The results are reported in Table II. Yields of selected components were determined in the acidic and neutral fractions using the internal standard method. Naphthalene and/or biphenyl were used as internal standards in the acidic fraction analysis and 2-methylnaphthalene was used in the neutral fraction analysis. The results are reported in Tables I and III.

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The Synthesis of a Large-Ring Ketone Containing a Lactone Function. The Dieckmann Condensation *vs.* the Thorpe–Ziegler Condensation[1]

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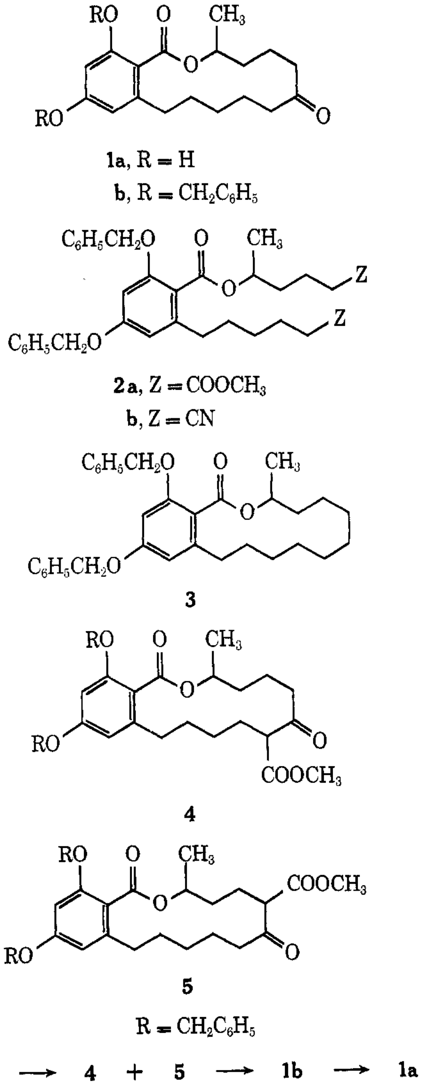
A method has been found for the synthesis in good yield of a large-ring ketone from an α,ω diester (**2a**) whose structure contains a third functional group that is susceptible to basic cleavage. This cyclization, an adaptation of the Dieckmann reaction, has been applied to the preparation of the 2,4-dibenzyl ethers of racemic 5′- and 7′-carbomethoxyzearalanone (**4** and **5**) which are necessary intermediates in the total synthesis of *R,S*-zearalanone (**1a**). This cyclization was compared to the Thorpe–Ziegler cyclization of the parallel α,ω-dinitrile (**2b**). In this case, the enamino nitriles first formed (**9** and **10**) were found to rearrange under the influence of base by nucleophilic attack of the enamino anion on the carbonyl carbon to give amides **11** and **12**. The physical and chemical properties of **11** and **12**, as well as those of the dimer (**19**) produced in this cyclization, are discussed.

SCHEME I


1a, R = H
b, R = $CH_2C_6H_5$
2a, Z = $COOCH_3$
b, Z = CN
3
4
5
R = $CH_2C_6H_5$
$$\mathbf{2a} \longrightarrow \mathbf{4} + \mathbf{5} \longrightarrow \mathbf{1b} \longrightarrow \mathbf{1a}$$

The Thorpe–Ziegler condensation has been known for many years as a principal method for syntheses of large-ring ketones. In contrast, the Dieckmann condensation appears to be little known as a source of large-ring ketones[3] even though its application in useful yields has been demonstrated with a series of α,ω diesters.[4] Many modern texts and references[5-7] still continue to state that the scope of the Dieckmann cyclization is restricted to formation of five- or six-membered rings.

To our knowledge there is no reference in the literature to the synthesis of a large-ring ketone from an α,ω-difunctional compound by either the Thorpe–Ziegler or the Dieckmann reactions, where the starting dinitrile or diester, respectively, has a structure in which there is a third functional group that is susceptible to basic cleavage.

The problem of cyclizing such a structure became real to us in completing a total synthesis of zearalanone[8] (**1a**), where it became necessary to cyclize either triester **2a** or ester dinitrile **2b** to a 14-membered lactone intermediate that could be converted readily to **1a** (Scheme I).

The Dieckmann Cyclization of 4-Carbomethoxy-1-methylbutyl 2,4-Bis(benzyloxy)-6-(5-carbomethoxypentyl)benzoate (2a).—The reaction conditions successfully used by Leonard and Schimelpfenig[4] for the cyclization of alkanedioic esters, namely, potassium *tert*-butoxide in refluxing xylene, did not appear promising for the cyclization of **2a**. The dibenzyl ether of zearalane (**3**) was completely destroyed in less than a day by this treatment, indicating that substantial

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[1] Part of this work was presented as a paper at the 157th National Meeting of the American Chemical Society, Minneapolis, Minnesota, April, 1969, MEDI 28.

[2] G. D. Searle International Co., P.O. Box 5486, Chicago, Ill. 60680.

[3] K. Ziegler, H. Eberle, and H. Ohlinger, *Justus Liebigs Ann. Chem.*, **504**, 94 (1933).

[4] N. J. Leonard and C. W. Schimelpfenig, Jr., *J. Org. Chem.*, **23**, 1708 (1958).

[5] J. Hendrickson, D. Cram, and G. Hammond, "Organic Chemistry," 3rd ed, McGraw-Hill, New York, N. Y., 1970, p 525.

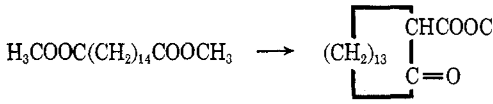
[6] S. Patai, Ed., "The Chemistry of the Carbonyl Group," Interscience, New York, N. Y., 1966, p 274.

[7] A. Liberles, "Introduction to Theoretical Organic Chemistry," Macmillan, New York, N. Y., 1968, p 550.

[8] The total synthesis of zearalanone is the subject of a paper by us in *J. Med. Chem.*, in press.

loss in yield of the desired cyclization product could be expected by way of basic attack either on the lactone function of the product or on the ester function of **2a**.

This problem was solved by substituting sodium bis(trimethylsilyl)amide, $[(CH_3)_3Si]_2NNa$ (**6**), for potassium *tert*-butoxide. Compound **6** is a strong base that is readily soluble in nonpolar organic solvents such as ether.[9] This latter property permitted us to have a homogeneous reaction system at moderate temperatures, and allowed the Dieckmann cyclization to proceed smoothly in good yield. Thus, under conditions of high dilution, a refluxing ether solution of **6** brought about cyclization of a model diester, dimethyl hexadecanedioate (**7**), into methyl 2-oxocyclopentadecanecarboxylate (**8**) in 64% yield, repeatedly.



$$\mathrm{H_3COOC(CH_2)_{14}COOCH_3} \longrightarrow \mathrm{(CH_2)_{13}}\left[\begin{array}{l}\mathrm{CHCOOCH_3}\\ |\\ \mathrm{C{=}O}\end{array}\right.$$

7 **8**

This was a reproducible improvement over the 48% yield of cyclopentadecanone obtained with potassium *tert*-butoxide in refluxing xylene.[4]

Reaction of triester **2a** with **6** in reluxing ether solution resulted in a product in 77% yield. Although this product could be considered to be the 2,4-dibenzyl ether of either 5′- or 7′-carbomethoxyzearalanone[10] (**4** or **5**), we believe that it is more reasonable to consider the product as a mixture of **4** and **5**. No attempt was made to separate this mixture, since the two components are equally useful in the total synthesis of **1b**. This yield was achieved by continuous, controlled addition of a very dilute ether solution of **2a** to a refluxing ether solution of **6** during 8 hr. As expected, more rapid addition (6.5 hr) caused a drop in yield to 57%.

Base **6** exhibits high nucleophilic reactivity.[11] With esters that have a reactive α hydrogen it reacts to form a sodium enolate and bis(trimethylsilyl)amine.[9] On the other hand, esters with no α hydrogen are reported to form imidic acid derivatives.[12] With triester **2a** there is afforded to base **6** the opportunity to react in either or both of the ways just described. No evidence of an imidic acid derivative was obtained during reaction of **2a** with **6**. Isolation of the mixture of **4** and **5** demonstrated that **2a** behaved as an ester with reactive α hydrogen.

The product (**4** and **5**) was saponified to the corresponding mixture of β-keto acids and then, without isolation, this mixture was decarboxylated by warming in acid to give the 2,4-dibenzyl ether of *R*,*S*-zearalanone (**1b**).[8]

The ease with which these macrocyclizations were carried out, the mild reaction conditions used, and the excellent yields obtained encourage us to suggest that this reaction should be more widely investigated as a valuable tool in the synthesis of complex macrocyclic structures. Preservation of the lactone function (**4** and **5**) under basic conditions by use of **6** at moderate temperatures leads us to speculate that this adaptation of the Dieckmann reaction might be useful in the preparation of other complex macrocycles with base-reactive functions.

Thorpe–Ziegler Cyclization of 4-Cyano-1-methylbutyl 6-(5-Cyanopentyl)-2,4-bis(benzyloxy)benzoate (2b).—Fry and Fieser first applied the Thorpe–Ziegler cyclization to the synthesis of a cyclic ketone fused to an aromatic ring.[13] In our hands, their reaction conditions[14] applied to dinitrile **2b**[8] gave a very small yield of a mixture of unidentified products and an equally small recovery of unreacted **2b**.

The importance of a soluble base for good yields in the nitrile cyclization at high dilution has long been recognized.[15,16] Since the condensing agent used by Fry and Fieser proved to be insoluble in ether, we turned to the ether-soluble agent developed by Ziegler and coworkers.[16] This agent, prepared from powdered sodium (2 g-atoms), styrene (1 mol), and *N*-methylaniline (2.5 mol) in ether, gave 65% total yields of products resulting from cyclization of **2b**.

We observed that when lactone **3** was exposed to this condensing agent in refluxing ether, it was nearly all recovered after 5 hr but was substantially decomposed to at least three unidentified products after 27 hr. To define further the relationship between yield and reaction time,[17] we reexamined[18] the cyclization of a model compound, hexadecanedinitrile, into 2-amino-1-cyclopentadecene-1-carbonitrile using $NaN(CH_3)C_6H_5$ in ether solution. For reaction times of 72, 6, and 4 hr, the yields of this cyclic enamino nitrile were 47, 34, and 20%, respectively.

Under conditions of high dilution, an ethereal solution of 1 molar equiv of **2b** was added at a constant rate in 6 hr to a refluxing ethereal solution of 10 molar equiv of sodio-*N*-methylaniline. Two products were obtained: a monomer (mol wt 566) and a dimer (mol wt 1040) in 20 and 45% yields, respectively. It was tempting at first to consider that the monomer was the expected mixture of isomeric enamino nitriles, **9** and **10** (mol wt 524) and that the dimer was a mixture of the macrocyclic products containing two lactone and two enamino nitrile functions (mol wt 1048) resulting from intermolecular condensation of **2b**. Such was not the case, however, and each of these products will be discussed in turn.

Monomer.—Both the molecular weight and combustion analysis of the monomer agree closely with structures **9** and **10**, or any other isomeric structure.

The ir spectrum presents an ambiguous picture. Absorptions at 2180, 3390, and 3310 cm^{-1} conform to a

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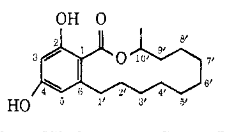
[9] C. R. Krüger and E. G. Rochow, *J. Organometal. Chem.*, **1**, 476 (1964).

[10] The numbering system used in this paper for the zearalane ring system is as follows.



[11] U. Wannagat and H. Niederprüm, *Chem. Ber.*, **94**, 1540 (1961).

[12] C. Krüger, E. G. Rochow, and U. Wannagat, *ibid.*, **96**, 2139 (1963).

[13] E. M. Fry and L. F. Fieser, *J. Amer. Chem. Soc.*, **62**, 3489 (1940).

[14] *N*-Methylaniline was converted to its sodium derivative with the use of naphthalene as an assistant, and this condensing agent was used in refluxing ether where it is mainly insoluble.

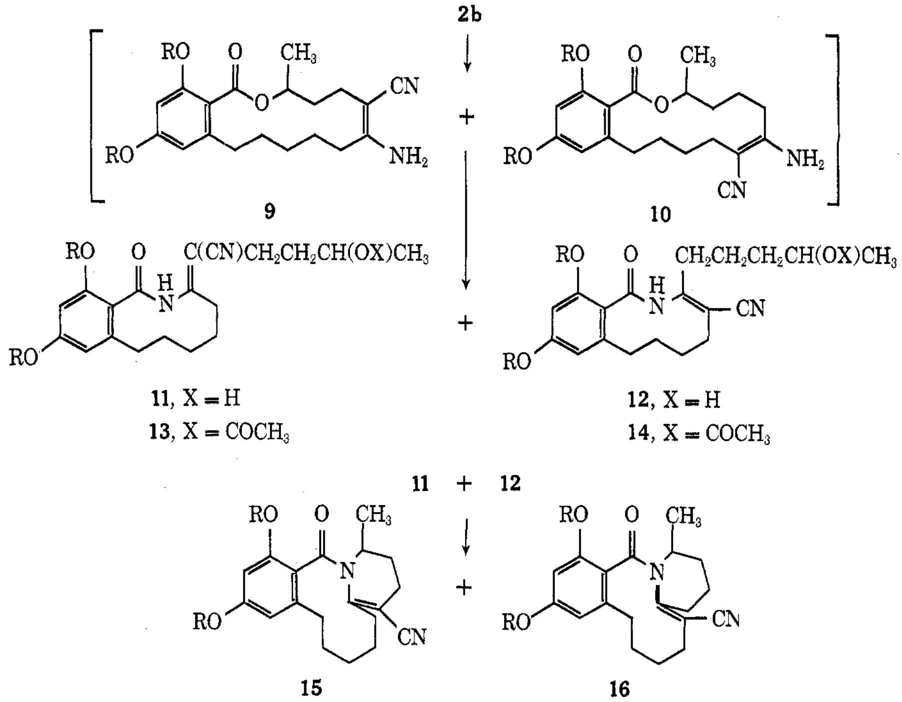
[15] K. Ziegler and H. Hall, *Justus Liebigs Ann. Chem.*, **528**, 151, 153 (1937).

[16] K. Ziegler, L. Jakob, and H. Wollthan, *ibid.*, **511**, 69, 70 (1934).

[17] Reaction time in the Thorpe–Ziegler cyclization is the time of addition, under conditions of high dilution, of a solution of the dinitrile to a refluxing solution of the condensing agent.

[18] The Thorpe–Ziegler cyclization of hexadecanedinitrile was first reported by L. Ruzicka, M. Stoll, and H. Schinz, *Helv. Chim. Acta*, **9**, 260 (1926).

SCHEME II



$R = CH_2C_6H_5$

very characteristic pattern of absorption for enamino nitriles,[19] but that at 3390 cm^{-1} could also represent an H-bonded OH stretching frequency and the absorption at 3310 cm^{-1} might represent a secondary amide NH stretching mode. Absorption at 2220 cm^{-1} is characteristic of an α,β-unsaturated nitrile. Carbonyl absorption at 1685 cm^{-1} is only moderately intense in contrast to the very intense absorption exhibited by the lactone carbonyl functions of **1a**, **1b**, **3**, and other zearalanone derivatives.

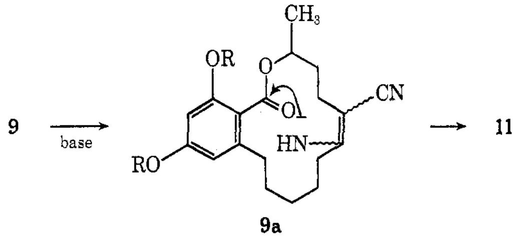
The nmr spectrum fails to support structures **9** and **10**, because there is no signal at δ 5.1, the usual position for a lactone proton, and no indication of $-NH_2$ protons, usually seen at 266 cps in enamino nitriles.[20] Instead, there is a multiplet (1 H) at δ 4.2 which disappears with D_2O, and a multiplet (1 H) at δ 3.3–3.9 which by decoupling was shown to couple with a methyl group.

This evidence suggests that the monomer has either structure **11** or **12**, its isomer (Scheme II). These structures are compatible with the known information on the monomer. In the nmr spectrum, for example, the multiplet at δ 4.2 represents –OH and the multiplet at δ 3.3–3.9 represents $CH_3C{=}H$.

We rationalize that the Thorpe reaction did occur to give the expected mixture of enamino nitriles, **9** and **10**, and that in the presence of base the lactone carbonyl in **9** and **10** each underwent nucleophilic attack by an enamino anion (such as **9a**) to give a mixture of **11** and **12**, respectively.

Structures **11** and **12** are also consistent with the chemical behavior of the monomer.

Enamino nitriles are generally hydrolyzed to the corresponding keto nitriles or ketones under acidic conditions, although exceptions are known.[21] When the monomer is warmed to 50° for 2 hr in a mixture of acetic acid, water, and phosphoric acid, a considerably less polar product is obtained whose nitrogen content and spectra show that it is not the β-keto nitrile, β-keto amide, or ketone that would be expected from **9** or **10**. Nitrogen analysis, as well as the ir and nmr spectra, agree with acetates **13** and **14** as the products arising from treatment of alcohols **11** and **12**, respectively, with this acidic mixture.



9a

Treatment of the monomeric mixture **11** and **12** with a warm mixture of methanol and concentrated HCl for several hours gave products for which we propose structures **15** and **16**. These fused-ring, N,N-disubstituted amides may be viewed as resulting by loss of water from hydroxy amides **11** and **12**, respectively, probably *via* an oxonium intermediate as shown in Scheme III.

Combustion analyses support these structures. A molecular weight determination (572) agrees with the view that water was lost intramolecularly and not intermolecularly by dimer formation.

The nmr spectrum of the mixture of **15** and **16** shows that no lactone proton or other hydrogen exchangeable with D_2O is present. The methyl doublet at δ 1.2 in the mixture of **11** and **12** becomes two sets

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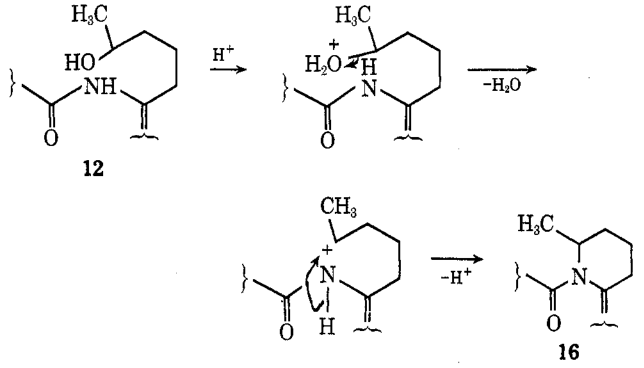
[19] Enamino nitriles exhibit their nitrile stretching frequency at the unusually low range of 2165–2190 cm^{-1}. They also show two bands in the NH-stretching region. For a review of this topic, see E. C. Taylor and A. McKillop, "The Chemistry of Cyclic Enaminonitriles and o-Aminonitriles," Interscience, New York, N. Y., 1970, p 4.

[20] S. Baldwin, *J. Org. Chem.*, **26**, 3288 (1961).

[21] Reference 19, p 60.

SCHEME III



of methyl doublets at δ 1.2–1.4 (J = 6 cps) in the mixture of **15** and **16**. Possibly this change is related to the conformation of the methyl group, where it is axial in one structure and equatorial in the other one. In quite a different family of compounds, derivations of 2-methylcyclohexanone and 4-methylcyclohexanone, it has been shown[22] that axial methyl groups occur at lower field than equatorial methyl groups in nmr spectra, irrespective of their ring position.

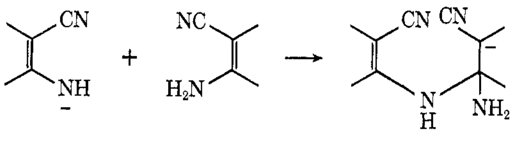
Since structures **15** and **16** contain *N*-acylenamino nitrile groups, it is pertinent to note that the products resulting from the above methanol–HCl treatment exhibit strong absorption at 2180 cm^{-1} in the ir spectrum. N,N-Disubstituted enamino nitriles are known to absorb at this wavenumber.[20]

Dimer.—The major product of the Thorpe–Ziegler cyclization exhibits an nmr spectrum very similar to that of the monomer. This fact rules out for the dimer the type of structure usually seen for this cyclization where each nitrile function of two molecules of dinitrile **2a** condenses intermolecularly to give a 28-membered ring, fused to two aromatic rings, and containing two lactone functions and two enamino nitrile groups.

The ir spectrum of the dimer also closely resembles that of the monomer, except that the carbonyl absorption at 1710 cm^{-1} is of strong rather than weak intensity.

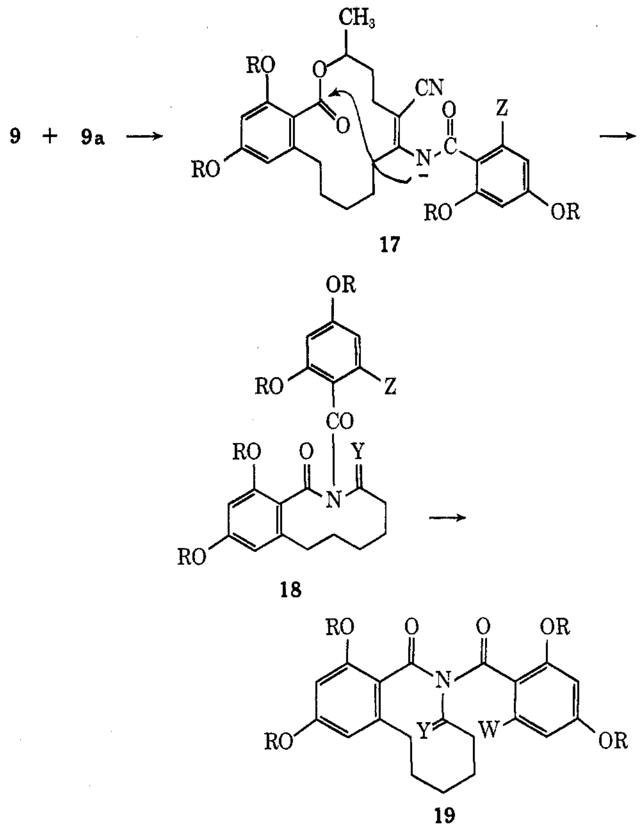
Combustion analysis indicates that in dimerization about one-fourth of the available nitrogen is lost.

These facts also rule out for the dimer the type of structure proposed by Thompson,[23] wherein the enamino anion of one molecule of enamino nitrile nucleophilically attacks a second molecule of enamino nitrile.



A possible course for the present dimerization begins with nucleophilic attack upon the lactone carbonyl of **9** by its anion **9a** to give an intermediate dimer anion **17** (Scheme IV), which, as an *N*-acylenamino nitrile, can undergo intramolecular nucleophilic attack at the remaining lactone carbonyl to give imide **18**. Acidic hydrolysis, an opportunity for which is afforded in the processing conditions of the Thorpe–Ziegler reaction mixture, might result in hydrolysis of the unsubstituted enamino nitrile function to a β-keto nitrile function, as shown in **19**.

SCHEME IV



R = $CH_2C_6H_5$
Z = $(CH_2)_5C(NH_2){=}C(CN)CH_2CH_2CH(OH)CH_3$
W = $(CH_2)_5COCH(CN)CH_2CH_2CH(OH)CH_3$
Y = $C(CN)CH_2CH_2CH(OH)CH_3$

Although we regard structure **19** as speculative, it is in agreement with the ir and nmr spectra, the results of combustion analyses, and a determination of molecular weight of the dimer.

Experimental Section

Infrared spectra were obtained with a Perkin-Elmer 21 spectrophotometer. Nuclear magnetic resonance spectra were obtained on a Varian A-60A spectrometer. Elemental analyses were obtained in our laboratories. Melting points were taken in a Thomas-Hoover capillary melting point apparatus, and are uncorrected. Molecular weights were determined using a Hewlett-Packard vapor pressure osmometer Model 302 calibrated with recrystallized benzil using chloroform as the solvent.

The preparation of compounds **2a** and **2b** is described in ref 8.

Mixture of the 2,4-Dibenzyl Ethers of Racemic 5′- and 7′-Carbomethoxyzearalanone, 4 and 5.—To a refluxing ethereal solution of 3.44 g (0.019 mol) of **6**[9,11] in 175 ml of dry ether, a solution of 1.85 g (0.003 mol) of triester **2a**[8] in 260 ml of dry ether was added continuously and uniformly over a period of 8 hr using the high-dilution technique described below. The reaction mixture was refluxed for an additional 15 min after addition was complete and cooled. Glacial acetic acid (25 ml) was added. The resulting mixture was washed three times with 80-ml portions of water, dried ($MgSO_4$), and stripped of ether to give 1.81 g of paste. This residue was passed through 60 g of a Silicar-CC-7 column with chloroform to obtain 1.33 g (77%) of the mixture of **7** and **8**: ir (film) 1725 (ester C=O), 1700 cm^{-1} (ketone C=O); nmr ($CDCl_3$) δ 1.01–1.09 (d, 3, $-OCHC\mathbf{H}_3$), 1.25–2.01 (m, 10, $-C\mathbf{H}_2C\mathbf{H}_2CHCOOCH_3$, $-CH_2C\mathbf{H}_2C\mathbf{H}_2C\mathbf{H}_2CH_2C{=}O$), 2.01–3.00 (m, 4, $-CH_2C{=}O$, benzylic CH_2), 3.63 (t, 4, $-CH_2C\mathbf{H}COOC\mathbf{H}_3$), 5.00 (d, 4, 2 $OC\mathbf{H}_2C_6H_5$), 5.1–5.3 (m, 1, $-OC\mathbf{H}CH_3$), 6.45 (s, 2, 2 aromatic H), 7.35 (d, 10, 2 $OCH_2C_6\mathbf{H}_5$).

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[22] F. Johnson, N. A. Starkovsky, and W. D. Guravitz, *J. Amer. Chem. Soc.*, **87**, 3492 (1965).

[23] Q. E. Thompson, *ibid.*, **80**, 5483 (1958).

To achieve high dilution, the rate of addition of the ethereal solution of **2a** was controlled by addition of fine droplets of mercury from a leveling bulb through a capillary tube into a reservoir containing the solution of **2a** in essentially the same manner as described by Ziegler and coworkers.[8] The solution of **2a** flowed from this reservoir into the high-dilution mixer described by Allen and VanAllan,[24] where it was first diluted by condensed ether from the refluxing reaction mixture. From this mixer, the diluted solution of **2a** flowed into the reaction flask.

2,4-Dibenzyl Ether of *R,S*-Zearalanone (1b).—A solution of 1.5 g of KOH in 3 ml of water and 27 ml of ethanol was prepared. A 7.5-ml aliquot of this solution (containing 0.375 g of KOH) was added to 200 mg (0.339 mmol) of the mixture of **4** and **5**. The resulting reaction mixture was refluxed for 1 hr, cooled, and acidified with 6 *N* HCl. The acidified mixture was warmed to 50° for 10 min, and then diluted with 75 ml of water. The diluted mixture was thrice extracted with 30-ml portions of ether. The combined ether extracts were washed with 20 ml of 5% $NaHCO_3$, then 20 ml of water, and finally dried ($MgSO_4$). Removal of ether left 130 mg of paste, which was passed through a column of 10 g of Silicar-CC-7 with chloroform to give 100 mg of paste. This paste crystallized slowly from methanol to give 90 mg (53.1%) of white **1b**, mp 104°. No depression in melting point was observed with the natural, authentic 2,4-dibenzyl ether of *S*-zearalanone (mp 104°).[25]

Anal. Calcd for $C_{32}H_{36}O_5$: C, 76.76; H, 7.24. Found: C, 76.93; H, 7.43.

Cyclization of 4-Cyano-1-methylbutyl 2,4-Bis(benzyloxy)-6-(5-cyanopentyl)benzoate (2b).—Dinitrile **2b**[8] (3.00 g, 0.006 mol) in 250 ml of dry ether was added continuously at a uniform rate in 6 hr to a stirred, refluxing 0.67 *M* solution (90 ml) of sodio-*N*-methylaniline[16] in ether using the high-dilution technique described for the preparation of the mixture of **4** and **5**. The mixture was then cooled and 25 ml of water was added to it. Most of the product separated as a thick oil. This oil was taken up in $CHCl_3$, and the $CHCl_3$ solution was washed with 20% phosphoric acid and dried (Na_2SO_4). Removal of $CHCl_3$ left 2.77 g of glassy solid which was put on a column (80 g) of Silicar-CC-7 in $CHCl_3$. Development of the column with $CHCl_3$ resulted in separation of 0.6 g (20%) of a mixture of **11** and **12**. Further development of the column with 2% methanol in chloroform gave 1.35 g of the dimer (**19**).

Mixture of the lactams of 4,6-dibenzyloxy-2-(6-amino-7-cyano-10-hydroxy-6-undecenyl)benzoic acid (11) and 4,6-dibenzyloxy-2-(6-amino-5-cyano-10-hydroxy-5-undecenyl)benzoic acid (12) had ir (film) 1685 (C=O), 2180 (conjugated CN), 2220 (unconjugated CN), 3310 (monosubstituted amide NH), 3390 cm^{-1} (H-bonded OH); nmr ($CDCl_3$) δ 1.2 (d, 3, $-OCHCH_3$), 3.3–3.9 (m, 1, $-OCHCH_3$), 4.2 δ (m, 1, OH). In this nmr spectrum, the multiplet at δ 3.3–3.9 was shown to couple with the methyl group by decoupling, and the multiplet at δ 4.2 disappeared with D_2O.

Anal. Calcd for $C_{33}H_{36}N_2O_4$: C, 75.75; H, 6.87; N, 5.34; mol wt, 524. Found: C, 75.58; H, 7.18; N, 5.24; mol wt, 566.

Dimer 19 had ir (film) 1700 (C=O), 2180 (conjugated CN), 2220 (unconjugated CN), 3365 cm^{-1} (H-bonded OH); nmr ($CDCl_3$) δ 3.5 (m, 1), 4.1 (m, 1).

Anal. Calcd for $C_{66}H_{71}N_3O_9$: C, 75.51; H, 6.76; N, 4.00; mol wt, 1050. Found: C, 75.22; H, 6.96; N, 3.66; mol wt, 1038.

Mixture of Lactams of 4,6-Dibenzyloxy-2-(6-amino-7-cyano-10-acetoxy-6-undecenyl)benzoic Acid (13) and 4,6-Dibenzyloxy-2-(6-amino-5-cyano-10-acetoxy-5-undecenyl)benzoic Acid (14).—The mixture of **11** and **12** (200 mg, 0.003 mol) was dissolved in a solution of 12 ml of glacial acetic acid, 1 ml of water, and 6 ml of 85% phosphoric acid. The reaction mixture was heated to 55° for 2 hr, cooled, and poured over ice. The resulting mixture was extracted with ether, the extract was dried ($MgSO_4$), and ether was removed from the dried extract to leave 180 mg of paste. This residue was taken up in $CHCl_3$, and the solution was passed through a column (10 g) of Silicar-CC-7 to give a mixture of **13** and **14** as a paste. *In the ir spectrum, intensity of absorption at* 1700 cm^{-1} (C=O) was increased, and intensity of absorption at 2180 cm^{-1} (conjugated CN) was the same in comparison with the ir spectrum of the starting mixture of **11** and **12**; nmr ($CDCl_3$) δ 2.00 (s, 3, $OCOCH_3$).

Anal. Calcd for $C_{35}H_{38}N_2O_5$: N, 4.94. Found: N, 4.67.

Mixture of Lactams of 4,6-Dibenzyloxy-2-[5-(5-cyano-2-methyl-1,2,3,4-tetrahydro-6-pyridyl)pentyl]benzoic Acid (15) and 4,6-Dibenzyloxy-2-[5-cyano-5-(6-methyl-2-piperidylidene)pentyl]-benzoic Acid (16).—The mixture of **11** and **12** (220 mg, 0.004 mol) was dissolved in 10 ml of methanol, concentrated hydrochloric acid (7 mmol) was added, and the resulting reaction mixture was stirred at 55° for 3 hr. Crushed ice was added, and the mixture was extracted with 5% sodium bicarbonate solution and water and then dried ($MgSO_4$). Removal of ether left a yellow, pasty residue (220 mg) which was taken up in $CHCl_3$. The $CHCl_3$ solution was passed through a 20-g column of Silicar-CC-7. Removal of $CHCl_3$ gave 180 mg of the mixture of **15** and **16**: ir (film) 1700 (weak, C=O), 2180 cm^{-1} (strong, conjugated CN); nmr ($CDCl_3$) δ 1.2–1.4 (2 d, 6, axial and equatorial CH_3 groups),[22] 4.0–4.4 (m, 1, $-CHCH_3$). The multiplet at δ 4.0–4.4 was shown to couple with the methyl group by decoupling. This nmr spectrum had no hydrogen exchangeable with D_2O.

Anal. Calcd for $C_{33}H_{34}N_2O_3$: C, 78.25; H, 6.71; N, 5.53. Found: C, 77.84; H, 6.78; N, 5.15.

Registry No.—**1b,** 37103-23-4; **11,** 37103-24-5; **12,** 37103-25-6; **13,** 37157-00-9; **14,** 37103-26-7; **15,** 37103-27-8; **16,** 37102-822; **19,** 37102-833.

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[24] C. F. H. Allen and J. A. VanAllan, *J. Org. Chem.*, **14**, 754 (1949).

[25] Unpublished data from the research laboratories of the Commercial Solvents Corp. For the preparation and other properties of *S*-zearalanone, see W. H. Urry, H. L. Wehrmeister, E. B. Hodge, and P. H. Hidy, *Tetrahedron Lett.*, 3109 (1966).