NEW ROUTE TO 7a-ANGULARLY SUBSTITUTED HYDROINDOLES

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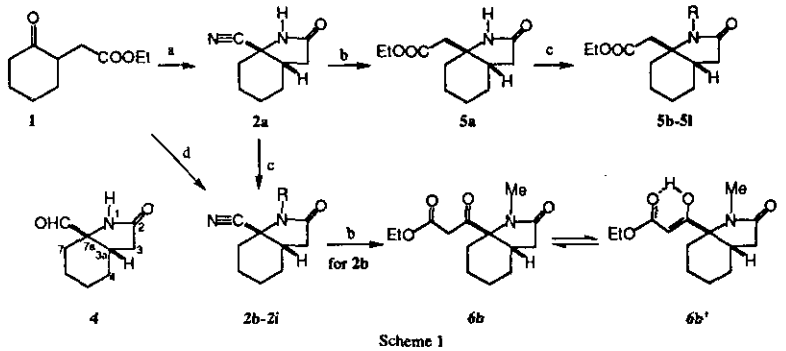
Abstract - Strecker type reaction of ethyl 2-oxocyclohexaneacetate with sodium cyanide and ammonium acetate gave 7a-cyano-octahydro-*cis*-1*H*-indol-2-one (**2a**) as a single product, which was alkylated to the *N*-alkyl derivatives. The cyano group in **2a** was convertible to ethoxycarbonylmethyl group by reaction with the Reformatsky reagent generated from ethyl bromoacetate. In the case of the *N*-methyl derivative **2b**, the cyano group was transformed into ethoxycarbonylacetyl group under the same reaction conditions.

Angularly substituted hydroindoles, particularly those with 7a-substituent appear in some alkaloids such as those of the genera *Stephania*[1] and *Erythrina*.[2] This paper deals with a facile method of synthesizing that type of skeleton from ethyl 2-oxocyclohexaneacetate (**1**) by application of Strecker amino-nitrile synthesis.[3] Our method is based on a modification of Glenn's synthesis of 5-cyano-γ-valerolactam from butyl 4-oxopentanoate,[4] but with the use of sodium cyanide instead of dangerous liquid hydrogen cyanide. The cyano group in the product can be converted by the anion-exchange reaction to a variety of functional groups affording useful synthetic intetrmediates.



Scheme 1

(a) NaCN, NH_4Cl or CH_3COONH_4; (b) Zn, $BrCH_2COOEt$, then dil-H_2SO_4; (c) KH, RX; (d) NaCN, RNH_2.

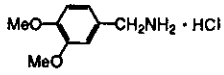
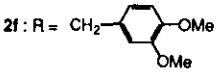
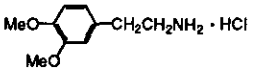
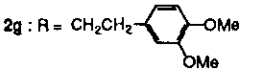
Heating of **1** with sodium cyanide and ammonium acetate in methanol-water at 120°C for 10 h yielded 7a-cyano-octahydro-1*H*-indol-2-one (**2a**) as a single product in 87% yield. The stereochemistry of **2a** was proved by converting it, upon catalytic hydrogenation over Raney Ni, to the corresponding aldehyde (**4**). It showed a cross-peak between 3a-H and the formyl proton in the NOESY, indicating that the ring

This paper is dedicated to 25th Anniversary of HETEROCYCLES.

juncture is *cis*.

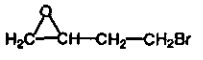
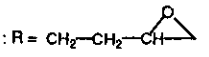
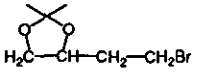
Similar reactions of **1** with primary amines and sodium cyanide also afforded corresponding *N*-alkyl derivatives (**2b-i**) (see Table 1). However, in these cases, the major products of *cis*-juncture were always contaminated with variable ratios of the *trans*-products (**3**), though the latters were not isolated except for **3d**, **3g** and **3i**. The presence and characterization of them are shown by the ^{13}C-NMR spectra, in which the ring juncture-carbons (3a and 7a) of the *trans*-isomers always appeared at a lower field by 7-8 and 5-6 ppm than those of the corresponding *cis*-isomers (see Table 3), respectively. Stereochemically pure *cis*-*N*-alkyl derivatives were obtained by *N*-alkylation of **2a** with alkyl halide in the presence of potassium hydride in THF (see Table 2).

Table 1 : Synthesis of 7a-Cyano-octahydro-1*H*-indol-2-ones (2)

Entry	Amine	Product	Yield (%)	Ratio (2:3)[a]
1	NH_4Cl	**2a** : R = H	54	
2	$MeCOONH_4$	**2a** : R = H	87	
3	$MeNH_2$ · HCl	**2b** : R = Me	94	11 : 1[b]
4	$EtNH_2$ · HCl	**2c** : R = Et	72	8.1 : 1
5	$EtOOCCH_2NH_2$ · HCl	**2d** : R = CH_2COOMe[c]	54	7.3 : 1
6	$EtOOCCH_2CH_2NH_2$ · HCl	**2e** : R = CH_2CH_2COOMe[d]	44	4.5 : 1
7		**2f** : R = 	40	1.2 : 1
8		**2g** : R = 	77[e]	1.3 : 1
9	CH_2=$CHCH_2NH_2$ · HCl	**2h** : R = CH_2CH=CH_2	15[e]	2.1 : 1
10	$HOCH_2CH_2CH_2NH_2$	**2i** : R = $CH_2CH_2CH_2OH$	92[e]	4.8 : 1

a) Determined by HPLC analysis [silica gel, AcOEt-hexane (10:1)]. b) The ratio was calculated from ^{13}C-NMR. Two isomers were inseparable in HPLC and ^{1}H-NMR. Methyl group were not separated in the ^{1}H-NMR spectra in $CDCl_3$ and benzene-d_6. c) The product is due to ester exchange during the reaction. d) The product is the carboxylic acid which was isolated as methyl ester after treatment with CH_2N_2. e) A small amount of **2a** was additionally obtained (for the reason, see text).

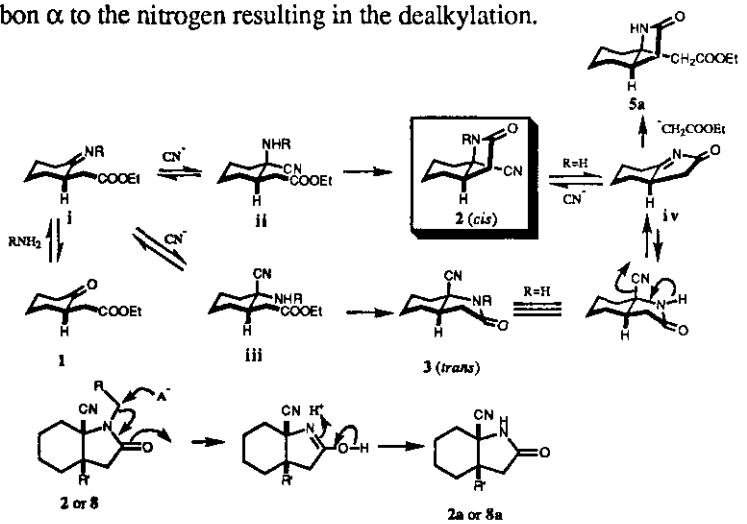
Table 2 : *N*-Alkylation of 7a-Cyano-octahydro-*cis*-1*H*-indol-2-one (2a)

Entry	R-X	Product (*cis* form)	Yield (%)
1	MeI	**2b** : R = Me	87
2	CH_2=$CHCH_2Br$	**2h** : R = CH_2CH=CH_2	66
3	$HOCH_2CH_2CH_2Br$	**2i** : R = $CH_2CH_2CH_2OH$	29
4	$EtOOCCH_2Br$	**2j** : R = CH_2CO_2Et	79
5	CH_2=$CHCH_2CH_2Br$	a)	
6		**2l** : R = 	48[b]
7		c)	

a) 2a was recovered because of decomposition of the reagent. b) Crude yield, the product was unstable on column chromatography. c) The reaction did not proceed because of steric hindrance of the *O,O*-isopropylidene group.

The above results indicate that the reaction proceeded as shown in Scheme 2. The reaction starts by the initial formation of the imine (**i**). Attack of the cyanide ion to **i** from the less hindered side (*anti* to the acetate side chain) gives the *cis*-ester (**ii**) preferentially over the *trans*-isomer (**iii**). Those cyclize to afford the lactams (**2** and **3**), respectively. However, when ammonia was used as a substrate (R=H in **2**

or **3**), they lose HCN readily affording the same intermediate (**iv**) from either compound. *Re*-attack of a cyanide ion to the intermediate imine (**iv**) regenerates **2a** and **3a**. Such equilibrium steps lead to converge the products to the thermodynamically more stable *cis*-isomer (**2a**). While, in the case of *N*-substituted compounds, elimination of HCN from the hydroindoles (**2** and **3**) is difficult, thus giving a mixture of **2** and **3** reflecting the initial *cis* / *trans* ratio (**ii** / **iii**). The participation of the imine intermediate was supported by the transformations of **2a** to **5a** (see below). It is also noticeable that dealkylated product (**2a**) was produced, though the amount is small, in the reactions of some primary amines (Table 1, Entries 8 - 10). We assume that this was produced by attack of a cyanide anion to the side chain methylene carbon α to the nitrogen resulting in the dealkylation.



Scheme 2

Table 3: ^{13}C-NMR Spectral Data for 7a-Cyano-octahydro-1*H*-indol-2-ones (**2**,**3**,**5** and **8**)

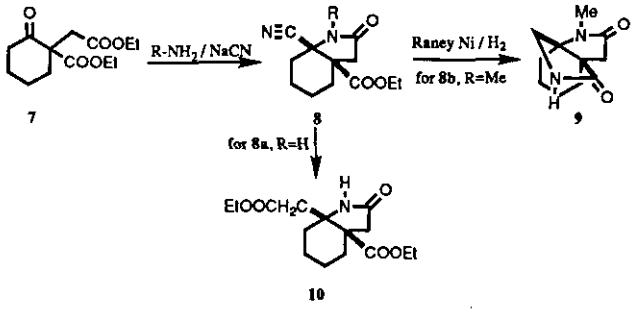
cis form	C2	C3	C3a	C4	C5	C6	C7	C7a	CN
2a	177.6	37.0	39.4	32.7	26.6	21.5	19.5	55.7	121.0
2b	174.1	36.8	38.0	31.4	27.4	22.3	20.5	61.0	120.3
2c	173.9	35.3	37.9	31.5	26.4	21.4	20.0	59.3	120.4
2d	174.3	35.0	38.3	31.9	26.2	21.2	20.0	60.1	119.5
2e	174.5	35.5	38.0	31.1	26.3	21.3	19.8	59.5	120.0
2f	174.4	36.8	38.2	32.9	26.6	21.7	19.5	60.3	119.7
2g	174.1	36.8	38.2	32.9	26.6	21.7	19.5	60.3	119.7
2h	174.0	35.6	38.5	32.0	25.9	21.5	20.0	60.0	121.0
2i	176.1	31.4	38.2	30.1	26.7	21.5	20.1	59.9	120.1
2j	174.0	34.8	38.2	31.8	26.1	21.1	19.9	60.0	119.4
5a	176.0	35.3	40.0	33.2	25.8	21.3	21.1	58.2	
5b	174.8	36.2	35.1	31.4	27.0	21.5	20.8	63.0	
5h	174.9	36.1	35.5	32.2	27.4	21.7	21.1	63.9	
5j	175.3	35.6	36.7	31.5	27.0	21.7	20.7	63.3	
8a	175.9	42.1	51.6	32.3	30.8	20.7	19.3	58.1	120.5
8b	172.2	40.4	48.5	31.7	28.1	19.9	18.7	61.2	117.8
8i	176.1	41.9	51.1	31.7	30.1	21.5	21.0	62.6	120.5
8j	172.8	41.5	49.7	31.7	29.1	20.0	18.8	61.2	118.2
8n	173.3	40.6	49.4	32.0	29.3	20.0	19.1	61.9	118.6

trans form	C2	C3	C3a	C4	C5	C6	C7	C7a	CN
3b	174.7	35.0	45.1	32.6	25.2	24.7	22.0	65.7	117.4
3c	174.4	35.1	45.9	33.1	25.2	24.7	22.1	65.0	118.6
3d	174.7	35.0	45.9	32.3	25.5	24.9	22.2	65.7	117.7
3e	175.1	36.7	45.9	32.7	26.5	22.0	21.5	65.2	121.0
3f	175.1	35.3	45.8	33.7	25.4	22.2	20.0	66.0	117.9
3g	175.0	34.4	45.9	33.2	25.5	24.8	22.2	65.5	118.5
3h	174.6	35.2	46.0	33.5	25.4	24.8	22.2	65.6	118.2
3i	176.2	32.9	46.0	31.0	25.2	24.6	22.0	65.4	118.2

Assignments of C4-C7 are arbitrary.

The cyano group in **2** was transformed into other functional groups by the following reactions. Treatment of **2a** with zinc and bromoacetate (Reformatsky reagent) resulted in the exchange of the cyano group to an ethyl acetate to afforded **5a** in 74% yield. The ring juncture of **5a** is also *cis* as indicated by

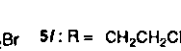
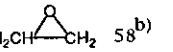
the cross-peak between 3a-H and the methylene proton in the acetate group in the NOESY. **5a** was alkylated to the corresponding *N*-alkyl derivatives (**5b-5*l***) (Table 4). An analogous reaction of the *N*-methyl derivative (**2b**) gave a different type of product (**6**) (which existed as an equilibrated mixture with its enol form **6'**). Formation of this product is explained by a Blaise type reaction with the ethyl acetate carbanion on the nitrile carbon followed by hydrolysis of the resulting imine.



7 8 9 10

Scheme 3

Table 4 : *N*-Alkylation of 7a-Ethoxycarbonylmethyl-octahydro-*cis*-1*H*-indol-2-one (5a)

Entry	R-X	Product	Yield (%)
1	MeI	**5b** : R = Me	87
2	CH_2=$CHCH_2Br$	**5h** : R = CH_2CH=CH_2	75
3	$HOCH_2CH_2CH_2Br$	a)	
4	$EtOOCCH_2Br$	**5j** : R = CH_2CO_2Et	82
5		**5*l*** : R = 	58[b]

a) The starting material was recovered. b) Crude yield, the product was unstable on column chromatography.

Table 5 : Synthesis of 7a-Cyano-3a-ethoxycarbonyl-octahydro-*cis*-1*H*-indol-2-one (8)

Entry	Amine	Product	Yield (%)
1	$MeCOONH_4$	**8a** : R = H	66
2	$MeNH_2$ · HCl	**8b** : R = Me	61
3	$HOCH_2CH_2CH_2NH_2$	**8i** : R = $CH_2CH_2CH_2OH$	54[a]
4		**8n** : R =	75
5	$EtOOCCH_2NH_2$ · HCl	**8a** : R = H[b]	34

a) **8a** was also obtained in low yield. b) See text.

Application of the above Strecker reaction to 2-ethoxycarbonyl-2-cyclohexanoneacetate (**7**) gave 7a-cyano-3a-ethoxycarbonyl-octahydro-*cis*-1*H*-indol-2-ones (**8**) in moderate yields. On catalytic hydrogenation over PtO_2, **8b** gave a tricyclic di-lactam (**9**) thus proving the stereochemistry. Treatment of **8a** (R=H) with a Reformatsky reagent gave the expected product (**10**), though the yield was not satisfactory (45%). The reaction of *N*-methyl derivative (**8b**) with the same reagent did not proceed and recovered the starting material. The reaction of **7** with ethyl glycinate hydrochloride and sodium cyanide unexpectedly gave only dealkylated lactam (**8a**) instead of **8j** (Table 5, Entry 5). This may be due to high susceptibility of the methylene group sandwiched by a carbonyl and nitrogen to the cyanide ion as discussed above. **8j** (R=CH_2COOEt) was prepared by the *N*-alkylation of **8a**.

EXPERIMENTAL

Melting points were determined on Yanaco micro hot stage melting point apparatus and are uncorrected. Unless otherwise stated, IR spectra were recorded on a JASCO IR-810 spectrophotometer in $CHCl_3$ solutions, and data are given in cm^{-1}. ^1H- and ^{13}C-NMR spectra were taken with a JEOL JNM-EX90 or a JNX-α500 spectrometer in $CDCl_3$ solutions with tetramethylsilane as an internal standard and the chemical shifts are given in δ values. Mass spectra (MS) and high resolution MS (HR-MS) were taken with a JEOL JMS D-300 machine and M^+ is indicated as *m/z*.

7a-Cyano-octahydro-*cis*-1*H*-indol-2-one (2a) A mixture of ethyl 2-oxocyclohexaneacetate (**1**) (8 g, 43.5 mmol) and ammonium acetate (6.03 g, 78 mmol) in MeOH (60 mL) was heaped on a frozen NaCN (3.82 g, 78 mmol) in water (6 mL) and the mixture was heated at 120°C for 10 h in a sealed tube. After acidification of the cooled mixture with 10% HCl to pH 5, it was extracted with $CHCl_3$. The organic layer was concentrated and the residue was purified by SiO_2 column chromatography (AcOEt:hexane=1:1) to yield **2a** (6.21 g, 87%) as colorless plates. mp 81-83°C (AcOEt-hexane). IR (KBr): 2240, 1700. ^{1}H-NMR: 7.50 (br s, 1H), 2.91-2.52 (m, 2H), 2.38-1.41 (m, 9H). *Anal.* Calcd for $C_9H_{12}N_2O$: C, 65.83; H, 7.37; N, 17.06. Found: C, 65.71; H, 7.32; N, 17.03.

1-Alkyl-7a-cyano-octahydro-*cis*-1*H*-indol-2-ones (2b-2*l*)

(1) Alkylation of 2a (General Procedure) A solution of **2a** (50 mg, 0.3 mmol) in THF (2 mL) was added to a suspension of KH (35% weight % dispersion in mineral oil, 41 mg, 0.36 mmol) in THF (5 mL) under Ar, and the mixture was stirred at 0°C for 0.5 h. Alkyl halide (0.42 mmol) was added to the mixture and the whole was brought to rt and stirred for 1 h. After addition of 5% HCl, the reaction mixture was extracted with AcOEt and the organic layer was concentrated to give the crude product, which was purified by passing a short SiO_2 column (AcOEt) to yield the *N*-alkyl derivatives (**2b**, **2h**, **2i**, **2j**, and **2*l***).

2b: Pale yellow oil. IR: 2240, 1715. ^{1}H-NMR: 2.85 (s, 3H), 2.83-1.47 (m, 11H). HR-MS: Calcd for $C_{10}H_{14}N_2O$: 178.1134. Found: 178.1107.

2h: Yellow oil. IR: 2240, 1710. ^{1}H-NMR: 6.10-5.66 (m, 1H), 5.41-5.17 (m, 2H), 4.05-3.94 (m, 2H), 2.79-2.51 (m, 2H), 2.33-2.05 (m, 3H), 2.51-1.26 (m, 6H). HR-MS: Calcd for $C_{12}H_{16}N_2O$: 204.1246. Found: 204.1261.

2i: Pale yellow oil. IR: 3400, 2250. 1700. ^{1}H-NMR: 3.79-3.37 (m, 4H), 3.31 (s, 1H), 2.83-2.55 (m, 2H), 2.36-1.26 (m, 11H). HR-MS: Calcd for $C_{12}H_{18}N_2O_2$: 222.1349. Found: 222.1366.

2j: Colorless oil. IR: 2240, 1760, 1720. ^{1}H-NMR: 4.22 (q, *J*=7.0 Hz, 2H), 4.21 (d, *J*=7.0 Hz, 1H), 4.02 (d, *J*=7.0 Hz, 1H), 2.68-1.53 (m, 11H), 1.29 (t, *J*=7.0 Hz, 3H). HR-MS: Calcd for $C_{13}H_{13}N_2O_3$: 250.1316. Found: 250.1316.

2*l*: Colorless oil. IR: 3060 (sh), 2230, 1720. ^{1}H-NMR: 4.17-3.65 (m, 1H), 3.57-3.24 (m, 4H), 2.81-2.51 (m, 2H), 2.36-1.19 (m, 11H).

(2) Strecker Reaction of 1 with Aliphatic Amines (General Procedure) A mixture of **1** (8 g, 43.5 mmol), primary amine (78 mmol), and NaCN (3.82 g, 78 mmol) in MeOH (60 mL)-water (6 mL) was heated in a sealed tube at 120°C for 10 h and the reaction mixture was worked up as described in **2a**. Compounds (**2b-2h**) were prepared by this method with contamination of the hardly separable corresponding *trans*-isomer (**3**) except for the cases of **2d**, **2g** and **2i** (Table 1), which were separated by chromatography.

2c: Pale yellow oil. IR: 2240, 1715. ^{1}H-NMR: 3.38 (m, 2H), 2.73-1.46 (m, 11H), 1.23 (t, *J*=7.2 Hz, 3H). HR-MS: Calcd for $C_{11}H_{16}N_2O$: 192.1241. Found: 192.1259.

2d: Pale yellow oil. IR: 2240, 1760, 1710. ^{1}H-NMR: 4.08 (s, 2H), 3,76 (s, 3H), 2.72-1.31 (m, 11H). HR-MS: Calcd for $C_{12}H_{16}N_2O_3$: 236.1151. Found: 236.1159.

2e: Pale yellow oil. IR: 2240, 1740, 1715. ^{1}H-NMR: 3.71 (s, 3H), 3.96-3.31 (m, 2H), 2.80-2.49 (m, 2H), 2.30-2.09 (m, 2H), 1.86-1.48 (m, 9H). HR-MS: Calcd for $C_{13}H_{18}N_2O_3$: 250.1298. Found; 250.1315.

2f: Light yellow oil. IR: 2850, 2240, 1715, 1600. ^{1}H-NMR: 6.89-6.81 (m, 3H), 4.79 (d, *J*=15.2 Hz, 1H), 4.71 (d, *J*=15.2 Hz, 1H), 3.86 (s, 3Hx2), 2.73-1.18 (m, 11H). HR-MS: Calcd for $C_{18}H_{22}N_2O_3$: 314.1669. Found: 314.1707.

2g: Colorless plates. mp 85-86°C (AcOEt-hexane). IR (KBr): 2860, 2225, 1700. ^{1}H-NMR: 6.80 (s, 3H), 3.89 (s, 3H), 3.86 (s, 3H), 3.72-1.48 (m, 15H). *Anal.* Calcd for $C_{19}H_{24}N_2O_3$: C, 69.49; H, 7.37; N, 8.53. Found: C, 69.23; H, 7.24; N, 8.63.

Data of *trans*-Isomers

3d: Colorless needles. mp 97-99°C (AcOEt-hexane). IR (KBr): 2250, 1755, 1720. ^{1}H-NMR: 4.40 (d, *J*=7.6 Hz, 1H), 3.77 (d, *J*= 7.6 Hz, 1H), 3.76 (s, 3H), 2.52-1.69 (m, 11H). HR-MS: Calcd for $C_{12}H_{16}N_2O_3$: 236.1151. Found: 236.1159.

3g: Light yellow oil. IR (film): 2850, 2240, 1700, 1600. ^{1}H-NMR: 6.90-6.69 (m, 3H), 3.88 (s, 3H), 3.86 (s, 3H), 3.73-1.24 (m, 15H). HR-MS: Calcd for $C_{19}H_{24}N_2O_3$: 328.1772. Found: 328.1785.

3i: Pale yellow oil. IR: 3450, 2225, 1680. ^{1}H-NMR: 3.74-3.41 (m, 4H), 3.16 (s, 1H), 2.49-2.22 (m, 2H), 2.18-1.66 (m, 11H). HR-MS: Calcd for $C_{12}H_{18}N_2O_2$: 222.1349. Found: 222.1369.

7a-Formyl-octahydro-*cis*-1*H*-indol-2-one (4) A solution of **2a** (164 mg, 1.0 mmol) and 30% ammonia (1 mL) in EtOH (5 mL) was hydrogenated over Raney nickel (100 mg) at 5 kg/cm^2 for 8 h. After removal of catalyst and solvent, the oily product was purified by SiO_2 column chromatography (AcOEt) to give the aldehyde (**4**) (25 mg, 15%) as a pale yellow oil. IR ($CHCl_3$): 1730, 1700. ^{1}H-NMR: 9.55 (s, 1H), 6.49 (br s, 1H), 2.47-1.18 (m, 11H). ^{13}C-NMR: 200.7, 178.2, 67.6, 37.2, 34.0, 27.8, 27.2, 22.2, 19.8. HR-MS: Calcd for $C_9H_{13}NO_2$: 167.0801. Found: 167.0943.

7a-Ethoxycarbonylmethyl-octahydro-*cis*-1*H*-indol-2-one (5a) A mixture of **2a** (230 mg, 1.0 mmol) and ethyl bromoacetate (835 mg, 5.0 mmol) in benzene (15 mL) was added dropwise over 1 h to a stirred suspension of Zn (325 mg, 5.0 mmol) in benzene (3 mL) at 95°C. After reflux for 4.5 h, the mixture was decomposed by addition of 10% H_2SO_4 (10 mL) and stirred for 0.5 h, then extracted with $CHCl_3$. The reddish oily product was purified by SiO_2 column chromatography (AcOEt:hexane =3:1) to give **5a** (234 mg, 74%) as a pale yellow oil. IR: 3240, 1725, 1710. ^{1}H-NMR: 6.61 (br s, 1H), 4.16 (q, *J*=7.3 Hz, 2H), 2.78 (d, *J*=15.7 Hz, 1H), 2.42 (d, *J*=15.7 Hz, 1H), 2.31-2.13 (m, 2H), 1.74-1.42 (m, 9H), 1.27 (t, *J*=7.3 Hz, 3H). HR-MS: Calcd for $C_{12}H_{19}NO_3$: 225.1383. Found: 225.1365.

1-Alkyl-7a-ethoxycarbonylmethyl-octahydro-*cis*-1*H*-indol-2-ones (5b-5*l*) (General Procedure) A solution of **5a** (50 mg, 0.22 mmol) in THF (2 mL) was added to a suspension of KH (35% weight % dispersion in mineral oil, 31 mg, 0.27 mmol) in THF (5 mL) under Ar at 0°C, and the mixture was stirred for 0.5 h at the same temperature. Alkyl halide (0.44 mmol) was added to the mixture and the whole was brought to rt and stirred for 1 h. The reaction mixture was worked up as described in *N*-alkylaion of **2a**, to yield the corresponding *N*-alkyl derivatives (**5b**, **5h**, **5j** and **5*l***.)

5b: Pale yellow oil. IR: 1740, 1700. ^{1}H-NMR: 4.06 (q, *J*=7.0 Hz, 2H), 2.68 (s, 3H), 2.54 (d, *J*=13.8 Hz, 1H), 2.34 (d, *J*=13.8 Hz, 1H), 2.26-1.33 (m, 11H), 1.18 (t, *J*=7.0 Hz, 3H). HR-MS: Calcd for

$C_{13}H_{21}NO_3$: 239.1514. Found: 239.1519.

5h: Colorless oil. IR: 1735, 1690. ^{1}H-NMR: 6.01-5.64 (m, 1H), 5.30-5.05 (m, 2H), 4.13 (q, *J*=7.3 Hz, 2H), 3.94-3.84 (m, 2H), 2.72 (d, *J*=13.8 Hz, 1H), 2.37 (d, *J*=13.8 Hz, 1H), 2.22-1.93 (m, 2H), 1.76-1.40 (m, 10H), 1.26 (t, *J*=7.3 Hz, 3H). HR-MS: Calcd for $C_{15}H_{23}NO_3$: 265.1655. Found: 265.1675.

5j: Colorless oil. IR: 1750, 1735, 1700. ^{1}H-NMR: 4.18 (q, *J*=7.0 Hz, 2H), 4.12 (q, *J*=7.0 Hz, 2H), 4.00 (d, *J*=2.6 Hz, 2H), 2.72 (d, *J*=2.6 Hz, 2H), 2.56-1.98 (m, 3H), 1.78-1.35 (m, 8H), 1.28 (t, *J*= 7.0 Hz, 3H), 1.26 (t, *J*= 7.0 Hz, 3H). HR-MS: Calcd for $C_{16}H_{25}NO_5$: 311.1718. Found: 311.1706.

5*l*: Colorless oil. IR: 3060 (sh), 1730, 1690. ^{1}H-NMR: 4.16 (q, *J*=7.0 Hz, 2H), 4.20-4.00 (m, 2H), 3.70-3.43 (m, 4H), 3.23-3.18 (m, 2H), 2.78 (d, *J*=16.0 Hz, 1H), 2.41 (d, *J*=16.0 Hz, 1H), 2.26-1.49 (m, 11H), 1.27 (t, *J*=7.0 Hz, 3H).

1-Methyl-7a-ethoxycarbonylacetyl-octahydro-*cis*-1*H*-indol-2-one (6b) Ethyl bromoacetate (167 mg, 1 mmol) was added to powdered zinc (327 mg, 5 mmol) suspended in THF (5 mL) under Ar at 70°C. The color of the solution changed to green. Then a mixture of **2b** (178 mg, 1 mmol) and ethyl bromoacetate (670 mg, 4 mmol) in THF (5 mL) was added dropwise to the suspension over 1 h. After the mixture was refluxed for 4 h, 10% HCl (10 mL) was added to the reaction mixture and which was stirred for 0.5 h. The mixture was extracted with $CHCl_3$ and the product was purified by SiO_2 column chromatography (AcOEt:hexane=3:1) to give a 2:1 mixture of **6b** and **6b'** (180 mg, 70%) as a pale yellow oil. IR: 1750, 1710, 1700. ^{1}H-NMR: **6b**: 4.20 (q, *J*=7.1 Hz), 3.52 (dd, *J*=39.4, 15.6 Hz), 2.80 (s), 1.283 (t, *J*=7.1 Hz). **6b'**: 12.44 (s), 4.95 (d, *J*=0.9 Hz), 4.17 (q, *J*=7.1 Hz), 2.79 (s), 1.276 (t, *J*=7.1 Hz). ^{13}C-NMR: **6b**: 177.5, 175.5, 172.7, 73.6, 61.7, 44.1, 36.2, 34.3, 27.5, 26.8, 26.4, 21.7, 20.5, 14.1. **6b'**: 175.8, 170.9, 166.6, 88.6, 67.6, 60.6, 37.4, 35.8, 28.8, 27.5, 25.7, 22.8, 20.7, 14.2. HR-MS: Calcd for $C_{14}H_{21}NO_4$: 267.1450. Found: 267.1468.

7a-Cyano-3a-ethoxycarbonyl-octahydro-*cis*-1*H*-indol-2-ones (8) (General Procedure) A mixture of ethyl 1-ethoxycarbonyl-2-cyclohexanoneacetate(7)(2.6 g, 10 mmol), ammonium acetate or primary amine (20 mmol), and NaCN (0.98 g, 20 mmol) in MeOH (15 mL)-water (2 mL) was heated at 120°C for 11 h , and the reaction mixture was worked up as described in **2**. Purification of the product obtained from the $CHCl_3$ extract by short SiO_2 column chromatography (AcOEt:hexane=1:1) gave **8a**, **8b**, **8i** and **8n** in the yields of Table 5.

8a: Colorless plates. mp 118-119°C (AcOEt-hexane). IR (KBr): 2350, 1720, 1680. ^{1}H-NMR: 7.08 (br s, 1H), 4.30 (q, *J*=7.0 Hz, 2H), 3.06 (d, *J*=16.7 Hz, 1H), 2.33 (d, *J*=16.7 Hz, 1H), 2.30-0.62 (m, 8H), 1.34 (t, *J*=7.0 Hz, 3H). *Anal.* Calcd for $C_{12}H_{16}N_2O_3$: C, 61.00; H, 6.83; N, 11.86. Found: C, 60.74; H, 6.75; N, 11.89.

8b: Colorless plates. mp 64-66°C (AcOEt-hexane). IR (KBr): 2360, 1720, 1710. ^{1}H-NMR: 4.30 (q, *J*=7.0 Hz, 2H), 2.86 (s, 3H), 2.95 (d, *J*=16.7 Hz, 1H), 2.38 (d, *J*=16.7 Hz, 1H), 2.34-1.02 (m, 8H), 1.34 (t, *J*=7.0 Hz, 3H). MS: m/z 250 (M^+). *Anal.* Calcd for $C_{13}H_{18}N_2O_3$: C, 62.38; H, 7.25; N, 11.19. Found: C, 62.16; H, 7.17; N, 11.13.

8i: Colorless oil. IR: 3450, 2400, 1730, 1700. ^{1}H-NMR: 4.28 (q, *J*=7.2 Hz, 2H), 3.82-3.17 (m, 6H), 3.00 (d, *J*=17.1 Hz, 1H), 2.39 (d, *J*=17.1 Hz, 1H), 2.16-1.53 (m, 9H), 1.33 (t, *J*=7.2 Hz, 3H). HR-

MS: Calcd for $C_{15}H_{22}N_2O_4$: 294.1603. Found: 294.1580.

8n: Light yellow oil. IR: 2400, 1730, 1710. ^{1}H-NMR: 7.27 (d, *J*=8.6 Hz, 2H), 6.84 (d, *J*=8.6 Hz, 2H), 4.68 (d, *J*=15.4 Hz, 1H), 4.27 (q, *J*=7.0 Hz, 2H), 4.26 (d, *J*=15.4 Hz, 1H), 3.79 (s, 3H), 3.11-1.42 (m, 10H), 1.31 (t, *J*=7.0 Hz, 3H). MS: m/z 356 (M^+).

2,4-Dioxo-1-methyl-2,3,4,5-tetrahydro-1*H*,6*H*-3a,6a-butanopyroro[2,3-*c*]pyrrole (9) A solution of **8b** (100 mg, 0.4 mmol) in AcOH (3 mL) was hydrogenated over PtO_2 (50 mg) under 4 kg/cm^2 for 5.5 h. After removal of catalyst and solvent, the solid residue was crystallized from $CHCl_3$-AcOEt to yield tricyclic di-lactam (**9**) (73 mg, 88%) as colorless plates. mp 212-214°C. IR (KBr): 1710, 1665. ^{1}H-NMR: 7.28 (br s, 1H), 3.37 (s, 2H), 2.77 (d, *J*=17.1 Hz, 1H), 2.75 (s, 3H), 2.36 (d, *J*=17.1 Hz, 1H), 2.16-1.29 (m, 8H). ^{13}C-NMR: 180.9, 172.5, 66.5, 46.8, 44.5, 35.4, 30.3, 28.5, 24.6, 21.1, 19.2. *Anal.* Calcd for $C_{11}H_{16}N_2O_2$: C, 63.44; H, 7.74; N, 13.45. Found: C, 63.12; H, 7.65; N, 13.36.

3a-Ethoxycarbonyl-7a-ethoxycarbonylmethyl-octahydro-*cis*-1*H*-indol-2-one (10) A mixture of **8a** (R=H, 50 mg, 0.2 mmol) and ethyl bromoacetate (167 mg, 1.0 mmol) in benzene (10 mL) was added dropwise over 40 min to a suspension of Zn (65 mg, 1.0 mmol) in benzene (2 mL) at 95°C. After reflux for 6 h, the mixture was decomposed by addition of 10% H_2SO_4 (2 mL) and stirred for 0.5 h, then extracted with $CHCl_3$. The oily product was purified by SiO_2 column chromatography (AcOEt:hexane =3:1) to give **10** (14 mg, net yield 45%) as a pale yellow oil and the starting material (**8a**) (25 mg, 50%). **10**: IR: 1730, 1710, 1700. ^{1}H-NMR: 6.10 (br s, 1H), 4.21 (q, *J*=7.0 Hz, 2H), 4.13 (q, *J*=7.1 Hz, 2H), 2.92 (d, *J*=16.8 Hz, 1H), 2.53 (s, 2H), 2.15 (d, *J*=16.8 Hz, 1H), 2.01-1.45 (m, 8H), 1.30 (t, *J*=7.0 Hz, 3H), 1.25 (t, *J*=7.1 Hz, 3H). ^{13}C-NMR: 174.6, 172.6, 170.8, 61.2, 60.9, 59.5, 50.5, 41.6, 41.3, 33.2, 30.5, 21.1, 20.3, 14.2, 14.1. HR-MS: Calcd for $C_{15}H_{23}NO_5$: 297.1584. Found: 297.1576.

1-Alkyl-7a-cyano-3a-ethoxycarbonyl-octahydro-*cis*-1*H*-indol-2-ones (8b-8j) (General Procedure) A solution of **8a** (100 mg, 0.4 mmol) in THF (4 mL) was added to a suspension of KH (35% weight % dispersion in mineral oil, 54 mg, 0.48 mmol) in THF (10 mL) under Ar at 0°C, and the mixture was stirred for 0.5 h at the same temperature. Alkyl halide (0.8 mmol) was added to the mixture and the whole was brought to rt and stirred for 1 h. The reaction mixture was worked up as described in *N*-alkylaion of **2a**, to yield the corresponding *N*-alkyl derivatives (**8b**, **8n** and **8j**).

8j: colorless oil. IR: 2400, 1750, 1740, 1730. ^{1}H-NMR: 4.30 (q, *J*=7.0 Hz, 2H), 4.23 (q, *J*=7.0 Hz, 2H), 4.02 (d, *J*=2.9 Hz, 2H), 3.01 (d, *J*=16.7 Hz, 1H), 2.44 (d, *J*=16.7 Hz, 1H), 2.22-1.46 (m, 8H), 1.34 (t, *J*=7.0 Hz, 3H), 1.30 (t, *J*=7.0 Hz, 3H). MS: m/z 322(M^+).

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