tive plate (2% MeOH in C_6H_6), there was obtained, in addition to more cis oxazoline, a small amount of *erythro*-*N*-benzoyl-β-*m*-nitrophenylserine methyl ester, mp 135–137°, which arose from oxazoline hydrolysis (and O → N acyl migration) during work-up. This component was not present in the original crystalline precipitate (a).

The residue (b), which consisted of three major components was separated on thick plates (6:1 C_6H_6–Et_2O, then 2% MeOH in C_6H_6). The most polar of the three was cis oxazoline, the major reaction product. Next was the isomeric trans oxazoline (ir, tlc), and least polar was *erythro*-*N*-benzoyl-β-chloro-β-(*m*-nitrophenyl)alanine methyl ester (melting point, ir, tlc).

***cis*-4-Carbomethoxy-5-*p*-methoxyphenyl-2-phenyl-2-oxazoline.**—An intimate mixture of 200 mg of *erythro*-*p*-methoxyphenylserine methyl ester, made by Fisher esterification of the more polar of the two *p*-methoxyphenylserines, and 200 mg of benziminoethyl ether hydrochloride was heated on the steam bath for 30 min.[6] Chromatography (3.5% MeOH in C_6H_6) gave 110 mg of crude product, the nmr of which clearly established the configuration as the cis oxazoline. The product was crystallized from ether–hexane. The same chromatography gave a vivid yellow fraction which was shown to be 4-*p*-methoxybenzylidene-2-phenyl-2-imidazolin-5-one: mp 295° dec from isopropyl alcohol (lit.[18] mp 289–290°); uv max (MeOH) 254 nm (log ε 4.39), 394 (4.54); M^+ 278, $C_{17}H_{14}N_2O_2$, mol wt 278.3.

***trans*-4-Carbomethoxy-5-*p*-methoxyphenyl-2-phenyl-2-oxazoline.**—When 400 mg of the threo isomer of *p*-methoxyphenylserine methyl ester underwent the same reaction as described directly above, there was obtained 124 mg of the title product, a light yellow oil, after chromatography on silica gel plates with 6·1 benzene–ether, then 2% methanol in benzene.

(18) A. R. Kidwai and G. M. Devasia, *J. Org. Chem.*, **27**, 4527 (1962).

Registry No.—Thionyl chloride, 7719-09-7; *threo*-β-*p*-methoxyphenylserine 32721-76-9; *erythro*-β-*p*-methoxyphenylserine, 32721-77-0; *erythro*-β-*p*-chlorophenylserine methyl ester hydrochloride, 32721-78-1; *erythro*-β-*p*-cyanophenylserine methyl ester hydrochloride, 32721-79-2; *threo*-β-*p*-cyanophenylserine methyl ester hydrochloride, 32721-80-5; *erythro*-β-*m*-chlorophenylserine methyl ester hydrochloride, 32721-81-6; methyl α-benzamido-*m*-chlorocinnamate, 32730-62-4; methyl α-benzamido-*p*-methoxycinnamate, 32730-63-5.

Acknowledgment.—We are grateful to Messrs. R. Zerfing, D. Harris, and especially Dr. A. W. Douglas who followed our reactions in the nmr, provided our spectra, and helped in correlating relationships. We also gladly acknowledge warm encouragement of Dr. P. I. Pollak.[19]

(19) Deceased, May 10, 1971.

Synthetic Indole Alkaloids. I. Synthesis of a Pentacyclic Lactam[1]

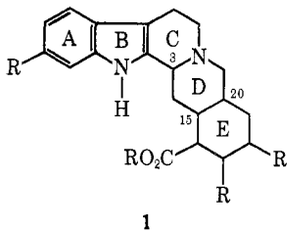
FREDERICK V. BRUTCHER, JR.,* WILLIAM D. VANDERWERFF, AND BARRY DREIKORN

Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104

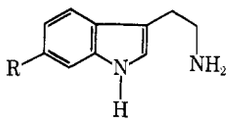
Received October 29, 1970

1,2,3,4,6,7,12,12b-Octahydro-2,4-diketoindolo[2,3-*a*]quinolizine (**3**), a tetracyclic keto lactam, has been prepared as an intermediate in the synthesis of pentacyclic indole alkaloids from tryptamine (**2a**) and citric acid. 6-Methoxytryptamine (**2b**) has also been used in place of **2a**. **3** has been reacted with carbethoxy methyl vinyl ketone (**15**) to produce the expected cyclized adduct, 1,2,3,4,5,7,8,13,13b,14-decahydrobenz[*g*]-1-carbethoxy-2,5-diketoindolo[2,3-*a*]quinolizine (**16**). **16** reduces smoothly with Pt and H_2 to produce the tetrahydro adduct **18**. Lithium aluminum hydride reduction of **18** produces a pentacyclic diol **21**. The stereochemistry of **21** is discussed.

Most of the total synthesis work in the reserpine[2] and the yohimbine[3] areas[4] (**1**) has involved preconstruction of the stereochemical relationships of the D/E rings before condensation with tryptamine (**2a**) or 6-methoxytryptamine (**2b**) to form the pentacyclic skeleton.



1



2a, R = H
b, R = OCH_3

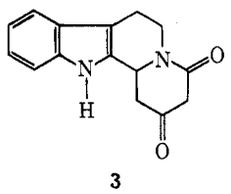
(1) (a) Supported in part by the National Institute of Mental Health. (b) Presented in part before the Division of Organic Chemistry, 159th National Meeting of the American Chemical Society, Houston, Tex., Feb 1970, Abstracts, No. ORGN 15.

(2) R. B. Woodward, F. Bader, H. Bickel, and R. Kierstead, *Tetrahedron*, **2**, 1 (1958).

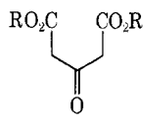
(3) E. Van Tamelen, M. Shamma, A. Burgstahler, J. Wolinsky, R. Tamm, and P. Aldrich, *J. Amer. Chem. Soc.*, **80**, 5006 (1958); **91**, 7315 (1969).

(4) (a) J. Poisson, *Ann. Chim. (Paris)*, **9**, 99 (1964); (b) R. H. F. Manske in "The Alkaloids, Chemistry and Physiology," Vol. VIII, R. H. F. Manske, Ed., Academic Press, New York, N. Y., 1965, p 694; (c) E. Schlittler in "The Alkaloids, Chemistry and Physiology," Vol. VIII, R. H. F. Manske, Ed., Academic Press, New York, N.Y., 1965, p 287; (d) I. Ernest and B. Kakac, *Chem. Ind. (London)*, 513 (1965); (e) for a different stepwise approach, see Cs. Szantay, L. Toke, and K. Honti, *Tetrahedron Lett.*, **No. 22**, 1665 (1965).

In this paper a stepwise construction of rings A through E is explored. In outline, it was envisaged that **2a** or **2b** might be combined with a modified β-oxoglutaric acid to yield a keto lactam of type **3** which then could be alkylated with a substituted methyl vinyl ketone and cyclized to yield a pentacyclic precursor of **1**.



3



4a, R = H
b, R = C_2H_5

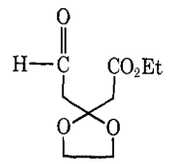
Synthesis Results.—Citric acid, an inexpensive starting material, was readily converted[5] to β-oxoglutaric acid (**4a**) which in turn was esterified[6] to yield **4b** as a preliminary to preparing the desired aldehydo ester **5**. To obtain **5**, **4b** was converted to the ketal ester **6a** which was converted to its disodium salt **6b**, and then cyclized with oxalyl chloride to give the anhydride **7**.[7] **7** was then transformed with ethanol to the acid es-

(5) R. Adams, H. M. Chiles, and C. F. Rassweiler, *Org. Syn.*, **5**, 5 (1925).

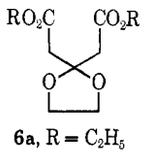
(6) R. Adams and H. M. Chiles, "Organic Syntheses," Collect. Vol. I, Wiley, New York, N. Y., 1947, p 237.

(7) R. Adams, *J. Amer. Chem. Soc.*, **42**, 599 (1920).

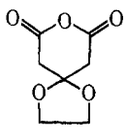
ter **8a** which on treatment, without purification, with oxalyl chloride gave **8b**. Rosenmund reduction[8] of **8b** again without purification gave the blocked aldehydo ester **5**.



5

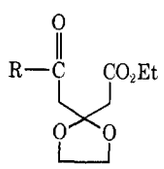


6a, R = C_2H_5
b, R = Na

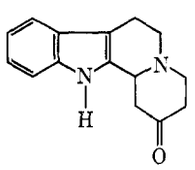


7

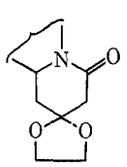
Condensation of **5** and tryptamine (**2a**) then proceeded smoothly without purification of intermediates to yield the keto lactam **3**. Thus **5** and **2a** reacted in glacial acetic acid to give a red gum whose infrared peaks indicated an ester at 1720 cm^{-1}, a ketal at 946 cm^{-1}, and a strong peak at 1626 cm^{-1} due to a C=N vibration. Solution of this Schiff's base in ethanolic hydrogen chloride and subsequent treatment with boiling 10% sulfuric acid converted it to **3** in an overall yield from **5** of 35%.



8a, R = OH
b, R = Cl

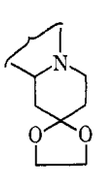


9

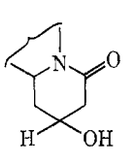


10

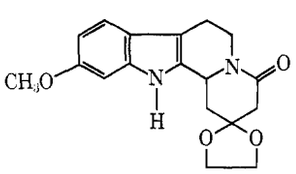
As a structure proof **3** seemed readily convertible to **9**, which had been earlier prepared by Swan[9] using a different route. Accordingly the keto lactam **3** was blocked to give the ketal **10**, which was then reduced to **11** and hydrolyzed to give **9** identical in every respect with an authentic sample kindly supplied by Dr. G. A. Swan. An additional sodium borohydride reduction of **3** gave the expected hydroxy lactam **12**. Our interest in the resperpine series led us to condense 6-methoxytryptamine (**2b**) and **5** under slightly different conditions to give the lactam **13** but with the ketal group still intact.[10]



11

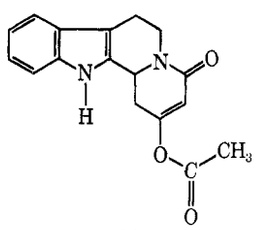


12

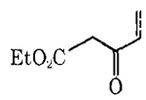


13

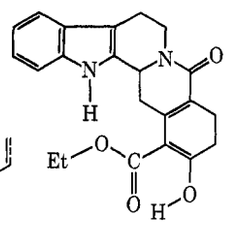
Although the physical properties of the tetracyclic keto lactam **3** generally corresponded closely to its assigned structure, it was most interesting to note that its β-dicarbonyl system failed to give a positive methanolic ferric chloride test[14] and that its ir spectrum in KBr had a good ketone peak at 1724 cm^{-1} certainly indicative of little if any enolic character under these conditions. However, **3** dissolved readily in aqueous base and also was converted with acetic anhydride to the enol acetate **14**.



14



15



16

Reaction with Carbethoxymethyl Vinyl Ketone (15).—The tetracyclic keto lactam (**3**), carbethoxymethyl vinyl ketone (**15**),[15] and a basic catalyst, potassium hydroxide in methanol,[16] were allowed to react in refluxing methanol to give after standing overnight a crystalline product which in time was shown to be the pentacyclic Michael adduct **16**. The ir spectrum of **16** had the peculiar property of having no carbonyl absorption[17] above 1635 cm^{-1}. Thus the saturated ester and ketone absorptions of **3** and **15** were replaced by strong absorptions at 1635, 1592, and 1558 cm^{-1}. The 1635 and 1592 cm^{-1} bands were interpreted to be representative of the chelated enol **16** in accordance with the work of Rhoads[18] on enolizable cyclic β-keto esters. The absence of higher frequency absorption associated with the keto form was rationalizable in terms of the report of Albright and Goldman[19] that α-yohimbinone (**17**) was completely enolic and had no absorption above 1642 cm^{-1}. **16** did have a peak in its nmr spectrum at δ 13.5 ppm which could be assigned to an enolic hydrogen,[19] but its mass spectrum was indeterminate since it decomposed in the instrument to low molecular weight fragments.

Hydrogenation of **16** proceeded smoothly with platinum oxide,[20] apparently accompanied by the uptake of four atoms of hydrogen, since the mass spectrum of the product **18** had a strong parent peak at 382 mass units corresponding to the molecular weight of **18**. The ir spectrum of the tetrahydro adduct **18** showed two strong saturated carbonyl absorptions at 1722 and

(8) E. Mosettig and R. Mozingo, *Org. React.*, **4**, 362 (1948).

(9) L. H. Groves and G. A. Swan, *J. Chem. Soc.*, 650 (1952).

(10) Several other approaches which did not lead to **3** or a variation of it include attempted reaction of diethyl ethylenedioxyglutarate (**6a**) or the corresponding dimethyl ester with tryptamine (**2a**) under a wide variety of conditions. Starting materials were generally recovered except in a sealed tube where the ditryptamide of β-ethylenedioxyglutaric acid was obtained in a low yield.[11] Reaction of tryptamine (**2a**) with β-ethylenedioxyglutaric anhydride (**7**) gave the expected glutaramic acid but it, or its ester or the derived glutarimide, could not be cyclized to form ring C.[12,13]

(11) E. Besthorn and E. Garben, *Ber.*, **33**, 3442 (1900).

(12) E. Schlittler and T. Allemann, *Helv. Chim. Acta*, **31**, 128 (1948).

(13) N. Itoh and S. Sugasawa, *Tetrahedron*, **1**, 45 (1957).

(14) R. L. Shriner, R. C. Fuson, and D. T. Curtin, "The Systematic Identification of Organic Compounds," 5th ed, Wiley, New York, N. Y., 1964, p 127.

(15) N. Nazarov and S. I. Zavylov, *J. Gen. Chem. USSR*, **23**, 1701 (1953).

(16) S. I. Zavylov, G. V. Kondratina, and L. F. Kudryantseva, *ibid.*, **31**, 3449 (1961); R. Hohenlohe-Oehingen, *Monatsh. Chem.*, **93**, 576 (1962); E. Wenkert, A. Afonso, J. B. Bredenberg, C. Kaneko, and A. Tahara, *J. Amer. Chem. Soc.*, **86**, 2038 (1964); S. W. Pelletier, R. L. Chappell, and S. Prabhakar, *ibid.*, **90**, 2889 (1968).

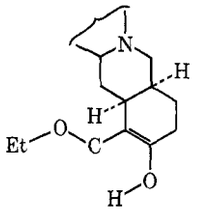
(17) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed, Wiley, New York, N. Y., 1958, p 34.

(18) S. J. Rhoads, A. W. Decora, J. C. Gilbert, T. Garland, M. J. Urbigkit, and R. J. Spangler, *Tetrahedron*, **19**, 1625 (1963). They also report that enolizable cyclic β-keto esters develop an instantaneous and intense blue to blue-purple coloration with Henecka's ferric chloride reagent. **16** gave an immediate dark blue color with this reagent. **3** gave no color at all and **15** was wine red. Rhoads, *et al.*, also reported a dark green color formed with ethanolic cupric acetate and their β-keto esters. **16** gave a similar dark green color with this reagent.

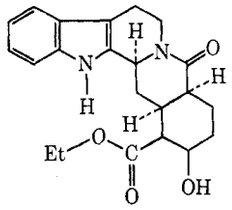
(19) J. D. Albright and L. Goldman, *J. Org. Chem.*, **30**, 1007 (1965).

(20) S. Siegel and G. V. Smith, *J. Amer. Chem. Soc.*, **82**, 6082, 6087 (1960). The double bond common to rings D and E at C_{15} and C_{20} in **16** might be expected to reduce smoothly cis under these conditions in view of the experiments of F. L. Weisenborn, *ibid.*, **79**, 4818 (1957), leading to synthetic 17-desmethoxydeserpidine.

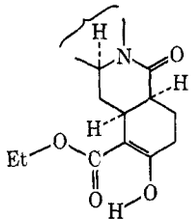
1610 cm^{-1} corresponding to a saturated ester and lactam, respectively. Since **18** had a secondary alcohol, back oxidation using the modified[19] *N,N'*-dicyclohexylcarbodiimide method of Pfitzer and Moffatt[21] produced the ketone **19**. **19** had no saturated carbonyl



17

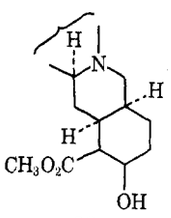


18

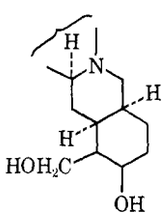


19

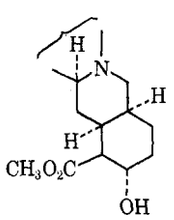
absorption at all, but rather a strong doublet at 1641 and 1617 cm^{-1} consistent with an enolized β-keto ester. This result, following Albright and Goldman,[19,22] can be used to assign a cis D/E ring junction in 19 and also in **18**. The mass spectrum of **19** had no parent peak; however, this was not surprising since the other β-keto ester **16** also had none. Reduction of **19** with platinum oxide and hydrogen, although on an extremely small scale, gave a dihydro-**19** which was identical in all respects with the tetrahydro Michael adduct **18**. Regeneration of **18** this way suggests that similar steric factors may be operating in the reduction of **18** and the Michael adduct **16**. If α-cis addition of hydrogen to the hindered enol is favored, as molecular models seem to indicate, then the carbethoxyl and hydroxyl groups would be β-cis. This conclusion, coupled with the likelihood that D/E in **18** is cis fused, places **18** in the alloyohimbine (**20**) family. If the C_3 hydrogen of **18** is α then it would be oriented as in alloyohimbine (**20**), but if it is β it would be as in epialloyohimbine.



20



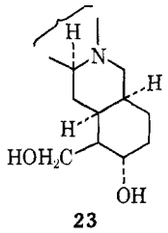
21



22

In order to get some idea as to the orientation of the C_3 hydrogen and also to remove the lactam carbonyl group at C_{21},[23] the lithium aluminum hydride reduction of **18** to yield **21** was accomplished. The crystalline diol **21** showed no absorption in the carbonyl region but had two bands in the CH region at 2805 and 2755 cm^{-1} which were not in **18**. These so-called Bohlmann bands have been suggested,[24,25] not without dissent,[26] to be indicative of an axial α-C_3 hydrogen. Since Wenkert[27] has suggested that a β-C_3 hydrogen might have an nmr peak at δ 4.6 ppm, the nmr spectrum of **21** was scrutinized. No peak other than from the deuterated dimethyl sulfoxide at 2.5 and 3.7 ppm could be found from 3.4 to 7 ppm, again indicating that the C_3 hydrogen of **21** was α. While the mass spectrum of **21** showed a parent peak equal to the molecular weight of the diol and the isotopic analysis was consistent with its empirical formula, it was of considerable importance to note the appearance of a large *m/e* M − 1 peak characteristic of yohimbine-like alkaloids[28] and arising from loss of the C_3 hydrogen. The elemental analysis required inclusion of 0.75 mol of ethanol to fit the combustion analysis. Solvation of this sort is also characteristic of the diols from yohimbine[29] and α-yohimbine.[30]

If the stereochemistry of the diol is that shown in *dl*-**21**, then alloyohimbine (**20**) is that alkaloid which should reduce to optically active **21**. Unfortunately it was not available. α-yohimbine (**22**) was, however, and, although the C_{17} hydroxyl was now α, the rest of the molecule was similar to **20**. Reduction of **22** yielded the diol **23**, which had the expected Bohlmann bands at 2795 and 2745 cm^{-1}; however, the rest of the ir spectrum of **23** showed that it was definitely different from synthetic diol **21**. Since the mass spectra of **21** and the diol from α-yohimbine **23** should be very similar, they were compared and found to be nearly



23

identical. However, there were definite slight differences in intensity of the peaks due in part to the slightly different stereochemistry and also to possible impurity differences.

Although other experiments were attempted, especially on the initial Michael adduct **16** or its immediate transformation products, they were indefinite due presumably to the two D/E double bonds in **16**. This generally mirrors the reported instability even toward recrystallization of $\Delta^{15(20)}$-yohimbine[31] due most likely to the double bond common to the D/E rings.

(21) K. E. Pfitzer and J. C. Moffatt, *J. Amer. Chem. Soc.*, **85**, 3027 (1963).

(22) Albright and Goldman[19] oxidized yohimbine, which has D/E trans, to yohimbinone and observed no enolic character, but α-yohimbine (**22**) with D/E cis on oxidation to a α-yohimbinone (**17**) was highly enolic.

(23) In this synthetic scheme the lactam carbonyl at C_{21} through its enol at C_{21}–C_{20} represents a way of converting the D/E junction from cis to trans and thereby entering, with the proper substituents, the reserpine and the yohimbine areas using a common synthetic plan.

(24) F. Bohlmann, *Chem. Ber.*, **91**, 2157 (1958).

(25) E. Wenkert and D. K. Roychaudhukl, *J. Amer. Chem. Soc.*, **78**, 6417 (1956).

(26) W. E. Rosen, *Tetrahedron Lett.*, **No. 14**, 481 (1961).

(27) E. Wenkert and B. Wickberg, *J. Amer. Chem. Soc.*, **84**, 4914 (1962).

(28) L. D. Antonaccio, N. A. Pereira, B. Gilbert, H. Vorbruegger, H. Budzikiewicz, J. M. Wilson, L. J. Durham, and C. Djerassi, *ibid.*, **84**, 2161 (1962).

(29) R. C. Elderfield and A. P. Gray, *J. Org. Chem.*, **16**, 506 (1951).

(30) A. Chatterjee and P. Karrer, *Helv. Chim. Acta*, **33**, 802 (1950); A. Chatterjee and S. C. Pakrashl, *J. Indian Chem. Soc.*, **36**, 684 (1959).

(31) K. T. Potts and D. R. Liljengren, *J. Org. Chem.*, **28**, 3066 (1963).

Experimental Section

All microanalyses were obtained from the Galbraith Laboratories, Knoxville, Tenn., or from Dr. Alfred Bernhardt, Microanalytical Laboratory, Max Planck Institute, Ruhr, West Germany. The melting points of all compounds up to and including **13** were determined on a calibrated apparatus heated at 1 deg/min and are corrected. All others were obtained on a Hoover–Thomas melting point apparatus heated at 1 deg/min and have not been corrected. All boiling points are uncorrected. The ir spectra were run on a Perkin-Elmer Infracord or Model 21, 421, or 521 recording ir spectrophotometer. The nmr spectra were run on a Varian HA-60 or HR-60 nmr instrument. The uv spectra were run on a Cary 14 recording uv spectrophotometer. The mass spectra were obtained from Morgan Schaffer Corp., Montreal, Canada.

Starting Materials.—Tryptamine (**2a**) was prepared from indole by the Brutcher and Vanderwerff modification [*J. Org. Chem.*, **23**, 146 (1958)] of the Speeter and Anthony[32] synthesis of substituted tryptamines. 6-Methoxytryptamine (**2b**) was synthesized using the Woodward method.[2] Conversion of citric acid to diethyl β-ethylenedioxyglutarate (**6a**)[33] was routine.[5,6]

Disodium β-Ethylenedioxyglutarate (6b).—A solution of 35.6 g (0.89 mol) of sodium hydroxide in 400 ml of hot absolute ethanol was added dropwise with stirring to a hot solution of 73.1 g (0.297 mol) of diethyl β-ethylenedioxyglutarate (**6a**) in 400 ml of ethanol over a 1-hr period. The mixture was refluxed for an additional hour, filtered hot through a sintered glass funnel, and washed with hot ethanol to give 67.7g (97.2%) of **6b** as a snow-white powder. Recrystallization from water–ethanol afforded colorless blades.

Anal. Calcd for $C_7H_8O_6Na_2$: C,35.91; H, 3.44. Found: C, 35.61; H, 3.42.

β-Ethylenedioxyglutaric Anhydride (7).—To a suspension of 52.8 g (0.22 mol) of the crude disodium salt **6b** in 1 l. of chloroform was added, with rapid stirring, a solution of 38.1 ml (0.45 mol) of oxalyl chloride in 300 ml of chloroform over a 5-min period. The mixture was maintained at 45–50° (water bath) for 1 hr, filtered hot through Celite, concentrated to one-third volume under vacuum, and heated to boiling followed by saturation with low-boiling petroleum ether (bp 30–60°) and chilling to yield 29.5 g of **7**. Concentration of the liquors yielded 3.3 g more of **7** for a combined yield of 85%. **7** on recrystallization from chloroform–petroleum ether gave colorless needles: mp 112–113°; ir ($CHCl_3$) 1828, 1779 (anhydride C=O), 1055 (CO), 952 cm^{-1} (ketal COC).

Anal. Calcd for $C_7H_8O_5$: C, 48.87; H, 4.67. Found: C, 48.86; H, 4.59.

4-Carbethoxy-3-ethylenedioxybutyric Acid (8a).—A mixture of 21.85 g (0.127 mol) of β-ethylenedioxyglutaric anhydride (**7**) and 14.8 ml (0.254 mol) of absolute ethanol was gently refluxed for 24 hr. After removal of the excess ethanol under vacuum there remained 26.58 g (96.0%) of the half-acid ester as a colorless, viscous oil which was always used for further reactions without purification. **8a** had in the ir spectrum ($CHCl_3$) 1720 (acid and ester C=O), 1365 (CH_3), 1035 (ester CO), and 950 cm^{-1} (ketal COC).

4-Carbethoxy-3-ethylenedioxybutyryl Chloride (8b).—To a solution of 26.58 g (0.12 mol) of unpurified half-acid ester **8a** in 250 ml of dry benzene was added 27 ml (0.30 mol) of oxalyl chloride and the mixture was refluxed for 2 hr, after which the solvent was removed under vacuum. The resulting oil was triturated several times with a total of 1 l. of low-boiling petroleum ether. The triturants were combined, treated with Darco, and filtered and the petroleum ether was removed under a stream of dry air on a water bath to yield 19.66 g (68.5%) of the acid chloride **8b** as a mobile, pale yellow liquid: ir ($CHCl_3$) 1785 (acid chloride C=O), 1720 (ester C=O), 1365 (CH_3), 1030 (ester CO), and 950 cm^{-1} (ketal COC). **8b** suffered complete decomposition on attempted distillation and was used further without purification.

4-Carbethoxy-3-ethylenedioxybutyraldehyde (5).—A mixture of 200 ml of dry xylene, 4.0 g of 5% palladium on barium sulfate,[8] and 40 mg of "quinoline sulfur"[8] was heated under a stream of hydrogen to remove traces of water, then cooled; 19.66 g (0.083 mol) of the unpurified acid chloride **8b** was added and the mixture was heated to reflux. When hydrogen chloride evolution ceased after 1 hr, the mixture was cooled and filtered through Celite and the solvent was removed under vacuum. There remained a residue which was distilled to yield 10.31 g (61.4%) of the almost colorless aldehyde **5**: bp 120–122° (1.3 mm); ir ($CHCl_3$) 1720 (ester and aldehyde C=O), 1360 (CH_3), 1030 (ester CO), 948 (ketal COC). The 2,4-dinitrophenylhydrazone of **5** after two recrystallizations from ethanol had mp 111.5–113.0°.

Anal. Calcd for $C_{15}H_{18}N_4O_8$: C, 47.12; H, 4.74; N, 14.66. Found: C, 47.35; H, 4.72; N, 14.55.

1,2,3,4,6,7,12,12b-Octahydro-2,4-diketoindolo[2,3-*a*]quinolizene (3). A. *N*-[β-(3-Indolyl)ethyl]-4-carbethoxy-2-ethylenebutylimine (Schiff's Base).—To a hot solution of 3.20 g (0.02 mol) of tryptamine (**2a**) in 25 ml of glacial acetic acid was added at once a solution of 4.04 g (0.02 mol) of the aldehyde ester **5** in 25 ml of glacial acetic acid. The mixture was refluxed for 2 hr, then cooled and poured into a large volume of ice–water. It was then extracted twice with chloroform using added sodium acetate to reduce emulsion formation, washed twice with water, dried (Na_2SO_4), and stripped of solvent under vacuum to give 5.18 g (75.2%) of the Schiff base as a red-orange oil which could not be crystallized: ir ($CHCl_3$) 1732 (ester C=O), 1638 (C=N), 1040 (ester CO), 948 cm^{-1} (ketal COC).

B.—To 5.18 g (0.015 mol) of the above Schiff's base in a 250-ml beaker was added 150 ml of 10% sulfuric acid. The mixture was heated on a hot plate with constant stirring until, after a few minutes of ebullition, the keto lactam product **3** began to precipitate. Heating was continued until this ceased and then the mixture was cooled, filtered, and washed (H_2O). The keto lactam **3** was freed from traces of the Schiff's base by trituration with cold ethanol. After final filtration and washing with ethanol, 0.96 g (25.2%) of **3** was obtained as a white solid. Recrystallization from ethanol–water gave **3** as clusters of colorless needles: mp 242° dec; ir (KBr) 1724 (ketone C=O), 1644, 1622 cm^{-1} (lactam C=O).

Anal. Calcd for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02. Found: C, 70.81; H, 5.74; N, 11.04.

The phenylhydrazone recrystallized from ethanol–water had mp 219° dec.

Anal. Calcd for $C_{21}H_{20}N_4O$: C, 73.23; H, 5.85; N, 16.27. Found: C, 73.27; H, 6.08; N, 16.27.

A solution of 2.67 g (0.00775 mol) of the above Schiff's base in a minimum amount of 20% ethanolic hydrogen chloride was allowed to stand for 24 hr at room temperature. The resulting tan crystals were filtered, washed first with ethanol and the with ether. to yield 1.19 g of an unstable tan intermediate. This product readily dissolved in 100 ml of 10% sulfuric acid, which was then heated on a hot plate for 10 min with accompanying ebullition. At the end of that time reasonable pure white crystalline keto lactam **3** separated out. Filtration and washing with water yielded 0.90 (46%) of **3**. Recrystallization from ethanol–water yielded **3** as white, flocculent crystals, mp 243–244° dec.

1,2,3,4,6,7,12,12b-Octahydro-2-ethylenedioxy-4-ketoindolo[2,3-*a*]quinolizine (10).—A solution of 1.00 g (0.00393 mol) of the keto lactam **3** and 40 mg of *p*-toluenesulfonic acid in 100 ml of tetrahydrofuran and 50 ml of 2-methyl-2-ethyl-1,3-dioxolane, prepared by a previously described method,[34] was refluxed for 21 hr, cooled, poured into benzene, washed twice with 10% sodium carbonate and twice with water, and dried (Na_2SO_4), and the solvent was removed under vacuum to give 0.20 g (17%) of the ketal **10** as a yellow, granular solid: ir ($CHCl_3$) 1628 (lactam C=O), 946 cm^{-1} (ketal COC). Further purification was not attempted.

1,2,3,4,6,7,12,12b-Octahydro-2-ketoindolo[2,3-*a*]quinolizine (9).—To a refluxing suspension of 0.5 g of lithium aluminum hydride in 50 ml of diethyl ether was added slowly a solution of 0.11 g (0.00037 mol) of the crude ketal **10** in 100 ml of diethyl ether. The mixture was refluxed for 1 hr and after cooling water was cautiously added. The resulting mixture was filtered through Celite and the filter cake was triturated several times with diethyl ether. After the combined filtrate and triturants were evaporated to dryness, the crude reduction product was dissolved in 10% sulfuric acid, refluxed for 18 hr, cooled, made basic with sodium hydroxide, extracted with chloroform, washed (H_2O), and dried (Na_2SO_4), and the solvent was removed under vacuum to give 0.02 g of the ketone **9**. Recrystallization from benzene–low boiling petroleum ether afforded **9** as yellow needles, mp 178.5–179° (lit.[9] mp 180–180.5°). A mixture melting point with an authentic sample of **9** kindly supplied by Dr. Swan[9] had a value of 181.5–182.2° and was therefore undepressed.

(32) N. E. Speeter and W. C. Anthony, *J. Amer. Chem. Soc.*, **76**, 6209 (1954).

(33) R. Kuhn, *J. Prakt. Chem.*, **139**, 156 (1940).

(34) H. J. Dauben, B. Löken, and H. J. Ringold, *J. Amer. Chem. Soc.*, **76**, 1359 (1954).

dl-**1,2,3,4,6,7,12,12b-Octahydro-2-hydroxy-4-ketoindolo[2,3-*a*]quinolizine (12).**—To a solution of 0.50 g (0.00197 mol) of the keto lactam **3** in 55 ml of absolute ethanol was added 0.50 g of sodium borohydride. The mixture was heated briefly to effect solution of the hydride and then allowed to stand for 45 min. A small volume of water was then added and the mixture was cautiously heated to boiling to destroy the excess hydride. While ebullition was maintained, 100 ml of water was added gradually to displace the ethanol. The solution was chilled, filtered to remove a faint cloudiness, and allowed to stand overnight, whereupon 0.19 g (40%) of colorless crystals of **12** were deposited. Recrystallization from ethanol–water gave colorless, feathery needles: mp 144–146° dec; ir (KBr) 1650, 1580 cm^{-1} (lactam C=O).

Anal. Calcd for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.35; H, 6.36; N, 10.99.

1,2,3,4,6,7,12,12-b-Octahydro-2-ethylenedioxy-4-keto-10-methoxyindolo[2,3-*a*]quinolizine (13).—Solutions of 0.42 g (0.00221 mol) of 6-methoxytryptamine (**2b**) prepared by the method of Woodward[2] and 0.45 g (0.00221 mol) of the ester aldehyde **3** each in 25 ml of benzene were combined and refluxed for 18 hr, 5 mg of *p*-toluenesulfonic acid was added, and the mixture was refluxed for another 2.5 hr. The solution was filtered hot, and the filtrate on standing deposited 0.19 g (26%) of **13** as tan granular crystals. Recrystallization of **13** from chloroform–low boiling petroleum ether gave **13** as clusters of almost white needles: mp 231–232°; ir (KBr) 1620 (lactam C=O), 945 cm^{-1} (ketal COC).

Anal. Calcd for $C_{18}H_{20}N_2O_4$: C, 65.84; H, 6.14; N, 8.53. Found: C, 65.60; H, 6.31; N, 8.42.

N-[*β*-(**3-Indolyl**)**ethyl**]-*β*-**ethylenedioxyglutaramic Acid.**—To a refluxing solution of 10.69 g (0.0667 mol) of tryptamine (**2a**) in 800 ml of chloroform was added dropwise with stirring over a 2 hr period a solution of 11.49 g (0.0667 mol) of *β*-ethylenedioxyglutaric anhydride (**7**) in 500 ml of chloroform. The mixture was then stirred for 2 hr with occasional application of heat to maintain the temperature just below reflux. Finally 700 ml of low-boiling petroleum ether was added and the mixture was chilled to give 21.39 g (96.6%) of the glutaramic acid which on recrystallization from ethyl acetate–petroleum ether gave almost white crystals: mp 166–167° dec; ir (KBr) 1721 (acid C=O), 1620, 1567 (amide C=O, 956 cm^{-1} (ketal COC).

Anal. Calcd for $C_{17}H_{20}N_2O_5$: C, 61.43; H, 6.07; N, 8.43. Found: C, 61.40; H, 6.03; N, 8.33.

N-[*β*-(**3-Indolylethyl**)]-*β*-**ethylenedioxyglutarimide.**—To a mixture of 50 g of phosphorus pentoxide and 250 g of sand suspended in 500 ml of dry pyridine at 75° (water bath) was added dropwise with vigorous stirring a solution of 5.00 g of the above glutaramic acid in 250 ml of pyridine over a period of 1 hr. During this time the temperature was increased to 85–90°. The mixture was stirred at this temperature for an additional 4 hr, then filtered hot, and the residue was washed with hot pyridine. The combined filtrate and washings were stripped of solvent under vacuum and the resulting oil was triturated with cold, saturated sodium bicarbonate solution. The resulting tan, granular product was filtered, washed, and dried to give 3.28 g (69.4%) of the glutarimide, which upon recrystallization from benzene–low boiling petroleum ether gave colorless crystals: mp 155.5–156°; ir ($CHCl_3$) 1734, 1681 (imide C=O), 948 cm^{-1} (ketal COC).

Anal. Calcd for $C_{17}H_{18}N_2O_4$: C, 64.95; H, 5.77; N, 8.91. Found: C, 64.99; H, 5.60; N, 8.74.

1,2,4,6,7,12,12b-Hexahydro-2-acetyl-4-ketoindolo[2,3-*a*]quinolizine (14).—To a mixture of 0.2 g (7.9×10^{-4} mol) of keto lactam and 0.2 g (2.6×10^{-3} mol) of sodium acetate was added 10 ml (0.09 mol) of acetic anhydride. The mixture was stirred overnight at room temperature and in the morning it was added to 40 ml of ice–water, stirred for 0.5 hr, and extracted twice with 50-ml portions of diethyl ether. The ether solution was dried over sodium sulfate, filtered, and concentrated on a Rotovap to yield finally 0.085 g (39.8%) of the crude enol acetate (**14**). **14** was recrystallized from anhydrous ether to give colorless, cubic crystals: mp 196–197 dec; ir (KBr) 1766 (acetyl C=O), 1652 (C=C), 1637, 1598 cm^{-1} (lactam C=O); uv max (95% EtOH) 289 mμ (ϵ 8.0×10^3), 282 (10.5×10^3), 273 (10.9×10^3), 223 (43.0×10^3).

Anal. Calcd for $C_{17}H_{16}N_2O_3$: C, 68.91; H, 5.44; N, 9.42. Found: C, 69.04; H, 5.51; N, 9.33.

1,2,3,4,5,7,8,13,13b,14-Decahydrobenz[*g*]-1-carbethoxy-2,5-diketoindolo[2,3-*a*]quinolizine (16).—To a solution of 1.0 g (3.9×10^{-3} mol) of keto lactam **3** in 50 ml of hot methanol was added first a solution of 0.03 g (5.2×10^{-4} mol) of potassium hydroxide in several milliliters of methanol and then 0.60 g (4×10^{-3} mol) of freshly prepared carbethoxymethyl vinyl ketone (**15**). The solution formed was gently refluxed under nitrogen for 0.5 hr and then allowed to cool overnight. In the morning the crystalline product was filtered, washed with 20 ml of cold methanol, and recrystallized from ethanol–water to yield 0.65 g (42.2%) of rhomboidlike crystals of the keto lactam adduct (**16**): mp 195° dec; ir (KBr) 1635, 1595, 1560 cm^{-1} (lactam and keto ester C=O, C=C); uv max (95% MeOH) 224 mμ (ϵ 46,000), 269 (17,000), 289 (10,000), 338 (6700); nmr (C_2D_6SO) δ 1.25 (t, 3), 2.6 (d, 3), 4.28 (d, 2), 7.25 (d, 2), 11.01 (s, 1), 13.4 (s, 1).

Anal. Calcd for $C_{22}H_{22}N_2O_4$: C, 69.83; H, 5.86; N, 7.40. Found: C, 69.83; H, 5.61; N, 7.48.

1,2,3,4,4a,5,7,8,13,13b,14,14a-Dodecahydrobenz[g]-1-carbethoxy-2-hydroxy-5-ketoindolo[2,3-*a*]quinolizine (18).—To a solution of 0.50 g (1.32×10^{-3} mol) of the keto lactam adduct **16** in 250 ml of absolute ethanol was added 50 mg of platinum oxide. The mixture was placed in a Parr hydrogenator, flushed with hydrogen four times, and shaken under 55 lb of pressure at room temperature for 12 hr. After filtration, the filtrate was concentrated on a Rotovap and the crude solid was then dissolved in hot methanol, treated with Darco, filtered, and allowed to crystallize. There was obtained 0.10 g (20.5%) of the tetrahydro adduct **18** as white rhomboid needles: mp 228–231° dec; ir (KBr) 3290 (indole NH), 1722 (ester C=O), 1610 cm^{-1} (lactam C=O); uv max 224 mμ (ϵ 40,000), 273 (8800), 283 (8700), 289 (6900); nmr (C_2D_6SO) δ 0.8 (t, 2), 1.54 (t, 3), 2.77 (d, 3), 3.68 (s, 3), 4.75 (s, 2), 7.05 (t, 1), 7.3 (m, 1); mass spectrum *m/e* 382, 364, 335, 291, 186, 170, 169, 144, 91, 55, 18.

Anal. Calcd for $C_{22}H_{26}N_2O_4$: C, 69.09; H, 6.85; N, 7.33. Found: C, 68.96; H, 6.75; N, 7.41.

1,2,3,4,4a,5,7,8,13,13b,14,14a-Dodecabenz[*g*]-1-carbethoxy-2,5-diketoindolo[2,3-*a*]quinolizine (19).—To 0.1 g (5.2×10^{-4} mol) of **18** was added 0.5 g (0.0024 mol) of *N*,*N*′-dicyclohexylcarbodiimide, 0.12 g (0.0012 mol) of crystalline orthophosphoric acid, and 0.3 ml of dimethyl sulfoxide, and the mixture was stirred for 24 hr at room temperature. To the orange-tan mixture was then added 5 ml of methanol–water (3:2) and stirring was continued for an additional 0.5 hr. The resulting slurry was filtered and the filter cake was washed with 5 ml more of the methanol–water solution. The filtrate was diluted with 40 ml of ice–water, made basic with aqueous ammonia, and filtered. The resulting filter cake was washed with water, dried, dissolved in hot methanol, treated with Darco, filtered, and allowed to crystallize to yield 0.035 g (34.1%) of the keto ester of the dihydro adduct **19** as white needles: mp 139–142°; ir (KBr) 3290 (indole NH), 1641, 1617 cm^{-1} (ester, ketone, lactam C=O, C=C).

Anal. Calcd for $C_{22}H_{24}N_2O_4$: C, 69.46; H, 6.36. Found: C, 69.32; H, 6.42.

1,2,3,4,4a,5,7,8,13,13b,14,14a-Dodecabenz[*g*]-1-hydroxymethyl-2-hydroxy[2,3-*a*]quinolizine (21).—**21** was obtained by the following precedure.

A solution of 0.1 g (2.62×10^{-4} mol) of tetrahydro adduct **18** in 15 ml of purified tetrahydrofuran was added dropwise to a stirred mixture of 0.1 g (0.004 mol) of $LiAlH_4$ in 25 ml of tetrahydrofuran under a nitrogen bed. The mixture, which turned pea-green, was refluxed for 1 hr, cooled, cautiously treated with 5 ml of water–tetrahydrofuran, and then refluxed for an additional 0.5 hr. It was then filtered hot through a Celite bed to give a filtrate which was dried (Na_2SO_4) and concentrated on a Rotovap. The crude solid residue was dissolved in hot ethanol, treated with Darco, filtered, and allowed to crystallize to give 0.061 g (71.5%) of the pentacyclic diol **21** as white crystals: mp 189–191° dec; ir (KBr) 3280 (indole NH), 2805 and 2755 cm^{-1} (Bohlmann[24] bands); uv max 224 mμ (ϵ 33,000), 275 (7100), 283 (7500), 289 (6100).

Anal. Calcd for $C_{20}H_{26}N_2O_2 \cdot {}^3/_4EtOH$: C, 71.54; H, 8.52; N, 7.76. Found: C, 71.42; H, 8.51; N, 7.77.

Registry No.—**3,** 32296-83-6; **3** phenylhydrazone, 32296-84-7; **5,** 32296-85-8; **5** 2,4-DNP, 32296-86-9; **6b,** 32296-87-0; **7,** 32296-88-1; **8a,** 32296-89-2; **8b,** 32367-46-7; **10,** 32296-90-5; **12,** 32296-91-6; **13,** 32296-92-7; **14,** 32296-93-8; **16,** 32296-94-9; **18,** 32296-95-0; **19,** 32296-96-1; **21,** 32296-97-2; *N*-[*β*-(3-indolyl)ethyl]-*β*-ethylenedioxyglutaramic acid, 32296-

98-3; *N*-[β-(3-indolylethyl)]-β-ethylenedioxyglutarimide, 32367-47-8.

Acknowledgment.—Thanks are due the Charles Pfizer and Company for a generous initial supply of β-oxoglutaric acid. Thanks are also due the National Institute of Mental Health for Public Health Grant MH-10106-01,02 and in addition to George M. J. Slusarczuk, Joseph Wreen, and John Harrison for their preparative assistance.

The Condensation of Aldehydes and Ketones with Dipeptides[1]

CHARLES A. PANETTA* AND MUNIR PESH-IMAM

Department of Chemistry, The University of Mississippi, University, Mississippi 38677

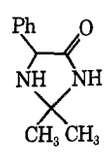
Received June 21, 1971

The interaction of simple peptides and carbonyl compounds has been investigated and found to be a fairly general reaction in weakly alkaline media. The reaction appears to be reversible and the most stable products have been obtained using alicyclic and acyclic ketones and acyclic aldehydes. In the present work, the sodium salts of several dipeptides were treated with ketones or aldehydes in refluxing methanolic or aqueous solutions. The products were shown to be imidazolidinyl peptides. This is apparently the first general investigation of what appears to be a common reaction of peptides.

The condensations of aldehydes and ketones with substances containing both amide and amine functional groups have been reported in the literature. The products of these reactions are generally heterocyclic compounds which have both the amide and amine nitrogen atoms in the new ring system.

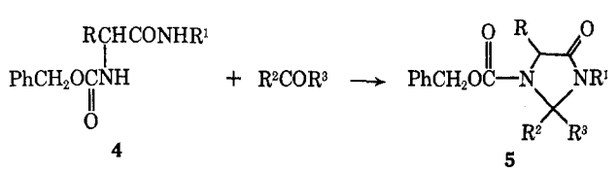
Davis and Levy[2] described the condensation of acetone with the α-phenylglycine amide (**1**) to yield an oxazolidine **2**, which rearranged, after treatment with pyridine, to a 4-imidazolidinone **3**. Similarly, other

1 **2**



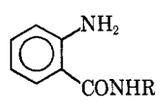
3

workers[3] found that isobutyraldehyde, benzaldehyde, and cyclohexanone reacted with the amides of carbobenzoxyamino acids **4** in the presence of a sulfonic acid catalyst to afford 1-carbobenzoxy-4-imidazolidinones **5** and other products. Primary and secondary amides

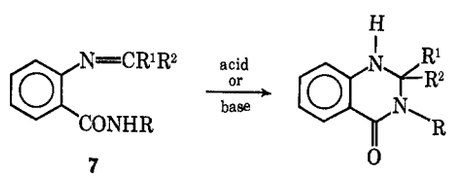


4 **5**

of 2-aminobenzoic acids **6** undergo the same type of condensation reaction with aldehydes[4] and ketones.[5] 1,2,3,4-Tetrahydro-4-quinazolones **8** were obtained after isomerization of the initially formed imine **7**. An imidazolidinone known as hetacillin (**10**) has been reported in other work.[6] It was prepared by the action of acetone on the commercially important penicillin,

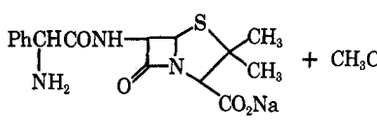


6

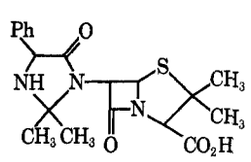


7 **8**

ampicillin (**9**), in a weakly basic aqueous medium. Aldehydes and other ketones were also successfully condensed with **9**.



9



10

The reaction of formaldehyde with proteins and peptides has been reviewed[7] and the formation of 4-imidazolidinone derivatives was postulated in some of the cases. Aside from this work, however, there has been no systematic and thorough study of the interaction of carbonyl compounds with peptides.

In this paper, we report on what appears to be a general condensation reaction of aldehydes and ketones with a variety of dipeptides. The reaction is appar-

(1) Presented at the Joint Southeast–Southwest Regional Meeting of the American Chemical Society, New Orleans, La., Dec 1970.

(2) A. C. Davis and A. L. Levy, *J. Chem. Soc.*, 3479 (1951).

(3) U. Zehavi and D. Ben-Ishai, *J. Org. Chem.*, **26**, 1097 (1961).

(4) T. A. K. Smith and H. Stephen, *Tetrahedron*, **1**, 38 (1957).

(5) G. F. Field, W. J. Zally, and L. H. Sternbach, *J. Org. Chem.*, **36**, 777 (1971).

(6) G. A. Hardcastle, Jr., D. A. Johnson, and C. A. Panetta, *ibid.*, **31**, 897 (1966).

(7) D. French and J. T. Edsall, *Advan. Protein Chem.*, **2**, 277 (1945).