydrous magnesium sulfate and removal of the solvent, the residue was fractionated to give 274 g. (62%) of 3-methyl-2-cyclohexene-1-one, b.p. 88–90° (18 mm.), and 31 g. of Hagemann's ester, b.p. 121–123° (4 mm.).

α,4-Dicyano-3-oxo-5-methyl-2-azabicyclo[3.3.1]nonaneacetamide (V).—An ice-cold mixture of 22 g. (0.2 mole) of 3-methyl-2-cyclohexene-1-one and 45 g. (0.4 mole) of ethyl cyanoacetate was added to 75 ml. of absolute alcohol saturated with ammonia at −10° (16 g. of ammonia) in a citrate bottle. The solution was allowed to stand four days at room temperature while the crystalline product separated on the sides of the flask. After filtration the solid was powdered and triturated twice with 100-ml. portions of hot 95% ethanol. The crude, alcohol insoluble product weighed 23.6 g. and melted at 260–268° dec. It was dissolved in hot dimethylformamide and after the addition of water the cooled solution deposited 21.4 g. (44%) of V, m.p. 269–273° dec. (sealed tube). An analytical sample was prepared by two more recrystallizations from dimethylformamide–water and melts at 274.5–276° dec. (sealed tube). Farmer and Ross reported a melting point of 275° for their diamide.[3]

Anal. Calcd. for $C_{13}H_{16}N_4O_2$: C, 59.98; H, 6.19; N, 21.54. Found: C, 59.91; H, 6.00; N, 21.60.

The compound is insoluble in all common organic solvents but soluble in hot dimethylformamide. It dissolves slowly in cold concentrated sulfuric acid. The ultraviolet absorption showed several shoulders at 222, 245 and 280 mμ with log ε 3.9 to 1.4. Infrared absorption, λ_{max}^{nujol} 3.02 μ, 3.20 μ (NH), 4.61 μ (CN), 5.90 μ, 6.05–6.15 μ (amide).

Cooling the hot alcohol extracts from the crude reaction product gave 7.1 g. of colorless prisms, m.p. 174–176°. An analytical sample was obtained by recrystallization from acetonitrile or isopropyl alcohol, m.p. 175.5–176.5°.

Anal. Calcd. for $C_{22}H_{31}N_5O_4$: C, 61.56; H, 7.28; N, 16.32. Found: C, 61.76, 61.76; H, 7.28, 7.30; N, 16.26, 16.04.

4-Carboxamide-3-oxo-5-methyl-2-azabicyclo[3.3.1]nonanemalonamide.—The Guareschi lactam (V), 5.2 g. (0.02 mole), was dissolved in 20 ml. of warm concentrated sulfuric acid and heated on the steam-bath for 30 minutes. The cooled solution was poured carefully on to 50 g. of ice and filtered from a small amount of insoluble material. Neutralization of the acid with sodium carbonate gave 3.4 g. (64%) of a solid melting at 311°. An analytical sample was prepared by recrystallization from water, m.p. 313–314° (sealed tube).

Anal. Calcd. for $C_{13}H_{20}N_4O_4$: C, 52.69; H, 6.80; N, 18.91. Found: C, 52.41; H, 6.76; N, 18.56.

3-Oxo-5-methyl-2-azabicyclo[3.3.1]nonaneacetic Acid (VIIa). a. Acid Hydrolysis.—A solution of 20.8 g. of the lactam (V) in 60 ml. of sulfuric acid was heated on the steam-bath for 30 min. It was then diluted with 250 ml. of water and heated to reflux for 36 hr. The hot solution was treated with charcoal and upon cooling 15.7 g. (91% yield) of the

(23) Analyses by the Microanalytical Laboratory of the Department of Chemistry, University of California. The ultraviolet absorption spectra were taken in 95% ethanol using a Beckman model DU spectrophotometer. All melting points are corrected.

(24) L. I. Smith and G. F. Roualt, THIS JOURNAL, **65**, 631 (1943).

lactam-acid (VIIa) separated in the form of small prisms, m.p. 203–205°. Two recrystallizations from acetonitrile–water gave an analytical sample, m.p. 206–207°.

Anal. Calcd. for $C_{11}H_{17}NO_3$: C, 62.55; H, 8.13; N, 6.63; neut. equiv., 211.5. Found: C, 62.74; H, 7.89; N, 6.80; neut. equiv., 213.

A solution of the lactam-acid in chloroform did not decolorize bromine nor aqueous potassium permanganate. It did not absorb hydrogen over Adams catalyst. Infrared absorption, λ_{max}^{nujol} 2.99μ (OH,NH), 5.89 μ (COOH), 6.20–6.25 μ (lactam).

b. **Alkaline Hydrolysis.**—The Guareschi lactam (V), 5.2 g. (0.02 mole), was heated in 75 ml. of refluxing 30% sodium hydroxide for three days. After acidification and treatment with charcoal the solution was extracted with ether in a continuous extractor for three days. Removal of the ether and sublimation of the residue, which decarboxylated at 160°, at 190–200° (0.5 mm.), gave 2.8 g. of sublimate, m.p. 205–206° and undepressed when mixed with a sample of the acid-lactam obtained by hydrolysis in acid solution.

Alkaline Hydrolysis of the Acid Lactam (VIIa).—The acid-lactam (VIIa), 2.1 g. (0.01 mole), was heated for 8 hours at 250° in 30 ml. of 2 *N* sodium hydroxide. Acidification of the solution with 35 ml. of 2 *N* hydrochloric acid gave an oil which solidified and redissolved upon heating the solution to boiling. Upon cooling the solution, 1.2 g. of the starting lactam separated, m.p. 198–203°. The aqueous solution was extracted with chloroform, the chloroform was removed and the residue was taken up in ether and filtered from another 0.1 g. of starting lactam-acid, m.p. 200–203°. The ether solution was dried and evaporated leaving an oil which solidified to give 0.65 g. of material melting at 88–95°. Several recrystallizations from hexane–ether raised the melting point to 104–108°. The analysis, neutral equivalent, and broad melting range indicate a mixture of isomers of 1-methyl-2-cyclohexene-1,3-diacetic acid.

Anal. Calcd. for $C_{11}H_{16}O_4$: C, 62.24; H, 7.60; neut. equiv., 106. Found: C, 62.20; H, 7.55; neut. equiv., 108.

Methyl 3-Oxo-5-methyl-2-azabicyclo[3.3.1]nonaneacetate (VIIb).—The methyl ester (VIIb) of the acid-lactam was prepared by refluxing for 16 hours a mixture of 13.5 g. of VIIa in 40 ml. of methanol, 40 ml. of chloroform and 4 ml. of concentrated sulfuric acid under a Soxhlet containing 10 g. of anhydrous magnesium sulfate. The solution was cooled, extracted with an excess of 8% bicarbonate solution and dried. Removal of the chloroform left an oil which solidified to give 14.5 g. (96%) of the crude ester, m.p. 73–75°. Recrystallization from hexane gave 12.5 g. of material, m.p. 74–75°. An analytical sample was prepared by sublimation and recrystallization from hexane, m.p. 75.8–76.5°.

Anal. Calcd. for $C_{12}H_{19}NO_3$: C, 63.97; H, 8.50; N, 6.22. Found: C, 64.18; H, 8.48; N, 6.10.

The lactam is sufficiently basic to prevent the extraction of the ester from an acid solution with ether. Infrared absorption, $\lambda_{max}^{CHCl_3}$ 2.96 μ (NH), 5.81 μ (ester), 6.05–6.10 μ (lactam); $\lambda_{max}^{CS_2}$ 2.89 μ, 3.09 μ, 3.23 μ (NH), 5.76 μ (ester), 6.00 μ (lactam); λ_{max}^{nujol} 3.12 μ, 3.23 μ (NH), 5.80 μ (ester), 6.00–6.15 μ (lactam).

Lithium Aluminum Hydride Reduction of VIIb.—To a suspension of 4 g. of lithium aluminum hydride in 150 ml. of anhydrous dioxane was added dropwise a solution of 9 g. (0.04 mole) of the methyl ester in 75 ml. of dioxane. The solution was heated to reflux for 48 hours and it was then cooled in an ice-bath. One hundred ml. of 30% sulfuric acid was added dropwise and the dioxane was removed by steam distillation. Extraction with chloroform and removal of the solvent left 2.7 g. of solid, m.p. 146–148°. The aqueous solution was basified and extracted with chloroform. Removal of the solvent and treatment of the residue with pentane gave an additional 0.36 g. of the lactam-alcohol, m.p. 147–150°. The total recovery of **3-oxo-5-methyl-2-azabicyclo[3.3.1]nonaneëthanol (VIII)** was 39%. An analytical sample was prepared by crystallization from benzene, m.p. 149–150°.

Anal. Calcd. for $C_{11}H_{19}NO_2$: C, 66.97; H, 9.71; N, 7.10. Found: C, 66.99; H, 9.64; N, 6.97.

After the removal of the lactam-alcohol the pentane was evaporated and the residue was sublimed at 80–90° (18 mm.) to give 1.4 g. (19%) of **5-methyl-2-azabicyclo[3.3.1]nonaneethanol (IX)**, m.p. 62–63°.

Anal. Calcd. for $C_{11}H_{21}NO$: C, 72.68; H, 11.40; N, 7.64. Found: C, 72.36; H, 11.40; N, 7.83.

The picrate was prepared in ether solution and was purified by recrystallization from benzene, m.p. 173.5–174.5°.

Anal. Calcd. for $C_{17}H_{24}N_4O_8$: C, 49.51; H, 5.87; N, 13.59. Found: C, 49.72; H, 5.76; N, 13.22.

In another reduction with lithium aluminum hydride and tetrahydrofuran as the solvent there was obtained a 60% yield of the lactam-alcohol and 10% of the amino-alcohol.

Hydrogenation of VIIb over Copper Chromite.—A solution of 1.13 g. of the methyl ester (VIIb) was shaken at 210° with 3 g. of copper chromite catalyst[25] under 150 atm. of hydrogen. Absorption of hydrogen ceased in an hour and after the removal of the catalyst the solvents were removed and the residue crystallized from ether and was recrystallized from benzene–petroleum ether to give 0.64 g. (65%) of VIII, m.p. 148.5–149.5°.

Lithium Aluminum Hydride Reduction of VIIa.—A suspension of 2.1 g. (0.01 mole) of VIIa and 1.2 g. of lithium aluminum hydride in 75 ml. of dioxane was stirred and heated to reflux for 24 hr. The solution was cooled in an ice-bath and hydrolyzed with 20 ml. of water followed by 50 ml. of 20% sulfuric acid. The dioxane was removed by steam distillation and the aqueous solution was extracted with chloroform. Removal of the chloroform and crystallization of the residue from water gave 1.1 g. (55%) of the lactam-alcohol (VIII), m.p. 148–149.5°.

The aqueous solution was poured into 100 ml. of 20% potassium hydroxide and it was then extracted with ether. Removal of the ether and sublimation of the residue gave 0.44 g. (24%) of the amino-alcohol (IX), m.p. 62–63°.

Lithium Aluminum Hydride Reduction of VIII.—The lactam-alcohol (VIII), 2 g. (0.01 mole), was dissolved in 50 ml. of hot dioxane and added dropwise to a stirred suspension of 1.2 g. of lithium aluminum hydride in refluxing dioxane. After 20 hours of refluxing, the solution was decomposed with water and sulfuric acid and, after the removal of the dioxane, the aqueous solution was continuously extracted with chloroform. Removal of the chloroform left 0.49 g. of starting acid. Basification of the aqueous solution and recovery of the amine by extraction with ether followed by sublimation gave 0.91 g. (48%) of IX, m.p. 62–63°.

α,4-Dicyano-3-oxo-5-ethyl-2-azabicyclo[3.3.1]nonaneacetamide.—A solution of 4.8 g. (0.039 mole) of 3-ethyl-2-cyclohexene-1-one, 10 g. (0.8 mole) of ethyl cyanoacetate and 8.5 g. (0.5 mole) of NH_3 in 40 ml. of alcohol was allowed to stand for 3 days. There was deposited 2.8 g. of large prisms. Recrystallization from 20 ml. of dimethylformamide and 30 ml. of water gave 2.7 g. (25% yield), of product, m.p. 275–280° dec. One more crystallization from DMF–water gave an analytical sample, m.p. 279–280° dec. (preheated block).

Anal. Calcd. for $C_{14}H_{18}N_4O_2$: C, 61.30; H, 6.62; N, 19.96. Found: C, 61.53; H, 6.68; N, 19.47.

4-Cyano-5-methyl-3-oxo-2-azabicyclo[3.3.1]nonanol (XI).—A solution of 2.42 g. (0.022 mole) of 3-methyl-2-cyclohexene-1-one, 3.7 g. (0.044 mole) of cyanoacetamide and 0.5 ml. of piperidine in 50 ml. of water was allowed to stand for 24 hr. The solid which had separated was filtered and washed with water. To the filtrate was added 0.5 ml. of piperidine and after 48 hr. a second crop of crystalline material was obtained. The total yield was 3.2 g. (77%), m.p. 187–190°. Two recrystallizations of a sample from isopropyl alcohol gave small prisms, m.p. 189–190°.

Anal. Calcd. for $C_{10}H_{14}N_2O_4$: C, 61.85; H, 7.27; N, 14.44. Found: C, 61.85; H, 6.98; N, 14.25.

Infrared absorption, λ_{max}^{nujol} 2.90, 3.2 μ (OH, NH); 4.63 μ (–CN); 6.10 μ (lactam).

In a similar experiment with 0.5 ml. of 30% potassium hydroxide as the catalyst in 125 ml. of water, a 24% yield of the condensation product was obtained.

N-Ethyl-4-cyano-5-methyl-3-oxo-2-azabicyclo[3.3.1]nonanol.—A solution of 35 g. (0.3 mole) of ethyl cyanoacetate and 30 g. (0.27 mole) of 3-methyl-2-cyclohexene-1-one in 150

(25) R. Connor, K. Folkers and H. Adkins, THIS JOURNAL, **54**, 1138 (1938).

ml. of 4 *N* ethylamine in 95% ethanol was allowed to stand tightly stoppered for 7 days and there was obtained 30 g. of a solid melting at 104–118°. Ten grams of this solid recrystallized from 200 ml. of boiling water gave 3 g. of large prisms, m.p. 166–169°. Three recrystallizations from isopropyl alcohol raised the m.p. to 170–171°.

Anal. Calcd. for $C_{12}H_{18}N_2O_2$: C, 64.82; H, 8.16; N, 12.60. Found: C, 64.56; H, 8.00; N, 12.78.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF ROCHESTER]

An Attempted Fries Reaction with Thiolesters. The Formation of Trithioörthoesters[1]

BY D. S. TARBELL AND A. H. HERZ[2]

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The Fries rearrangement of favorably substituted aryl thiolesters has not been realized, even in the presence of the strong Lewis acid, aluminum bromide. Instead, trithioörthoesters may be formed by partial cleavage of the thiolester, followed by the addition of the thiophenol to the ester carbonyl. Thus, phenyl thiolacetate upon treatment with boron fluoride or aluminum bromide yielded phenyl trithioörthoacetate (I). Structure I had been previously assigned to a compound obtained by the action of thiophenol on 1,1,1-trichloroethane; however, the product of that reaction has been shown to be 1,2-diphenylthioethane (VI). A number of orthotrithioesters have been prepared by treating an acyl chloride or thiolester with thiophenol in the presence of boron fluoride; similarly, a mixed orthothioester (II) was obtained by the action of *m*-thiocresol on phenyl thiolacetate. Since 4-acetylthiophenol and boron fluoride gave a mercaptole-type of condensation product, it is concluded that in general, under the acidic conditions of the Fries reaction, acylthiophenols would be expected to condense to polymercaptoles. The failure of the Fries reaction to occur is attributed to deactivation of the aromatic ring by contributions from resonance forms in which sulfur has expanded its valence shell.

Several reports[3] indicate that the Fries reaction has not been realized with esters of thiophenols, RCOSAr. We have reinvestigated this problem, because it seemed possible that the use of a very strong Lewis acid, such as aluminum bromide,[4] and a suitably substituted thiophenol ester, might bring about the desired rearrangements. Such a result would make possible a kinetic study of the reaction, and thus might yield some information about the mechanism of the Fries reaction with oxygen esters, which is not very well understood.[5] As indicated below, the reaction has not been successful in our hands, but under the experimental conditions used the aryl thiolacetates may be partially converted to aryl trithioörthoacetates, $CH_3C(SAr)_3$(I).

Treatment of analytically pure phenyl thiolacetate with boron fluoride, either alone or in acetic acid, yielded only a crystalline compound, of m.p. 145–146°. The composition of this material agreed with the phenyl trithioörthoacetate structure I, and its chemical properties supported this view; the latter included conversion by alcoholic mercuric chloride to phenylthiomercuric chloride, and and quantitative oxidation by peroxide to benzenesulfonic acid. Furthermore, the infrared and ultraviolet spectra (see Table I) of the 146° compound agreed very closely with those of phenyl trithioörthoformate,[6] $HC(SC_6H_5)_3$. However, structure I had been assigned to a compound of m.p. 71.5°, obtained by the action of 1,1,1-trichloroethane on thiophenol[7]; this product was reported to yield a trisulfone of m.p. 180°, which we were unable to obtain from the 146° compound.

$RC(SAr)_3$

I, Ar = C_6H_5, R = CH_3

II, $(Ar)_2$ = *m*-$CH_3C_6H_4$, Ar = C_6H_5, R = CH_3

III, Ar = *m*-$CH_3C_6H_4$, R = CH_3

IV, Ar = $CH_2C_6H_5$, R = CH_3

V, Ar = C_6H_5, R = C_6H_5

TABLE I

INFRARED ABSORPTION MAXIMA IN NUJOL

S, strong, M, medium, W, weak absorption

$(C_6H_5S)_3C-CH_3$		$(C_6H_5S)_3C-H$	
691 cm.$^{-1}$	M	691 cm.$^{-1}$	S
704	S	704	M
..		725	W
756	S	759	S
920	W	..	
999	W	999	W
1024	M	1024	M
1059	M	1059	M
1176	W	1176	W
1300	M	1300	W

ULTRAVIOLET ABSORPTION IN METHYLCYCLOHEXANE

$(C_6H_5S)_3C-CH_3$		$(C_6H_5S)_3C-H$	
mμ	log ε	mμ	log ε
Max. 236	4.161	Max. 236	4.115
Min. 257	3.779	Min. 256	3.991
Max. 268	3.843	Max. 264	4.009

It appeared probable, from a consideration of the m.p.'s, and the percentage compositions, that Laves' compounds were actually 1,2-diphenylthioethane,[8] m.p. 69°, (VI) and the corresponding disulfone,[9] m.p. 180°.

$$CH_3CCl_3 \xrightarrow{C_6H_5SH} C_6H_5SCH_2CH_2SC_6H_5 \quad \text{(VI)}$$

This compound might have been formed from an

(1) Presented at the 122nd Meeting of the American Chemical Society, Atlantic City, N. J., September, 1952.

(2) Eastman Kodak Fellow, 1952–1953.

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(4) *Cf.* (a) Pfeiffer and Haack, *Ann.*, **460**, 156 (1928); (b) D. P. Harnish and D. S. Tarbell, THIS JOURNAL, **70**, 4123 (1948); (c) D. S. Tarbell and J. C. Petropoulos, *ibid.*, **74**, 244 (1952).

(5) For review, see A. H. Blatt, in "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942, p. 342; *cf.* D. S. Tarbell and P. E. Fanta, THIS JOURNAL, **65**, 2169 (1943), and C. R. Hauser and R. H. Man, *J. Org. Chem.*, **17**, 390 (1952).

(6) B. Holmberg, *Ber.*, **40**, 1740 (1907).

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(9) (a) R. Otto, *Ber.*, **13**, 1280 (1880); (b) H. Gilman and N. J. Beaber, THIS JOURNAL, **47**, 1451 (1925).