Stereoselective Syntheses of Isoquinuclidones. II[1]

JOHN WITTE AND V. BOEKELHEIDE*

Department of Chemistry, University of Oregon, Eugene, Oregon 97403

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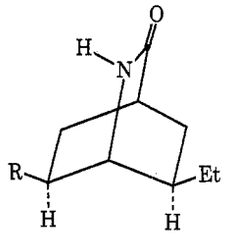
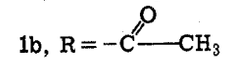
Syntheses of indole derivatives followed by cleavage of the indole ring is shown to be a convenient method of preparing 2,4,6-trisubstituted anilines. Hydrogenation of such 2,4,6-trisubstituted anilines over a ruthenium catalyst occurs in an all cis fashion, providing a stereoselective synthesis of isoquinuclidone derivatives.

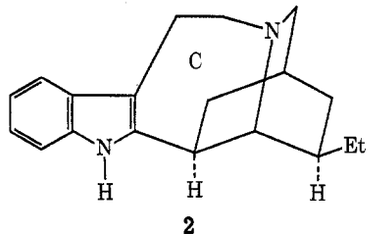
In an accompanying paper we have described the stereoselective synthesis of the isoquinuclidine moiety (**1**) of the ibogamine molecule (**2**) by hydrogenation appropriate 2,4,6-trisubstituted anilines over a ruthenium catalyst.[2] Important to the success of such a scheme is the availability of convenient syntheses of appropriately substituted anilines. In our previous study,[2] such syntheses were accomplished *via* conversion of a substituted aniline to the corresponding isatin followed by cleavage of the isatin ring and hydrolysis. This scheme, although efficient, is limited to the synthesis of 6-carbethoxy isoquinuclidones (**1a**) or easily derived analogs (**1b**). For a total synthesis of ibogamine and the related iboga alkaloids, it would be desirable to have a more flexible synthesis of 2,4,6-trisubstituted anilines which would allow the stereoselective synthesis of an isoquinuclidine moiety such as **3**, containing the seven-membered C ring of ibogamine (**2**). The present report describes a study directed toward this end utilizing indole derivatives as intermediates.



1a, R = $-CO_2Et$



1b, R = $-C(=O)-CH_3$



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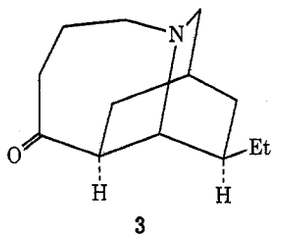

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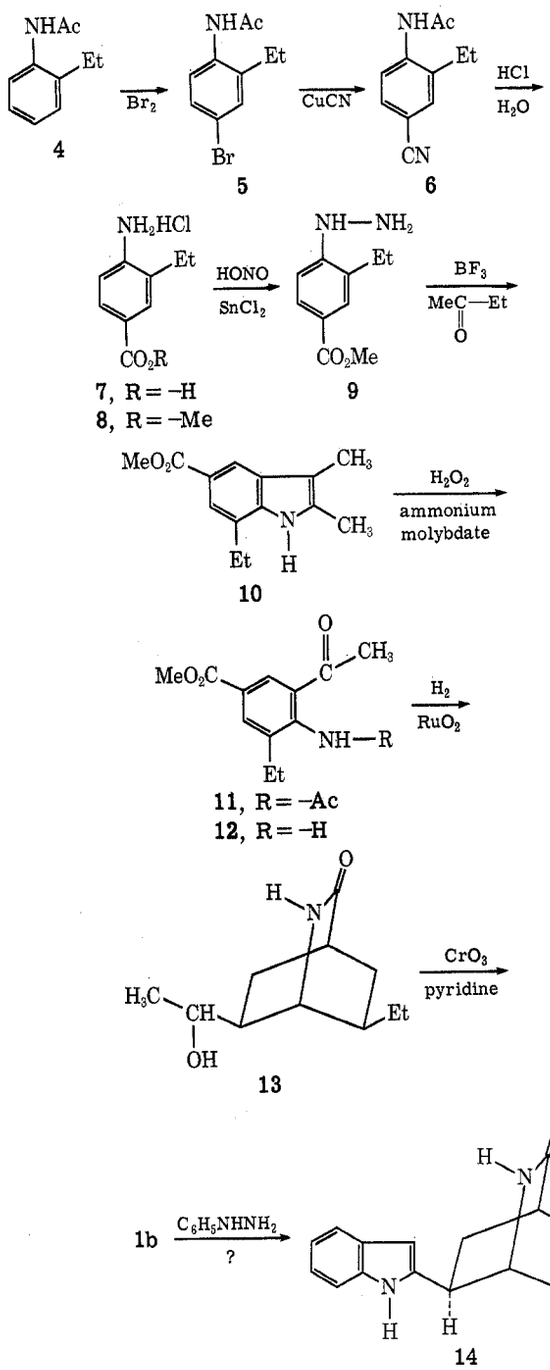
To explore the use of indoles as intermediates the first experiments were directed toward preparing the 6-acetyl-7-ethylisoquinuclidone (**1b**), previously synthesized *via* the isatin route.[2] For this purpose and as shown in Scheme I, 2-ethylacetanilide (**4**) was brominated to give 4-bromo-2-ethylacetanilide (**5**) in 93% yield and this in turn was converted in 77% yield *via* a von Braun reaction to the corresponding 4-cyano-2-ethylacetanilide (**6**). Hydrolysis of **6** proceeded quantitatively to the 4-carboxy-2-ethylaniline hydrochloride (**7**). Diazotization and reduction of the corresponding methyl ester (**8**) led in 90% yield to 4-carboethoxy-2-ethylphenylhydrazine (**9**). Reaction of **9** with methyl ethyl ketone under conditions of the Fischer indole synthesis then gave 2,3-dimethyl-5-carbomethoxy-7-ethylindole (**10**) in 68% yield.

SCHEME I



(1) We thank the Public Health Service, National Heart Institute Grant No. 5-ROI-HE 09813, for financial support of this investigation.

(2) V. A. Snieckus, T. Onouchi, and V. Boekelheide, *J. Org. Chem.*, **37**, 2845 (1972).

At this stage it was necessary to develop a procedure for cleavage of the indole nucleus. Oxidative methods have been investigated extensively.[3-7] The use of chromium trioxide in acetic acid, as studied by Koelsch,[4] is very effective but appears to be useful only for 2-acylinodoles. The elegant method of Dolby and Booth using periodate apparently is only moderately successful when electron-withdrawing substituents are present at the 5 position,[7] as in the present case. Therefore, we chose the hydrogen peroxide and ammonium molybdate procedure of Mentzen and Berguer.[5] Under their conditions **10** gave the corresponding acetanilide **11** in 60% yield. Hydrolysis of **11** then led to the desired 2,4,6-trisubstituted aniline (**12**). Although this route requires seven steps, all of them proceed in high yield and are convenient to carry out.

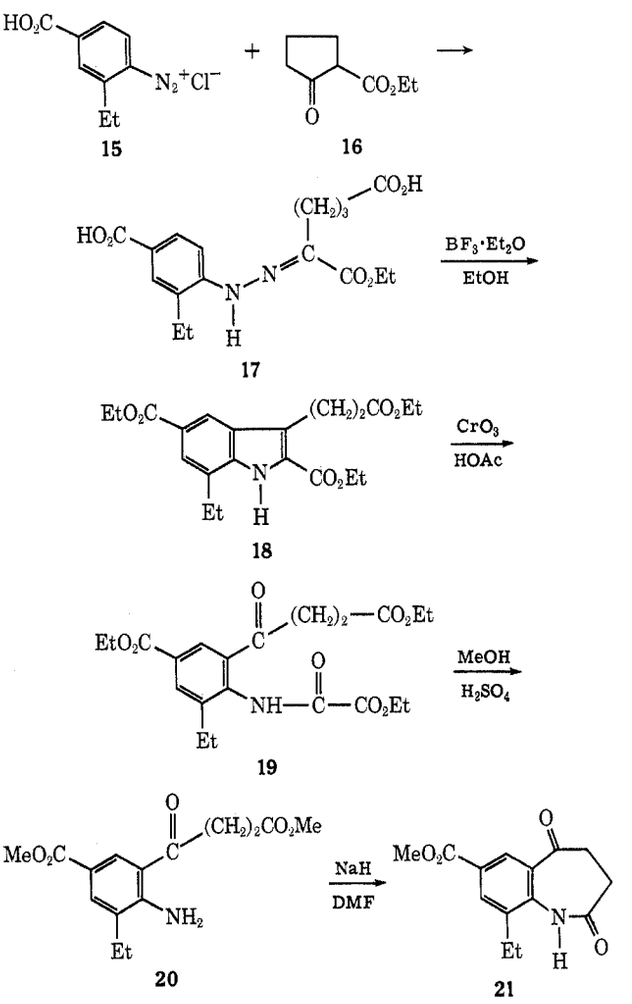
Catalytic hydrogenation of **12** over a ruthenium oxide catalyst at 150° and 2000 psi proceeded smoothly to yield the isoquinuclidone **13**. Oxidation of **13** with chromium trioxide–pyridine readily regenerated the ketone and provided **1b** in 50% yield overall from **12**.

Various experimental procedures were investigated for the conversion of **1b** *via* its phenylhydrazone to the indole derivate **14**, Although ultraviolet spectral data on the crude products indicated the presence of indole derivatives, the yield of **14**, if formed, was too low to be useful. We then turned to exploring the possibility for utilizing the indole approach for the synthesis of **3**. For this purpose **7** was diazotized and the corresponding diazonium salt (**15**) was allowed to react with 2-carbethoxycyclopentanone (**16**) in a Japp–Klingemann reaction. This gave the phenylhydrazone **17** in 77% yield overall from **7**. The Fischer indole cyclization of **17** was then accomplished in 65% yield using boron trifluoride etherate in ethanol, which simultaneously effected esterification of the carboxyl groups to give **18**. In this case with a carbethoxyl group present at the 2 position, oxidative cleavage with chromium trioxide in acetic acid was selected preferentially for cleavage of the indole nucleus and proceeded in 60% yield to give **19**. Hydrolysis of **19** readily gave the free aniline derivative **20** (Scheme II).

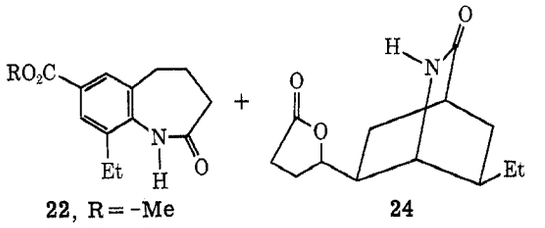
Although the cyclization of *o*-(β-carbethoxypropionyl)anilines has been reported to occur readily on sublimation or heating in boiling decalin,[8] **20** was recovered unchanged after subjection to these conditions. Apparently, the carbethoxyl group in the 4 position has a marked deactivating effect on such cyclizations to the amino group. To overcome this **20** was treated with sodium hydride in dimethylformamide and the resulting anion readily cyclized in 67% yield to give **21**.

It was hoped that hydrogenation of **21** might occur as before to give directly the isoquinuclidone skeleton of **3**. However, when **21** was subjected to hydrogenation over a ruthenium oxide catalyst at 135° and 2000 psi, three products were obtained in yields of 17, 15, and 42%. Based on their spectral data and elementary composition, the three products have been assigned structures **22**, **23**, and **24**. Apparently, spontaneous ring closure to the isoquinuclidone moiety does not occur with amides but rather requires a free, basic, amino group.

SCHEME II



21 $\xrightarrow[RuO_2]{H_2}$

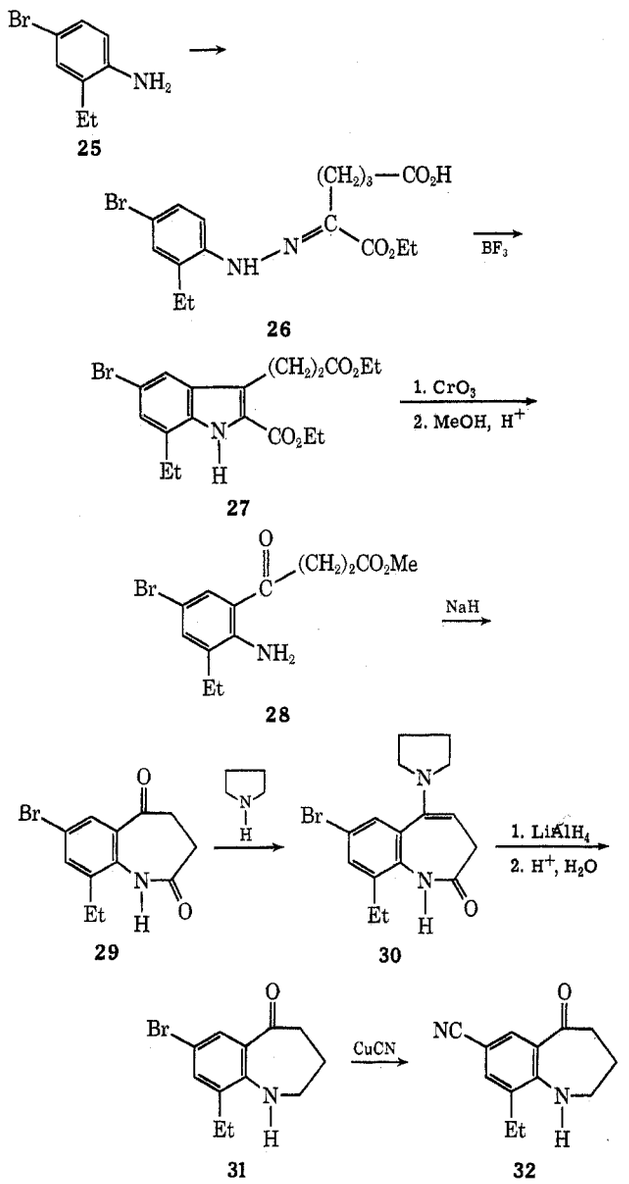


With this outcome it seemed necessary to modify the synthetic sequence to provide a basic amine prior to catalytic hydrogenation so that spontaneous cyclization to the isoquinuclidone moiety would occur. With this goal in mind we converted 4-bromo-2-ethylaniline (**25**) to its diazonium salt and subjected this to a Japp–Klingemann reaction with 2-carbethoxycyclopentanone. The resulting hydrazone derivative **26**, formed in 81% yield, was then cyclized with boron trifluoride etherate in ethanol to give **27**. Oxidation of **27** with chromium trioxide in acetic acid followed by methanolysis of the product yielded **28**. This was cyclized as before with sodium hydride to give **29**. At this stage it was desired to reduce the amide linkage

(3) B. Witkop and S. Goodwin, *J. Amer. Chem. Soc.*, **75**, 337 (1953).
(4) C. F. Koelsch, *J. Org. Chem.*, **8**, 295 (1943).
(5) C. Mentzen and Y. Berguer, *Bull. Soc. Chim., Fr.*, 218 (1952).
(6) L. J. Dolby and D. L. Booth, *J. Amer. Chem. Soc.*, **88**, 1049 (1966).
(7) D. L. Booth, Doctoral Dissertation, University of Oregon, 1965.
(8) A. H. Rees, *J. Chem. Soc.*, 3111 (1959).

while leaving the ketone carbonyl intact. To do this **29** was first converted to the corresponding enamine **30** with pyrrolidine and then **30** was subjected to reduction with lithium aluminum hydride. Hydrolysis of this product gave the desired keto amine **31** in 85% yield. Treatment of **31** with cuprous cyanide in a von Braun reaction gave the cyano derivative **32** in 75% yield (Scheme III).

SCHEME III



Work was discontinued at this stage in view of the reports of total syntheses of ibogamine by other investigators.[9]

Experimental Section[10]

4-Cyano-2-ethylacetanilide (6).—The reaction of bromine in acetic acid with *o*-ethylacetanilide at 5° gave 4-bromo-2-ethylacetanilide (5) in 93% yield as white needles: mp 147.0–147.5°.[11] A solution of **5** and 4.5 g of cuprous cyanide in 50 ml of *N*-methyl-2-pyrrolidone was boiled under reflux for 3 hr. The cold solution was then poured into a mixture of 100 ml of concentrated ammonium hydroxide and 400 ml of water, causing the separation of a brown solid. This was collected, treated with activated charcoal in ethanol, and recrystallized from a water–ethanol mixture to give 5.8 g (77%) of colorless needles: mp 177–178°; ir ($CHCl_3$) 3520 cm^{-1} (NH), 2250 (C≡N), and 1715 (C=O).

Anal. Calcd for $C_{11}H_{12}N_2O$: C, 70.23; H, 6.38; N, 14.89. Found: C, 70.42; H, 6.43; N, 14.52.

3-Ethyl-4-aminobenzoic Acid Hydrochloride (7).—A suspension of 5.0 g of **6** in 25 ml of concentrated hydrochloric acid was boiled under reflux for 12 hr. During this time the suspended solid went into solution and then reprecipitated. The precipitate was collected and recrystallized from water to give 5.2 g (99%) of white crystals: mp 210–211°.

Anal. Calcd for $C_9H_{12}ClNO_2$: C, 53.63; H, 5.95; N, 6.95. Found: C, 53.59; H, 6.03; N, 7.01.

2-Ethyl-4-carbomethoxyphenylhydrazine (9).—A solution of 20.0 g of **7** in 250 ml of methanol saturated with dry hydrogen chloride was boiled under reflux for 2 hr and then concentrated to dryness. The white crystalline residue (**8**) was dissolved in 100 ml of concentrated hydrochloric acid, cooled to −10°, and stirred vigorously while adding a solution of 6.9 g of sodium nitrite in 100 ml of water dropwise over a period of 1.0 hr. The stirring was continued during the addition of a cold solution of 90.0 g of stannous chloride in 90 ml of concentrated hydrochloric acid, the rate of addition being adjusted so that the temperature of the reaction mixture never rose above −5°. After the addition was complete, the pH of the reaction mixture was brought to 14 and the product was extracted with chloroform. When the chloroform extract had been washed with water and dried, concentration gave a white solid which, after recrystallization from an ether–cyclohexane mixture, yielded 17.5 g (90%) of white needles: mp 75–76°; ir ($CHCl_3$), 3450 cm^{-1} (broad NH) and 1690 (C=O); nmr ($CDCl_3$) τ 2.00–2.30 (m, 2 H, Ar*H*), 3.00 (d, 1 H, Ar*H*), 5.10–5.50 (m, 6 H, –N*H* and CH_3O–), 6.53 (q, 2 H, $ArCH_2$–), and 8.75 (t, 3 H, $-CH_2CH_3$).

Anal. Calcd for $C_{10}H_{14}N_2O_2$: C, 61.86; H, 7.22; N, 14.44. Found: C, 62.13; H, 7.01; N, 14.71.

2,3-Dimethyl-5-carbomethoxy-7-ethylindole (10).—A mixture of 17.5 g of **9**, 10.8 g of methyl ethyl ketone, and 0.2 ml of acetic acid in 200 ml of methanol was boiled under reflux for 2 hr. After concentration to remove most of the methanol, 50 ml of boron trifluoride etherate was added and the reaction mixture was heated at 130° for 10 min. It was then added to 300 ml of cold water and extracted with chloroform. After the chloroform extract had been washed with water and dried, it was concentrated to give a brown oil. This was taken up in benzene and chromatographed over silica gel. The white solid obtained from the main fraction of eluate was recrystallized from methanol to give 14.1 g (68%) of white needles: mp 77–78°; ir ($CHCl_3$) 3450 cm^{-1} (NH) and 1700 (C=O); nmr ($CDCl_3$) τ 1.73 (broad s, 1 H, N*H*), 1.90 (d, 1 H, Ar*H*), 2.31 (d, 1 H, Ar*H*), 6.10 (s, 3 H, $-OCH_3$), 7.19 (q, 2 H, $ArCH_2$–), 7.67 (s, 3 H, CH_3), 7.79 (s, 3 H, CH_3), and 8.80 (t, 3 H, $-CH_2CH_3$).

Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.67; H, 7.32; N, 5.95.

***N*-Acetyl-2-acetyl-4-carbomethoxy-6-ethylaniline** (11).—To a suspension of 13.8 g of **10** and 300 mg of ammonium molybdate in 300 ml of acetic acid there was added dropwise with stirring over a period of 0.5 hr 50 ml of a 30% aqueous hydrogen peroxide solution. The reaction mixture was held at 35° until all of the suspended indole had dissolved and then it was stirred at room temperature for an additional 8 hr. After dilution with 1.0 l. of water, it was extracted with chloroform. The chloroform extract was washed successively with water, dilute aqueous sodium bicarbonate, and water, before drying. Concentration of the chloroform extract gave a brown oil which was chromatographed over silica gel using benzene for elution. The yellow solid from the main fraction of eluate was recrystallized from a methanol–water mixture to give 9.4 g (60%) of yellow needles: mp 132–133°; nmr ($CDCl_3$) τ 0.63 (broad s, 1 H, N*H*,), 1.84 (d, 1 H,

(9) (a) G. Büchi, D. L. Coffen, K. Kocsis, P. E. Sonnet, and F. E. Ziegler, *J. Amer. Chem. Soc.*, **87**, 2073 (1965); *ibid.*, **88**, 3099 (1966); (b) Y. Ban, T. Wakamatsu, U. Fujimoto, and T. Oishi, *Tetrahedron Lett.*, 3383 (1968); (c) W. Nagata, S. Hirai, T. Okumura, and K. Kawata, *J. Amer. Chem. Soc.*, **90**, 1650 (1968); (d) S. Sallay, *ibid.*, **89**, 6762 (1967); (e) J. P. Kutney, W. J. Cretney, P. LeQueane, B. McHague, and E. Piers, *ibid.*, **88**, 4756 (1967); (f) J. Harley-Mason, Alta-ur-Rahman, and J. A. Beisler, *Chem. Commun.*, 743 (1966); *ibid.*, 208 (1967).

(10) Elemental analyses are by Bernhardt Laboratories and MicroTech Laboratories. Infrared spectra were measured with a Perkin-Elmer Model 202 spectrophotometer, ultraviolet and visible spectra with a Cary 15, nmr spectra with a Varian A-60, and mass spectra by Morgan-Schaffer Corp.

(11) A. Kövendi and M. Kircz, *Chem. Ber.*, **97**, 1896 (1964).

ArH), 2.01 (d, 1 H, ArH), 6.08 (s, 3 H, $-OCH_3$), 7.07–7.66 (m, 5 H), 7.68 (s, 3 H, $-CH_3$), and 8.83 (t, 3 H, $-CH_2CH_3$).

Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.86; H, 6.51; N, 5.32. Found: C, 63.77; H, 6.38; N, 5.27.

2-Acetyl-4-carbomethoxy-6-ethylaniline (12).—A solution of 9.1 g of **11** and 10 ml of concentrated sulfuric acid in 200 ml of absolute methanol was boiled under reflux for 4 hr. After the solution had been poured into 1.0 l. of water, it was brought to pH 5 and extracted with chloroform. Concentration of the chloroform extract gave a yellow solid which was chromatographed over silica gel using a 1:1 benzene–chloroform mixture for elution. The crystalline solid from the main fraction of eluate was recrystallized from methanol to give 5.1 g (68%) of yellow needles: mp 114–115°; ir ($CHCl_3$) 3450 and 3350 cm^{-1} (NH_2) and 1690 (broad C=O); nmr ($CDCl_3$) τ 1.58 (d, 1 H, ArH), 2.12 (d, 1 H, ArH), 2.5 (broad s, 1 H, NH), 6.04 (s, 3 H, $-OCH_3$), 7.22–7.71 (m, 5 H), and 8.88 (t, 3 H, $-CH_2-CH_3$).

Anal. Calcd for $C_{12}H_{15}NO_3$: C, 65.16; H, 6.79; N, 6.34. Found: C, 65.11; H, 6.85; N, 6.25.

6-Acetyl-7-ethyl-2-azabicyclo[2.2.2]octan-3-one (1b).—A solution of 5.0 g of **12** in 100 ml of isopropyl alcohol containing 1.0 g of a ruthenium oxide catalyst was subjected to hydrogenation at 150° and 2000 psi for 8 hr. After removal of the catalyst and solvent, the colorless, residual oil was added to a solution of 35.6 g of the dipyridine–chromium(VI) oxide complex in 700 ml of methylene chloride. The mixture was stirred at room temperature for 15 min before adding 5 ml of isopropyl alcohol and stirring an additional 5 min. The mixture was then filtered and the filtrate concentrated. The resulting dark oil was chromatographed over alumina (Woelm, activity I) using chloroform for elution. The main eluate fraction gave 2.6 g (54%) of a colorless oil: ir ($CHCl_3$) 1720 cm^{-1} (ketone C=O) and 1680 (–C(O)–NH); nmr ($CDCl_3$) τ 7.82 (s, 3 H, $-C(O)-CH_3$) and 9.09 (t, 3 H, $-CH_2-CH_3$).

Anal. Calcd for $C_{11}H_{17}NO_2$: C, 67.69; H, 8.71; N, 7.23. Found: C, 67.58; H, 8.77; N, 7.12.

A solution of 1.5 g of **1b** plus 1 drop of acetic acid and 840 mg of phenylhydrazine in 5 ml of benzene was heated for a short period of time. After removal of the benzene, the residue was dissolved in 2.0 g of polyphosphoric acid and heated at 100–110°. Work up of the reaction mixture followed by thin layer chromatography over silica gel using a 5% ethanol–chloroform mixture for elution gave three spots. The material corresponding to the spot of highest R_f was resubjected to preparative tlc chromatography several times. A sample of this material showed a typical indole ultraviolet spectrum (uv maxima at 225 and 275 nm) but it was insufficient in amount and purity for further characterization.

2-Ethyl-4-carboxyphenylhydrazone of Ethyl δ-Carboxy-α-oxovalerate (17).—To a solution of 51.0 g of 3-ethyl-4-aminobenzoic acid hydrochloride (**7**) in a mixture of 10 ml of concentrated hydrochloric acid and 500 ml of water held at 0° there was added dropwise with stirring a solution of 17.5 g of sodium nitrite in 40 ml of water. Then, with continued stirring, a solution of 50 g of sodium acetate in 100 ml of water was added dropwise. This was followed by addition of 46.5 g of 2-carbethoxycyclopentanone with vigorous stirring. Over the course of 1 hr of stirring a yellow oil deposited and crystallized. This yellow solid was removed by decantation and added to 400 ml of a boiling 7% aqueous sodium carbonate solution. After 2 min the solution was cooled and acidified. The yellow solid, which separated, was collected and recrystallized from ethanol to give 77.3 g (77%) of yellow crystals, mp 218–219°.

Anal. Calcd for $C_{17}H_{22}N_2O_6$: C, 58.27; H, 6.34; N, 8.00. Found: C, 58.01; H, 6.25; N, 7.82.

2,5-Dicarbethoxy-7-ethyl-3-(β-carbethoxyethyl)indole (18).—A suspension of 35.0 g of **17** in 200 ml of absolute ethanol containing 100 ml of boron trifluoride etherate was boiled under reflux until solution was complete and then for an additional 0.5 hr. After removal of most of the solvent, the residue was poured onto cracked ice and extracted with dichloromethane. When the dichloromethane extract had been washed with water and dried, it was concentrated giving a yellow-brown solid. This was chromatographed over alumina (Woelm, activity I) using ether for elution. The solid from the main eluate fraction was recrystallized from an ethanol–water mixture to give 25.2 g (65%) of white needles: mp 125–126°; ir ($CHCl_3$) 3650 cm^{-1} (NH) and 1760 (C=O); nmr ($CDCl_3$) τ 0.43 (broad s, 1 H, NH), 1.67 (d, 1 H, ArH), 2.15 (d, 1 H, ArH), 5.65 (q, 4 H, $-OCH_2CH_3$), 6.82 (q, 2 H, $-CH_2CH_3$), and 8.68 (m, 12 H, $-CH_2CH_3$).

Anal. Calcd for $C_{21}H_{27}NO_6$: C, 63.68; H, 7.15; N, 3.71. Found: C, 64.10; H, 7.11; N, 3.50.

Ethyl β-(5-Carbethoxy-3-ethyl-2-ethoxalylaminobenzoyl)propionate (19).—To a suspension of 5.0 g of **18** in 25 ml of acetic acid there was added dropwise with stirring a solution of 3.85 g of chromium trioxide and 2 ml of water in 13 ml of acetic acid. After the reaction had been stirred overnight at room temperature, it was diluted with water and extracted with chloroform. The chloroform extract was washed successively with water, aqueous sodium carbonate, and water. The yellow solid resulting on concentration of the chloroform extract was recrystallized from an ethanol–water mixture to give 3.3 g (60%) of yellow crystals: mp 69–70°; ir ($CHCl_3$) 3450 cm^{-1} (NH) and 1754–1690 (broad C=O); nmr ($CDCl_3$) τ −0.28 (s, 1 H, NH), 1.68 (d, 1 H, ArH), 1.88 (d, 1 H, ArH), 5.75 (m, 6 H, $-OCH_2CH_3$), 6.67 (m, 2 H, $-C(O)-CH_2-$), 7.25 (q, 2 H, $-CH_2CH_3$), and 8.67 (m, 12 H, $-CH_2CH_3$).

Anal. Calcd for $C_{21}H_{27}NO_8$: C, 59.86; H, 6.41; N, 3.33. Found: C, 60.43; H, 6.37; N, 3.14.

Methyl β-(2-Amino-3-ethyl-5-carbomethoxybenzoyl)propionate (20).—A solution of 8.4 g of **19** and 5 ml of concentrated sulfuric acid in 100 ml of absolute methanol was boiled under reflux for 3 hr. The reaction mixture was then cooled, poured on to 500 g of ice, made basic, and extracted with chloroform. After the chloroform extract had been washed with water and dried, it was concentrated to give a yellow solid. This was recrystallized from a methanol–water mixture to yield 5.2 g (90%) of yellow crystals: mp 87–88°; ir ($CHCl_3$) 3530 and 3345 cm^{-1} (NH_2) and 1720 and 1700 (C=O); nmr ($CDCl_3$) τ 1.57 (d, 1 H, ArH), 2.16 (d, 1 H, ArH), 6.13 (s, 3 H, OCH_3), 6.20 (s, 3 H, $-OCH_3$), 6.62 (m, 4 H, $-C(O)-CH_2-$), 7.42 (q, 2 H, $-CH_2CH_3$), and 8.75 (t, 3 H, $-CH_2CH_3$).

Anal. Calcd for $C_{15}H_{19}NO_5$: C, 59.40; H, 6.27; N, 4.62. Found: C, 59.19; H, 6.25; N, 4.51.

2,3,4,5-Tetrahydro-7-carbomethoxy-9-ethyl-2,5-dioxobenz[f]azepine (21).—To a suspension of 2.4 g of sodium hydride in 200 ml of tetrahydrofuran held at −40° there was added dropwise with stirring a solution of 15.0 g of **20** in 20 ml of dimethylformamide. The mixture was allowed to warm to room temperature while being stirred over a period of 1.5 hr. It was then poured onto ice, brought to pH 4 with acetic acid, and extracted with chloroform. After concentration of the chloroform extract, the resulting brown solid was chromatographed over Florisil using an 80% hexane–chloroform mixture for elution. The pale yellow solid from the main fraction of eluate was recrystallized from an ethanol–water mixture giving 10.0 g (67%) of yellow crystals: mp 161–162°; ir ($CHCl_3$) 3450 cm^{-1} (NH) and 1725 and 1670 (C=O); nmr ($CDCl_3$) τ 1.53 (s, 1 H, NH), 7.15 (m, 6 H), and 8.68 (t, 3 H, $-CH_2CH_3$).

Anal. Calcd for $C_{14}H_{15}NO_4$: C, 64.75; H, 5.75; N, 5.36. Found: C, 64.37; H, 6.00; N, 5.18.

Catalytic Hydrogenation of 21.—A mixture of 1.0 g of **21** and 200 mg of a ruthenium oxide catalyst in 50 ml of ethanol was subjected to hydrogenation at 135° and 2000 psi for 12 hr. After removal of the catalyst and solvent, the residual oil was taken up in chloroform and chromatographed over silica gel. Elution with a 1% methanol–chloroform mixture (fraction A) gave a white solid. This was recrystallized from a methanol–water mixture to yield 170 mg (17%) of white crystals: mp 111–112°; ir ($CHCl_3$) 3470 cm^{-1} (NH), 1730 (–C(O)–O), and 1658 (–C(O)–NH). This has been assigned structure **22**.

Anal. Calcd for $C_{14}H_{23}NO_2$: C, 66.40; H, 9.09; N, 5.53. Found: C, 66.56; H, 8.93; N, 5.42.

Further elution with a 3% methanol–chloroform mixture (fraction B) gave a second white solid. This, on recrystallization from benzene, yielded 420 mg (42%) of white crystals: mp 199–200°; ir ($CHCl_3$) 3340 cm^{-1} (NH), 1770 (γ-lactone C=O), and 1670 (–C(O)–NH); nmr ($CDCl_3$) τ 3.10 (broad s, 1 H, –C(O)–NH–). This has been assigned structure **24**.

Anal. Calcd for $C_{13}H_{19}NO_3$: C, 65.27; H, 8.79; N, 5.86. Found: C, 65.09; H, 8.80; N, 6.01.

Finally, elution with a 6% methanol–chloroform mixture (fraction C) gave a third white solid. This, on recrystallization from a methanol–water mixture yielded 150 mg (15%) of white crystals: mp 133–134°; ir ($CHCl_3$) 3280 cm^{-1} (broad, OH and NH), 1695 (broad, –C(O)–OH and –C(O)–NH–); nmr ($CDCl_3$) τ −1.34 (broad s, 1 H, –C(O)–OH) and 2.02 (d, 1 H, –NH). This has been assigned structure **23**.

Anal. Calcd for $C_{13}H_{21}NO_3$: C, 65.27; H, 8.79; N, 5.86. Found: C, 65.23; H, 8.75; N, 5.98.

2-Ethyl-4-bromophenylhydrazone of Ethyl δ-Carboxy-α-oxovalerate (26).—To a solution of 100.0 g of 4-bromo-2-ethylaniline in 1.0 l. of water and 190 ml of concentrated hydrochloric acid held at 0° there was added dropwise with stirring a solution of 34.5 g of sodium nitrite in 200 ml of water. After the mixture had been stirred an additional 0.5 hr at 0°, there was added 400 g of sodium acetate followed by 80.0 g of 2-carbethoxycyclopentanone. The yellow oil which separated was extracted with chloroform. Concentration of the chloroform extract gave a residual yellow oil which was added to 600 ml of a 7% aqueous sodium carbonate solution and boiled for 2 min. The solution was then cooled, brought to pH 2, and again extracted with chloroform. The combined chloroform extracts were washed with water, dried, and concentrated. The resulting yellow solid was recrystallized from an ethanol–water mixture to give 172 g (81%) of yellow crystals: mp 133–134°.

Anal. Calcd for $C_{16}H_{21}N_2O_4Br$: C, 49.91; H, 5.45; N, 7.27. Found: C, 49.74; H, 5.37; N, 7.53.

2-Carbethoxy-3-(β-carbethoxyethyl)-5-bromo-7-ethylindole (27).—A solution of 30.0 g of **26** and 65 ml of boron trifluoride etherate in 250 ml of absolute ethanol was boiled under reflux for 1 hr. After concentration to remove most the solvent, the reaction mixture was poured into ice water and extracted with chloroform. The chloroform extract was washed with water, dried, and concentrated. The residual oil was taken up in ether and chromatographed over neutral alumina (Woelm, activity I). The solid from the main fraction of eluate was recrystallized from an ethanol–water mixture to give 21.0 g (59%) of white crystals: mp 117–118°; nmr ($CDCl_3$) τ 1.13 (s, 1 H, N*H*), 2.32 (d, 1 H, Ar*H*), 2.80 (d, 1 H, Ar*H*), 5.32–6.12 (m, 4 H, ArC*H*$_2$–), 6.66 (t, 2 H, –C*H*$_2$C(O)–), 6.99–7.55 (m, 4 H), and 8.35–9.05 (m, 6 H).

Anal. Calcd for $C_{18}H_{22}NO_4Br$: C, 54.58; H, 5.55; N, 3.53. Found: C, 54.27; H, 5.52; N, 3.46.

Methyl γ-(2-Amino-3-ethyl-5-bromobenzoyl)propionate (28).—To a solution of 36.0 g of chromium trioxide and 18 ml of water in 120 ml of acetic acid there was added dropwise with stirring a solution of 43.7 g of **27** in 230 ml of acetic acid. The temperature of the reaction mixture was maintained at 25–30° during the addition and stirring was continued for 4 hr at that temperature after the addition was complete. Then the reaction mixture was diluted with 1.0 l. of water and extracted with chloroform. After the chloroform extract had been washed successively with water, dilute aqueous acid, and water, it was concentrated, leaving a brown oil. This was dissolved in 500 ml of methanol containing 40 ml of concentrated sulfuric acid and boiled under reflux for 18 hr. The reaction mixture was then poured into ice water and the brown solid which separated was collected. This was recrystallized from methanol to give 10.0 g (54%, based on **27**) of yellow plates: mp 87–88°; nmr ($CDCl_3$) τ 2.24 (d, 1 H, ArH), 2.75 (d, 1 H, Ar*H*), 6.33 (s, 3 H, –OC*H*$_3$), 6.76 (t, 2 H, –C*H*$_2$–C(O)–), 7.42 (m, 4 H), and 8.78 (t, 3 H, –CH$_2$C*H*$_3$).

Anal. Calcd for $C_{13}H_{16}NO_3Br$: C, 49.68; H, 5.10; N, 4.46; Br, 25.48. Found: C, 49.77; H, 4.97; N, 4.23; Br, 25.52.

2,3,4,5-Tetrahydro-7-bromo-9-ethyl-2,5-dioxobenz[*f*]azepine (29).—To a suspension of 3.6 g of sodium hydride in 150 ml of tetrahydrofuran held at −45° there was added dropwise with stirring a solution of 23.6 g of **28** in 100 ml of dimethylformamide. After the addition was complete, the reaction mixture was allowed to warm to room temperature and was stirred for an additional 0.5 hr. It was then poured into 300 ml of water and extracted with chloroform. Concentration of the chloroform extract gave a yellow solid which was chromatographed over silica gel using chloroform for elution. The solid obtained from the main fraction of eluate was recrystallized from methanol to give 13.6 g (66%) of yellow needles: mp 92–93°; ir ($CHCl_3$) 3430 cm^{-1} (NH) and 1680 (broad C=O); nmr ($CDCl_3$) τ 1.25 (s, 1 H, NH), 2.27 (d, 1 H, Ar*H*), 2.50 (d, 1 H, Ar*H*), 6.80–7.50 (m, 6 H), and 8.78 (t, 3 H, –CH$_2$C*H*$_3$).

Anal. Calcd for $C_{12}H_{12}NO_2Br$: C, 51.06; H, 4.25; N, 4.96; Br, 28.37. Found: C, 51.13; H, 4.17; N, 5.01; Br, 28.08.

2,3,4,5-Tetrahydro-7-bromo-9-ethyl-5-oxobenz[*f*]azepine (31).—A solution of 5.0 g of **29**, 3.6 g of pyrrolidine, and 5 mg of *p*-toluenesulfonic acid in 100 ml of toluene was boiled under reflux until no further water was collected in a Dean–Stark trap attached to the system. The mixture was concentrated to less than half-volume, 200 ml of ether was added, and then 1.1 g of lithium aluminum hydride was added. The reaction mixture was boiled under reflux for 8 hr before adding an aqueous saturated sodium sulfate solution dropwise to effect separation of the metallic hydroxides as a granular precipitate. After filtration, the filtrate was concentrated to give a yellow oil. This was taken up in 3 *N* aqueous hydrochloric acid and allowed to stand at room temperature for 3 hr. The solution was then made basic and extracted with chloroform. After concentration of the chloroform extract, the resulting yellow solid was chromatographed over silica gel using a 50% chloroform–benzene mixture for elution. The yellow solid from the main fraction of eluate was recrystallized from methanol to give 4.0 g (85%) of yellow plates: mp 91–92°; ir ($CHCl_3$) 3490 cm^{-1} (NH) and 1665 (C=O); nmr ($CDCl_3$) τ 2.28 (d, 1 H, Ar*H*), 2.79 (d, 1 H, Ar*H*), 5.93 (broad s, 1 H, N*H*), 6.67–8.06 (m, 8 H), 8.73 (t, 3 H, –CH$_2$C*H*$_3$).

Anal. Calcd for $C_{12}N_{14}NOBr$: C, 53.73; H, 5.41; N, 5.41. Br, 29.85. Found: C, 53.48; H, 5.28; N, 5.27; Br, 30.19

2,3,4,5-Tetrahydro-7-cyano-9-ethyl-5-oxobenz[*f*]azepine (32).—A solution of 3.5 g of **31** and 1.8 g of cuprous cyanide in 25 ml of *N*-methyl-2-pyrrolidone was heated at 200° for 2.5 hr. After the reaction mixture had been cooled, it was poured into 100 ml of an aqueous 10% sodium cyanide solution and extracted with chloroform. The chloroform extract was washed with water, dried, and concentrated. The residual brown solid was chromatographed over silica gel using a 50% chloroform–benzene mixture for elution. The crystalline solid obtained from the main fraction of eluate was recrystallized from methanol to give 2.1 g (75%) of yellow crystals: mp 95–96°; ir ($CHCl_3$) 3450 cm^{-1} (NH), 2250 (C≡N), and 1670 (C=O); nmr ($CDCl_3$) τ 2.10 (d, 1 H, Ar*H*), 2.67 (d, 1 H, Ar*H*), 4.33 (broad t, 1 H, NH), 6.39–7.87 (m, 8 H), and 8.87 (t, 3 H, –CH$_2$CH$_3$).

Anal. Calcd for $C_{13}H_{14}N_2O$: C, 72.89; H, 6.54; N, 13.08. Found: C, 73.05; H, 6.33; N, 12.97.

Registry No.—**1b**, 34921-72-7; **6**, 34921-76-1; **7**, 34921-77-2; **9**, 34921-78-3; **10**, 34921-79-4; **11**, 34921-80-7; **12**, 34921-81-8; **17**, 34921-82-9; **18**, 34934-81-1; **19**, 34921-83-0; **20**, 34921-84-1; **21**, 34921-85-2; **22**, 34921-86-3; **23**, 34921-87-4; **24**, 34921-88-5; **26**, 34921-89-6; **27**, 34921-90-9; **28**, 34921-91-0; **29**, 34921-92-1; **31**, 34921-93-2; **32**, 34921-94-3.