manner. The distillation residues were combined and taken up in ether. Undissolved solid material was removed by filtration and washed with ether. The combined ethereal solutions were concentrated *in vacuo*. The concentrate was pyrolyzed under 110 mm. pressure and the distillation terminated under 20 mm. pressure. Most of the pyrolysate was obtained at 165–170°/110 mm. Toward the end of this and similar pyrolysis runs, small amounts of solid material were obtained which were identified as 4-oxo-2-alkenoic acids, corresponding to keto acid adducts (IV). Distillation of the pyrolysate gave a fraction, b.p. 123–127°/17 mm., which upon redistillation yielded the lactone as a colorless oil, b.p. 110–111°/10 mm. (20.15 g., yield 59%); sapon. equiv. calcd. and found: 138.

In a repeat run in which the stripped and redistilled solvent was used, a 68% yield, b.p. 119–121°/15 mm., was obtained.

(*C*) *From anthracene adducts* (*R″ = 9,10-anthraceno-*). Lactone (VI), (8.0 g., 0.025 mole) was pyrolyzed at 240–260° under 12 mm. pressure. The distillate consisted of copious amounts of anthracene and a yellow oil. Low boiling petroleum ether was added to the mixture, and the solution was filtered and concentrated. Distillation yielded a colorless oil, b.p. 110–112°/11 mm. (1.9 g., yield 54%); sapon. equiv. calcd., 138; found, 142.

2,4-Octadienoic acid by saponification of 4-hydroxy 2,4-octadienoic acid γ-lactone. The lactone (1.35 g., 0.0098 mole) was dissolved in a little acetone, and treated with 1*N* sodium hydroxide (10 ml.). Enough acetone was added to the mixture to make it homogeneous. After standing at room temperature for 15 min. the solution was neutralized to the phenolphthalein end point with 0.1*N* hydrochloric acid, extracted twice with small amounts of methylene chloride, acidified with 3*N* hydrochloric acid and extracted with ether. The ethereal solution was separated, washed with water, and allowed to evaporate at room temperature. The residue was taken up in a small amount of isopropyl ether containing a trace of iodine. Crystallization began within a few hours; when it appeared complete, the mass was filtered, washed with a mixture of isopropyl ether and low boiling petroleum ether and finally with petroleum ether. Air-drying resulted in a 64% yield (0.98 g.) of colorless needles, m.p. 108° (reported[9] m.p. 105–106°); neut. equiv. calcd. and found: 156.

Acknowledgment. The author is indebted to Mr. S. J. Tassinari for the reported microanalyses, and to Mr. Berruti for ultraviolet absorption data.

OAKDALE, N. Y.

(9) F. L. Breusch and H. Keskin, *Arch. Biochem.*, **18**, 314 (1948).

[CONTRIBUTION FROM THE RESEARCH LABORATORIES DIVISION, NATIONAL DAIRY PRODUCTS CORPORATION]

Potential Antimicrobial Agents. III. 4-Methylamino-2,4-alkadienoic Acid γ-Lactams[1]

HENRY M. WALTON

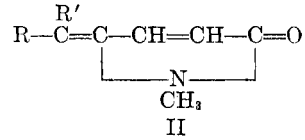
Received September 17, 1956

4-Methylamino-2,4-alkadienoic acid γ-lactams are structurally analogous to the antibiotic, protoanemonin. For this new class of lactams, a convenient one-step method of preparation is presented, consisting of the reaction of Grignard reagents with N-methylbicyclo[2.2.1]5-heptene-2,3-dicarboximide, followed by pyrolysis of the resulting Diels-Alder lactam adducts.

The structures of protoanemonin[2] and patulin[3] have attracted attention to 4-hydroxy-2,4-alkadienoic acid γ-lactones (I) as potential antimicrobial agents.[4] The preceding paper in this series[1] describes a general method for the preparation of lactones (I). It seemed also of interest to determine what effect the replacement of the lactone ring oxygen by nitrogen might have on physiological action.

This paper is concerned with the preparation of a new class of lactams (II) structurally analogous to lactones (I), in which the N-methyl group takes the place of the lactone ring oxygen.

The method presented here is based on the use of

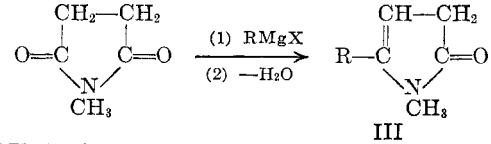


II

R, R′ = H, alkyl, cycloalkyl

the Diels-Alder adduct of N-methyl maleimide and cyclopentadiene, N-methylbicyclo[2.2.1]5-heptene-2,3-dicarboximide (IV), which is easily accessible, through reaction of the commercially available bicyclo[2.2.1]5-heptene-2,3-dicarboxylic anhydride[5] with methylamine.

Lukes[6] has shown that Grignard reagents react with N-methyl succinimide to yield lactams (III):



III

(1) Preceding paper in this series: H. M. Walton, *J. Org. Chem.*, **22**, 312 (1957).

(2) E. Shaw, *J. Am. Chem. Soc.*, **68**, 2510 (1946).

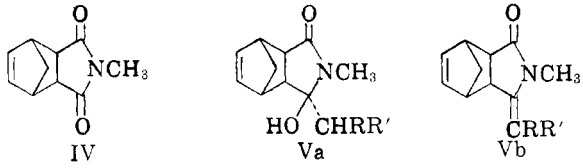
(3) R. B. Woodward and G. Singh, *J. Am. Chem. Soc.*, **71**, 758 (1949).

(4) For a discussion of the antimicrobial activity of unsaturated lactones, see L. J. Haynes, *Quart. Rev.*, **2**, 46 (1948); C. J. Cavallito, Antibiotics from Plants, in C. M. Suter, *Medicinal Chemistry*, John Wiley and Sons, New York, 1951, Vol. I, pp. 224–235.

(5) Nadic Anhydride, National Aniline Division, Allied Chemical and Dye Corporation.

(6) R. Lukes, *Coll. Czechoslov. Chem. Comm.*, **1**, 119 (1929); *Chem. Abstr.*, **23**, 4469 (1929).

Similarly the reaction of Grignard reagents with imide adduct (IV) yielded lactams (Vb), with or without isolation of their hydrated precursors (Va.)



A number of Diels-Alder adducts similar to (IV) are known to be thermally unstable and to undergo retrogression[7] at elevated temperatures with the liberation of the corresponding maleimides.[8] It was found that the new adducts (Vb) easily undergo pyrolytic retrogression at 180–200°.

The amide adduct (IV) reacted readily with Grignard reagents derived from primary, secondary, cycloalkyl, and benzyl halides. In the reaction of Grignard reagents of primary alkyl halides, adducts (Vb) were obtained in 65–90% yield. Efficient stirring was essential for optimal yield. After working up the reaction mixture, adducts (Va, Vb) or lactams (II) were obtained depending upon conditions encountered during isolation.

In a number of cases, when low temperatures could be maintained during isolation, adducts (Va) resulted. Their separate dehydration and conversion into adducts (Vb) was easily effected by refluxing their benzene solutions containing small amounts of p-toluenesulfonic acid, and azeotropic water removal.

When moderate temperatures were encountered during isolation, the dehydrated product (Vb) resulted directly, *e.g.*, when following hydrolysis the benzene solution of the crude reaction product was concentrated on the steam bath. Also, in a few cases involving lower molecular weight adducts (Vb), the distilled product contained unreacted imide adduct (IV) which could not be completely removed although it tended to partly crystallize from the distillate.

Attempted distillations of the Grignard reaction product at still pot temperatures of 175° and higher resulted in varying degrees of retrogression with the formation of lactams (II).

Table I lists a series of intermediate lactam adducts (Va, Vb).

TABLE I

LACTAM ADDUCTS (Va, Vb)

R	R'	M.P. or B.P. °C./Mm.	Formula[a,b]	Analyses C Calcd.	C Found	H Calcd.	H Found
n-C_3H_7	H	123.5–125.5°/1.5	$C_{14}H_{19}NO^{b,c}$	77.38	76.56	8.81	8.62
n-C_3H_7	H	126–127°[d]	$C_{14}H_{21}NO_2{}^{a,e}$	71.42	71.87	8.99	8.91
n-C_5H_{11}	H	117–119.5°/0.2	$C_{16}H_{23}NO^{b}$	78.32	78.10	9.45	9.38
n-C_7H_{15}	H	158–161°/0.3	$C_{18}H_{27}NO^{b}$	79.06	78.74	9.96	9.83
n-$C_{11}H_{23}$	H	65–66[f]	$C_{22}H_{37}NO_2{}^{a}$	76.03	76.00	10.73	10.58
CH_3	CH_3	149–150°[d]	$C_{13}H_{19}NO^{b}$	70.65	70.89	8.65	8.41
C_6H_5	H	170–175° dec.[g]	$C_{17}H_{19}NO_2{}^{a}$	75.81	75.92	7.11	7.10
—$(CH_2)_5$—		168–169°[d]	$C_{16}H_{23}NO_2{}^{a}$	73.53	73.41	8.87	8.70

[a] Structure (Va). [b] Structure (Vb). [c] Analysis suggests the admixture of (Va) or of (IV). [d] Recrystallized from methyl ethyl ketone. [e] Analysis suggests the presence of (Vb). [f] Recrystallized from isopropyl ether, then from ether-petroleum ether mixture. [g] Recrystallized from isopropyl alcohol.

The lactam adducts appear to be somewhat more heat-stable than the corresponding adducts of lactones (I). The *crude* lactams may be pyrolyzed directly. The new method essentially consists of one step affording lactams (II) in 50–85% overall yields.

Lactams (II) and lactam adducts (Vb) were usually obtained as colorless to pale yellow oils, which, in the absence of precautions, tended to thicken and discolor upon storage. However, little deterioration was observed when these materials were stored under nitrogen at about 4°. Solid adducts (Va) were stored at room temperature for two years without apparent change.

The skeletal structure of lactams (II) was confirmed by conversion of 4-methylamino-2,4-octadienoic acid γ-lactam (VI) and 4-methylamino-3-octenoic acid γ-lactam (VII) to sodium 4-methylamino octanoate (VIII) *via* parallel reaction series, and characterization of the corresponding acids as N-3,5-dinitrobenzoyl derivatives. The 3,5-dinitrobenzamides so obtained had m.p. 57–58°, separate and admixed.

Lactam (VI) in isopropyl alcohol had λ_{max} 262 mμ, ε 9924, with a secondary peak at 300 mμ. This compares with the following absorption maxima of lactones of related structure: protoanemonin,[2] λ_{max} 260 mμ; patulin,[3] λ_{max} 276 mμ; 4-hydroxy-2,4-nonadienoic acid γ-lactone,[1] λ_{max} 275 mμ.

(7) For a discussion of the retrogressive Diels-Alder reaction see M. C. Kloetzel, *Org. Reactions*, **IV**, 9 (1948).

(8) E. J. Prill, U. S. Patent 2,524,136; *Chem. Abstr.*, **45**, 1162 (1951); P. O. Tawney, U. S. Patent 2,524,145; *Chem. Abstr.*, **45**, 1162 (1951); *cf.* St. C. Harvey, *J. Am. Chem. Soc.*, **71**, 1121 (1949); J. A. Berson and R. Swidler, *J. Am. Chem. Soc.*, **76**, 2835 (1954).

TABLE II

LACTAMS (II)

R	R′	M.P. or B.P. °C./Mm.	Formula	Analyses C Calcd.	C Found	H Calcd.	H Found
C_2H_5	H	122–124°/15	$C_8H_{11}NO$	70.04	70.14	8.08	7.81
n-C_3H_7	H	132–133°/11	$C_9H_{13}NO$	71.49	71.84	8.66	8.34
n-C_5H_{11}	H	154°/10	$C_{11}H_{17}NO$	73.38	73.34	9.56	9.54
n-C_7H_{15}	H	177–179°/12	$C_{13}H_{21}NO$	75.31	74.28	10.21	9.84
CH_3	CH_3	98–99°[a]	$C_8H_{11}NO$	70.04	70.02	8.08	8.01
CH_3	n-C_6H_{13}	190°/17	$C_{13}H_{21}NO$	75.31	75.04	10.21	10.03
—$(CH_2)_5$—		117–118°[b]	$C_{11}H_{15}NO$	74.54	74.83	8.53	8.36

[a] Recrystallized from isopropyl ether. [b] Recrystallized from isopropyl ether-methyl ethyl ketone.

In view of their ready accessibility, attempts were made to convert lactams II into methyl 4-oxo-2-alkenoates, as an alternative to the method described earlier for the preparation of these esters.[9] Numerous attempts failed to bring about a satisfactory conversion by means of methanol and acids.

EXPERIMENTAL

All melting points were determined on a Fisher-Johns melting point apparatus, thermometer calibration with Keufler "Testsubstanzen."

N-Methylbicyclo[2.2.1]5-heptene-2,3-dicarboximide (IV). With intermittent stirring, 40% methylamine (120 g., 1.55 mole) was added in several portions to bicyclo[2.2.1]5-heptene-2,3-dicarboxylic anhydride (164 g., 1.0 mole). The resulting reaction was moderated by cooling the mixture in a water bath. During the addition of the amine the anhydride went into solution. Shortly afterwards the flask contents solidified. They were heated in an oil bath at 160–180° until the distillation of water ceased (about 30 min.). The crystalline mass obtained on cooling was taken up in hot isopropyl alcohol. When the solution was filtered and cooled it deposited the product (148 g., 85% yield) of colorless crystals, m.p. 107°; reported m.p. 105–107°.[10]

Lactam (Va) (RR' = —$(CH_2)_5$—). The preparation of all Grignard reagents and their reaction with imide (IV) were carried out under dry nitrogen. An efficient stainless steel stirrer was used to maintain stirring throughout. Cyclohexylmagnesium bromide was prepared in the usual manner from magnesium (4.0 g., 0.165 g. atom) and cyclohexyl bromide (freshly distilled, 28.0 g., 0.172 mole) in ether (100 ml.). The reaction was initiated with the aid of a small amount of methylmagnesium iodide solution and completed with stirring and heating under reflux for several hours. The imide (IV) (26.6 g., 0.15 mole) dissolved in benzene (130 ml.) was added with stirring to the Grignard solution at a rate sufficient to maintain spontaneous refluxing. The precipitate formed during addition of the imide solution became very viscous, and rendered stirring difficult, when the addition was about half completed. With continued stirring and addition of the imide solution, the viscous mass gradually became granular and the fluidity of the mixture was restored. Following the addition, stirring and heating under reflux were continued for 8.5 hr. The reaction mixture was allowed to cool and stand at room temperature overnight. It was decomposed by the cautious addition with external cooling of water (50 ml.), followed by 3N hydrochloric acid (55 ml.). The resulting crystalline precipitate was removed by filtration and washed with water and ether. The washed solid (30 g., m.p. 165–173°) was dissolved in hot methyl ethyl ketone and allowed to crystallize. Coarse needles, m.p. 168–169°, were obtained.

Anal. Calcd. for $C_{16}H_{23}O_2N$: C, 73.53; H, 8.87. Found: C, 73.41; H, 8.70.

Additional material was obtained by working up the filtrates.

Lactam (Vb) (R = n-C_5H_{11}, R' = H). The Grignard reagent was prepared from magnesium (7.3 g., 0.30 g. atom) and n-hexyl chloride (36.5 g., 0.33 mole) in ether (150 ml.) and reacted with imide (IV) (44.3 g., 0.25 mole) dissolved in benzene (220 ml.) as described above. After completion of the addition the mixture was stirred and heated under reflux for 1.5 hr. It was cooled and decomposed by the gradual addition, with stirring and external cooling, of 3N hydrochloric acid (100 ml.). The aqueous layer was separated and extracted with ether. The combined ethereal solutions were washed with several small portions of water, dried over magnesium sulfate and concentrated *in vacuo* (water bath to 80°). A light yellow oil (60.4 g.) was obtained. A portion of the oil (9.1 g.) was distilled and yielded a pale yellow oil, b.p. 117.5–119.5°/0.2 mm. (5.1 g., corresponding to a 76% yield).

Anal. Calcd. for $C_{16}H_{23}NO$: C, 78.32; H, 9.45. Found: C, 78.10; H, 9.38.

Lactam (II) (R = n-C_3H_7, R' = H). The corresponding adduct (Vb) (5.5 g., 0.025 mole) was heated to 190–200° under about 60 mm. pressure and the distillation was completed under 15 mm. pressure. Redistillation of the pyrolysate yielded a colorless oil (2.7 g., yield 71%), b.p. 132–133°/11 mm., n_D^{25} 1.5472, which was stored under nitrogen.

Anal. Calcd. for $C_9H_{13}NO$: C, 71.49; H, 8.66, 2 double bonds. Found: C, 71.84; H, 8.34. H_2 uptake, 2.0 mole.

Other adducts similarly were pyrolyzed.

4-Methylaminooctanoic acid γ-lactam from 4-methylamino-2,4-octadienoic acid γ-lactam (VI). The solution of the unsaturated lactam, b.p. 130°/10 mm. (16.0 g.) in alcohol (50 ml.) was hydrogenated at room temperature using an initial pressure of 27.5 lb. and a 10% palladium on charcoal catalyst. Hydrogen uptake was quantitative. Filtration and distillation resulted in the quantitative yield of a colorless oil, b.p. 120°/10 mm., n_D^{25} 1.4695.

Anal. Calcd. for $C_9H_{17}ON$: C, 69.63; H, 11.04. Found: C, 69.99; H, 10.48.

Despite the apparently quantitative hydrogen uptake, analyses and refractive index indicated the presence of incompletely hydrogenated lactam VI.

4-Methylaminooctanoic acid γ-lactam from 4-methylamino-3-octenoic acid γ-lactam (VII). By the foregoing procedure the unsaturated lactam,[3] b.p. 120–122°/8 mm., yielded a colorless oil, b.p. 121–124°/11 mm., n_D^{25} 1.4670.

Anal. Calcd. for $C_9H_{17}ON$: C, 69.63; H, 11.04. Found: C, 69.34; H, 10.89.

N-3,5-Dinitrobenzoyl-4-methylaminooctanoic acid. Both saturated lactams were treated as follows:

(9) Paper I in this series, H. M. Walton, *J. Org. Chem.*, **22**, 308 (1957).

(10) H. W. Arnold and N. E. Searle, U. S. Patent 2,462,835; *Chem. Abstr.*, **43**, 4421 (1949).

The lactam (3.4 g.) was dissolved in 3*N* hydrochloric acid (8 ml.) and allowed to stand at room temperature for 40 hr. To the resulting mixture 3*N* sodium hydroxide (15 ml.) was added and the precipitated oil redissolved by the addition of water (total weight of solution: 40 g.).

A portion of this solution (10 ml.) was stirred with 3,5-dinitrobenzoyl chloride (2 g.). After a few minutes the mixture was filtered and acidified with hydrochloric acid. The resulting solid material was filtered off, washed with water and ether, and dissolved in a small amount of hot benzene. The benzene solution was concentrated on the steam bath and the residue crystallized from a mixture of isopropyl ether and ligroin. Recrystallization from the same solvent mixture yielded faintly yellow crystals, m.p. 57–58°, in both reaction series. The same melting point was observed with a mixture of the two specimens.

Anal. (specimen derived from lactam VI). Calcd. for $C_{16}H_{21}N_3O_7$: C, 52.03; H, 5.73. Found: C, 51.81; H, 5.31.

Acknowledgment. The author is indebted to Mr. S. J. Tassinari for microanalyses and to Mr. R. Berruti for ultraviolet absorption data.

OAKDALE, N. Y.