Synthesis and Reactions of Isoquinuclidone Diesters[1]

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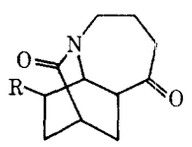
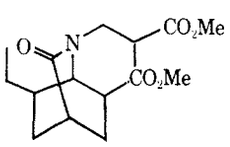
3-Oxo-6-carbomethoxy-2-azabicyclo[2.2.2]octane (**13**) and its 7-ethyl derivative **15** were prepared by heating the amino diesters **8** and **9** in the presence of 1 equiv of sodium methoxide. Treating the isoquinuclidones with methyl acrylate in the presence of sodium gave the N-substituted diesters **17** and **18**. All attempts at Dieckmann cyclization of **17** were unsuccessful. On attempted acyloin condensation of **18** the major product formed was that resulting from retro-Michael reaction and reduction of the 6-carbomethoxy group. This material was isolated as its acetate, **21**.

As part of a program leading to a general synthesis of the iboga alkaloids several routes to the preparation of the tricyclic ketone **1a** and its desethyl counterpart **1b** were investigated. One approach which has recently been described[3] led to **1b** and thus, to desethylibogamine. It was felt, however, that the diester **2**, an oxidative degradation product of ibogaine,[4] would also be a useful intermediate in the synthesis of **1a** since either Dieckmann cyclization followed by ring expansion or acyloin condensation and reduction could be envisioned as reasonable routes for this conversion. Thus, efforts were expended on developing a synthesis of **2** and investigating its cyclization reactions.



1a, R = Et
b, R = H



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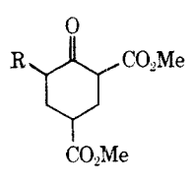
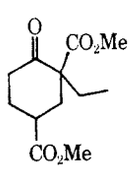
Alkylation of 2,4-dicarbomethoxycyclohexanone[5] (**3**) with ethyl iodide and potassium *t*-butoxide[6] followed by refluxing the alkylated material **4** with sodium methoxide in toluene[7] gave a very good yield of the 2,4,6-trisubstituted cyclohexanone **5**. The nmr spectrum of **5** indicated that both ethyl epimers (ethyl group *cis* and *trans* to the 4-carbomethoxy group) were present in about equal amounts.



3, R = H
5, R = Et



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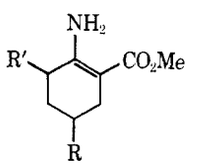
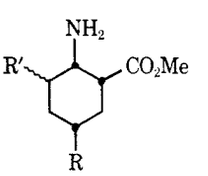
Both **3** and **5** were converted to their respective enamines **6** and **7** by passing a vigorous stream of ammonia through the β-keto ester at elevated temperatures in the presence of a trace of ammonium nitrate.[8] Hydrogenation of these enamines over palladium[9] gave the aminocyclohexane diesters **8** and **9**. Hydrogenation of the tetrahydroanthranilic ester **10**[10] over rhodium has been reported to give the *cis*-2-aminocyclohexanecarboxylate **11**.[11] This same product is obtained from palladium-catalyzed hydrogenation of **10**.[9] Thus, in both **8** and **9** it can be assumed that the amino group and the ester at C-2 are *cis* to each other.



6, R = CO_2Me; R′ = H
7, R = CO_2Me; R′ = Et
10, R = R′ = H



8, R = CO_2Me; R′ = H
9, R = CO_2Me; R′ = Et
11, R = R′ = H

The stereochemistry of the ester group at C-4, however, remains to be established. It was previously shown that the presence of the 4-carbomethoxy group makes the hydrogenation of **6** considerably more difficult than the saturation of the double bond in **10**.[9] A comparison of the spectra obtained from **6** and **10** also revealed some interesting data. The ultraviolet spectrum of **6** exhibited a maximum at 284 mμ with an extinction coefficient of 20,000; **10** also absorbed at 283 mμ, but had an extinction coefficient of only 15,000. The nmr spectrum of **6** displayed a broad singlet at δ 6.3 (378 Hz) for the N–H protons, but the peak for the analogous set of protons from **10** was observed at δ 6.0 (361 Hz). The unreactive ring double bond, enhanced extinction coefficient, and deshielded N–H protons of **6** can be interpreted as the result of a special type of field effect known as a supraannular effect.[12] With this

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(2) (a) NDEA Fellow 1965–1968. (b) Taken from the dissertation submitted by R. F. B. to Seton Hall University in partial fulfillment of the requirements for the Ph.D. degree, 1968.

(3) R. L. Augustine and W. G. Pierson, *J. Org. Chem.*, **34**, 1070 (1969).

(4) M. F. Bartlett, D. F. Dickel, and W. I. Taylor, *J. Amer. Chem. Soc.*, **80**, 126 (1958).

(5) H. T. Openshaw and R. Robinson, *J. Chem. Soc.*, 912 (1946).

(6) G. Stork and S. M. McElvain, *J. Amer. Chem. Soc.*, **68**, 1053 (1946).

(7) W. L. Meyer, A. P. Lobo, and E. T. Marquis, *J. Org. Chem.*, **30**, 181 (1965); L. Nicole and L. Berlinguet, *Can. J. Chem.*, **40**, 353 (1962).

(8) H. G. Becker, *J. Prakt. Chem.*, **12**, 294 (1961).

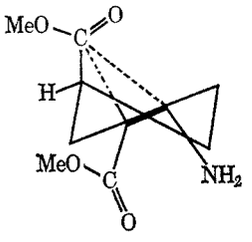
(9) R. L. Augustine, R. F. Bellina, and A. J. Gustavsen, *J. Org. Chem.*, **33**, 1287 (1968).

(10) V. Prelog and U. Geyer, *Helv. Chim. Acta*, **28**, 1677 (1945).

(11) K. J. Liska, *J. Pharm. Sci.*, **53**, 1427 (1964).

(12) G. P. Kugatova-Shemyakina and Yu. A. Ovchinnikov, *Tetrahedron*, **18**, 697 (1962); G. P. Kugatova-Shemyakina, G. M. Nikolaev, and V. M. Andreev, *ibid.*, **23**, 2721 (1967); G. P. Kugatova-Shemyakina and G. M. Nikolaev, *ibid.*, **23**, 2987 (1967).

effect in operation the vinylogous urethan **6**, contrary to expectation, would exist preferentially in the conformation **12**, in which the 4-carbomethoxy group is in an



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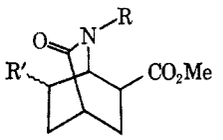
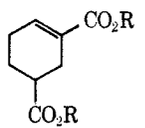
axial position and is near enough to the ring double bond to give rise to an intramolecular interaction between the π electrons of the latter and the electrophilic carbon of the former. Thus, hydrogenation of the double bond of **6** would be expected to give the all-*cis* product **8**. Products resulting from a similar type of *trans* attack have also been obtained from epoxidation[13] and hydroboration[14] of a number of carbonyl-substituted cyclohexenes.

This stereochemical assignment is strengthened by the ease of deamination of **8** and **9** as compared to that of **11**. The preferred conformation for the all-*cis* isomer **8** would have the amine group in an axial configuration,[15] and, thus, it would be expected to be readily eliminated. The preferred arrangement of stereoisomers of **8** having either or both of the ester groups *trans* to amine function would have the amino group predominantly or exclusively in the equatorial conformation and, therefore, less easily involved in an elimination reaction.

Because of this ease of deamination the cyclization of **8** to the isoquinuclidone **13** proved troublesome. Heating a dilute solution of **8** gave, as the major isolable material, the unsaturated diester **14a**, which was identified by hydrolysis to the known[16] tetrahydroisophthalic acid **14b**. However, cyclization could be effected in



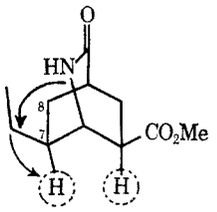
13, R = R′ = H
15, R = H; R′ = Et
17, R = $CH_2CH_2CO_2Me$; R′ = H
18, R = $CH_2CH_2CO_2Me$; R′ = Et



14a, R = Me
b, R = H

reasonably good yield by heating a methanol solution of **8** at 185° for 8 min in a sealed bomb in the presence of 1 equiv of sodium methoxide. The use of less base and/or longer reaction times resulted in the formation of less isoquinuclidone. The nmr spectrum of **13** exhibited two closely spaced singlets in a 3:2 ratio which have been assigned to the protons of the *exo* and *endo*[17] methyl ester groups, respectively.

Cyclization of **9** gave the substituted isoquinuclidone **15** as a nearly equal mixture of *exo* and *endo*[17] ethyl epimers. In contrast to what was observed with **13** the nmr spectrum of **15** showed only one clean singlet for the carbomethoxy protons indicating that only one ester epimer was present. Clearly, the isomer of **15** possessing an *endo* ethyl group would exist preferentially with the epimerizable carbomethoxy group in an *exo* configuration. The reasons why the carbomethoxy group preferred the *exo* position when the ethyl group was *exo* were not apparent. However, if the steric repulsion between the heterocyclic bridge and the *exo* ethyl group were great it would force rotation about the 7,8 carbon–carbon bond resulting in the 7-hydrogen being thrust toward the 6-*endo* group as depicted in **16**.



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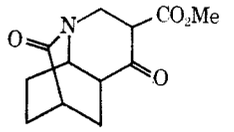
Since the 6-carbomethoxy group has a greater steric requirement than the 6-hydrogen, the carbomethoxy entity would prefer the *exo* position.

The isoquinuclidones **13** and **15** were treated with methyl acrylate in the presence of sodium metal to give the diesters **17** and **18**, respectively. Compound **18** had infrared spectral characteristics identical with those reported for **2**[4] but was, obviously, a mixture of ethyl epimers. The presence of two three-proton singlets in the nmr spectrum of **18** indicated that the 6-ester group was still in the *exo* configuration. With **17**, however, four carbomethoxy singlets were observed showing that this material was still a mixture of 6-carbomethoxy isomers.

The Dieckmann cyclization was attempted originally on **17** since it was felt that under the basic reaction conditions used ester epimerization would occur and, thus, the stereochemistry at C-6 was not important. All attempts to cyclize **17** under a wide variety of reaction conditions failed to give the desired β-keto ester, **19**. However, when the addition of methyl acrylate to **13** was run in the presence of a small amount of methanol a very small quantity (~1% yield) of **19** was obtained. It is



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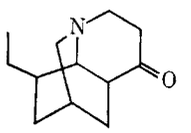

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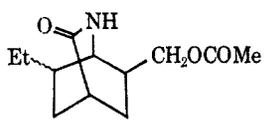
probable that the trigonal nature of the lactam nitrogen imparts considerable strain to a tricyclic system such as **19**, and, thus, cyclization does not take place for steric reasons. On the other hand the tricyclic amino ketone **20**, which is readily obtained by degradation of ibogaine, is relatively strain free.

Attention was then turned to the acyloin condensation of these isoquinuclidone diesters. Because of competitive Dieckmann cyclization the acyloin condensation is normally not very useful for the formation of seven-membered rings.[18,19] However, in the present

(13) H. B. Henbest and B. Nicholls, *J. Chem. Soc.*, 221 (1959).
(14) J. Klein, E. Dunkelblum, and A. Avrahami, *J. Org. Chem.*, **32**, 935 (1967).
(15) J. Hirsch, "Topics in Stereochemistry," Vol. 1, N. L. Allinger and E. L. Eliel, Ed., Interscience Publishers, Inc., New York, N. Y., 1967, 199.
(16) W. H. Perkin and S. S. Pickles, *J. Chem. Soc.*, 87 (1905).
(17) An *exo* substituent is defined as one which is *cis* to the lactam bridge of the isoquinuclidone, and an *endo* substituent is *trans* to this bridge.
(18) P. D. Gardner, G. R. Haynes, and R. L. Brandon, *J. Org. Chem.*, **22**, 1206 (1957).
(19) K. T. Finley, *Chem. Rev.*, **64**, 573 (1964).

instance this competitive reaction does not take place and, therefore, the acyloin condensation was expected to occur readily. The diester **18** was used in these reactions since this material had the 6-carbomethoxy group in the proper configuration. The condensation of **18**, using a liquid ammonia–tetrahydrofuran solvent system, gave a product which failed to exhibit an ester carbonyl band in the infrared spectrum. The crude product was acetylated and chromatographed on silicic acid. The major component, which was present in about 60–70% yield, exhibited bands in the infrared spectrum at 3425 (*NH*CO), 1680 (lactam carbonyl), 1735 (acetate carbonyl), and 1250–1230 cm^{-1} (acetate C–O stretching frequency). The nmr spectrum of this compound displayed a three-proton singlet at δ 2.05 anticipated for an acetate methyl, a two-proton doublet (J = 7.5 Hz) at δ 3.94 corresponding to an entity such as $CHCH_2OAc$, and a broad singlet at about δ 7.4 for the lactam proton. These data, coupled with the elemental analysis, lead to the conclusion that this compound was the isoquinuclidone acetate **21**. Thus un-



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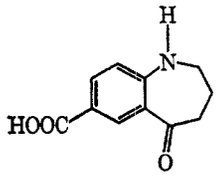
expected product apparently arises from retro-Michael reaction of the N-alkyl ester and reduction of the 6-carbomethoxy group, followed by acetylation of the resulting alcohol. The proton required for this unusual reduction is thought to originate from the α position of the N-alkyl ester. The formation of a small quantity of an alcohol under acyloin conditions has been previously reported.[18] A thin layer chromatographic and infrared spectral study of all of the fractions from the column chromatography failed to indicate the presence of any acyloin product. In addition to the acetate **21** a small quantity of a crystalline material was isolated which displayed a very intense band at 1705 cm^{-1} in the infrared spectrum. The structure of this compound has not been ascertained.

The failure of **18** to cyclize is probably due primarily to the action of the facile retro-Michael reaction and not to any steric factors since the tricyclic material **23** has been previously obtained in very good yield on hydrogenative cyclization of the amino acid **22**.[20]



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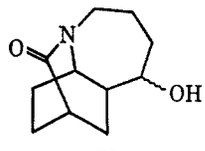

23

It is apparent, then, that these cyclizations cannot be used to synthesize **1** as desired and that other approaches to this problem need to be developed.[21,22]

(20) Y. Ban, T. Wakamatsu, Y. Fujimoto, and T. Oishi, *Tetrahedron Letters*, 3383 (1968).

(21) Two syntheses of the amine analog of **1** have recently been reported.[20,22]

(22) S. I. Sallay, *J. Amer. Chem. Soc.*, **89**, 6762 (1967).

Experimental Section[23]

1,3,3,5-Tetracarbomethoxypentane (24).—To a mixture of 200 g (1.52 moles) of dimethyl malonate and 5.0 g (0.22 g-atom) of sodium in 250 ml of dry benzene was added, with stirring, 312.7 g (3.64 moles) of methyl acrylate in 300 ml of dry benzene over a 3-hr period. After addition the mixture was stirred an additional 3 hr and refrigerated overnight. The benzene solution was washed with cold 10% hydrochloric acid and water, dried, filtered, and evaporated to give 475 g of a colorless oil which crystallized while cooling. Two recrystallizations from methanol gave large colorless crystals, mp 54–57°.

Anal. Calcd for $C_{13}H_{20}O_8$: C, 51.31; H, 6.62. Found: C, 51.00; H, 6.72.

1,3,5-Pentanetricarboxylic Acid (25).—The tetraester **24** (220 g, 0.72 mole) was refluxed for 14 hr in 1100 ml of concentrated hydrochloric acid. The residue obtained on evaporation was heated at 200° for 2.5 hr. Recrystallization of this residue from acetone–chloroform gave 145.5 g (95%) of product, mp 109–111°. A second recrystallization from acetone furnished crystals, mp 111–113° (lit.[5] mp 113–114°).

1,3,5-Tricarbomethoxypentane (26).—A mixture of 125.2 g (0.61 mole) of **25**, 180 g (5.53 mole) of absolute methanol, 60 ml of concentrated sulfuric acid, and 300 ml of dry benzene was refluxed for 18 hr. The benzene layer was separated and replaced by 300 ml of fresh dry benzene and 20 ml of concentrated sulfuric acid. After the mixture was refluxed an additional 4 hr, the benzene phase was separated and combined with the first benzene solution. The combined solution was washed with cold saturated aqueous sodium bicarbonate solution, dried, filtered, and evaporated to give 145.6 g of the triester. The sulfuric acid phase was neutralized with potassium carbonate and extracted twice with ether to yield an additional 5.0 g of product. Distillation of 270 g of this material gave 250.2 g (93%) of a colorless oil, bp 119° (0.5 mm) [lit.[5] bp 162° (12 mm)].

2-Ethyl-2,4-dicarbomethoxycyclohexanone (4).—To a solution of potassium *t*-butoxide (prepared from 7.86 g (0.20 g-atom) of potassium metal and 200 ml of dry *t*-butyl alcohol) was added 43.1 g (0.20 mole) of the β-keto ester **3**[5] in 200 ml of dry *t*-butyl alcohol. The mixture was refluxed for 45 min and allowed to cool to room temperature. Ethyl iodide [62.4 g (0.40 mole)] was added in one portion and the mixture refluxed with stirring for 24 hr. Most of the alcohol was removed by evaporation under reduced pressure. The supernatant alcohol was decanted and the residue was washed three times with ether. The ethereal washings were combined with the supernatant alcohol, and the combined solution was washed with ice-cold 10% hydrochloric acid, saturated aqueous sodium bicarbonate solution, and saturated brine. Evaporation of the solvent after drying left 46.1 g (95%) of a colorless oil which did not give a color reaction with ferric chloride. Distillation of 50 g gave 47.3 g (90%) of product: bp 135.5–138° (0.7 mm); $n^{20}D$ 1.4696; infrared spectrum (film), 1740 strong shoulder (2-COOMe), 1735 strong (4-COOMe), and 1715 cm^{-1} (six-membered ring CO); nmr spectrum, 3 H triplet at δ 0.90 (J = 7.0 Hz) (CH_2CH_3) and 6 H singlet at 3.83 (both CO_2Me).

Anal. Calcd for $C_{12}H_{18}O_5$: C, 59.49; H, 7.49. Found: C, 59.33; H, 7.38.

The 2,4-dinitrophenylhydrazone was recrystallized from methanol, mp 148–149°.

Anal. Calcd for $C_{18}H_{22}N_4O_8$: C, 51.18; H, 5.25; N, 13.26. Found: C, 50.99; H, 5.19; N, 13.21.

6-Ethyl-2,4-dicarbomethoxycyclohexanone (5).—Dry toluene (150 ml) was added to 5.94 (0.11 mole) of sodium methoxide. To this rapidly stirred slurry was added 24.0 g (0.099 mole) of the β-keto ester **4** in 150 ml of dry toluene over a 1-hr period. The mixture was refluxed for 8 hr after which the solvent was distilled until its boiling point rose to 110° (about 30 min). After cooling, the reaction mixture was diluted with 100 ml of benzene, and washed with ice-cold 10% hydrochloric acid. The acidic

(23) All melting points were determined in open capillary tubes using a Mel-Temp apparatus and are uncorrected. All boiling points are uncorrected. The infrared spectra were recorded on a Beckman Model IR-10 recording spectrophotometer in chloroform solution unless otherwise indicated. The ultraviolet spectra were recorded in absolute methanol on a Beckman Model DK-2 ratio recording spectrophotometer. The nuclear magnetic resonance were determined on a Varian Associates Model A-60A recording spectrometer in deuteriochloroform unless otherwise specified. Tetramethylsilane (TMS) was used as the internal standard and all signals are given in parts per million (δ) relative to TMS at δ 0.

washings were saturated with sodium chloride and extracted twice with benzene. The combined benzene solution was washed with 4 ml of saturated aqueous sodium bicarbonate solution and three times with 6 ml of saturated brine, dried, and evaporated to give a pale orange oil. Distillation of the crude product gave 14.6 g (61%) of product, bp 125–134° (0.07–0.1 mm), which gave a very intense ferric chloride test. A fraction of the colorless oil which had bp 128–130° (0.07 mm) and $n^{20}D$ 1.4764 served as the analytical sample; infrared spectrum ($HCCl_3$), 1740 (2-**COO**Me), 1735 (4-**COO**Me), 1660 (-HOC=C**O**C**O**Me), and 1620 cm^{-1} (enolic C=C); nmr spectrum, overlapping 3 H triplets at *ca.* δ 1.0 (J = 6.0 Hz) (epimric $CH_2\mathbf{CH_3}$), 3 H singlet at 3.72 (4-COO**Me**), 3 H singlet at 3.78 (2-COO**Me**), and 0.6 H singlets of approximately equal intensities at 12.21 and 12.37 (indicative of enolic OH protons in different chemical environments).

Anal. Calcd for $C_{12}H_{18}O_5$: C, 59.49; H, 7.49. Found: C, 59.45; H, 7.40.

Methyl 4-carbomethoxy-6-ethyl-3,4,5,6-tetrahydroanthranilate (7) was prepared following the procedure used to synthesize the desethyl analog 6[9] except that the required reaction temperature was 115–125°. The product, which was obtained in quantitative yield, did not react with ferric chloride reagent. The viscous oil resisted all attempts at crystallization. An attempt to distil this material led to extensive decomposition. The infrared spectrum (film) of the crude material showed bands at 3460 (nonbonded N–H), 3330 (bonded N–H), 1730 (4-**COO**Me), 1670 (2-**COO**Me), and 1615 cm^{-1} (C=C); the nmr spectrum had overlapping 3 H triplets of approximately equal intensities centered at *ca.* δ 1.10 (J = 6.5 Hz) (epimeric $CH_2\mathbf{CH_3}$), 3 H singlet at 3.68 (4-COO**Me**), 3 H singlet (2-COO**Me**), and overlapping broad singlets centered at *ca.* 6.50 which integrated for 2 H ($\mathbf{NH_2}$).

2,4-Dicarbomethoxy-6-ethylcyclohexylamine (9) was prepared by the hydrogenation of 7 by the previously described procedure.[9] The amino diester 9 was obtained as a thick, viscous oil which resisted crystallization and decomposed on distillation. All attempts to derivatize 9 as the hydrochloride salt, the *p*-nitrobenzamide, or the 3,5-dinitrobenzamide led only to extensive deamination. This material showed infrared absorption (film) at 3350 (N–H) and 1735 cm^{-1} (both -**COO**Me), but no absorption at 1655 (NH_2C=C**COO**Me) or at 1618 cm^{-1} (C=C).

3-Oxo-6-carbomethoxy-2-azabicyclo[2.2.2]octane (13).—Into a 35-ml stainless steel bomb was placed 4.0 g (0.19 mole) of the amino diester 8 in 15 ml of dry methanol and 1.0 g (0.19 mole) of sodium methoxide in 15 ml of dry methanol. The vessel was sealed, vigorously shaken, and immersed in an oil bath at 185 ± 5° for 7–10 min. The bomb was removed from the oil bath, allowed to cool for 15 min at room temperature, and subsequently placed in a freezing mixture until very cold at which time the reaction vessel was opened.

Small pieces of Dry Ice and 10 ml of water were added to a flask containing the methanolic reaction mixtures from two runs. The solution was acidified to pH 4–6 by the dropwise addition of concentrated hydrochloric acid and the acidified reaction mixture was extracted thoroughly with chloroform which was dried, filtered, and evaporated to furnish an orange oil. This residue was taken up in methanol and filtered through a pad of Norit, and the solvent was evaporated to give 6.5 g of a pale yellow oil. Infrared analysis indicated that the oil contained the desired isoquinuclidone and some unsaturated side product which resulted from deamination of the starting material.

This crude product (6.5 g) was taken up in 25 ml of water. The aqueous solution was extracted twice with 10-ml portions of ether. The combined ethereal solution was back extracted with two 10-ml portions of water. The ethereal solution (A) was set aside for further study. The aqueous extracts were combined with the original aqueous solution. This combined solution was saturated with sodium chloride and extracted four times with 25-ml portions of methylene chloride. The combined methylene chloride extract was dried, filtered, passed through a Norit pad, and evaporated to give 4.0 g (56%) of nearly colorless product. All attempts to induce this oil to crystallize failed.

This oil was placed on a small silica gel column and eluted with ether to remove the trace impurity. The isoquinuclidone product was removed from the column with methanol. The methanol was evaporated and the residue was distilled from a metal block distillation apparatus at 175–225° *in vacuo*. Thin layer chromatographic studies (silica gel) of the distillate using chloroform, ether, and methanol as eluents indicated the presence of only one component: infrared spectrum ($HCCl_3$), 3425 (**NH**CO), 3230 broad (clathrated H_2O), 1735 (**COO**Me), and 1685 cm^{-1} strong (**NHCO**); nmr spectrum, broad 4 H singlet at δ 1.78 (CH_2CH_2), singlets at 3.73 and 3.76 integrating for a total of 3 H (epimeric COO**Me**), 0.8 H broad singlet centered at 4.0 (clathrated H_2O), and a broad 1 H singlet centered at 7.65 (**NH**CO).

Anal. Calcd for $C_9H_{13}NO_3 \cdot 0.6H_2O$: C, 55.69; H, 7.38; N, 7.22. Found: C, 55.68; H, 7.38; N, 7.09.

Identification of the Major Side Product from the Isoquinuclidone Synthesis.—The ethereal solution (A) from the previous reaction was filtered through Norit, dried, and evaporated to yield 1.88 g of pale yellow oil which rapidly decolorized a bromine–carbon tetrachloride solution and had infrared absorption (film) at 1735 (CH**COO**Me), 1715 (C=C**COO**Me), and 1650 cm^{-1} (C=C). A small quantity of this compound was hydrolyzed by refluxing in 15% hydrochloric acid for 8 hr. White crystals, mp 237–241°, formed while the acidic solution was cooling. The Δ^3-tetrahydroisophthalic acid **14b** so obtained was recrystallized from water, mp 245.5–248° (lit.[16] mp 243–244°). Running the cyclization of **8** for longer times on in the presence of smaller amounts of base gave more **14a** and considerably less of the desired **13**.

3-Oxo-6-*exo*-carbomethoxy-7-ethyl-2-azabicyclo[2.2.2]octane (15). (1) **Sodium Methoxide Method.**—The procedure used to synthesize **15** was the same as that which was employed for the preparation of the desethyl analog **13**. Twelve grams of the amino diester **9** were cyclized in four portions to furnish the isoquinuclidone product in 53% yield (5.4 g). All attempts to induce the product to crystallize failed. A sample of the isoquinuclidone was distilled nearly quantitatively from a metal block distillation apparatus to give a viscous, colorless oil; infrared spectrum ($HCCl_3$), 3425 (**NH**CO), 1730 (**COO**Me), and 1680 cm^{-1} (**NHCO**); nmr spectrum, 3 H overlapping triplets centered *ca.* δ 0.97 (J = 6.0 Hz) (epimeric $CH_2\mathbf{CH_3}$), 3 H singlet at 3.73 (COO**Me**), and a broad 1 H singlet at *ca.* 7.47 (NHCO).

Anal. Calcd for $C_{11}H_{17}NO_3$: C, 62.54; H, 8.11; N, 6.63. Found: C, 62.29; H, 8.23; N, 6.52.

(2) **Hydrogenation–Cyclization Method.**—To 1.6 g of 5% ruthenium-on-charcoal catalyst which was thoroughly moistened with dry dioxane, was added, with caution, a solution of 1.5 g (0.0062 mole) of the vinylogous urethan **7** in 60 ml of absolute methanol. This mixture was hydrogenated at 1800 psig and 120° for 24 hr and then at 1900 psig and 175° for an additional 12 hr and the catalyst was removed by filtration. Evaporation of the solvent under reduced pressure afforded an oil which was taken up in ether and filtered through a sintered-glass funnel. The ethereal filtrate was thoroughly extracted with small portions of water and the aqueous extracts combined. The combined aqueous solution was thoroughly extracted with methylene chloride, the methylene chloride extracts were combined, dried, filtered, and evaporated under reduced pressure to furnish 0.25 g (19%) of the isoquinuclidone **15**, which was identical with that prepared by method 1.

N-(β-Methyl propionate)-3-oxo-6-carbomethoxy-2-azabicyclo[2.2.2]octane (17).—A mixture of 1.58 g (0.0087 mole) of the isoquinuclidone **13**, 0.05 g (0.0022 g-atom) of sodium (cut into small pieces), and 7 ml of dry benzene was stirred at room temperature for 10 min. The mixture was chilled in an ice bath and 0.86 g (0.01 mole) of methyl acrylate was added in one portion with stirring. The solution was cooled for 15 min after the addition, and then the reaction was allowed to stir at room temperature for 24 hr. The solution was decanted from the unreacted sodium and the reaction flask was rinsed several times with a few milliliters of benzene. The combined benzene solution was washed with a small volume of 10% hydrochloric acid. The acidic washings were saturated with sodium chloride and extracted twice with 10-ml portions of benzene. The benzene extracts were added to the original benzene solution and the combined solution was washed with saturated aqueous sodium bicarbonate solution and saturated brine, dried, filtered, and evaporated to give 2.1 g (92%) of product as a colorless cloudy oil which was further purified by filtering a methanolic solution of it through a Norit pad. The analytical sample was prepared by distillation from a metal block distillation apparatus at 125–160° *in vacuo*; infrared spectrum ($HCCl_3$), 1735 (**COO**Me) and 1660 cm^{-1} (**NCO**); the nmr spectrum showed a 4 H broad singlet at δ 1.76 ($CHCH_2\mathbf{CH_2}CH$), and four very close singlets at 3.67–3.76 which integrate for a total of 6 H (*exo* and *endo* COO**Me**, *cis* and *trans* $-N(CH_2)_2$COO**Me**).

Anal. Calcd for $C_{13}H_{19}NO_6$: C, 57.98; H, 7.11; N, 5.20. Found: C, 57.87; H, 7.24; N, 5.07.

N-(β-Methyl propionate)-3-oxo-*exo*-6-carbomethoxy-7-ethyl-2-azabicyclo[2.2.2]octane (18) was prepared by using the same procedure as employed for the preparation of the desethyl analog **17**. Alkylation of 1.9 g (0.0090 mole) of **15**, with 0.95 g (0.011 mole) of methyl acrylate, afforded 2.21 g (83%) of nearly pure product as a colorless oil. The analytical sample distilled cleanly from a metal block distillation apparatus at 180–230° *in vacuo*; infrared spectrum (film), 1740 (ester CO) and 1678 cm^{-1} (lactam CO) [lit.[4] 1742 (ester CO) and 1678 cm^{-1} (lactam CO) for **2**]; nmr spectrum, poorly resolved triplet at δ 0.97 (J = 6.0 Hz) (epimeric $CH_2\mathbf{CH_3}$), 3 H singlet at 3.70 ($CH_2CH_2\mathbf{COOMe}$), and a 3 H singlet at 3.73 (CHCOO**Me**).

Anal. Calcd for $C_{15}H_{23}NO_5$: C, 60.59; H, 7.80; N, 4.71. Found: C, 60.46; H, 7.61; N, 4.87.

Preparation of the Tricyclic Ketolactam 19.—A mixture of 0.50 g (0.0027 mole) of the isoquinuclidone **13**, 0.06 g (0.0027 g-atom) of sodium, 0.24 g (0.0028 mole) of methyl acrylate, 2 drops of absolute methanol, and 10 ml of dry benzene was stirred for 30 min at room temperature. The yellow solution was then refluxed with stirring for 7 hr under dry nitrogen. The solvent was distilled until the boiling point of the distillate reached 80° (about 30 min) and the cooled reaction mixture was diluted with 40 ml of benzene. The reaction mixture was washed with a small portion of ice-cold 10% hydrochloric acid. The acidic wash was extracted twice with 5-ml portions of methylene chloride. All organic phases were combined, washed with saturated aqueous sodium bicarbonate solution, dried, and evaporated to give 0.48 g of a viscous orange oil. The crude product was taken up in methanol, filtered through a Norit pad, and evaporated under reduced pressure to furnish 0.37 g of a pale yellow oil which gave a positive ferric chloride test.

The oil[24] was chromatographed on 15 g of silicic acid and eluted with absolute ether. The ether eluent afforded about 9 mg of a crystalline material. Chloroform ws used to recover starting material and the alkylated, but uncyclized isoquinuclidone, **17**. The crystalline solid was sublimed at 70–90° (1 mm); mp 80–120°; infrared spectrum ($HCCl_3$), 3370 (enolic OH), 1730 (COCH**COO**Me), 1710 (COCHCOOMe), 1680 shoulder (–HOC=COCOMe), 1670 (**NCO**), and 1614 cm^{-1} (C=C); ultraviolet spectrum, λ_{max}^{MeOH} 250 mμ, λ_{max} (methanol plus a trace of sodium hydroxide) 280 mμ.

Anal. Calcd for $C_{12}H_{15}NO_4$: C, 60.75; H, 6.37. Found: C, 60.40; H, 6.63.

Attempted Acyloin Cyclization of the Lactam Diester 18.—The lactam diester **18** was placed on a hot-water bath under high vacuum for 10 hr prior to use to remove any trace of water or methanol which may have been present. A 1-l. three-neck flask equipped with a Dry Ice condenser, mechanical stirrer, addition funnel, and a dry nitrogen system was thoroughly flamed-out before being used. All incoming predried gases were passed through potassium hydroxide drying towers as a precautionary step. The exit port of the system was similarly protected from moisture. A positive nitrogen pressure was maintained at all times, and all additions to the reaction flask were made against the stream of nitrogen.

(24) A similar oil was obtained by treating **17** with 1 equiv of sodium methoxide in refluxing toluene after which the solvent was distilled until its boiling point rose to 110°. Both of these oils displayed a minor, but identical ferric chloride active spot on tlc (silica gel) using several solvents of varying polarity as eluents.

To the reaction flask was added 350 ml of anhydrous liquid ammonia and 220 ml of freshly distilled anhydrous tetrahydrofuran. In this solvent system was dissolved 1.36 g (0.059 g-atom) of freshly cut sodium. A solution of the diester [2.50 g (0.0084 mole)] in 220 ml of anhydrous tetrahydrofuran was added with stirring over 90 min. The stirring was continued as the reaction slowly warmed to room temperature. The reaction was allowed to stand overnight under a slow stream of nitrogen.

The unreacted sodium was destroyed by the addition of 8 ml of methanol followed by 30 min of stirring. Two 10-ml portions of cold 10% hydrochloric acid were added and the mixture was vigorously shaken. The tetrahydrofuran was removed under reduced pressure at 25°. The remaining aqueous phase was saturated with sodium chloride and extracted four times with 40-ml portions of methylene chloride. The extracts were dried, filtered, and evaporated to give 1.60 g of a viscous yellow oil.

This crude product was dissolved in a solution of 9.5 ml of acetic anhydride and 15.8 ml of pyridine and allowed to stand at room temperature for 40 hr. The dark red residue obtained on evaporation of the reaction mixture was taken up in methylene chloride, washed twice with 5-ml portions of 5% hydrochloric acid, dried, filtered, and evaporated to give a red oil. The crude acetate was chromatographed on 20 g of silicic acid as a preliminary purification step. Only two fractions, which were eluted with chloroform–methanol (10:1), contained material which exhibited infrared spectral characteristics which were in accord with the anticipated acetylated product. These fractions were combined and evaporated to furnish 0.78 g of an oil which was then rechromatographed on 100 g of silicic acid.

From the chloroform eluent was obtained 171 mg of a crystalline solid. With considerable material loss, the solid was recrystallized from ether–hexane; mp 96–98°; infrared spectrum ($HCCl_3$), 1755 cm^{-1} (ketone?); mol wt (cryoscopic) 116.

Anal. Found: C, 57.04; H, 7.30.

A reasonable structure to account for these data has not been ascertained.

From the ether eluent was obtained 130 mg of a cloudy oil which was taken up in methanol and filtered through a Norit pad. Evaporation of the solvent left a clear oil which was distilled from a metal block distillation apparatus at 150–200° *in vacuo*. This compound was assigned structure **21** from the following data: infrared spectrum ($HCCl_3$), 3425 (**NH**CO), 1735 (**OCO**Me), 1680 (NH**CO**), and 1250–1210 cm^{-1} (acetate C–O stretch); nmr spectrum, 3 H singlet at δ 2.05 (OCO**Me**), 2 H doublet at 3.94 ($CH\mathbf{CH_2}OCOMe$), and a 1 H broad singlet at *ca.* 7.36.

Anal. Calcd for $C_{12}H_{19}NO_3$: C, 63.98; H, 8.50. Found: C, 63.73; H, 8.48.

A thin layer and vapor phase chromatographic estimate of all of the fractions from both column chromatographies indicated that 60–70% of the crude reaction mixture consisted of this compound.

This experiment was repeated several times varying the conditions including the solvent system (ether–ammonia); however, none of the desired acyloin product was detected at any time.

Registry No.—**4**, 19766-30-4; **4** (2,4-dinitrophenylhydrazone), 19766-31-5; **5**, 19766-32-6; **13**, 19795-95-0; **15**, 19766-07-5; **17**, 19766-33-7; **18**, 19766-08-6; **19**, 19766-34-8; **21**, 19766-35-9; **24**, 19766-36-0.