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Indoles. V.[1] Syntheses and Reactions of Cycloalkanon-[c,d]indole Derivatives

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A convenient synthetic method for cycloalkanon[*c*,*d*]indoles (**1** and **8**) and some of their reactions were examined.

The Friedel-Crafts reaction of 1-acetylindol-3-ylpropionic acids (**4b** and **4c**) gave cyclopent[*b*]indoles (**5b** and **5c**). This result indicates the general tendency of cyclization of 1-acetylindol-3-ylalkanoic acid, different from only one example reported previously by Szmuszkovicz,[3k] who prepared benz[*c*,*d*]indole derivative (**3**) from 1-acetylindol-3-yl-succinic anhydride (**2**).

The Friedel-Crafts reaction of 2-ethoxycarbonylindol-3-ylalkanoic acids (**7b**, **7c**, and **7d**), which were obtained in a good yield from easily available starting materials, gave cycloalkanon[*c*,*d*]indoles (**8a**, **8c**, and **8e**) in 24, 66, and 73% yield, respectively. Saponification and decarboxylation of **8a** and **8e** gave Uhle's ketone (**1a**) and a new ketone (**1b**), respectively.

The Beckmann rearrangement of oximes (**9a** and **9b**) with polyphosphoric acid gave lactams (**10a** and **10b**) resulting from aryl migration. This is different from Bowman's example,[3p] in which lactams (**11a** and **11b**) resulting from alkyl migration are obtained by the Beckmann rearrangement of oximes (**9c** and **9d**) with thionyl chloride. Saponification and decarboxylation of **10a** and **10b** gave azepino[*c*,*d*]indolone (**10c**) and azocino-[*c*,*d*]indolone (**10d**) in 50 and 55% yield, respectively.

5-(3-Ethoxycarbonyl-5-oxo-2-pyrrolin-1-yl)-6(1*H*)-oxo-3,4,5,6-tetrahydrocyclohept-[*c*,*d*]indole (**15b**) was obtained from **1b** by Stoll's method[3d] and its structure was elucidated from its nuclear magnetic resonance and mass spectra.

1) Part IV: T. Nagasaka and S. Ohki, *Yakugaku Zasshi*, **92**, 777 (1972).
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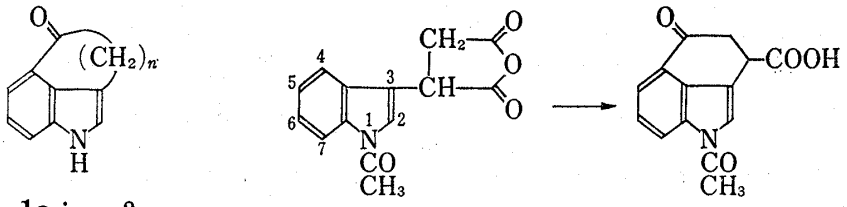
3) *a*) W.A. Jacobs and R.G. Gould, Jr., *Science*, **85**, 248 (1937); W.A. Jacobs and R.G. Gould, Jr., *J. Biol. Chem.*, **120**, 141 (1937); *idem*, *ibid.*, **130**, 407 (1939); *b*) F.C. Uhle, *J. Am. Chem. Soc.*, **71**, 761 (1949); F.C. Uhle, C.G. Vernick, and G.L. Schmir, *J. Am. Chem. Soc.*, **77**, 3334 (1955); F.C. Uhle and S.H. Robinson, *J. Am. Chem. Soc.*, **77**, 3544 (1955); F.C. Uhle, C.M. McEwen, Jr., H. Schröter, C. Yuan, and B.W. Baker, *J. Am. Chem. Soc.*, **82**, 1200 (1960); *c*) C.A. Grob and J. Voltz, *Helv. Chim. Acta*, **33**, 1796 (1950); C.A. Grob, B. Hofer, and P. Payot, *Experientia*, **7**, 373 (1951); C.A. Grob and B. Hofer, *Helv. Chim. Acta*, **35**, 2095 (1952); C.A. Grob and P. Payot, *Helv. Chim. Acta*, **36**, 839 (1953); C.A. Grob and B. Hofer, *Helv. Chim. Acta*, **36**, 847 (1953); C.A. Grob, H. Kappeler, and W. Meier, *Helv. Chim. Acta*, **44**, 1517 (1961); C.A. Grob, W. Meier, and E. Renk, *Helv. Chim. Acta*, **44**, 1525 (1961); C.A. Grob and E. Renk, *Helv. Chim. Acta*, **44**, 1531 (1961); *d*) A. Stoll, J. Rutschmann, and Th. Petrzilka, *Helv. Chim. Acta*, **33**, 2257 (1950); A. Stoll and J. Rutschmann, *Helv. Chim. Acta*, **34**, 382 (1951); *idem*, *ibid.*, **35**, 141 (1952); A. Stoll and Th. Petrzilka, *Helv. Chim. Acta*, **36**, 1125, 1137 (1953); *e*) F.G. Mann and A.J. Tetlow, *Chem. Ind.* (London), **1953**, 823; F.G. Mann and A.J. Tetlow, *J. Chem. Soc.*, **1957**, 3352; *f*) A. Cohen, B. Health-Brown, and A.H. Rees, *Chem. Ind.* (London), **1953**, 1152, 1179; *g*) J.A. Barltrop and D.A.H. Taylor, *J. Chem. Soc.*, **1954**, 3399, 3403; *h*) E.C. Kornfeld, E.J. Fornefeld, G.B. Kline, M.J. Mann, R.G. Jones, and R.B. Woodward, *J. Am. Chem. Soc.*, **76**, 5256 (1954); *idem*, *ibid.*, **78**, 3087 (1956); *i*) H. Plieninger and K. Suhr, *Chem. Ber.*, **90**, 1980, 1984 (1957); H. Plieninger and W. Müller, *Chem. Ber.*, **93**, 2029, (1960); H. Plieninger, H. Bauer, W. Buchler, J. Kurze, and L. Learch, *Ann.*, **680**, 69 (1964); H. Plieninger and W. Lehnert, *Chem. Ber.*, **100**, 2427 (1967); *j*) J.A. Moore and M. Rahm, *J. Org. Chem.*, **26**, 1109 (1961); *k*) J. Szmuszkovicz, *J. Org. Chem.*, **29**, 843 (1964); *l*) A.B. A. Jansen, J.M. Johnson, and J.R. Surtees, *J. Chem. Soc.*, Supple. No. 1, 5573 (1964); *m*) M. Julia, G.F. Le, J. Igolen, and M. Baillarge, *Bull. Soc. Chim. Fr.*, **1968**, 1071; M. Julia, G.F. Le, J. Igolen, and M. Baillarge, *Tetrahedron Lett.*, **1969**, 1569; *n*) K. Pelz, M. Rajsner, J.O. Jilek, M. Protiva, *Collect. Czech. Chem. Commun.*, **33**, 2111 (1968); *o*) B. Zeeh, *Chem. Ber.*, **102**, 678 (1969); *p*) R.E. Bowman, D.D. Evans, J. Guyett, H. Nagy, J. Weale, D.J. Weyell, and A.C. White, *J. Chem. Soc.*, Perkin Trans. 1, **1972**, 1121, 1926; *idem*, *ibid.*, **1973**, 438, 760.

Keywords——acetylindolylalkanoic acids; cycloalkanonindoles; Japp–Klingemann reaction; Fischer indolization; Friedel–Crafts reaction; Beckmann rearrangement; azepinoindolone; azocinoindolone

Cycloalkanon[*c*,*d*]indoles (**1**) are tricyclic system compounds related to lysergic acid derivatives. In order to synthesize lysergic acid derivatives with a pharmacological activity, a convenient synthetic method for **1**, a key intermediate, and its reactions were examined. It seems that the synthesis of **1** is comparatively difficult.[3)]

The first example of the synthesis of this tricyclic system was that of 5-oxo-1,3,4,5-tetrahydrobenz[*c*,*d*]indole (Uhle's ketone) (**1a**) reported by Uhle,[3b)] which was derived from 2-chloro-6-nitrotoluene through multiple steps. Compounds with this skeleton have later been synthesized by several groups.[3)] The most notable among these is Szmuszkovicz's work[3k)] obtaining 1-acetyl-5-oxo-1,3,4,5-tetrahydrobenz[*c*,*d*]indole-3-carboxylic acid (**3**) by the Friedel–Crafts reaction of 1-acetylindol-3-ylsuccinic anhydride (**2**) (Chart 1). This is interesting because of the only synthesis of the skeleton of **1** by direct cyclization to the 4-position of indole.[4)] As this method seemed convenient for the synthesis of **1**, we attempted its synthesis by the Friedel–Crafts reaction using a few kinds of indol-3-ylalkanoic acids.



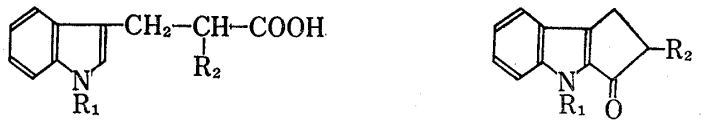
1a : $n=2$
1b : $n=3$

2 **3**

Chart 1

Cyclization of 3-(1-Acetylindol-3-yl)propionic Acid (4b)

In general, nucleophilic activity of 2-position of indole is very marked. For example, cyclization of indol-3-ylpropionic acid (**4a**) takes place at the 2-position to give only 3-oxo-1,2,3,4-tetrahydrocyclopent[*b*]indole[5)] (**5a**) (Chart 2). Cyclization of **2** at 4-position may be due to the decreased nucleophilic activity of 2-position by the acetylation of 1-position. Consequently, it should be possible to synthesize **1** by the Friedel–Crafts reaction of 1-acetylindol-3-yl-alkanoic acids. We chose 3-(1-acetylindol-3-yl)propionic acid (**4b**) as the most simple model compound. Synthesis of **4b** was comparatively difficult and several conditions were examined. The best result was obtained by esterification of **4a** with *tert*-butanol and trifluoroacetic anhydride in dry benzene,[6)] acetylation of this *tert*-butyl ester with sodium



4a : $R_1=R_2=H$
4b : $R_1=COCH_3$, $R_2=H$
4c : $R_1=COCH_3$, $R_2=-N$(CO, CO)

5a : $R_1=R_2=H$
5b : $R_1=COCH_3$, $R_2=H$
5c : $R_1=COCH_3$, $R_2=-N$(CO, CO)

Chart 2

4) Direct cyclization from 3- to 4-position of indoline derivatives is known.[3h,3m)]
5) *a*) K. Ishizumi, T. Shioiri, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **15**, 863 (1967); *b*) K.F. Jennings, *J. Chem. Soc.*, **1957**, 497.
6) The same esterification of indol-3-ylbutyric acid with trifluoroacetic anhydride gave 2,3,4,9-tetrahydro-1-carbazolone quantitatively.

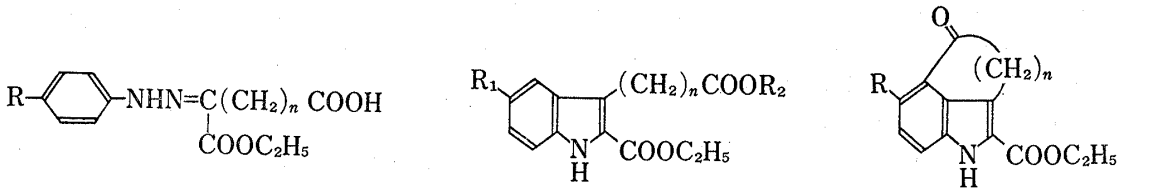
hydride and acetyl chloride in dry dimethylformamide, and hydrolysis of this ester with trifluoroacetic acid. **4b** was obtained in an overall yield of 41% from **4a**.

The Friedel–Crafts reaction of the acid chloride of **4b** gave **5b** as a sole product in 60% yield.

Since we previously obtained **5c** from **4c**,[7] it can be concluded that cyclization of 1-acetylindol-3-ylalkanoic acids by the Friedel–Crafts reaction occurs at 2-position in general. Cyclization of **2** at 4-position should be regarded as a unique example. Although it can be considered that the carbonyl group of the side chain of **2** influences the direction of cyclization, the mechanism is not clear.

Cyclization of 3-(2-Ethoxycarbonylindol-3-yl)alkanoic Acids: Synthesis of 1

Cyclization of the compounds having a substituent at 2-position was attempted to avoid cyclization at 2-position. Although such an attempt has already been made, using 2-acetylindol-3-ylpropionic acid,[5b] 2-carboxy-3-(2-methylindol-3-yl)propionic acid,[8] and 1-acetyl-2-ethoxyindol-3-ylsuccinic anhydride,[9] cyclization to the 4-position did not take place in any case of these compounds. We therefore chose the 2-ethoxycarbonylindole compound as a synthetic key intermediate, because introduction of an ester function at 2-position protects 2-position from cyclization and decreases the susceptibility of the indole ring to acidic treatment, including especially Friedel–Crafts reaction.



6a: R=H, n=3
6b: R=OCH_3, n=3
6c: R=H, n=4
6d: R=H, n=5

7a: R_1=H, R_2=C_2H_5, n=2
7b: R_1=H, R_2=H, n=2
7c: R_1=OCH_3, R_2=H, n=2
7d: R_1=H, R_2=H, n=3
7e: R_1=H, R_2=H, n=4

8a: R=H, n=2
8b: R=OCH_3, n=2
8c: R=OH, n=2
8d: R=$OCH_2C_6H_5$, n=2
8e: R=H, n=3

Chart 3

Phenylhydrazones (**6a**, **6b**, **6c**, and **6d**) were obtained in a good yield by the Japp-Klingemann reaction[10] of corresponding 2-ethoxycarbonylcycloalkanones with benzenediazonium salts. These were mixture of *E*- and *Z*-forms, but used in the next reaction without separation. Manske and Robinson[11] had obtained a diester (**7a**) by the Fischer indolization of crude **6a** with sulfuric acid in ethanol. By the use of zinc chloride as a condensation agent in acetic acid, promising monoester (**7b**, **7c**, **7d**, and **7e**), which were suitable for the next cyclization, were obtained in respective overall yield of 65, 42, 30, and 9%[12] (Chart 3).

7b was derived to its acid chloride with thionyl chloride and submitted to the Friedel-Crafts reaction with aluminum chloride in dichloroethane.[13] The crude product thereby obtained was purified by silica gel chromatography and the objective 2-ethoxycarbonyl-5-oxo-1,3,4,5-tetrahydrobenz[*c*,*d*]indole (**8a**) was obtained as yellow needles in 24% yield.

7) S. Ohki and T. Nagasaka, *Chem. Pharm. Bull.* (Tokyo), **19**, 545 (1971).
8) H. Plieninger, *Chem. Ber.*, **86**, 404 (1953).
9) H. Plieninger and D. Wild, *Chem. Ber.*, **99**, 3063 (1966).
10) R.R. Philips, "Organic Reactions," Vol. 10, ed. by R. Adams, John Wiley, and Sons, Inc., New York, 1959, pp. 143—178; B. Robinson, *Chem. Rev.*, **63**, 373 (1963); *idem*, *ibid.*, **69**, 227 (1969).
11) R.H. Manske and R. Robinson, *J. Chem. Soc.*, **1927**, 240.
12) Saponification of **7a** with 1 molar equivalent of a base (NaOH) gave only ethyl 3-(2-carboxyindol-3-yl)-propionate.
13) When nitromethane or carbon disulfide was used in place of dichloroethane, **8a** could not be obtained.

Hydrolysis of **8a** with alkali and decarboxylation yielded Uhle's ketone (**1a**) as crystals melting at 165°.

By the same method, **8b** and **8c** were obtained from **7c**. Under the condition of stirring for 13 hr at room temperature, **8c** was obtained in 66% yield but a reaction for 2 hr gave **8b** in 70% yield.[14] Methylation of **8c** to **8b** or its benzylation to **8d** did not occur in a favorable yield.[15]

By the same method, a compound with a new skeleton, 2-ethoxycarbonyl-6(1*H*)-oxo-3,4,5,6-tetrahydrocyclohept[*c*,*d*]indole (**8e**) was obtained in 73% yield from **7d**. From the comparison of cyclization of **7b** and **7d**, it was found that the formation of a 7-membered ring is easier than that of a 6-membered ring in the cyclization from 3- to 4-position of the indole ring. Hydrolysis and decarboxylation of **8e** afforded **1b** in 84% yield.

As described above, we obtained the monoester (**7**) and hereby succeeded in the synthesis of **1** by the Friedel–Crafts reaction of **7** in a comparatively good yield. Compared with former methods,[3] this is a convenient synthetic method with an advantage of a few steps from easily available starting materials.

The Friedel–Crafts reaction of **7e** failed to induce the objective intramolecular cyclization to the 4-position and gave only a small amount of a product assumed to be a trimer which showed a parent peak at *m/e* 811 in its mass spectrum.

Reaction of Cycloalkanon[*c*,*d*]indoles

Some reactions of cycloalkanon[*c*,*d*]indoles (**1** and **8**), which can easily be synthesized, were then carried out. Uhle's ketone (**1a**) is known to be unstable and easily undergoes isomerization to a naphthalenoid system.[3] The ethoxycarbonyl group in **8** may be expected to control this isomerization.

1) Syntheses of Azepino- (**10c**) and Azocino-indolones (**10d**): In order to derive **8** to pharmacological active compounds, syntheses of azepino-[16] (**10c**) and azocino-indolones[17] (**10d**) by the Beckmann rearrangement were carried out. The Beckmann rearrangement of oximes (**9a** and **9b**), obtained in high yields from **8a** and **8e**, with polyphosphoric acid (PPA)[18] gave lactams (**10a** and **10b**) in 45% and 61% yield, respectively (Chart 4). Their nuclear magnetic resonance (NMR) spectra (in d_6-dimethyl sulfoxide) showed signals at δ 2.72 and 2.25 for the methylene protons adjacent to the carbonyl group,[19] respectively, and a signal for one aromatic proton, shifted to a higher magnetic field, at δ 6.65 and 6.67, respectively. As these shifted signals were not seen in the starting ketones (**8a** and **8e**), this fact indicates that the amino group is adjacent to the aromatic ring. The structures of 2-ethoxycarbonyl-5(1*H*)-oxo-3,4,5,6-tetrahydroazepino[4,3,2-*c*,*d*]indole for **10a** and 2-ethoxycarbonyl-6-oxo-1,-3,4,5,6,7-hexahydroazocino[4,3,2-*c*,*d*]indole for **10b** can be suggested. For the confirmation of these structures, **10a** and **10b** were saponified and then decarboxylated to give 5(1*H*)-oxo-3,4,5,6-tetrahydroazepino[4,3,2-*c*,*d*]indole (**10c**) and 6-oxo-1,3,4,5,6,7-hexahydroazocino-[4,3,2-*c*,*d*]indole (**10d**) in 50% and 55% yield, respectively. **10c** is identical with the known

14) The yield of **8b** and **8c** varies with the reaction scale and the amount of aluminum chloride. Contamination of **8b** in **8c**, or *vice versa*, sometimes cannot be avoided.

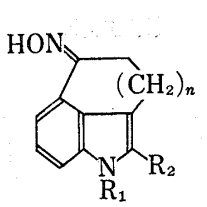
15) Difficulty of alkylation of **8c** might be due to the strong intramolecular hydrogen bonding of the hydroxyl and carbonyl groups. The *Rf* value [thin-layer chromatography (TLC)] of **8c** is larger than that of **8b**.

16) Some azepinoindoles having pharmacological activity in the central nervous system are known: J.B. Hester, Jr., A.H. Tang, H.H. Keasling, and W. Veldkamp, *J. Med. Chem.*, **11**, 101 (1968).

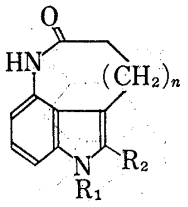
17) Azocinoindoles are little known: O. Yonemitsu, P. Cerutti, and B. Witkop, *J. Am. Chem. Soc.*, **88**, 3941 (1966); T. Kobayashi, T.F. Spande, H. Aoyagi, and B. Witkop, *J. Med. Chem.*, **12**, 636 (1969).

18) The same reaction of **9a** and **9b** with thionyl chloride gave only impure amorphous products. See ref. 3*p* for the Beckmann rearrangement with thionyl chloride.

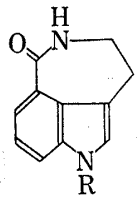
19) In general 1-tetralone oximes give mainly the lactams resulting from aryl migration by the usual Beckmann rearrangement (PPA) and chemical shifts of methylene protons adjacent to the carbonyl group of lactams are in δ 2.2—2.9 (in $CDCl_3$); see P.T. Lansbury and N.R. Mancuso, *J. Am. Chem. Soc.*, **88**, 1205 (1966).



9a: R_1=H, R_2=$COOC_2H_5$, n=1
9b: R_1=H, R_2=$COOC_2H_5$, n=2
9c: R_1=$COCH_3$, R_2=H, n=1
9d: R_1=Ts, R_2=H, n=1
9e: R_1=$COCH_3$, R_2=H, n=2



10a: R_1=H, R_2=$COOC_2H_5$, n=1
10b: R_1=H, R_2=$COOC_2H_5$, n=2
10c: R_1=R_2=H, n=1
10d: R_1=R_2=H, n=2
10e: R_1=$COCH_3$, R_2=H, n=2



11a: R=$COCH_3$
11b: R=Ts
11c: R=H

Ts=CH_3-  -SO_2-

Chart 4

compound in the melting point and spectroscopic data (infrared and ultraviolet spectra), which was derived from diethyl (4-aminoindol-3-yl)methylmalonate by Hester.[20]

On the other hand, Bowman and others[3p] obtained lactams (**11a** and **11b**) resulting from alkyl migration by the Beckmann rearrangement of the oximes (**9c** and **9d**) with thionyl chloride and derived **11a** to 6(1*H*)-oxo-3,4,5,6-tetrahydroazepino[5,4,3-*c*,*d*]indole (**11c**), an isomer of **10c**. The difference in the behavior of our and their compounds must be elucidated by further examination.[21]

2) Attemted Introduction of Nitrogen Function in α-Position of Ketones: We then attempted to introduce an amino group in α-position of the carbonyl group in **8** for derivation to lysergic acid derivatives. Bromination of **8a** and **8e** with pyridinium hydrobromide perbromide in acetic acid gave **12a** and **12b** in respective yields of 76% and 95% (Chart 5). Presence of bromine in the α-position of the carbonyl was confirmed from their NMR spectra. Substitution reaction of the bromine atom of **12a** with methylaminoacetone ethylene ketal[3h] was attempted but ended only in the elimination of hydrogen bromide to give 2-ethoxycarbonyl-1,5-dihydro-5-oxobenz[*c*,*d*]indole (**13**). The reaction of methylaminoacetone ethylene ketal in a sealed tube with 4-bromo-2-ethoxycarbonyl-5-hydroxyl-1,3,4,5-tetrahydrobenz-[*c*,*d*]indole (**14**), prepared by the reduction of **12a** with sodium borohydride, gave the ketone (**8a**) in 38% yield and failed to substitute the bromine atom with an amino group.[22]

Stoll, *et al.*[3d] had reported the synthesis of 4-(3-ethoxycarbonyl-5-oxo-2-pyrrolin-1-yl)-5-oxo-1,3,4,5-tetrahydrobenz[*c*,*d*]indole (**15a**) through nitrosation of **1a** with potassium *tert*-

20) J.B. Hester, Jr., *J. Org. Chem.*, **32**, 4095 (1967).

21) When the oxime (**9e**), an analog of **9c**, was submitted to the Beckmann rearrangement with thionyl chloride, the lactam (**10e**) resulting from aryl migration was obtained as a sole product. Saponification of **10e** gave **10d**, which was identical with the compound previously obtained from **10b**. It should be considered that some factors (such as ring size of benzcycloalkanones, strain of transition state intermediates, stereochemistry and isomerization of oximes, effect of substituents in the aromatic ring, and rearrangement agents) influence the rearrangement; L.G. Donaruma and W.Z. Heldt, "Organic Reactions," Vol. 11, ed. by R. Adams, John Wiley and Sons, Inc., New York, 1960, pp 1—156; P.A.S. Smith, "Molecular Rearrangement," ed. by P. de Mayo, Interscience Publishers, New York, 1963, Chapter 8; A.L.J. Beckwith, "Chemistry of Amides," ed. by J. Zabicky, Interscience Publishers, 1970, pp. 73—185; see also ref. 19.

22) It is reported that the reaction of 2-bromo-1,2,3,4-tetrahydro-1-naphthol (*trans*) with aliphatic amines or with alcoholic potassium hydroxide gave 2-alkylamino-1,2,3,4-tetrahydro-1-naphthols in a good yield [J.F. Lontz, US Patent, 2654759 (1953); *Chem. Abstr.*, **48**, 10774 (1954)] or 1,2-epoxy-1,2,3,4-tetrahydronaphthalene quantitatively [F. Strauss and A. Rohrbadher, *Chem. Ber.*, **54B**, 40 (1921)]. This result suggests that the stereochemistry of bromine and hydroxyl of this bromohydrin (**13**) should be *cis*, because the elimination of hydrogen bromide is presumably predominant in the case of *cis*; see P.D. Bartlett, *J. Am. Chem. Soc.*, **57**, 224 (1935).

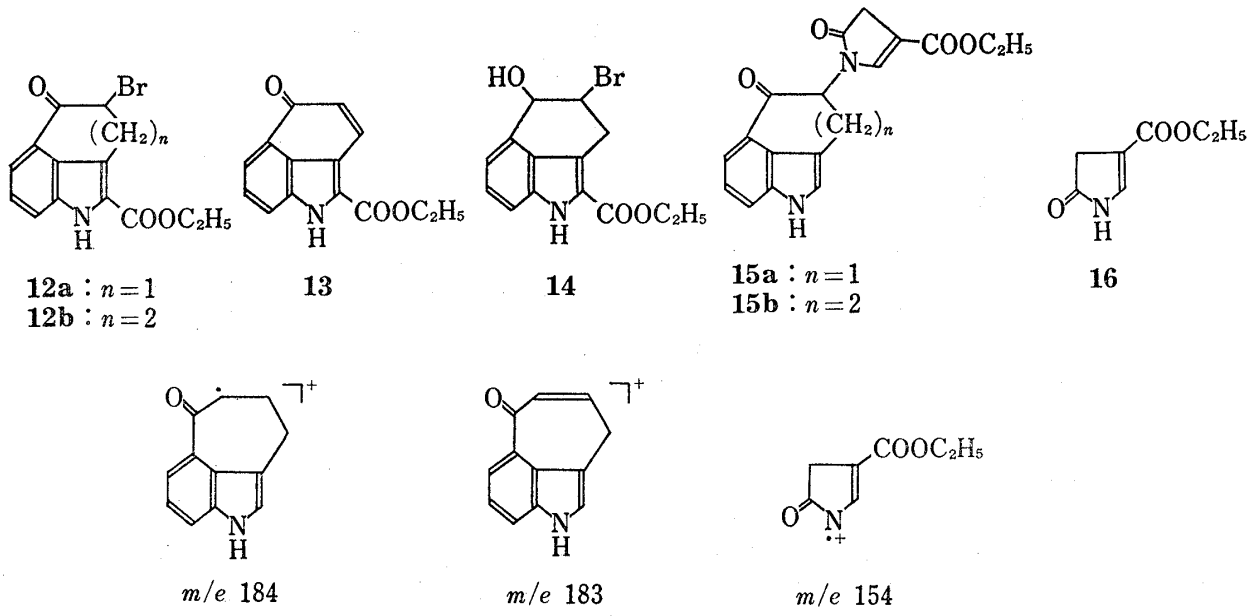


Chart 5

butoxide and isoamyl nitrite, reduction with zinc and acetic acid to amine, condensation with formylsuccinate, and finally cyclization with potassium *tert*-butoxide in *tert*-butanol. This reaction should be noteworthy as a synthetic example that the nitrogen of a heterocyclic compound was introduced into α-position of the carbonyl. They presented at first 9-ethoxycarbonylergol-6,9-diene-8-carboxylic acid (having a skeleton of ergoline) as the structure of **15a**[3d] in 1950, but corrected its structure from the chemical character[3d] in 1952. As we can prepare **15b**, an analog of **15a**, from **1b** by the same method, we report the confirmation of the structure of **15b** by analytical, chemical, and spectroscopic method. Namely, **15b** is unreactive with 2,4-dinitrophenylhydrazone, as **15a** is, because of the steric hindrance of pyrrolinone, but the mass spectrum exhibits M^+(*m/e* 338) and fragmented ion peaks at *m/e* 184, 183, and 154, which may be considered to be those shown above (Chart 5). (These fragments were confirmed by high-resolution mass spectra). NMR spectrum of **15b** (in $CDCl_3$) shows a signal at δ 3.47 (2H, singlet) as methylene protons (4-position) of 2-pyrrolinone. This result agrees with the fact that the NMR spectrum of 3-ethoxycarbonyl-5-oxo-2-pyrroline (**16**) (in $CDCl_3$) shows a signal at δ 3.40 (2H, singlet) as methylene protons.[23]

As mentioned above, we examined some reactions of cycloalkanon[*c*,*d*]indoles (**1** and **8**) and were able to synthesize azepinoindolone (**10c**), azocinoindolone (**10d**), and pyrrolinonylindole (**15b**). However, a route to the skeleton of lysergic acid derivatives must await future investigations.

Experimental[24]

3-(1-Acetylindol-3-yl)propionic Acid (4b)——To a suspension of indol-3-ylpropionic acid (**4a**) (4.0 g, 21 mmol) in benzene (200 ml), $(CF_3CO)_2O$ (22 g, 100 mmol) was added under cooling. After the mixture was stirred at room temperature for 10 min, *tert*-BuOH (40 ml) was added and the whole mixture was stirred

23) J. Bordner and H. Rapoport, *J. Org. Chem.*, **30**, 3824 (1965).

24) Melting points were determined on a micro-melting point apparatus (Yanagimoto) and are uncorrected. NMR spectra were obtained on a JNM-4H-100 spectrometer (Japan Electron Optics Laboratory Co.) and the chemical shifts are reported in ppm from TMS as an internal standard. The following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, b=broad, Infrared (IR) spectra were obtained on a EPI-GII spectrophotometer (Hitachi). Ultraviolet (UV) spectra were obtained on a EPS-II spectrophotometer (Hitachi). Mass spectra (MS) were determined on a RMU-7L spectrometer (Hitachi).

at the same temperature for 30 min. After removal of excess $(CF_3CO)_2O$ under reduced pressure, the benzene solution was washed with cold 10% NaOH and H_2O, and dried over Na_2SO_4. The solvent was evaporated to give colorless crystals (crude *tert*-butyl indol-3-ylpropionate). Yield, 4.49 g (87%). NMR ($CDCl_3$) δ: 1.42 [9H, s, $C(C\underline{H}_3)_3$], 2.60 (2H, m, $C\underline{H}_2CO$), 3.06 (2H, m, $C\underline{H}_2CH_2CO$), 7.00 (1H, s, C_2–H), 7.05—7.50 (3H, m, aromatic protons), 7.65 (1H, d-d, C_4–H), 8.00 (1H, b, N<u>H</u>).

The solution of this *tert*-butyl ester in dry dimethylformamide (DMF; 10 ml) was added gradually to a solution of NaH (4.4 g, 180 mmol) in dry DMF (30 ml) and the mixture was stirred at 40—50° for 1 hr. CH_3COCl (15 g, 190 mmol) was added dropwise to the mixture during 20 min under cooling, and the whole mixture was stirred at room temperature for 1 hr. After excess NaH was decomposed with a small quantity of EtOH and H_2O with caution, the reaction mixture was extracted with EtOAc (50 ml × 5). The extract was washed with H_2O, dried over Na_2SO_4, and the solvent was evaporated to a brown viscous oil (crude *tert*-butyl 1-acetylindol-3-ylpropionate). Yield, 4.9 g. IR ($CHCl_3$) ν_{max} cm^{-1}: 1710 (C=O), no NH band.

When the solution of this material in CF_3CO_2H (10 ml) was allowed to stand at room temperature for 4 hr, a precipitate appeared, which was collected by filtration and washed with ether. Its recrystallization from $CHCl_3$ gave colorless crystals, mp 159—160°. Yield, 2.0 g (overall yield from **4a**; 41%). MS *m/e*: 231.0876 (M^+) (Calcd. for $C_{13}H_{13}NO_3$: 231.0895), 189 ($M^+ - CH_2{=}C{=}O$), 130 (base). IR ν_{max} cm^{-1}: 3000—2200 (CO<u>O</u>H), 1730 (acetyl C=O), 1700 (acid C=O). NMR (CF_3CO_2H) δ: 2.78 (3H, s, $COC\underline{H}_3$), 2.85—3.30 (4H, m, $C\underline{H}_2C\underline{H}_2CO$), 7.20—7.70 (3H, m, aromatic protons), 8.40 (1H, m, C_7–H).

General Procedure for Phenylhydrazones (6)——A typical procedure is described for phenylhydrazone of ethyl hydrogen 2-oxo-adipate (**6a**): Benzenediazonium chloride solution was prepared by mixing aniline (3.8 g, 41 mmol), conc. HCl (10 ml, 114 mmol), ice (20 g), and $NaNO_2$ (2.8 g, 41 mmol) under cooling at 0°. Alkaline solution was prepared by dissolving KOH (7.2 g, 130 mmol) in H_2O (80 ml) and cooled in an ice bath. 2-Ethoxycarbonylcyclopentanone (6.3 g, 40 mmol) was shaken vigorously with one-half of the above alkaline solution (40 ml) in a separator and the unreacted ketone was extracted with cold benzene (10 ml). The alkaline layer was poured on ice (40 g) and then one-half of the above diazonium solution (17 ml) was added. After the mixture was stirred for 1 min, the remaining half of the alkaline solution (40 ml), which was shaken with the above benzene extract, and the remaining half of the diazonium solution (17 ml) were added. After stirring for 5 min under ice cooling, conc. HCl (11 ml) was added to the reaction mixture, giving a red oil, which solidified on standing. Aqueous layer was removed by decantation and the solid was washed several times with H_2O and dried. Yield, 9.21 g (82%), mp 97—100°. Recrystallization from EtOH–H_2O gave orange crystals, mp 106°. IR ν_{max}^{KBr} cm^{-1}: 1720 (C=O), 1680 (C=N).

Crude phenylhydrazones prepared by this method are mixture of *E*- and *Z*-forms, which are revealed by TLC and NMR spectrum. When a solution of crude mixture in $CHCl_3$ is allowed to stand at room temperature for several hours, the *Z*-form isomerizes quantitatively to *E*-form having an intramolecular hydrogen bond, which can be isolated. Crude phenylhydrazones (**6**) were used for the synthesis of **7** without isomerization and purification.

General Procedure for 2-Ethoxycarbonylindol-3-ylalkanoic Acids (7)——A typical procedure is described for 3-(2-ethoxycarbonylindol-3-yl)propionic acid (**7b**): A mixture of the crude hydrazone (**6a**) (80 g, 286 mmol), $ZnCl_2$ (40 g, 295 mmol), and glacial AcOH (200 ml) was heated for 1 hr under atmospheric pressure with removal of AcOH (150 ml). After the reaction mixture was poured on ice, the solid formed was collected by filtration and washed with H_2O. When a solution of this solid in $CHCl_3$ (150 ml) was shaken vigorously with H_2O (100 ml) in a separator, white crystals appeared gradually, which were collected by filtration and washed with a small amount of $CHCl_3$. Yield, 56 g, mp 194°. The $CHCl_3$ filtrate was washed with H_2O, dried over Na_2SO_4, concentrated, and allowed to stand in a refrigerator, and additional crystals (3 g), mp 192°, were obtained. Total yield, 59 g (65% overall yield from aniline). Recrystallization from EtOH gave colorless plates, mp 200—202°. *Anal.* Calcd. for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79; N, 5.36. Found: C, 64.66; H, 5.85; N, 5.45. IR ν_{max}^{KBr} cm^{-1}: 3500 (NH), 1720 (ester C=O), 1700 (acid C=O). NMR [$(CD_3)_2CO$] δ: 1.38 (3H, t, $CH_2C\underline{H}_3$), 2.65 (2H, t, $C\underline{H}_2CO$), 3.42 (2H, t, $C\underline{H}_2CH_2CO$), 4.38 (2H, q, $OC\underline{H}_2CH_3$), 7.00—7.85 (4H, m, aromatic protons), 10.60 (1H, b.s, COO<u>H</u>).

3-(2-Ethoxycarbonyl-5-methoxyindol-3-yl)propionic acid (**7c**) was obtained in 42% overall yield from *p*-anisidine as yellow prisms (from $CHCl_3$–EtOH), mp 191°. *Anal.* Calcd. for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88; N, 4.81. Found: C, 61.78; H, 6.05; N, 4.55. IR ν_{max}^{KBr} cm^{-1}: 3310 (NH), 1710 (ester C=O), 1690 (acid C=O).

4-(2-Ethoxycarbonylindol-3-yl)butylic acid (**7d**) was obtained in 30% overall yield as colorless prisms (from benzene), mp 135°. *Anal.* Calcd. for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.11; H, 6.12; N, 5.07. IR ν_{max}^{KBr} cm^{-1}: 1720 (ester C=O), 1680 (acid C=O).

5-(2-Ethoxycarbonylindol-3-yl)valeric acid (**7e**) was obtained in 9% overall yield as brown prisms (from benzene), mp 146—147°. *Anal.* Calcd. for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.85. Found: C, 66.48; H, 6.83; N, 4.53. NMR ($CDCl_3$) δ: 1.46 (3H, t, $CH_2C\underline{H}_3$), 1.74 (4H, m, $CH_2C\underline{H}_2C\underline{H}_2CH_2$), 2.39 (2H, m, $CH_2C\underline{H}_2$-CO), 3.12 [2H, m, $C\underline{H}_2(CH_2)_2CH_2CO$], 4.40 (2H, q, $OC\underline{H}_2CH_3$), 7.22 (3H, m, aromatic protons), 7.66 (1H, d, C_7–H), 8.91 (1H, s, N<u>H</u>), 9.95 (1H, b, COO<u>H</u>).

Ethyl 3-(2-ethoxycarbonylindol-3-yl)propionate (**7a**) was obtained in 74% overall yield by refluxing a solution of **6a** in EtOH with conc. H_2SO_4 for 2.5 hr. Colorless prisms (from benzene), mp 93—94° (reported[11] mp 95—96°). *Anal.* Calcd. for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.66; H, 6.68; N, 4.67.

UV λ_{max}^{EtOH} nm: 230, 297. IR ν_{max}^{KBr} cm^{-1}: 1740 (ester C=O), 1700 (conjugated ester C=O).

General Procedure for the Friedel-Crafts Reactions——A typical procedure is described for 2-ethoxycarbonyl-5-oxo-1,3,4,5-tetrahydrobenz[*c,d*]indole (**8a**): When a suspension of **7b** (620 mg, 2.4 mmol) and $SOCl_2$ (900 mg, 7.5 mmol) in $CHCl_3$ (10 ml) was warmed on a steam bath, **7b** dissolved with a bubble of gas within 30 min. Evaporation of the solvent under reduced pressure gave the acid chloride (white needles), which was stirred with $AlCl_3$ (1.3 g, 10 mmol) in dichloroethane (50 ml) at room temperature for 2 hr and then at 60° for 30 min. The reaction mixture was poured into conc. HCl (1 ml) containing ice (200 g), and the organic layer was separated. Aqueous layer and the solid were extracted several times with $CHCl_3$. Combined $CHCl_3$ layer was washed with H_2O, dried over Na_2SO_4, and the solvent was evaporated to a yellow viscous oil (300 mg), which was purified by chromatography over silica gel eluted with $CHCl_3$. Yellow crystals (from EtOH), mp 189—191°, were obtained. Yield, 142 mg (24%). *Anal.* Calcd. for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76. Found: C, 69.40; H, 5.47; N, 5.71. IR ν_{max}^{KBr} cm^{-1}: 3250 (NH), 1705 (ester C=O), 1663 (ketone C=O). UV λ_{max}^{EtOH} nm: 262, 272, 338. NMR ($CDCl_3$) δ: 1.41 (3H, t, $CH_2C\underline{H}_3$), 2.97 (2H, t, $CH_2C\underline{H}_2CO$), 3.50 (2H, t, $C\underline{H}_2CH_2CO$), 4.43 (2H, q, $OC\underline{H}_2CH_3$), 7.30—7.70 (3H, m, aromatic protons), 9.11 (1H, b.s, NH).

2-Ethoxycarbonyl-6-methoxy-5-oxo-1,3,4,5-tetrahydrobenz[*c,d*]indole (**8b**) was obtained from **7c** in 70% yield by a short reaction time (2 hr) at room temperature. Yellow prisms (from EtOH), mp 197—200°. *Anal.* Calcd. for $C_{15}H_{15}NO_4$: C, 65.92; H, 5.53; N, 5.13. Found: C, 66.03; H, 5.69; N, 4.98. IR ν_{max}^{KBr} cm^{-1}: 3240 (NH), 1710 (ester C=O), 1650 (ketone C=O). NMR ($CDCl_3$) δ: 1.45 (3H, t, $CH_2C\underline{H}_3$), 2.94 (2H, t, $C\underline{H}_2CO$), 3.47 (2H, t, $C\underline{H}_2CH_2CO$), 4.00 (3H, s, $OC\underline{H}_3$), 4.45 (2H, q, $OC\underline{H}_2CH_3$), 7.10 (1H, d, C_7–$\underline{H}$), 7.58 (1H, d, C_8–$\underline{H}$), 8.95 (1H, b.s, N$\underline{H}$).

2-Ethoxycarbonyl-6-hydroxy-5-oxo-1,3,4,5-tetrahydrobenz[*c,d*]indole (**8c**) was obtained from **7c** in 66% yield by a long reaction time (13 hr) at room temperature. Yellow prisms (from EtOH), mp 208°. *Anal.* Calcd. for $C_{14}H_{13}NO_4$: C, 64.86, H, 5.05; N, 5.40. Found: C, 64.57; H, 5.28; N, 5.15. IR ν_{max}^{KBr} cm^{-1}: 3320 (NH), 1695 (ester C=O), 1640 (ketone C=O). NMR ($CDCl_3$) δ: 1.46 (3H, t, $CH_2C\underline{H}_3$), 2.95 (2H, t, $C\underline{H}_2CO$), 3.47 (2H, t, $C\underline{H}_2CH_2CO$), 4.45 (2H, q, $OC\underline{H}_2CH_3$), 6.97 (1H, d, C_7–$\underline{H}$), 7.54 (1H, d, C_8–$\underline{H}$), 8.95 (1H, b.s, N$\underline{H}$).

8b appeared as a blue spot (Rf=0.2) on a TLC plate (silica gel–$CHCl_3$) by a fluorescent lamp, while **8c** appeared green (Rf=0.6). **8b** and **8c** were easily separated by column chromatography (silica gel) by elution with $CHCl_3$.

2-Ethoxycarbonyl-6(1*H*)-oxo-3,4,5,6-tetrahydrocyclohept[*c,d*]indole (**8e**) was obtained from **7d** in 73% yield. Pale yellow prisms (from EtOH), mp 154—156°. *Anal.* Calcd. for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found: C, 69.96; H, 5.98; N, 5.74. IR ν_{max}^{KBr} cm^{-1}: 3350 (NH), 1695 (ester C=O), 1665 (ketone C=O). NMR ($CDCl_3$) δ: 1.43 (3H, t, $CH_2C\underline{H}_3$), 2.20 (2H, m, $CH_2C\underline{H}_2CH_2$), 3.05 (2H, m, $C\underline{H}_2CO$), 3.40 (2H, m, $C\underline{H}_2CH_2CH_2CO$), 4.45 (2H, q, $OC\underline{H}_2CH_3$), 7.30—7.72 (2H, m, aromatic protons), 8.04 (1H, d, C_7- or C_9–$\underline{H}$), 9.19 (1H, b.s, N$\underline{H}$).

4-Acetyl-3-oxo-1,2,3,4-tetrahydrocyclopent[*b*]indole (**5b**) was obtained in 60% yield by the Friedel–Crafts reaction of **4b** and in 51% overall yield by acetylation (Ac_2O and AcONa) of **5a**, which was prepared by cyclization of **4a** with PPA.[5a] Yellow needles, mp 149—150°. *Anal.* Calcd. for $C_{13}H_{11}NO_2$: C, 73.22; H, 5.20; N, 6.57. Found: C, 73.18; H, 5.42; N, 6.64. NMR ($CDCl_3$) δ: 2.91 (3H, s, $COC\underline{H}_3$), 3.06 (4H, s, $C\underline{H}_2C\underline{H}_2CO$), 7.30—7.75 (3H, m, aromatic protons), 8.61 (1H, d, C_5–$\underline{H}$).

6-Benzyloxy-2-ethoxycarbonyl-5-oxo-1,3,4,5-tetrahydrobenz[*c,d*]indole (**8d**)——A mixture of **8c** (259 mg, 1 mmol), K_2CO_3 (170 mg, 1.2 mmol), $PhCH_2Cl$ (160 mg, 1.2 mmol), and dry DMF (5 ml) was stirred at room temperature for 1 hr and then at 120—130° for 30 min. This reaction mixture was poured into H_2O and extracted with ether (30 ml×5). The extract was washed with H_2O, dried over Na_2SO_4, and ether was evaporated to a brown viscous oil (270 mg), which was purified by chromatography over silica gel eluted with $CHCl_3$. The first fraction gave the starting material (150 mg) and the second fraction gave **8d** as yellow needles (from EtOH), mp 192—194°. Yield, 50 mg (14%). *Anal.* Calcd. for $C_{21}H_{19}NO_4$: C, 72.19; H, 5.48; N, 4.01. Found: C, 72.27; H, 5.77; N, 3.88. IR ν_{max}^{KBr} cm^{-1}: 3300 (NH), 1660 (C=O). NMR ($CDCl_3$) δ: 1.45 (3H, t, $CH_2C\underline{H}_3$), 2.96 (2H, t, $C\underline{H}_2CO$), 3.50 (2H, t, $C\underline{H}_2CH_2CO$), 4.45 (2H, q. $OC\underline{H}_2CH_3$), 5.30 (2H, s, $PhC\underline{H}_2$), 7.14 (1H, d, C_7–$\underline{H}$), 7.25—7.70 (6H, m, aromatic protons), 8.95 (1H, b.s, N$\underline{H}$).

5-Oxo-1,3,4,5-tetrahydrobenz[*c,d*]indole (**1a**)——A mixture of **8a** (265 mg, 1.1 mmol), KOH (130 mg, 2.3 mmol), and 95% EtOH (15 ml) was stirred at room temperature for 23 hr. After evaporation of EtOH, the residue was dissolved in H_2O (30 ml), acidified with 5% HCl, and extracted with EtOAc (the insoluble material was removed by filtration). The extract was washed with H_2O, dried over Na_2SO_4, and EtOAc was evaporated to give yellow crystals (65 mg), which were heated at 220—230° for 20 min with a small amount of Cu powder and quinoline (2 ml). When cooled, the mixture was poured into conc. HCl containing ice and extracted with ether. The extract was washed with H_2O, dried over $CaCl_2$, and ether was evaporated to give yellow crystals (15 mg), which were purified by chromatography over silica gel eluted with $CHCl_3$. Yellow needles (10 mg), mp 160—165° (reported[3h] mp 165—166°). IR ($CHCl_3$) ν_{max} cm^{-1}: 3470 (NH), 1680 (C=O), 1620. (superimposable with the IR spectrum of **1a** in lit.[3h]). NMR ($CDCl_3$) δ: 2.92 (2H, m, $C\underline{H}_2CO$), 3.28 (2H, m, $C\underline{H}_2CH_2CO$), 7.10 (1H, s, C_2–$\underline{H}$), 7.3—7.7 (3H, m, aromatic protons), 8.30 (1H, b.s, N$\underline{H}$).

6(1*H*)-oxo-3,4,5,6-tetrahydrocyclohept[*c,d*]indole (**1b**)——A mixture of **8e** (1.0 g, 3.9 mmol), KOH (330 mg, 5.9 mmol), and 95% EtOH (50 ml) was refluxed for 3 hr. After evaporation of the solvent, the residue was dissolved in a small amount of H_2O and acidified with 5% HCl to give a white solid. After removal of

H_2O under reduced pressure, the residual solid was heated at 220—230° for 1 hr with Cu powder (300 mg) and quinoline (8 ml). By the same work-up as above, yellow crystals (from $CHCl_3$), mp 176—177°, were obtained. Yield, 605 mg (84%). *Anal.* Calcd. for $C_{12}H_{11}NO$: C, 77.81; H, 5.99; N, 7.56. Found: C, 77.52; H, 6.10; N, 7.49. IR ($CHCl_3$) ν_{max} cm^{-1}: 3470 (NH), 1665 (C=O), 1615. NMR ($CDCl_3$) δ: 2.15 (2H, m, $CH_2C\underline{H}_2CH_2$), 3.10 (4H, m, $C\underline{H}_2CH_2C\underline{H}_2CO$), 7.19 (1H, s, C_2–H), 7.17—7.34 (1H, m, C_8–H), 7.58 (1H, d, C_9–H), 7.95 (1H, d, C_7–H), 8.50 (1H, b.s, NH).

General Procedure for Oximes (9)——A typical procedure is described for the oxime (**9a**) of 2-ethoxycarbonyl-5-oxo-1,3,4,5-tetrahydrobenz[*c,d*]indole (**8a**): A mixture of **8a** (500 mg, 2.05 mmol), $NH_2OH\cdot HCl$ (240 mg, 3.45 mmol), and K_2CO_3 (140 mg, 1 mmol) in 95% MeOH (30 ml) was refluxed for 3 hr. After evaporation of the solvent, the residue was washed with H_2O and dried. Yellow prisms, mp 200—207°, were obtained. Yield, 530 mg (100%). Recrystallization from EtOH gave a sample of mp 214—216° for analysis. *Anal.* Calcd. for $C_{14}H_{14}N_2O_3$: C, 65.10; H, 5.46; N, 10.85. Found: C, 64.85; H, 5.41; N, 10.89. NMR [$(CD_3)_2SO$] δ: 1.37 (3H, t, $CH_2C\underline{H}_3$), 3.22 (4H, m, $C\underline{H}_2C\underline{H}_2$), 4.35 (2H, q, $OC\underline{H}_2CH_3$), 7.37 (3H, s, aromatic protons), 11.32 (1H, s), 11.39 (1H, b.s, N<u>H</u> or NO<u>H</u>).

Oxime (**9b**) of 2-ethoxycarbonyl-6-oxo-3,4,5,6-tetrahydro-1*H*-cyclohept[*c,d*]indole (**8e**) was obtained in 97% yield as yellow prisms (from EtOH), mp 226—227° (dec.). *Anal.* Calcd. for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N, 10.29. Found: C, 66.17; H, 5.98; N, 10.05. IR ν_{max}^{KBr} cm^{-1}: 3300 (NH and NOH), 1675 (C=N). NMR [$(CD_3)_2SO$] δ: 1.35 (3H, t, $CH_2C\underline{H}_3$), 1.90 (2H, m, $CH_2C\underline{H}_2CH_2$), 2.97—3.25 (4H, m, $C\underline{H}_2CH_2C\underline{H}_2$), 4.35 (2H, q, $OC\underline{H}_2CH_3$), 7.1—7.5 (3H, m, aromatic protons), 11.19 (1H, s), 11.63 (1H, s, N<u>H</u> or NO<u>H</u>).

Oxime (**9e**) was obtained in 63% yield from 1-acetyl-6-oxo-3,4,5,6-tetrahydro-1*H*-cyclohept[*c,d*]indole, which was prepared in 89% yield by acetylation of **1b** with Ac_2O and AcONa. **9e**: Yellow prisms (from EtOH), mp 188—192°. *Anal.* Calcd. for $C_{14}H_{14}N_2O_2$: C, 69.40; H, 5.83; N, 11.56. Found: C, 69.41; H, 5.83; N, 11.46. IR ν_{max}^{KBr} cm^{-1}: 3500 (NOH), 1710 (C=O). 1-Acetyl-6-oxo-3,4,5,6-tetrahydro-1*H*-cyclohept-[*c,d*]indole: Yellow prisms (from EtOH), mp 150—152°. *Anal.* Calcd. for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 73.87; H, 5.86; N, 5.97. IR ν_{max}^{KBr} cm^{-1}: 1700 (amide C=O), 1660 (ketone C=O). NMR ($CDCl_3$) δ: 2.10 (2H, m, $CH_2C\underline{H}_2CH_2$), 2.62 (3H, s, $COC\underline{H}_3$), 3.20 (4H, m, $C\underline{H}_2CH_2C\underline{H}_2$), 7.31 (1H, s, C_2–H), 7.40 (1H, t, C_8–H), 8.10 (1H, d, C_7– or C_9–H), 8.70 (1H, d, C_7– or C_9–H).

General Procedure for the Beckmann Rearrangements——A typical procedure is described for 2-ethoxycarbonyl-5-oxo-3,4,5,6-tetrahydro-1*H*-azepino[4,3,2-*c,d*]indole (**10a**): The oxime (**9a**) (500 mg, 1.9 mmol) was stirred with PPA (5 g) at 110—120° for 30 min. After saturated $NaHCO_3$ was added gradually to alkaline condition, the mixture was extracted with EtOAc (50 ml × 4). The extract was washed with H_2O, dried over Na_2SO_4, and the solvent was evaporated to give a yellow solid. Recrystallization from EtOH gave yellow prisms, mp 262—264°. Yield, 226 mg (45%). *Anal.* Calcd. for $C_{14}H_{14}N_2O_3\cdot 1/2C_2H_5OH$ (a half molecular EtOH was confirmed by NMR spectrum): C, 64.04; H, 6.09; N, 9.96. Found: C, 63.85; H, 5.94; N, 9.70. NMR [$(CD_3)_2SO$] δ: 1.37 (3H, t, $CH_2C\underline{H}_3$), 2.72 (2H, m, $C\underline{H}_2CO$), 3.33 (2H, m, $C\underline{H}_2CH_2CO$), 4.34 (2H, q, $OC\underline{H}_2CH_3$), 6.65 (1H, d-d, C_7–H), 7.30 (2H, m, aromatic protons). IR ν_{max}^{KBr} cm^{-1}: 3230, 3150, 3100, 1670 (ester C=O), 1640 (amide C=O).

2-Ethoxycarbonyl-6-oxo-1,3,4,5,6,7-hexahydro-azocino[4,3,2-*c,d*]indole (**10b**) was obtained from **9b** in 61% yield. Yellow prisms (from EtOH), mp 259—260°. *Anal.* Calcd. for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N, 10.29. Found: C, 66.01; H, 6.13; N, 10.28. IR ν_{max}^{KBr} cm^{-1}: 3330, 3180, 3080, 1715 (ester C=O), 1660 (amide C=O). NMR [$(CD_3)_2SO$] δ: 1.35 (3H, t, $CH_2C\underline{H}_3$), 1.85 (2H, m, $CH_2C\underline{H}_2CH_2$), 2.25 (2H, m, $C\underline{H}_2CO$), 4.34 (2H, q, $OC\underline{H}_2CH_3$), 6.67 (1H, d-d, C_8–H), 7.25 (2H, m, aromatic protons), 9.88 (1H, s, N<u>H</u>), 11.53 (1H, s, N<u>H</u>).

1-Acetyl-6-oxo-1,3,4,5,6,7-hexahydro-azocino[4,3,2-*c,d*]indole (**10e**) was obtained from **9e** in 50% yield by the method[3p] using $SOCl_2$. Brown needles (from acetone), mp 222—230°. *Anal.* Calcd. for $C_{14}H_{14}N_2O_2$: C, 69.40; H, 5.83; N, 11.56. Found: C, 69.81; H, 6.03; N, 11.87. IR ν_{max}^{KBr} cm^{-1}: 3200 (N<u>O</u>H), 1695 (C=O), 1675 (C=O). NMR [$(CD_3)_2SO$] δ: 2.5—3.0 (6H, m, $C\underline{H}_2C\underline{H}_2C\underline{H}_2$), 2.60 (3H, s, $COC\underline{H}_3$), 6.88 (1H, d-d, C_8–H), 7.26 (1H, t, C_9–H), 7.68 (1H, s, C_2–H), 8.17 (1H, d, C_{10}–H). UV λ_{max}^{EtOH} nm; 242, 275, 305, 313.

5-Oxo-3,4,5,6-tetrahydro-1*H*-azepino[4,3,2-*c,d*]indole (10c)——By the procedure described for **1b**, **10c** was obtained from **10a** in 50% yield as yellow needles (from acetone), mp 213—216° (reported[20] mp 213—214°). *Anal.* Calcd. for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.05. Found: C, 71.04; H, 5.31;. N, 1560. UV λ_{max}^{EtOH} nm: 231, 304. IR ν_{max}^{KBr} cm^{-1}: 3220 (NH), 1645 (amide C=O), 1620. NMR [$(CD_3)_2SO$] δ: 2.40 (2H, m, $C\underline{H}_2CO$), 2.70 (2H, m, $C\underline{H}_2CH_2CO$), 6.58 (1H, d-d, C_7–H), 6.95 (3H, m, aromatic protons).

6-Oxo-1,3,4,5,6,7-hexahydro-azocino[4,3,2-*c,d*]indole (10d)——**10d** was obtained from **10b** in 55% yield by the procedure described for **1b** and quantitatively by saponification of **10e**. Yellow prisms (from acetone), mp 274—281° (dec.). *Anal.* Calcd. for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 71.64; H, 6.30; N, 13.52. IR ν_{max}^{KBr} cm^{-1}: 3400, 3240, 3100, 3050, 1650 (C=O). NMR [$(CD_3)_2SO$] δ: 1.80 (2H, m, $CH_2C\underline{H}_2CH_2$), 2.25 (2H, m, $CH_2C\underline{H}_2CO$), 2.80 (2H, m, $C\underline{H}_2CH_2CH_2CO$), 6.58 (1H, d-d, C_8–H), 6.90—7.25 (3H, m, aromatic protons), 9.97 (1H, s, N<u>H</u>), 10.89 (1H, s, N<u>H</u>). UV λ_{max}^{EtOH} nm: 229, 296.

4-Bromo-2-ethoxycarbonyl-5-oxo-1,3,4,5-tetrahydrobenz[*c,d*]indole (12a)——To a solution of the ketone (**8a**) (210 mg, 0.86 mmol) in AcOH (4 ml), pyridinium hydrobromide perbromide (280 mg, 0.87 mmol) was added with stirring at room temperature. The reaction mixture was warmed at 50° for 10 min (HBr gas

bubbled and a precipitate appeared). When cooled, the solid was collected by filtration and washed with a small amount of AcOH to give yellow crystals (230 mg). The filtrate was poured into H_2O and the solid formed (40 mg) was collected. The combined cryatals were recrystallized from EtOH to yellow needles, mp 170° (dec.). Yield, 210 mg (76%). *Anal.* Calcd. for $C_{14}H_{12}BrNO_3$: C, 52.19; H, 3.75: N, 4.37. Found: C, 52.77; H, 3.82; N, 4.20. IR ν_{max}^{KBr} cm^{-1}: 1700 (ester C=O), 1650 (ketone C=O). UV λ_{max}^{EtOH} nm: 275, 360. NMR ($CDCl_3$) δ: 1.42 (3H, t, $CH_2C\underline{H}_3$), 3.99 (2H, d, $C\underline{H}_2CHBr$), 4.42 (2H, q, $OC\underline{H}_2CH_3$), 4.90 (1H, t, CH_2-$C\underline{H}Br$), 7.4—7.8 (3H, m, aromatic protons), 8.95 (1H, b.s, N$\underline{H}$).

5-Bromo-2-ethoxycarbonyl-6(1*H*)-oxo-3,4,5,6-tetrahydrocyclohept[*c*,*d*]indole (12b)——By the procedure described above, **12b** was obtained from **8e** in 95% yield. Yellow needles (from EtOH), mp 204—207° (dec.). *Anal.* Calcd. for $C_{15}H_{14}BrNO_3$: C, 53.59; H, 4.20; N, 4.17. Found: C, 53.65; H, 4.23; N, 4.18. IR ν_{max}^{KBr} cm^{-1}: 3310 (NH), 1690 (ester C=O), 1643 (ketone C=O). NMR [$(CD_3)_2SO$] δ: 1.40 (3H, t, $CH_2C\underline{H}_3$), 4.41 (2H, q, $OC\underline{H}_2CH_3$), 5.30 (1H, t, $CH_2C\underline{H}Br$), 7.3—8.0 (3H, m, aromatic protons).

Reaction of Bromide (12a) with Methylaminoacetone Ethylene Ketal[3h]——A solution of bromoketone (**12a**) (161 mg, 0.5 mmol) and methylaminoacetone ethylene ketal (200 mg, 1.5 mmol) in dry benzene (30 ml) was refluxed for 5 hr in N_2. Crystals were collected by filtration, washed with benzene, and dried. This was a mixture of yellow and white crystals (154 mg). Recrystallization from EtOH gave 2-ethoxycarbonyl-1,5-dihydro-5-oxobenz[*c*,*d*]indole (**13**) as orange prisms, mp 214—215° (dec.). Yield, 30 mg (25%). *Anal.* Calcd. for $C_{14}H_{11}NO_3$: C, 69.70; H, 4.59; N, 5.80. Found: C, 69.72; H, 4.51; N, 5.75. IR ν_{max}^{KBr} cm^{-1}: 1720 (ester C=O), 1630 (ketone C=O). UV λ_{max}^{EtOH} nm: 275, 286, 318, 375, 421. NMR [$(CD_3)_2SO$] δ: 1.42 (3H, t, $CH_2C\underline{H}_3$), 4.45 (2H, q, $OC\underline{H}_2CH_3$), 6.42 (1H, d, J=10 Hz, C_4-$\underline{H}$), 7.5—8.1 (4H, m, C_3-$\underline{H}$ and aromatic protons).

The mother liquor of recrystallization (EtOH) was evaporated to dryness and the residue was extracted with H_2O. The extract was washed with benzene and evaporated to give a solid (60 mg), which was recrystallized from EtOH–H_2O to give colorless needles (methylaminoacetone ethylene ketal hydrobromide), mp 159—161°. *Anal.* Calcd. for $C_6H_{13}NO_2 \cdot HBr$: C, 33.98; H, 6.65; N, 6.60. Found: C, 34.24; H, 6.91; N, 6.47.

Reduction of Bromoketone (12a) with Sodium Borohydride——A mixture of the bromoketone (**12a**) (200 mg, 0.62 mmol) and $NaBH_4$ (500 mg, 130 mmol) in EtOH (25 ml) was stirred at room temperature for 3 hr. After excess $NaBH_4$ was decomposed with 5% HCl (30 min), the reaction mixture was concentrated under reduced pressure, diluted with H_2O, and extracted with $CHCl_3$ (15 ml×4). The extract was washed with H_2O, dried over Na_2SO_4, and the solvent was evaporated to give yellow crystals, which were recrystallized from EtOH to give the bromohydrin (**14**) as colorless needles, mp 159—167° (dec.). Yield, 194 mg (97%). *Anal.* Calcd. for $C_{14}H_{14}BrNO_3 \cdot C_2H_5OH$ (one molar EtOH was confirmed by NMR spectrum): C, 51.90; H, 5.44; N, 3.78. Found: C, 52.15; H, 5.27; N, 3.97. NMR [$(CD_3)_2SO$] δ: 1.33 (3H, t, $CH_2C\underline{H}_3$), 3.64 (2H, m, $C\underline{H}_2CHBr$), 4.33 (2H, q, $OC\underline{H}_2CH_3$), 4.85 (1H, m, C$\underline{H}$Br), 5.10 (1H, d, C$\underline{H}$OH), 7.00 (1H, m, aromatic proton), 7.17 (2H, m, aromatic protons), 11.45 (1H, s, N$\underline{H}$).

Reaction of Bromohydrin (14) with Methylaminoacetone Ethylene Ketal——A mixture of the bromohydrin (**14**) (35 mg, 0.11 mmol) and methylaminoacetone ethylene ketal (56 mg, 0.43 mmol) in dry benzene (1.5 ml) was heated at 150° for 5 hr in a sealed tube. When cooled, the crystals formed were collected by filtration, and this was identified with methylaminoacetone ethylene ketal hydrobromide. The benzene filtrate was washed with H_2O, dried over Na_2SO_4, and benzene was evaporated to give a brown viscous oil, which was purified by chromatography over silica gel eluted with $CHCl_3$. The ketone (**8a**) was obtained in 38% yield (10 mg).

5-(3-Ethoxycarbonyl-5-oxo-2-pyrrolin-1-yl)-6(1*H*)-oxo-3,4,5,6-tetrahydrocyclohept[*c*,*d*]indole (15b)——To a solution of *tert*-BuOK (prepared from 170 mg, 4.3 mmol of K) in *tert*-BuOH (15 ml), the ketone (**1b**) (760 mg, 4.1 mmol) was added. Stirring was continued at room temperature for 10 min and then at 60° for 15 min. Isoamyl nitrite (750 mg, 6.4 mmol) was added at room temperature and the reaction mixture was stirred for 35 min (brown precipitate appeared). After ice (14 g), AcOH (7 ml), and Zn (1.3 g) were added, the mixture was stirred for 15 min. AcONa (13 g) and formyl succinate (1.4 ml) were added under ice cooling and the whole solution was stirred at 0° for 2 hr. After addition of H_2O, the reaction mixture was extracted with $CHCl_3$ (20 ml×5). The extract was washed with saturated $NaHCO_3$ and H_2O, dried over Na_2SO_4, and the solvent was evaporated to give a brown oil (1.8 g). After this oil was washed with petroleum ether (3 times), the insoluble viscous oil was stirred at room temperature for 3 hr with *tert*-BuOK (from 360 mg of K) in *tert*-BuOH (30 ml). After addition of H_2O and then 5% HCl, the solid formed was extracted with $CHCl_3$ (20 ml×4). The extract was washed with H_2O, dried over Na_2SO_4, and the solvent was evaporated to give a viscous oil (1 g), which was purified by chromatography over silica gel eluted with $CHCl_3$ to give the starting material (45 mg) from the first fraction and a yellow viscous oil (160 mg) from the second fraction. When a solution of this oil in $CHCl_3$–benzene was allowed to stand, yellow prisms, mp 206—207°, were obtained. Overall yield, 9.4% (130 mg). *Anal.* Calcd. for $C_{19}H_{18}N_2O_4$: C, 67.44; H, 5.36; N, 8.28. Found: C, 67.48; H, 5.46; N, 8.13. MS *m/e*: 338.127 (M^+) (Calcd. for $C_{19}H_{18}N_2O_4$: 338.125); 184.074 (Calcd. for $C_{12}H_{10}NO$: 184.076); 183.068 (Calcd. for $C_{12}H_9NO$: 183.068). IR ν_{max}^{KBr} cm^{-1}: 3370 (NH), 1695 (ester C=O), 1675 (C=O), 1615. UV λ_{max}^{EtOH} nm: 228. NMR ($CDCl_3$) δ: 1.33 (3H, t, $CH_2C\underline{H}_3$), 2.23 [2H, m, $C\underline{H}_2CH(N)$], 3.15 [2H, m, $C\underline{H}_2CH_2$-

CH(N)], 3.47 (2H, s, $C\underline{H}_2$ at 4-position of 2-pyrrolin-5-one), 4.25 (2H, q, $OC\underline{H}_2CH_3$), 5.30 [1H, q, $COC\underline{H}(N)$], 7.1—7.7 (4H, m, aromatic protons), 7.90 (1H, d-d, C_7–$\underline{H}$), 8.97 (1H, b.s, $N\underline{H}$).

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