SYNTHESIS OF 4-SUBSTITUTED ß-CARBOLINES

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Abstract - Various 4-substituted ß-carbolines are synthesized and further modified by electrophilic substitution reactions. The regioselectivity of electrophilic attack is demonstrated for a number of different reactions and strategies are outlined to achieve substitution at positions unaccessible by electrophilic attack.

Ethyl ß-carboline-3-carboxylate, isolated from human urine by Braestrup and coworkers[1], was found to exhibit high affinity for benzodiazepine receptors. This observation has stimulated the search for new ß-carboline derivatives with benzodiazepine-type activity[2,3]. First results obtained in our synthetic programme revealed that introduction of 4-substituents into the carboline skeleton was often associated with a considerable increase in receptor binding affinities. Our report, therefore, concentrates upon synthetic methodology leading to 4-substituted ß-carbolines and their further transformation.

Table I lists up a number of characteristic compounds which were synthesized according to three general pathways:

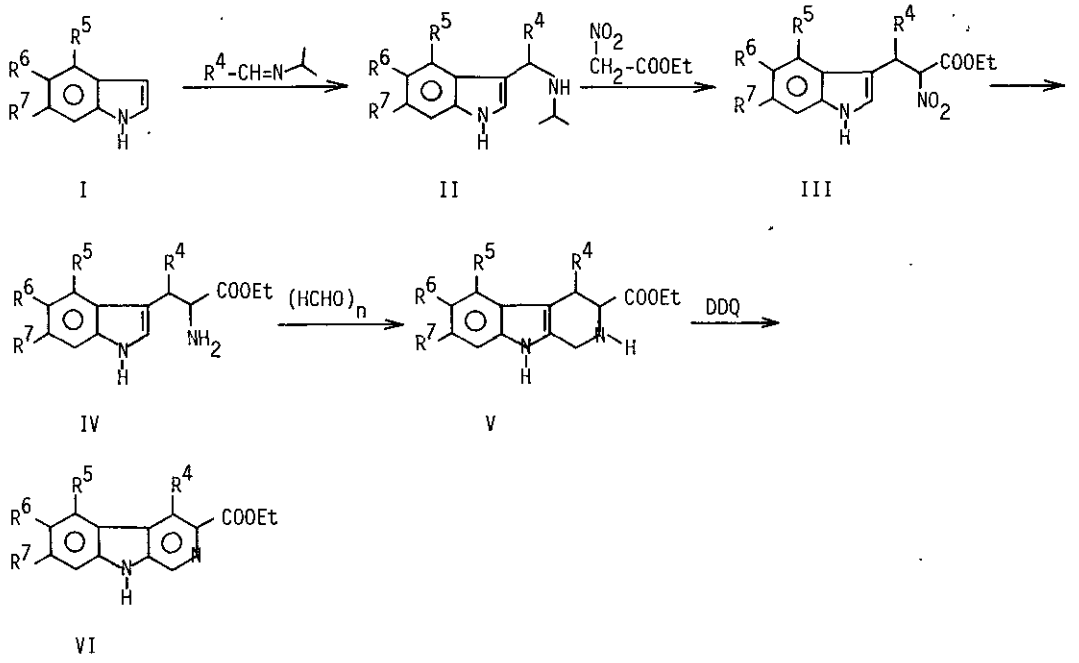
Path a

1. Path a represents the most convenient entry into the class of 4-substituted ß-carbolines. The synthesis, outlined in the scheme below, employs standard methods of indole chemistry: aldimines were prepared by Campbell's procedure[4] and reacted with indoles in analogy to Snyder's reaction mode[5]. Condensation with nitroacetic acid ester was performed as described by Lyttle and Erofeev[6]. Hydrogenation in the presence of Raney-Ni gave tryptophan derivatives IV, isolated

as mixtures of isomers. Pictet-Spengler reaction using Sandrin's modification[7] produced tetrahydro-ß-carbolines V, which - without further purification or isomer separation - were subjected to oxidation by DDQ, sulfur or palladium. Pictet-Spengler reaction was the only unsatisfactory step in this sequence of reactions, the yields (IV-V) being in the range of 30-50%. In several cases much better yields were obtained by reacting tryptophan derivatives IV with glyoxylic acid to produce a mixture of tetrahydro- and dihydro-ß-carboline-1-carboxylic acids which - prior to dehydrogenation - had to be decarboxylated in a separate step.

Although path a is applicable to a great diversity of substituted indoles, some limitations deserve a comment: 4-cyano- and 5-cyanoindoles could not be transformed to the corresponding ß-carbolines via pathway a; obviously, nucleophilicity at C-3 is decreased to such an extent that conventional methods of gramine-type formation must fail[+].

Path a:

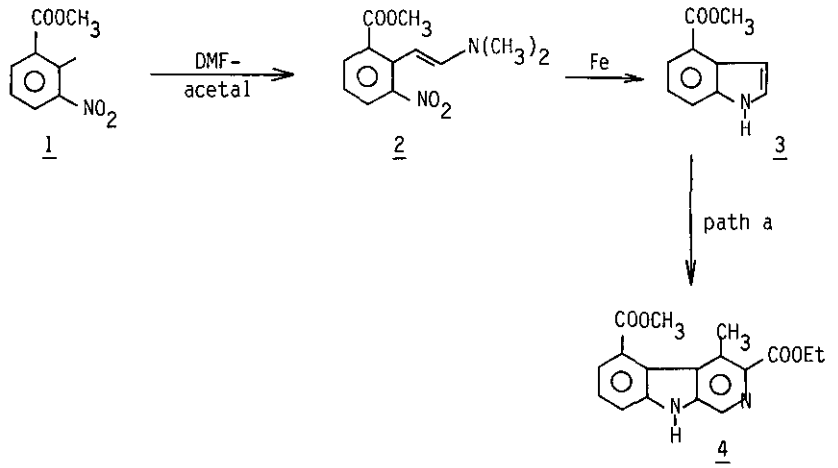


I II III IV V VI

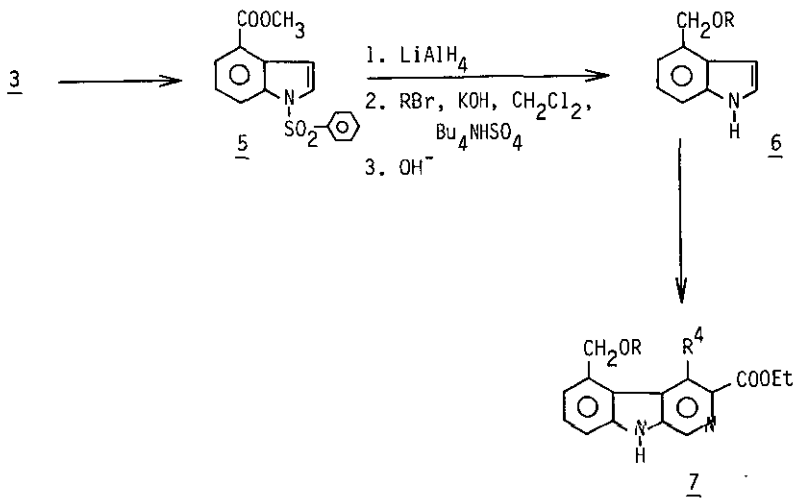
[+] The reaction sequence of path a is, however, applicable in the case of R^4 = H, R^5 = CN, $R^{6,7}$ = H; see F.C. Uhle and L.S. Harris, J. Am. Chem. Soc. 79, 102 (1957).

2. 5-Alkoxycarbonyl substitution

In contrast to the behavior of 4-cyanoindole , a 4-methoxycarbonyl-substituted indole[3] could be converted to ß-carboline 4 via path a. Starting indole 3 was conveniently prepared via Leimgruber's sequence[8] from nitrotoluene 1. Indole 3 served as starting material for a number of further transformations leading to 5-alkoxymethyl-substituted ß-carbolines of type 7.



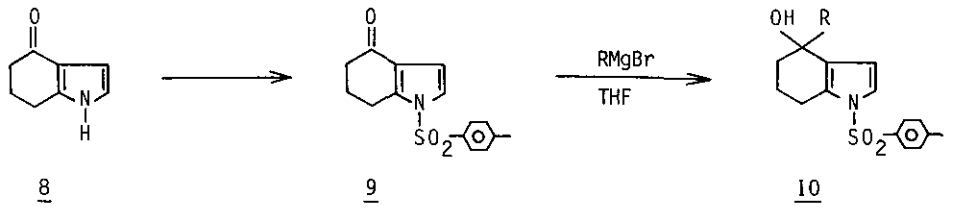
1 2 3 4



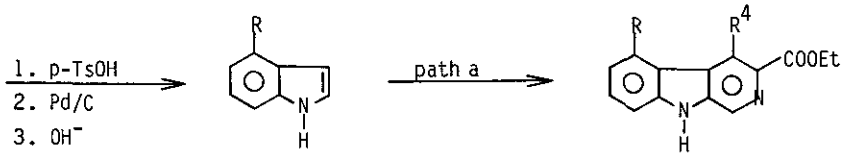
5 6 7

3. 5-Alkyl substitution

Tetrahydro-oxindole 8 is a readily available material[9] which could easily be transformed to 4-alkylindoles by Grignard reaction and dehydration/dehydrogenation. Thus, 5-methyl- and 5-ethyl-ß-carbolines were made accessible following path a.



8 9 10

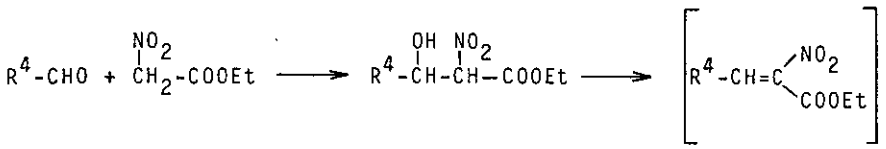


12 13

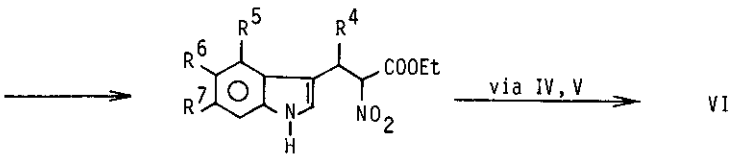
Path b

1. Several gramine derivatives of type II tended to condense with excess indole to produce dimers of type XI. This obstacle could be overcome by following path b, which involved condensation of aldehydes VII with nitro ester VIII followed by Michael-type addition of indole to produce intermediates III.

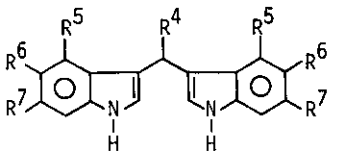
Path b (general scheme):



VII VIII IX X



III

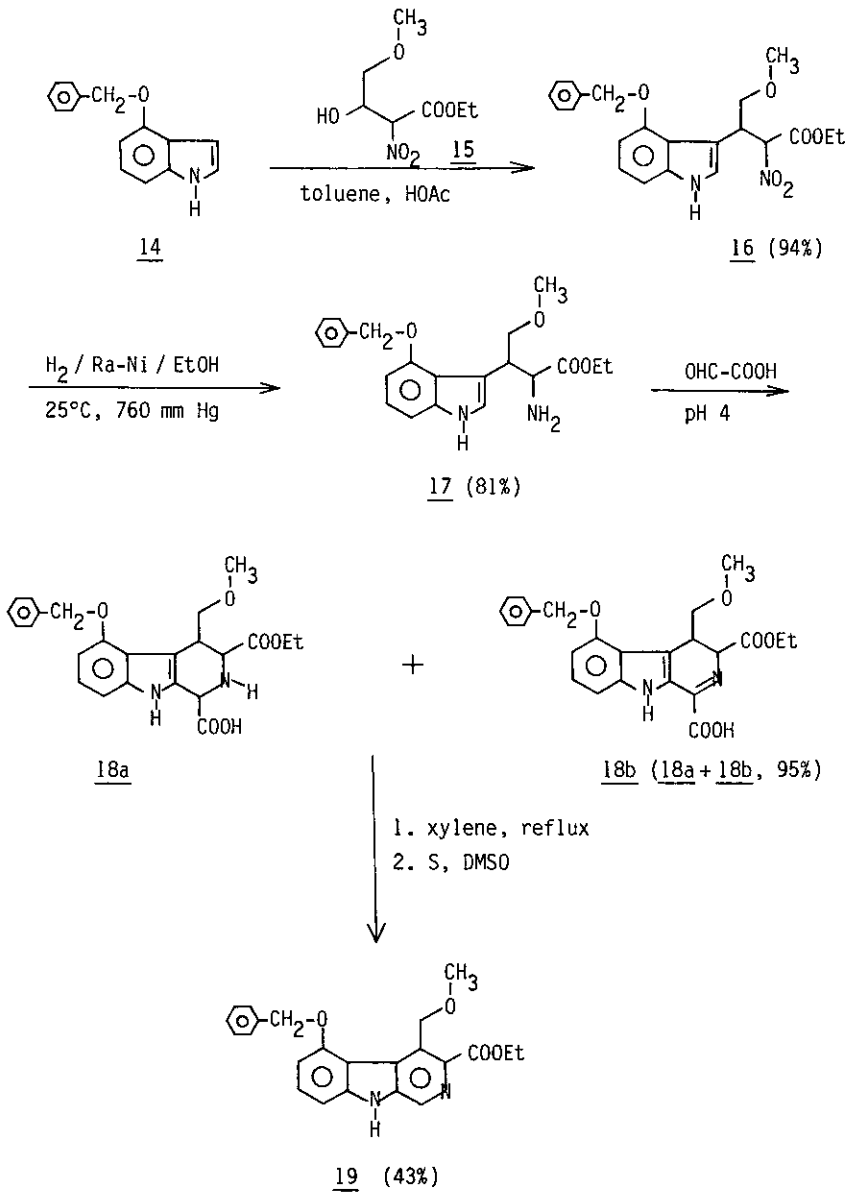


XI

As attempts to purify intermediates IX and X by distillation led to considerably decreased yields, dehydration of IX and indole addition were exercised as a one-pot reaction, simply by heating IX and indoles in toluene under acid catalysis or with azeotropic removal of water. Path b was effectively applied to the synthesis of 4-methoxymethyl- and 4-furyl-substituted ß-carboline derivatives.

The synthesis of 5-benzyloxy-4-methoxymethyl-ß-carboline 19, a compound with remarkable anticonvulsive activity[10], is described in detail (see scheme below).

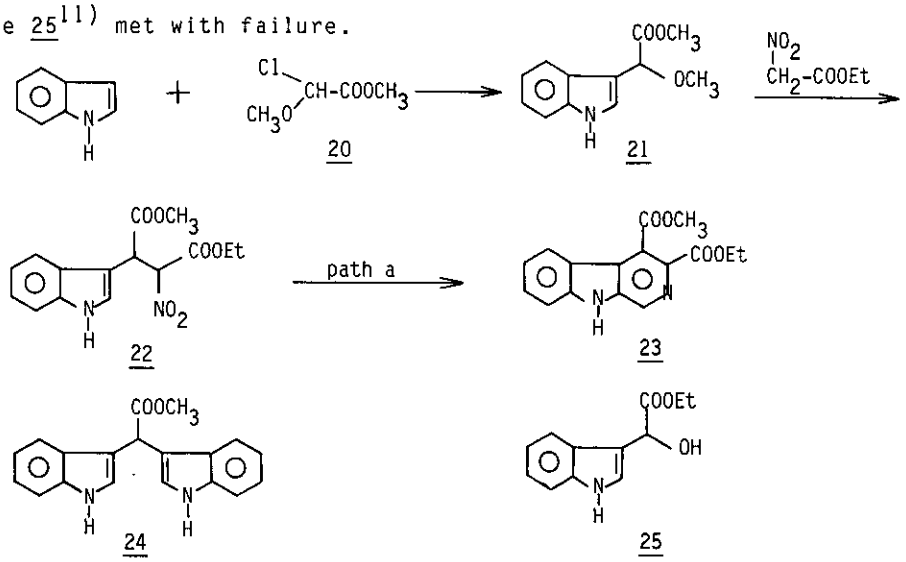
Synthesis of 5-benzyloxy-4-methoxymethyl-ß-carboline-3-carboxylic acid ethyl ester



2. 4-Methoxycarbonyl substitution

A 4-methoxycarbonyl derivative resulted from alkylation of indole with chloromethoxy ester 20. Intermediate 21 is very sensitive to traces of acid, condensing with excess indole under formation of dimer 24. So, our first attempts, reacting indole with 20 in the presence of tri-n-butyl amine, produced only traces of 21. Addition of dicyclohexylcarbodiimide - in order to capture traces of HCl irreversibly - raised the yield of 21 to 62%. Condensation of 21 with nitro acetic acid ester required more drastic conditions than the parent aldimine reactions, but, nonetheless, produced 22 in a 76% yield. Transformation of 22 to ß-carboline 23 was routinely exercised according to pathway a.

Various other attempts directed towards the synthesis of 23 via known intermediate 25[11] met with failure.



Path c (substitution reactions)

Pathway c summarizes synthetic procedures differing from paths a and b and includes electrophilic substitution reactions of preformed ß-carbolines and their subsequent derivatization.

1. nitriles
2. halogenation
3. side chain functionalization
4. nitro- and amino-substitution, thioureas, ureas, sulfonamides

1. Nitriles

As previously pointed out, 5- or 6-cyano-ß-carbolines were not accessible via paths a,b starting with 4- or 5-cyanoindoles. We, therefore, attempted to effect nitrile substitution via the Sandmeyer procedure and could, indeed, convert some 6-amino carbolines into the corresponding nitriles; yields were, however, in the range of 20%. An alternative method, namely reacting 6-iodo precursors with CuCN in DMF (reflux, 60 min) proved more efficient giving 6-cyano-ß-carbolines in 65-80% yields.

2. Halogenation

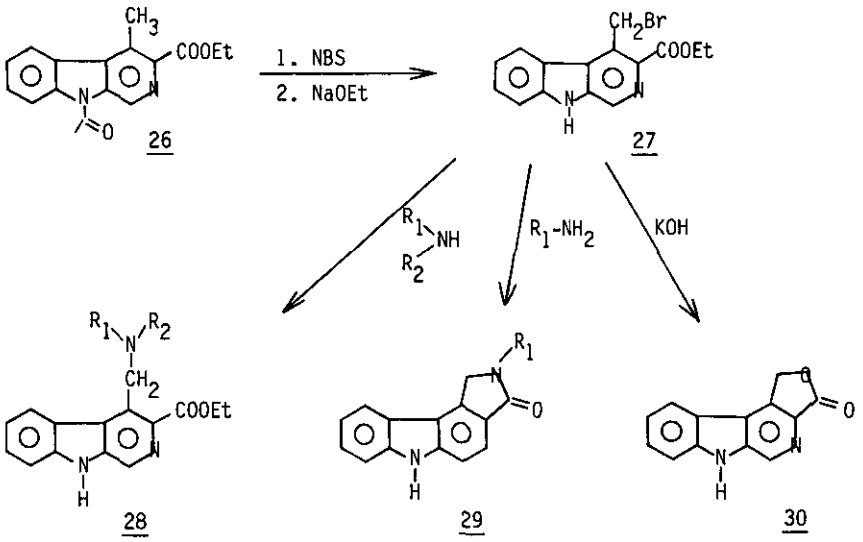
Standard bromination (Br_2, CH_2Cl_2, pyridin, 0°C) produced 6-bromo derivatives; excess bromine or reaction at elevated temperatures led to formation of 6,8-dibromo compounds. Bromination of a 6-methoxy-ß-carboline smoothly proceeded with formation of the expected 8-bromo derivative.
6-Chloro compounds were obtained by dissolving ß-carbolines in methylene chloride or chloroform presaturated with chlorine. Iodination was best carried out by treating methylene chloride solutions of ß-carbolines with a five-fold molar excess of iodine chloride for 20 hours at room temperature; the yields of 6-iodo derivatives, however, remained in the range of 40-60%.
Fluoro derivatives were mostly prepared along the lines of pathway a, since fluoro-substituted indole precursors were either commercially available or accessible by Leimgruber's excellent route[8] starting with fluoro-substituted α-nitro toluenes. In one case, a 6-fluoro compound was prepared by Schiemann reaction[12], i.e. transformation of a 6-amino precursor to its diazonium fluoroborate and thermolysis to form the 6-fluoro compound in a deplorable yield of less than 15%.

3. Side chain functionalization

N-Bromosuccinimide reaction (NBS, CCl_4, azobisisobutyronitrile, hν, reflux) of ß-carbolines led to bromination of the aromatic nucleus at positions C-6 and C-8. Side chain bromination required protection of the indole moiety as its acetyl

derivative. With this precaution, exclusive attack at the benzylic position of the 4-alkyl side chain was achieved. After removal of the N-acetyl group (NaOEt, EtOH, reflux) nucleophilic exchange of bromine could easily be effected with various amines, whereas exchange versus oxygen nucleophiles failed, except for intramolecular lactone formation.

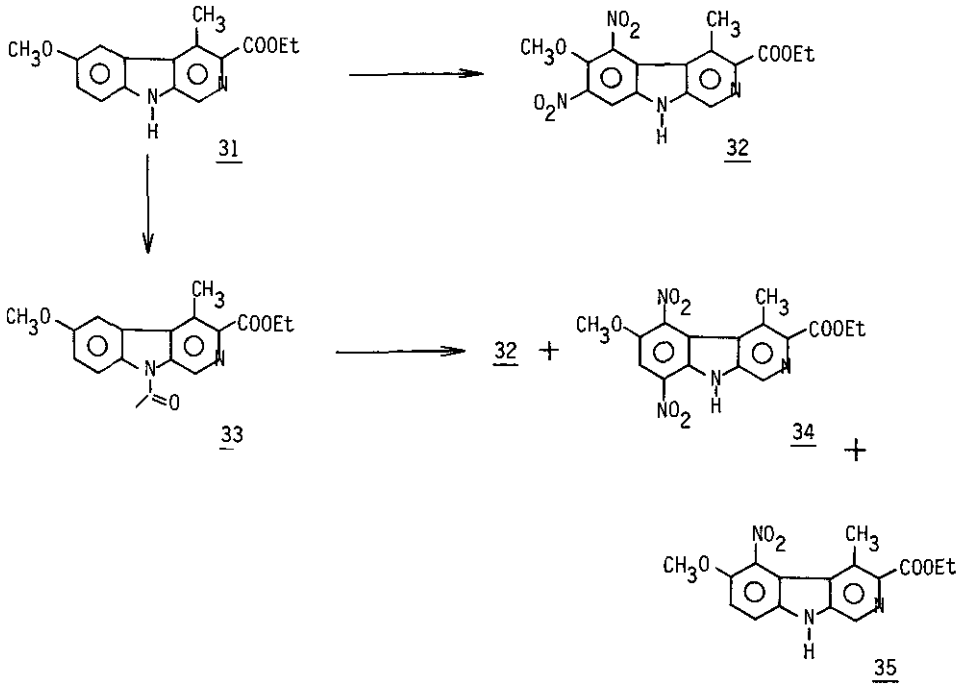
A 4-vinyl and a 4-acetyl derivative were obtained using NBS-bromination of a 4-ethyl-ß-carboline and subsequent dehydrobromination (DBU, THF) or, respectively, Kornblum oxidation (DBU, DMSO) - concomitant lactone formation being a serious side reaction in both cases.



4. Nitro- and amino-substitution, thioureas, ureas, sulfonamides

Treatment of ß-carbolines with a mixture of concentrated and fumic nitric acid at temperatures below 10°C produced 6-mononitro derivatives, generally accompanied by small amounts of 6,8-dinitro compounds. More complex results were obtained when position C-6 was already occupied by an electron-donating substituent. 6-Methoxy-4-methyl-ß-carboline 31, on nitration with 80% nitric acid, was rapidly converted to 5,7-dinitro derivative 32. Acylation of the indole nitrogen prior to nitration resulted in a mixture of products consisting of 5,7-dinitro

compound 32 (80%), 5,8-dinitro compound 34 (10%) and 5-mononitro derivative 35 (10%). Cleavage of the N-acetyl group occurred on aqueous work-up.



Hydrogenation of 6-mononitro derivatives in THF in the presence of Pd/C cleanly produced the corresponding 6-amino compounds which were selectively transformed to various 6-dialkylamino derivatives by reaction with alkyl bromides in the presence of Hünig base[13] in ethanol. Thioureas were conveniently synthesized using Staab's reagent (N,N-thiocarbonyldiimidazole)[14]. Acylation and urea formation proceeded under standard conditions. 6-Sulfonamides were prepared by reacting ß-carbolines with chlorosulfonic acid (2 equiv., 25°C, 2h) in methylene chloride and subsequent amine addition to produce the corresponding sulfonamides in nearly quantitative yields.

EXPERIMENTAL SECTION[16)]

a. representative example for path b: 5-Benzyloxy-4-methoxymethyl-ß-carboline-3-carboxylic acid ethyl ester

1. 3-Hydroxy-2-nitro-5-oxa-hexanoic acid ethyl ester 15

To a solution of 74.08 g (1 mol) of methoxyacetaldehyde[15)] in 100 ml of ethanol is added 1.0 g of sodium acetate dissolved in 8 ml of distilled water. After cooling to 5°C, 133.1 g (1 mol) of nitroacetic acid ethyl ester is added dropwise within a period of 2 h. After addition stirring is continued for 1 h at 10°C and for another 3 h at room temperature. The ethanolic solvent is distilled off in vacuo (15 mm Hg, bath temp. 30°C) and the residue taken up in 300 ml of diethyl ether. The ethereal phase is washed with 10% NaH_2PO_4-solution and brine and dried over $CaSO_4$. Evaporation of the solvent results in 170 g of a yellow liquid with a refractory index $n_{20}^{D} = 1.439$. ^{1}H-nmr analysis shows the product to be a mixture of equal amounts of 15 and nitroacetic acid ethyl ester. As this mixture is thermally unstable, it is used in the next step without further purification.

2. 3-(4-Benzyloxy-indol-3-yl)-2-nitro-5-oxa-hexanoic acid ethyl ester 16

A solution consisting of 60 g (0.258 mol) of 4-benzyloxyindole 14, 140 g of hydroxy nitro ester 15 (mixture obtained above), 1700 ml of toluene and 170 ml of glacial acetic acid is stirred under argon for 4 h at 110°C. After this period an additional quantity of hydroxy nitro ester 15 (70 g) is added and stirring continued for another 2.5 h. Thin layer chromatography then shows complete disappearance of starting indole 14. The solvent is evaporated in vacuo at a bath temperature not exceeding 50°C; acetic acid remaining in the crude product is removed azeotropically by several distillations with toluene. Column chromatography on silica gel with methylene chloride as eluent gives 99 g of a dark brown oil; representing an isomeric mixture which is transferred to the next step as such.

3. 3-(4-Benzyloxy-indole-3-yl)-2-amino-5-oxa-hexanoic acid ethyl ester 17

A suspension of 20 g of 16 and 30 g of Raney-Ni in 400 ml of ethanol is hydrogenated at room temperature and atmospheric pressure. After 1 h the theoretical amount of hydrogen is consumed, the catalyst is filtered off and the filtrate evaporated in vacuo. The residue is chromatographied on a silica gel column using methylene chloride/ethanol (10:1) as eluent. The main fraction (15 g), a semi-solid mixture of isomers, is used without further purification.

4. 5-Benzyloxy-3-ethoxycarbonyl-4-methoxymethyl-1,2,3,4-tetrahydro-ß-carboline-1-carboxylic acid 18a and 5-Benzyloxy-3-ethoxycarbonyl-4-methoxymethyl-3,4-dihydro-ß-carboline-1-carboxylic acid 18b

A solution of 10.8 g (0.118 mol) of glyoxylic acid (monohydrate) in 120 ml of water is added dropwise to a vigorously stirred solution of 37.6 g (0.098 mol) of amino ester 17 in 250 ml of ethyl acetate. The acidity of the mixture is adjusted to a pH-value of 4.0 by dropwise addition of 15 ml of a 10% K_2CO_3-solution. The yellow precipitate formed after 14 h of stirring at room temperature is filtered off, washed with a small quantity of ethyl acetate and dried to give a yellow powder (fraction I, 17.5 g).

A second fraction is obtained by separating the organic phase from the filtrate. Drying over Na_2SO_4 and evaporation gives 19.0 g of a yellow oil which slowly solidifies on standing (fraction II). Both fractions - according to nmr-analysis - consist of almost equal amounts of 18a and 18b.

5. 5-Benzyloxy-4-methoxymethyl-ß-carboline-3-carboxylic acid ethyl ester 19

Mixture 18a,b (17.5 g) is suspended in 175 ml of xylene and refluxed for 1 h. The solvent is removed in vacuo and the residue newly dissolved in 100 ml of dimethyl sulfoxide. Addition of 2.56 g of sulfur (powder) is followed by stirring for 1.5 h at a bath temperature of 140°C. DMSO is then distilled off and the remaining crude product chromatographed on silica gel with methylene chloride and methylene chloride/ethanol 20:1. The main fraction is crystallized from ethyl acetate/diethyl ether to give 6.7 g (43%) of 19, m.p. 186-188°C.

b. 4-Methoxycarbonyl-substitution

1. Methyl (3-indolyl)methoxyacetate 21

Methyl chloromethoxy acetate 20 (14.1 g, 0.102 mol) is slowly dropped to a stirred solution of 10 g (0.085 mol) of indole in 100 ml of toluene and 20 ml of tri-n-butylamine at 25 °C. After addition of 1.05 g (0.005 mol) of dicyclohexylcarbodiimide the reaction mixture is stirred under argon for 5 h at 80°C. The solution is then cooled to room temperature, poured into sat. $NaHCO_3$-solution and extracted with ethyl acetate. The crude product is chromatographed on silica gel with hexane/ethyl acetate. Crystallization of the main fraction from diisopropyl ether gives 11.5 g (62%) of 21, m.p. 127-128°C.

2. 3-(3-Indolyl)-3-methoxycarbonyl-2-nitro-propionic acid ethyl ester 22

A solution of 6 g (0.027 mol) of 21, 5.8 ml (0.036 mol) of nitroacetic acid ethyl ester and 0.5 ml of diisobutylamine in 100 ml of xylene is refluxed for 10 h under argon atmosphere. After cooling the mixture is diluted with ethyl acetate, washed with 0.5N-HCl and brine, dried (Na_2SO_4) and evaporated. Chromatography of the crude product yields 6.22 g (72%) of 22 as an isomeric mixture.

c. N-Bromosuccinimide functionalization (representative example)

9-Acetyl-4-bromomethyl-6-methoxy-ß-carboline-3-carboxylic acid ethyl ester

9-Acetyl-6-methoxy-4-methyl-ß-carboline-3-carboxylic acid ethyl ester (1.07 g, 0.0033 mol) is dissolved in 100 ml of tetrachloromethane. After addition of 1.75 g (0.0098 mol) of N-bromosuccinimide and 25 mg of azobisisobutyronitrile the solution is refluxed for 2.5 h under external irradition (photolamp, 200 W). The warm reaction mixture is diluted with 200 ml of ethyl acetate, washed successively with NaH_2PO_4-solution (10%), $Na_2S_2O_3$-solution (5%) and brine, dried ($MgSO_4$) and evaporated to give a crude product (1.4 g) which is crystallized from ethyl acetate to yield 930 mg (69.6%) of the title compound, m.p. 176.5-178°C.

d. Nitration (representative example)

4-Methoxymethyl-6-nitro-ß-carboline-3-carboxylic acid ethyl ester

Concentrated nitric acid (65%, 19.3 ml) and fumic nitric acid (9.65 ml) are carefully mixed at 0°C. 4-Methoxymethyl-ß-carboline-3-carboxylic acid ethyl ester (2.0 g, 0.007 mol) is added portionwise followed by stirring for 3 h at 5°C. The reaction mixture is slowly dropped into ice-water and then neutralized by careful addition of conc. ammonia solution. The precipitate is collected by filtration, washed with water and dried. In order to remove impurities, the crude product is suspended in 70 ml of ethyl acetate and refluxed on a steam bath for 30 min. Filtration of the hot solution results in pure 6-nitro derivative (1.95 g, 84.2%), m.p. 274-276°C.

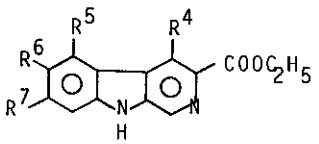
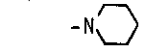
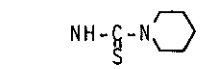
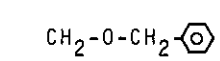


Table I

R_4	R_5	R_6	R_7	mp.	path
CH_3	H	H	H	235-239	a
CH_3	H	NO_2	H	272-275	c
CH_3	H	NH_2	H	238 (Decomp.)	c
CH_3	H	$NH-\overset{O}{\overset{\|}{C}}-CH_3$	H	273-279	c
C_2H_5	H	H	H	192	a
i-C_3H_7	H	H	H	163-167	a
n-C_3H_7	H	H	H	195-197	a
C_2H_5	H	Br	H	255-257	c
	H	H	H	226-232	a
	H	H	H	182-185	a
CH_3	H	Br	H	231-232	c
CH_3	H	Cl	H	225-228	c

R_4	R_5	R_6	R_7	mp.	path
C_2H_5	H	NO_2	H	274-282	c
CH_3	H	OCH_3	OCH_3	234-238	a
C_2H_5	O-CH_2- 	H	H	192-193	a
C_2H_5	O-C(=O)-CH_3	H	H	143-145	c
CH_3	O-C(=O)-CH_3	H	H	161-163	c
C_2H_5	OH	H	H	188-190	c
CH_2OCH_3	H	I	H	204-206	c
CH_2OCH_3	H	NH_2	H	199-201	c
C_2H_5	H	OCH_3	OCH_3	205-207	a
C_2H_5	OCH_3	H	H	166-167	a
C_2H_5	F	H	H	161-165	a
CH_3	F	H	H	189	a
CH_3	OCH_3	H	H	199-203	a
C_2H_5	H	NH_2	H	235-240	c
CH_2-$N(CH_3)_2$	H	OCH_3	H	171-175	c
$CH{=}CH_2$	H	H	H	193-195	c
C(=O)-CH_3	H	H	H	211-214	c
CH_2-OCH_3	H	-N 	H	212-214	c
CH_3	H	SO_2-NH_2	H	297-300	c
CH_3	H	F	H	212-214	a
CH_2OCH_3	H	H	H	118-119	a or b
C_2H_5	H	F	H	200-202	a
CH_2-CH_2-OCH_3	H	Br	H	208-210	c
C_2H_5	H	OCH_3	H	180-183	a
CH_3	O-CH_2- 	H	H	190-192	a
CH_2OCH_3	H	NO_2	H	274-276	c
CH_2OCH_3	H	Br	H	207-209	c
C_2H_5	H	OCH_3	OCH_3	232-233	a
CH_2OCH_3	H	OCH_3	OCH_3	163-164	a
CH_2OCH_3	H	SO_2-$N(CH_3)_2$	H	191-193	c
CH_3	H	OH	H	270-273	c
CH_3	NO_2	OCH_3	H	247-251	c

R_4	R_5	R_6	R_7	mp.	path
CH_2Br	H	OCH_3	H	340	c
CH_2-CH_2-OCH_3	H	H	H	181-183	a
$COOCH_3$ 	H	H	H	211-214	c
	H	H	H	221-225	b
CH_3	H	NH-SO_2-CH_3	H	242-244	c
C_2H_5	H	Cl	H	258-261	c
CH_3	H	NH-CHO	H	244-246	c
CH_3	H	SO_2-$N(CH_3)_2$	H	253-256	c
CH_3	H	SO_2-$N(C_2H_5)_2$	H	272-274	c
CH_3	H	SO_2-N  N-CH_3	H	247-251	c
n-C_3H_7	H	Br	H	251-255	c
$COOCH_3$	H	Br	H	250-253	c
CH_3	CH_3	H	H	160-163	a
CH_3	H	OCH_3	H	206-210	a
C_2H_5	H	SO_2-$N(CH_3)_2$	H	211-214	c
C_2H_5	H	CN	H	264-267	c
CH_2OCH_3	H	CN	H	252-255	c
CH_3	H	H	F	268-273	a
CH_3	H	NH-C(=O)-$N(CH_3)_2$	H	223 (Decomp.)	c
C_2H_5	H	H	F	250-252	a
CH_3	H	-N	H	244-251	c
CH_2-N 	H	OCH_3	H	194	c
C_2H_5	H	-N	H	218	c
CH_2OCH_3	O-CH_2	H	H	185-188	b
CH_2OCH_3	H	Cl	H	209-210	c
CH_2OCH_3	CH_3	H	H	151-152	a or b
CH_3	H	$N(CH_3)_2$	H	199-201	c
C_2H_5	CH_3	H	H	151-153	a
CH_3	-N	H	H	214-217	c
CH_2OCH_3	H	OCH_3	H	175-177	a
CH_3	$COOCH_3$	H	H	204-208	a

R_4	R_5	R_6	R_7	mp.	path
CH_3	C_2H_5	H	H	181-183	a
CH_3	H		H	219-224	c
CH_3	$CH_2OC_2H_5$	H	H	134-136	a
CH_3	CH_2-OCH_3	H	H	133-135	a
CH_3	H		H	178-182	c
CH_3		H	H	120-122	a

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