of one-half of the solvent and subsequent cooling. The total crude yield was, therefore, 21.27 g. (45.0%). The crude material was recrystallized twice from acetonitrile, and 19.3 g. (41%) of pure product, m.p. 150.0–150.5° (cor.), was obtained.

Anal. Calcd. for $C_{24}H_{26}Cl_2N_3OP$: N, 8.87. Found: N, 9.04.

Acknowledgments.—The authors wish to acknowledge the assistance of Mr. Richard A. Awl and Mr. Stephen C. Johnson in preparing some of the intermediates. Thanks are also due Drs. H. W. Bond, R. B. Ross, and J. E. Leiter of the CCNSC for their cooperation and for making the screening data available.

Hexahydro-11H-pyrrolo[2,1-*a*]-β-carbolines and Tetrahydro-13H-isoindolo[1,2-*a*]-β-carbolines

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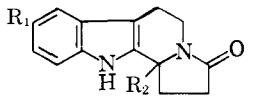
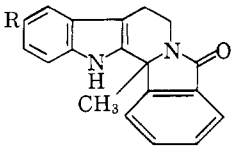
In previous work[2] the preparation of 1-substituted β-carbolines from DL-tryptophan and tryptamines and various phthaldehydic acids for testing as hypotensive agents has been described. The reaction has now been extended to various tryptamines and γ-keto acids. This type of reaction has, thus far, been reported only for cyclohexanone-2-acetic acid and tryptamine,[3] and α-ketoglutaric acid and 5-methoxytryptamine.[4]

The condensation of tryptamine, 5-methoxytryptamine, and 5-chlorotryptamine, with levulinic acid in refluxing technical xylene and with β-benzoylpropionic acid in refluxing *p*-cymene (b.p. 175°), gave the substituted 1,2,3,5,6,11b-hexahydro-3-oxo-11H-pyrrolo-[2,1-*a*]carbolines (Ia–f) in yields of 40–70%. The corresponding condensation of the three amines with *o*-acetylbenzoic acid in xylene gave higher yields of the substituted 5,7,8,13b-tetrahydro-5-oxo-13H-isoindolo-[1,2-*a*]-β-carbolines (IIa–c), required less vigorous



Ia, R_1 = H; R_2 = CH_3
b, R_1 = H; R_2 = C_6H_5
c, R_1 = OCH_3; R_2 = CH_3
d, R_1 = OCH_3; R_2 = C_6H_5
e, R_1 = Cl; R_2 = CH_3
f, R_1 = Cl; R_2 = C_6H_5

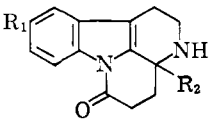


IIa, R = H
b, R = OCH_3
c, R = Cl

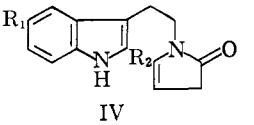
condition, and gave cleaner products than the condensation involving levulinic and β-benzoylpropionic acids. The water formed had to be removed to obtain a successful reaction and amounted to 2 moles.

An extensive investigation to obtain optimum conditions for the condensation was not carried out, but when the product yield was low, the time and/or temperature of the reaction were increased until no significant improvement in the yield was noted.

The position of the lactam ring was demonstrated by the lack of basicity of the condensation products. Lactam formation at the indole nitrogen would give the pyrido[1,2,3-*l*,*m*]-β-carboline (III), which would form salts with dilute acids. The indole nitrogen will



III



IV

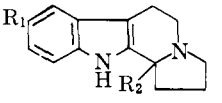
not form salts under these conditions. Structures I and II are further substantiated by the ultraviolet spectra which are similar to that of indole derivatives and unlike the spectra of N-acylindoles.[5]

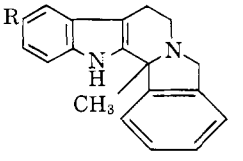
Compounds I and II did not give the Ehrlich's test in agreement with their β-carboline structure.

A precursor of this structure (IV) was isolated when β-benzoylpropionic acid and tryptamine were refluxed together for 8 hr. in toluene. The product (IV) after extensive purification gave a positive Ehrlich test and showed infrared bands at 1680 and 1645 cm.$^{-1}$ corresponding to the lactam carbonyl and enamine absorptions, respectively.

The same condensation in Butyl Cellosolve gave the lactam (Ib) and only small amounts of IV.

The lactams I and II were reduced to the corresponding tertiary amines V and VI with lithium aluminum hydride in 46–81% yields. These compounds (V and VI) were sensitive to air and precautions against oxidation were necessary to obtain good yields.





Va, R_1 = H; R_2 = CH_3
b, R_1 = H; R_2 = C_6H_5
c, R_1 = OCH_3; R_2 = CH_3
d, R_1 = OCH_3; R_2 = C_6H_5
e, R_1 = Cl; R_2 = CH_3
f, R_1 = Cl; R_2 = C_6H_5

VIa, R = H
b, R = OCH_3
c, R = Cl

The tertiary amine structure (Vc) was confirmed further by forming the methiodide; only one methyl group was introduced.

In rat dose range studies, compounds Ic and Ie in a 300-mg./kg. (*p.o.*) dose produced a moderate decrease in motor activity. Moderate hypersensitivity and slight hypertonicity were also observed in the rats treated with compound Ie. The remaining lactams in the series I and II produced no overt effects at dosage levels of 200–300 mg./kg.

Compound Ia in oral doses up to 300 mg./kg. did not produce ptosis or depletion of adrenal catechol amines in mice and hence does not resemble reserpine in these actions.

At oral doses of 200–300 mg./kg. in the rat, compounds Vb, Vd, and VIb produced signs of central stimulation. Convulsions occurred in the animals treated with similar doses of the other members of series V and VI.

(1) (a) Abstracted in part from the Ph.D. Thesis of J. D. Nordstrom, February 1963. (b) National Science Foundation Predoctoral Fellow, 1960–1962.

(2) S. Wawzonek and G. E. Nelson, *J. Org. Chem.*, **27**, 1377 (1962).

(3) A. Mondon and G. Hasselmeyer, *Chem. Ber.*, **92**, 2552 (1959).

(4) R. G. Taborsky and W. M. McIssac, *J. Med. Chem.*, **7**, 135 (1964).

(5) M. F. Bartlett and W. I. Taylor, *J. Am. Chem. Soc.*, **82**, 5941 (1960).

TABLE I

HEXAHYDRO-3-OXO-11H-PYRROLO[2,1-*a*]-β-CARBOLINES (I) AND TETRAHYDRO-5-OXO-13H-ISOINDOLO[1,2-*a*]-β-CARBOLINES (II)

Compd.	Solvent	Reflux time, hr.	Yield, %	M.p., °C.	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
Ia	Xylene	4	69.7	264–266[a]	$C_{15}H_{16}N_2O$	74.97	6.71	11.66	74.83	6.85	11.54
Ib	Butyl Cellosolve	20	46.0	263–264[b]	$C_{20}H_{18}N_2O$	79.44	6.00	9.26	79.72	6.39	9.27
Ic	Xylene	22	61.4	200–201	$C_{16}H_{18}N_2O_2$	71.09	6.71	10.37	71.06	6.67	10.55
Id	*p*-Cymene	22	50.4	258–259[b]	$C_{21}H_{20}N_2O_2$	75.88	6.07	8.44	75.63	6.31	8.77
Ie	Xylene	70	41.3	229–230[a]	$C_{15}H_{15}ClN_2O$	65.57	5.51	10.20	65.51	5.99	10.31
If	*p*-Cymene	72	39.7	266–267[b]	$C_{20}H_{17}ClN_2O$	71.31	5.09	8.32	71.49	4.77	8.08
IIa	Xylene	6	62.8	282–283[c]	$C_{19}H_{16}N_2O$	79.14	5.59	9.72	78.93	5.38	9.69
IIb	*p*-Cymene	4	81.2	143–153[b,d]							
				242–247 dec.	$C_{20}H_{18}N_2O_2$	75.45	5.70	8.80	75.63	5.57	9.03
IIc	Xylene	7.5	77.0	292–294[c]	$C_{19}H_{15}ClN_2O$	70.69	4.68	8.68	70.15	4.86	8.85

[a] Recrystallized from dioxane. [b] Recrystallized from a benzene–ethanol mixture. [c] Recrystallized from nitromethane. [d] Softening range.

TABLE II

HEXAHYDRO-11H-PYRROLO[2,1-*a*]-β-CARBOLINES (V) AND TETRAHYDRO-13H-ISOINDOLO[1,2-*a*]-β-CARBOLINES (VI)

Compd.	Yield, %	M.p., °C.	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
Va	80.9	122.5–124	$C_{15}H_{18}N_2$	79.60	8.02	12.38	79.77	8.04	12.39
Vb	56.7	145–147	$C_{20}H_{20}N_2$	83.29	6.99	9.72	83.41	6.99	9.39
Vc	76.0	105–115[a] 115–119	$C_{16}H_{20}N_2O$	74.96	7.87	10.93	75.21	7.82	10.99
Vd	56.3	133–138[a] 138–141	$C_{21}H_{22}N_2O$	79.21	6.97	8.80	79.01	6.77	8.65
Ve	80.0	153–153.5	$C_{15}H_{17}ClN_2$	69.08	6.53	10.75	69.09	6.54	10.95
Vf	78.9	138–141[a] 141–143	$C_{20}H_{19}ClN_2$	74.40	5.93	8.68	74.74	6.02	8.47
VIa	47.2	180–181	$C_{19}H_{18}N_2$	83.17	6.61	10.21	82.79	6.61	10.48
VIb	46.2	165–168	$C_{20}H_{20}N_2O$	78.91	6.62	9.21	78.93	6.49	9.11
VIc	55.8	190–191	$C_{19}H_{17}ClN_2$	73.89	5.55	9.07	73.99	5.75	8.98

[a] Softening point range.

Compound Va at a dose of 200 mg./kg. lowered rectal temperature in 75% of yeast-fevered rats. Derivatives Vc, Vf, and VIc showed no activity in this test procedure and also did not potentiate tryptamine-induced convulsions in the rat.

Experimental[6]

β-Benzoylpropionic acid,[7] *o*-acetylbenzoic acid,[8] tryptamine,[9] 5-methoxytryptamine,[10] and 5-chlorotryptamine[11] were prepared according to methods described in the literature.

1,2,3,5,6,11b-Hexahydro-8-methoxy-11b-methyl-3-oxo-11H-pyrrolo[2,1-*a*]-β-carboline (Ic).—5-Methoxytryptamine (3.80 g., 0.020 mole) and levulinic acid (2.56 g., 0.022 mole) were refluxed in 175 ml. of mixed xylenes (b.p. 135–140°) under a nitrogen atmosphere, with vigorous stirring, for 22 hr. The water released in the reaction was removed by a modified Dean–Stark water separator. After cooling, the xylene was removed under reduced pressure and the red residue was dissolved in 100 ml. of chloroform. The chloroform solution was washed with 40 ml. of 2 *N* HCl, 40 ml. of 2 *N* NaOH, and 40 ml. of water. Evaporation of the chloroform solution gave an oily residue, which was dissolved in 20 ml. of benzene and transferred to a column of 100 g. of alumina. Twelve ethyl acetate eluted fractions (40 ml.) were collected. Upon standing, 1.58 g. of white needles (m.p. 200–201°) precipitated from the first six fractions. Reducing the volume of these fractions to one-third yielded another 1.16 g. of needles (m.p. 198–200°). All of the fractions were evaporated to dryness, and the residue was recrystallized from benzene to give 0.58 g. of white needles (m.p. 200–201°). The total yield of lactam was 3.31 g. (61.4%); infrared spectrum (Nujol mull): 3260 (NH), 1667 (C=O), 1220, 1032 ($ArOCH_3$), 803 cm.$^{-1}$ (trisubstituted benzene); ultraviolet spectrum (95% ethanol): λ_{max} 226 mμ (log ε 4.47), 278 (3.96); λ_{infl} 293 mμ (log ε 3.86), 3.06 (363); λ_{min} 249 mμ (log ε 3.46).

The other β-carbolines were prepared in a similar fashion; the yields, conditions, and properties are listed in Table I.

The tryptamine derived lactams show λ_{max} at 225, 274, 280, and 290 mμ and λ_{min} near 250 mμ. The lactams of 5-chlorotryptamine show λ_{max} at 230, 283, 290, and 301 mμ with λ_{min} at 256 mμ. The infrared spectra show the NH stretching frequencies of indolic compounds at 2.9 to 3.05 μ and the carbonyl absorptions in the 1660 to 1675 cm.$^{-1}$ region.

1,2,3,5,6,11b-Hexahydro-8-methoxy-11b-methyl-11H-pyrrolo-[2,1-*a*]-β-carboline (Vc).—A solution of 2.15 g. of 1,2,3,5,6,11b-hexahydro-8-methoxy-11b-methyl-3-oxo-11H-pyrrolo[2,1-*a*]-β-carboline in 175 ml. of tetrahydrofuran was added dropwise to a refluxing slurry of 1.1 g. of lithium aluminum hydride in 75 ml. of tetrahydrofuran. The slurry was refluxed and stirred for 4 hr. under nitrogen. The reaction was cooled and decomposed with NaOH and water. After filtration, the clear solution was evaporated under reduced pressure. The oily residue was transferred to a column of 50 g. of alumina in 20 ml. of absolute ether. Ten ether-eluted fractions (40 ml.) were collected. The combined fractions were evaporated under nitrogen. The partially crystalline residue was crystallized by refluxing in 50 ml. of oxygen-free hexane. The white powdery solid (1.55 g., 76.0%) melted at 115–119° (softening at 105–115°) after vacuum drying.

The other members in this series were prepared in a similar fashion; the yields and properties are listed in Table II. Hexane was used for the recrystallization of all the compounds except Vf and VIb; ether was used for these examples.

(6) All melting points are corrected.

(7) L. F. Somerville and C. F. H. Allen, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 81.

(8) H. L. Yale, *J. Am. Chem. Soc.*, **69**, 1547 (1947).

(9) E. H. P. Young, *J. Chem. Soc.*, 3493 (1958).

(10) R. A. Abramovitch and D. Shapiro, *ibid.*, 4589 (1956).

(11) R. A. Abramovitch, *ibid.*, 4593 (1956).

The infrared spectra of the reduction products retained the indolic NH stretching frequencies and the ultraviolet spectra were similar to those of the parent lactams which were shown to have the indole chromophore.

Heating an ethanol solution of the amine with an excess of picric acid gave bright orange crystals of the picrate melting at 243–244° dec. after recrystallization from ethanol.

Anal. Calcd. for $C_{22}H_{23}N_5O_8$: C, 54.43; H, 4.77; N, 14.43. Found: C, 54.23; H, 4.84; N, 14.23.

The methiodide, prepared by refluxing the amine with an excess of methyl iodide in benzene for 5 min., was a colorless crystalline compound, melting at 267–268° after recrystallization from ethyl acetate–benzene.

Anal. Calcd. for $C_{17}H_{23}IN_2O$: C, 51.26; H, 5.82; N, 7.04. Found: C, 51.30; H, 6.11; N, 6.76.

N-β-(3-Indolyl)ethyl-2-phenyl-5-oxo-Δ²-pyrroline (IV, R_1 = H; R_2 = C_6H_5).—A mixture of 3.00 g. of tryptamine (0.019 mole), 3.45 g. of β-benzoylpropionic acid (0.020 mole), and 175 ml. of dry toluene was refluxed for 8 hr. in a flask fitted with a Dean–Stark water trap. Complete solution was attained after 5 hr. and 0.67 ml. of water (0.037 mole) had collected. After evaporating the solvent under reduced pressure, a red-yellow amorphous solid was obtained. Two recrystallizations from methanol gave 0.47 g. of yellow powder melting at 178–192°. Trituration with methanol gave a yellow powder melting at 197–200° dec. This material was shown to be present in at least 60% yield when column chromatography was used to separate the condensation product. The Ehrlich color test produced a deep red color, indicating the 2-position of the indole moiety is unsubstituted. The infrared spectrum showed major absorptions at 3300 (NH), 1680 (C=O), 1645 (enamine), and 698 cm.$^{-1}$ (aromatic).

Anal. Calcd. for $C_{20}H_{18}N_2O$: C, 79.44; H, 6.00; N, 9.26. Found: C, 79.57; H, 6.00; N, 9.25.

Acknowledgment.—The authors wish to express appreciation to Smith Kline and French Laboratories for a fellowship which supported part of this investigation, for a gift of 1,2,3,4-tetrahydro-1-oxo-6-methoxy-β-carboline, and for the pharmacological data.

A Carbocyclic Analog of Glyceraldehyde Dimer

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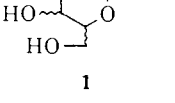
Received October 16, 1964

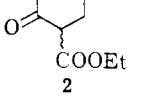
This note presents the synthesis of 2,5-dihydroxycyclohexane-1,4-dimethanol (**4**), a carbocyclic analog of racemic glyceraldehyde dimer (**1**) in which methylene groups replace the ring oxygen linkages. Due to complex side reactions the starting material, diethyl 2,5-diketohexahydroterephthalate (**2**), could not be reduced directly to **4** using lithium aluminum hydride. Catalytic reduction to the intermediate diol diester (**3**) was at first ineffective. If, however, **2** were freshly sublimed, reduction at 1 atm. using platinum oxide in methanol proceeded steadily and in 2 days the calculated amount of hydrogen was utilized. Crystallization from carbon tetrachloride gave **3** which, because of the general course of catalytic reduction over platinum,[1] is given the all *cis* configuration illustrated. Support for this stereochemistry was derived also from the n.m.r. spectrum of this substance as a 10 mole % solution in dimethyl sulfoxide[2] which shows two nonequivalent secondary OH groups (a doublet at δ = 4.72 p.p.m., 1.5-c.p.s. splitting, and a doublet at δ = 4.80 p.p.m., 3.5-c.p.s. splitting), a result consistent with a chair form of the all *cis* isomer.

This diol diester also resisted reduction by lithium aluminum hydride. It was hoped that a reagent with only one replaceable hydride atom would have less complexing tendencies and permit reduction of the two carbethoxy groups of **3**. Lithium tri-*t*-butoxyaluminohydride[3] proved effective for this purpose and, although the product was chelated, the chelate was cleavable by mild treatment with dilute hydrofluoric acid. The tetrol **4**, after evaporative distillation and recrystallization, was isolated in 50% yield. Epimerization of **3** by the lithium tri-*t*-butoxyaluminohydride could have produced three optically inactive tetrols. Despite examination of the mother liquors by thin layer chromatography, no other isomer was isolated, suggesting that the steric relations of **3** had been retained. Support for this configuration was found in the n.m.r. spectrum of **4** as a 10 mole % solution in dimethyl sulfoxide. Two nonequivalent primary alcohol triplets were found at δ = 4.18 (4-c.p.s. splitting) and 4.34 p.p.m. (2.5-c.p.s. splitting). Nonequivalent secondary alcohol protons gave signals at δ = 4.46 and 4.53 p.p.m. All of these signals were removed on exchange with deuterium oxide. This pattern is compatible with a chair conformation of **4** in which neither the primary nor the secondary alcohol groups are equivalent. (Sirupy D- and crystalline DL-glyceraldehyde do not give resolved OH proton signals when determined under these conditions.)

Since DL-glyceraldehyde dimer has been shown to have biological activity (inhibition of glycogen phosphorolysis[4]), it became desirable to evaluate **4**, a close structural analog of this dimer, for antitumor activity. In tests conducted by the Cancer Chemotherapy National Screening Center, **4** was nontoxic and inactive at a dose level of 200 mg./kg. against lymphoid leukemia L1210 and P1798 lymphosarcoma and also against Dunning ascites leukemia at 100 mg./kg. It was rated inactive against KB cell culture in which its ED_{50} was greater than 1000 γ/ml.



1



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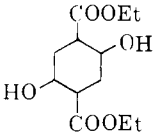

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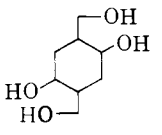

4

Experimental[5]

1,4-Dicarbethoxy-2,5-dihydroxycyclohexane (3).—Freshly sublimed [125° (20 μ)] **2** (5.8 g.) was mixed with 1.18 g. of plati-

(1) J-F. Sauvage, R. H. Baker, and A. S. Hussey, *J. Am. Chem. Soc.*, **82**, 6090 (1960), and references cited therein.

(2) O. L. Chapman and R. W. King, *ibid.*, **86**, 1256 (1964).

(3) H. C. Brown and R. F. McFarlin [*ibid.*, **80**, 5372 (1958)] report no reduction of esters with the reagent but this was under much milder conditions.

(4) H. Lehmann and J. Needham, *Enzymologia*, **5**, 95 (1938).

(5) Melting points were taken in capillaries using a Hershberg apparatus and are corrected. N.m.r. spectra were determined by Mrs. Josephine Goodwin on a Varian A-60 instrument using tetramethylsilane as internal reference. Microanalyses were performed by Miss Paula M. Parisius under the direction of Dr. William C. Alford.