Synthetic Studies on Indoles and Related Compounds. XXVI.[1] The Debenzylation of Protected Indole Nitrogen with Aluminum Chloride. (2)[2]

Toshiko WATANABE, Atsushi KOBAYASHI, Michiko NISHIURA, Hiroyuki TAKAHASHI, Tomoko USUI, Izumi KAMIYAMA, Naomi MOCHIZUKI, Kumiko NORITAKE, Yuusaku YOKOYAMA and Yasuoki MURAKAMI*

School of Pharmaceutical Sciences, Toho University, 2–2–1, Miyama, Funabashi, Chiba 274, Japan. *Received November 15, 1990*

A new debenzylation method using aluminum chloride in benzene or anisole, which had been developed by us for *N*-benzyl-2-acyl- and -2-ethoxycarbonylindoles, was applied to benzyl derivatives of other types of indoles and related compounds. Among them, *N*-benzyl derivatives of fully aromatized indoles, carbazoles and *β*-carbolines, and some benzamides were debenzylated successfully, whereas those of oxindoles and heterocyclic amides were not. As to the effect of a *p*-substituent on the benzyl group, it was found that an electron-donating substituent accelerates deprotection, whereas an electron-attracting substituent delays or prevents deprotection.

Keywords debenzylation; aluminum chloride; indole; benzamide; benzene; anisole

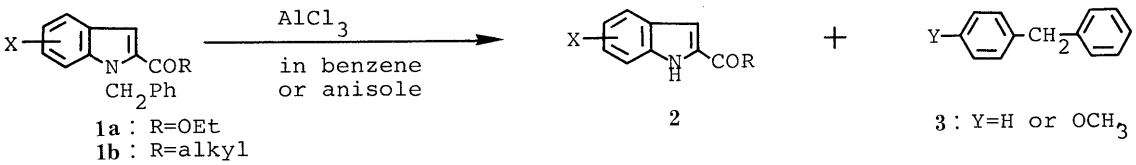
Some years ago we reported[2] a novel method for the debenzylation of protected nitrogen of indoles using aluminum chloride in benzene or anisole. In this reaction *N*-benzylindoles (**1a**, **b**) were easily converted to the corresponding NH-indoles (**2a**, **b**) under mild conditions, and the benzyl cation thus formed was trapped with benzene or anisole to form diarylmethane derivatives (**3**). The mechanism proposed in the case of ethyl 1-benzyl-1*H*-indole-2-carboxylate is shown in Chart 1, and is reminiscent of the Fries rearrangement. However, this method was applied only to the *N*-benzyl derivatives of ethyl indole-2-carboxylates (**2a**) and 2-acylindoles (**2b**). In this paper we describe the application of this method to other types of indoles and related compounds to examine its scope and limitations. If the expected debenzylation proceeds, the method is expected to be practically useful, because it has been reported that removal of the *N*-benzyl group from an amide by catalytic hydrogenolysis is rather difficult.[3]

The required unknown *N*-benzyl derivatives (**5**) were prepared by benzylation of the corresponding NH compounds (**4**) or by other methods, as shown in Table I, and their characteristics are listed in Table II.

Debenzylation reaction was carried out under the conditions used for the previous experiment[2]; that is, *N*-benzyl compounds (**5**) (1 eq) were allowed to react with aluminum chloride (4—6 eq) in benzene, or anisole at 0—50 °C. The results are summarized in Table III, and represent the highest yield obtained for each benzyl compound after many trials. The products, NH-compounds (**4**), were identical with authentic samples in terms of infrared (IR) and ^{1}H-nuclear magnetic resonance (^{1}H-NMR) spectra, and melting points. The compounds which did not undergo debenzylation are given below Table III.

Run 1 shows that a 3-acyl group in the ethyl indole-2-carboxylate skeleton does not prevent debenzylation. However, the reaction was accompanied with formation of 3-acetyl-1*H*-indole-2-carboxylic acid (**9**) (9%) by hydrolysis, and some starting material (**5a**) was recovered (8%). Run 2 shows that the 2-amide group in place of the 2-ethoxycarbonyl group was also effective for debenzylation, although anisole gave a better result than benzene as a solvent. Successful debenzylation of the 3-acyl-2-unsubstituted indoles (**5c**) (run 3) shows that the presence of a 2-acyl group is not essential for debenzylation.

It is noteworthy that *N*-benzyl derivatives of fully aromatized indoles, carbazole and *β*-carboline (**5d** and **5e** in runs 4 and 5) were debenzylated easily in almost the same manner as 2-alkoxycarbonyl- and 2-acylindoles[2] (**1a**, **b**). On the basis of this knowledge, this method was successfully applied to the synthesis of crenatine,[4] a new kind of



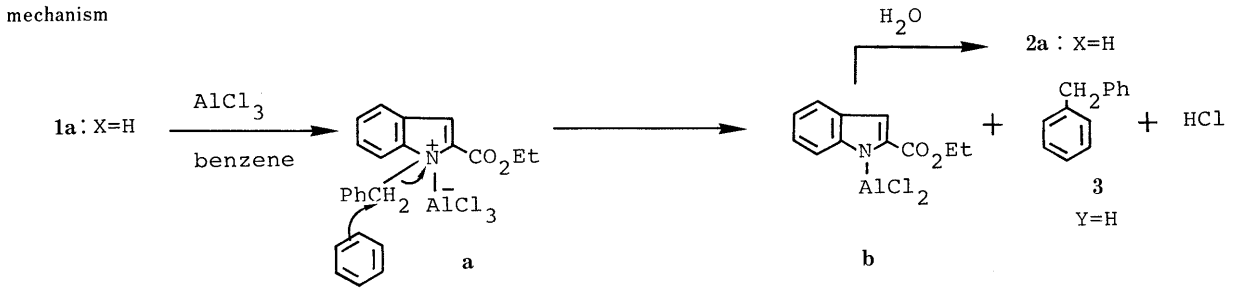
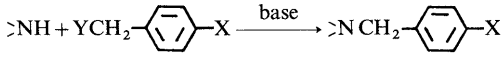


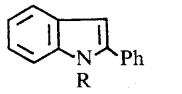
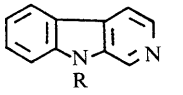
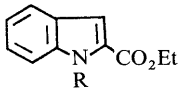
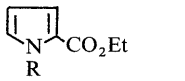
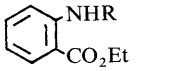
Chart 1

TABLE I. Preparation of *N*-Benzylindoles

A. *N*-Benzylation of NH Derivatives

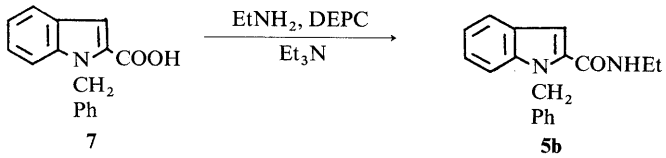


4 6 5

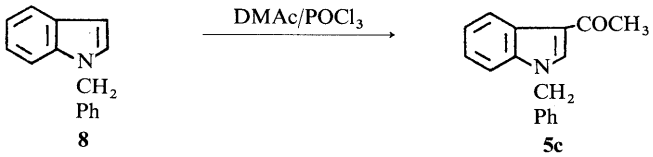
Run	Starting material 4 (R=H)	X	Y	Base	Solvent	Temperature	Time	Yield (%) of 5 (R=CH$_2$-C$_6$H$_4$-X)
1	 (4n)	H	Cl	NaH	DMF	r.t.	2 h	75
2	 (4e)	H	Cl	NaH	DMSO	50 °C	0.5 h	69
3	 (2a)	OMe	Cl	NaH	DMSO	50 °C	0.5 h	57
4	2a	NO_2	Br	K_2CO_3	Acetone	Reflux	14 h	71[a]
5	 (4g)	H	Cl	NaH	DMSO	50 °C	20 min	58
6	 (4w)	H	Cl	—	EtOH	Reflux	12.5 h	70

a) Yield was low (41%) when the reagent used was NaH in DMSO.

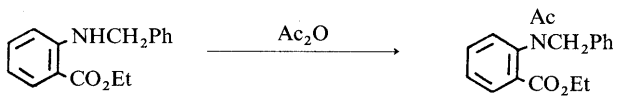
B. By other methods

i) 

7 5b

ii) 

8 5c

iii) 

5w 5x

β-carboline alkaloid, and would also be applicable to our synthesis[5] of ellipticine, in which the debenzylation step was carried out by means of the troublesome Birch reduction. In the present debenzylation the product was sometimes contaminated with a small amount of "C_x-benzyl-NH compounds," which would be formed by the attack of benzyl cation at the carbon moiety of the debenzylated NH-product. This was observed by mass spectrometry (MS, same molecular weight as starting material), ^{1}H-NMR spectroscopy (the presence of an isolated $-CH_2-$ and an NH group), and IR spectroscopy (the presence of an NH group) in the case of **5g**.

N-Benzyl-1,2,3,4-tetrahydrocarbazole (**5f**, run 6) seemed to undergo debenzylation but gave a mixture of many products, when checked by thin layer chromatography (TLC), probably because **5f** and the expected product (NH-compound), which has similar reactivity to usual indoles (indoles which are not stabilized by an electronegative substituent), are susceptible to acid (aluminum chloride) to give a mixture of products. Ethyl 1-benzyl-1*H*-pyrrole-2-carboxylate (**5g**, run 7) showed a similar reactivity to **5f**; that is, the reaction in benzene gave a mixture of several products. From the mixture, only a C-benzyl-NH product was isolated in low yield, but the position of the benzyl group was uncertain. *N*-Benzylisatin (**5h**, run 8) did not undergo debenzylation but two equivalents of benzene reacted at the 3-position to give 1-benzyl-3,3-diphenyloxindole in 88% yield. The reaction of isatin with aluminum chloride in benzene was reported to give the same kind of compound, 3,3-diphenyloxindole.[6] Other indolic com-

TABLE II. Characterization of *N*-Benzyl Compounds

Compound	Melting point or boiling point (°C)	Recrystallization solvent (Crystal form)	Formula	Analysis (%) Calcd (Found)			^{1}H-NMR (NCH_2Ar) δ ppm (in $CDCl_3$)
				C	H	N	
5c	115—116	Benzene–hexane (Colorless needles)	$C_{17}H_{15}NO$	81.90 (81.72	6.06 6.18	5.62 5.55)	5.30 (s)
5n	96.5—98.5	Ethyl acetate–hexane (Colorless prisms)	$C_{21}H_{17}N$	89.01 (89.23	6.05 6.13	4.94 4.90)	5.33 (s)
5b	124—125	Benzene (Colorless needles)	$C_{18}H_{18}N_2O$	77.67 (77.90	6.52 6.51	10.06 10.04)	5.77 (s)
5e	118—120	Benzene–hexane (Colorless needles)	$C_{18}H_{14}N_2$	83.69 (83.47	5.46 5.50	10.84 11.09)	5.48 (s)
5l	45—47.5	Ethyl acetate–pentane (Colorless needles)	$C_{19}H_{19}NO_3$	73.77 (73.53	6.19 6.16	4.53 4.66)	5.72 (s)
5m	102—104	Benzene–hexane (Colorless needles)	$C_{18}H_{16}N_2O_4$	66.66 (66.69	4.97 4.98	8.64 8.58)	5.91 (s)
5g	bp 155 °C/17 mmHg	Colorless oil	$C_{14}H_{15}NO_2$		229.1099[a] (229.1093)		5.50 (s)
5w	—	Colorless oil	$C_{16}H_{17}NO_2$		255.1255[a] (255.1251)		4.42 (d)
5x	54.5—56	Benzene–hexane (Yellow plates)	$C_{18}H_{19}NO_3$	72.71 (72.82	6.44 6.48	4.71 4.71)	4.17 and 5.35 (d)

a) High-resolution mass spectral data.

pounds, *N*-benzyl-2-phenyl-1*H*-indole (**5n**), *N*-benzyloxindole (**5o**), and related heterocycles (**5p** and **5q**) did not undergo debenzylation at all. On the other hand *N*-benzylbenzamide derivatives (**5i**, **5j**, and **5k**, runs 9—11) underwent debenzylation successfully. In them, a more electronegative group on the benzene ring accelerated debenzylation. However, the *N*-methyl derivative of **5i** (**5u**), phthalimide (**5r**), benzylanilides (**5s** and **5t**), *N*-benzyldiphenylamine (**5v**), ethyl *N*-benzylanthranilate (**5w**), and the *N*-acetyl derivative of **5w** (**5x**) did not undergo debenzylation.

The effect of Lewis acids other than aluminum chloride, that is, boron trifluoride etherate, titanium chloride, stannic chloride, and ferric chloride, was examined. The reaction of ethyl 1-benzyl-1*H*-indole-2-carboxylate (**1a**, X=H) with the former three Lewis acids gave only recovered starting material, while the reaction with ferric chloride gave only a mixture of C-benzyl-NH products.

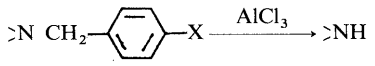
Finally, we examined the effect of a substituent on the benzyl group. Two kinds of ethyl 1-(*p*-substituted)benzylindole-2-carboxylate (**5l** and **5m**), were allowed to react under the same debenzylation conditions. Although the *p*-nitrobenzyl group was not removed at all, the *p*-methoxybenzyl group was removed easily to the same extent as the benzyl group.[2] Apparently a big substituent effect exists, suggesting that the stability of the benzyl cation ($X\text{–}C_6H_4CH_2^+$) determines the rate of deprotection. However, as the extent of removal of *p*-methoxybenzyl and benzyl groups is at the same level, the benzyl group is better for practical use.

In conclusion, the present method can be reliably applied to benzyl derivatives of 2-acyl, 2-alkoxycarbonyl, and fully aromatized indoles, as well as some benzamides. Before we started the present examination, we had suspected that our method might be applicable only to 2-carbonylindoles, in which aluminum chloride could react easily with indolic nitrogen owing to assistance of the neighboring carbonyl group. The present result shows that the debenzylation does not require 2-carbonyl group assistance and thus is not restricted to 2-acylindoles. Though no assistance of the 2-carbonyl group was required for debenzylation, the presence of this group is expected to favor debenzylation to some extent by its weak coordination with aluminum chloride. The reaction seems to be influenced by the basicity and steric crowdedness of nitrogen, because basic compounds (**5q**, **5v**, and **5w**) did not undergo debenzylation, and *N*-alkyl-*N*-benzylbenzamides (**5u**) did not, while corresponding *N*-benzyl-NH-benzamides (**5i**, **5j**, and **5k**) did. This steric crowdedness would be responsible for the non-reactivity of 1-benzyl-2-phenyl-1*H*-indole (**5n**). Usual indoles (not stabilized indoles) and oxindoles are not suitable substrates for this debenzylation. Although *N*-benzyl derivatives of other heterocycles and other amides are usually hard to debenzylate, a trial of the debenzylation process is advisable for every *N*-debenzylation, as the reactions of some benzylbenzamides were successful. As to the solvent (which has a trapping ability for the benzyl cation formed), the relative merits of benzene and anisole cannot be explained straightforwardly. Anisole seems to be better than benzene for trapping the benzyl cation, whereas anisole would combine weakly with aluminum chloride in an acid–base interaction to weaken the reactivity of aluminum chloride. Generally speaking, benzene is recommended due to its general applicability and easy handling. It may be worth trying both in any particular case.

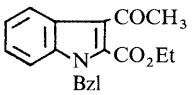
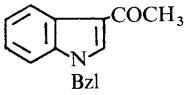
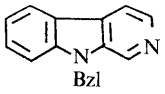
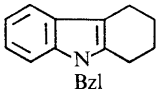
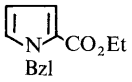
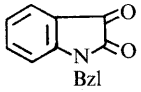
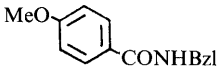
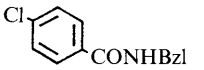
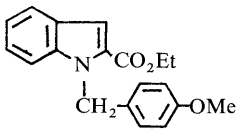
Experimental

All melting points were measured on a micro melting point hot stage (Yanagimoto) and are uncorrected. IR spectra were recorded in Nujol mulls (unless otherwise stated) on a Shimadzu IR 400 instrument. ^{1}H-NMR spectra were recorded in $CDCl_3$ (unless otherwise stated) on a Hitachi R-24B spectrometer (60 MHz). In the ^{1}H-NMR spectra, chemical shifts are given in δ values referred to internal tetramethylsilane, and the assignment of all NH and OH signals was confirmed by the disappearance of their signals after addition of D_2O. Mass spectra (MS) were measured by the direct inlet system on JEOL JMS-01-GS-2 spectrometer. For column

TABLE III. Results of Debenzylation Reaction

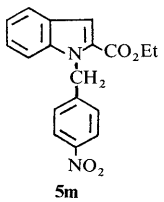


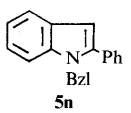
5 4

Run	*N*-Benzyl compound 5		Temperature	Time	$AlCl_3$(eq)/ solvent[a]	Yield (%) of 4	Melting point (°C) (Reported)	Starting material recovered (%)	Other products
1		(5a)[7]	r.t.	24 h	6/B	84	97—102 (96—97.5)[7]	8	(9, 9%)
2		(5b)	0 °C r.t.	30 min 2 h	4/B 4/A	25 70	185—188.5 (183)[21]	70 11	
3		(5c)	r.t.	15 h	4/B	90	191—194 (188—192)[b]		
4		(5d)[8]	r.t. r.t.	4 h 3 h	4/B 4/A	— 85	218—220 (245—247)[b]	—	Many spots on TLC
5		(5e)	r.t. r.t.	40 min 24 h	4/B 4/A	61 —	193—195 (198—200)[b]	 60	
6		(5f)[9]	r.t.	24 h	4/B	—	—	—	Many spots on TLC
7		(5g)	r.t. r.t.	4 h 24 h	4/B 4/A	— —	— —	— 65	(10, 18%)
8		(5h)[10]	r.t.	30 min	4/B	—	—	—	(11, 88%)
9		(5i)[b]	r.t.	3.5 h	4/B	74	129—130 (128—129)[b]		
10		(5j)[11]	50 °C	6 h	4/B	40	169—170 (164—167)[b]	—	(12, 25%)
11		(5k)[12]	50 °C	2 h	4/B	91	181.5—183 (172—176)[b]		
12		(5l)	0 °C	10 min	4/A	74 (Yield of 2a)	117—121 (122—125)[b]		

a) A = anisole, B = benzene. *b*) Commercially available.

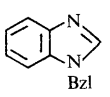
Compounds which did not undergo debenzylation were as follows.

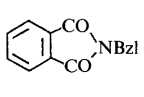

5m

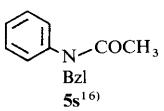

5n

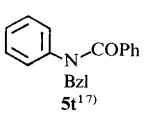

5o[10]


5p[13]

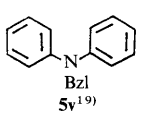

5q[14]

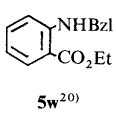

5r[15]

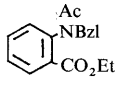

5s[16]


5t[17]

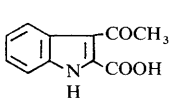

5u[18]

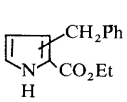

5v[19]

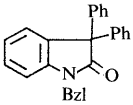

5w[20]

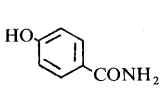

5x

By-products


9[7]


10


11


12[b]

chromatography, silica gel (Kiesel gel 60, 70—230 mesh, Merck), and for TLC, Kiesel gel GF_{254}, Merck, were used. The abbreviations used are as follows: s, singlet; d, doublet; dd, double doublet; t, triplet; q, quartet; m, multiplet; dif, diffused; br, broad; arom, aromatic.

General Procedure for *N*-Benzylation as Exemplified by Benzylation of 2-Phenylindole (5n) A solution of 2-phenylindole (1.544 g, 8 mmol) in dimethylformamide (DMF) (15 ml) was added to a suspension of 60% NaH (0.32 g, 8 mmol) in DMF (10 ml) under ice-cooling and under an Ar atmosphere. The mixture was stirred for 0.5 h at 0 °C, and then benzyl chloride (0.92 ml, 8 mmol) was added. The whole mixture was stirred for 2 h at room temperature, poured into ice-water, and extracted with AcOEt. The organic layer was washed with 10% HCl, saturated $NaHCO_3$, and brine, dried over $MgSO_4$, and evaporated to dryness *in vacuo*. The residue was chromatographed on SiO_2 with benzene–hexane (1 : 5) to afford colorless prisms (1.706 g, 75%), mp 96.5—98.5 °C, which were recrystallized from AcOEt–hexane.

General Procedure for Debenzylation of *N*-Benzyl Compounds A solution of a benzyl compound (1.0 mmol) in benzene or anisole (1—14 ml) was added to a suspension of $AlCl_3$ (4—6 eq relative to the benzyl compound) in benzene or anisole (0.5—4.5 ml) under ice-cooling. The mixture was stirred under the conditions shown in Table III. The reaction mixture was poured into water and extracted with benzene or ethyl acetate. The organic layer was washed successively with 5% $NaHCO_3$ and brine, dried over $MgSO_4$, and evaporated to dryness *in vacuo*. The residue was chromatographed on SiO_2 to give the NH-compound; a by-product was also obtained in some cases as shown in Table III.

***N*-Ethyl-1-benzyl-1*H*-indole-2-carboxamide (5b)** A solution of ethylamine hydrochloride (1.469 g, 18 mmol) in DMF (5 ml) was added to a solution of 1-benzyl-1*H*-indole-2-carboxylic acid (**7**) (3.027 g, 12 mmol) in DMF (4 ml). Then triethylamine (5.018 ml, 36 mmol) and diethylphosphorocyanidate (DEPC) (3.262 g, 18 mmol) were added. The whole mixture was stirred at room temperature for 2 h, then poured into ice-water and extracted with AcOEt. The organic layer was washed with water, dried over $MgSO_4$, and evaporated to dryness *in vacuo*. The residue was chromatographed on SiO_2 with benzene–AcOEt to give colorless needles (2.49 g, 75%), which were recrystallized from benzene, mp 142—143.5 °C. *Anal.* Calcd for $C_{18}H_{18}N_2O$: C, 77.67; H, 6.52; N, 10.06. Found: C, 77.90; H, 6.51; N, 10.04. IR ν_{max} cm^{-1}: 3440 (NH), 1660 (C=O). ^{1}H-NMR δ: 1.17 (3H, t, J=8 Hz, $CH_2C\underline{H}_3$), 3.16—3.61 (2H, m, $NC\underline{H}_2CH_3$), 5.77 (2H, s, NCH_2Ph), 6.10 (1H, br s, NH), 6.80 (1H, s, C_3-H), 6.90—7.70 (9H, m, arom H). MS *m/z* (%): 91 (100), 278 (M^+, 52).

3-Acetyl-1-benzyl-1*H*-indole (5c) Phosphorus oxychloride (1.4 ml, 15 mmol) was added dropwise to dimethylacetamide (DMAc, 6 ml) under ice-cooling. A solution of *N*-benzylindole (**8**) (1.036 g, 5 mmol) in DMAc (4 ml) was added to this solution, and the whole was stirred at 95 °C for 2 h. A solution of NaOH (3.5 g) in water (10 ml) was added, and the reaction mixture was stirred at 95 °C for 10 min, then extracted with AcOEt. The organic layer was washed with saturated NaCl, dried over $MgSO_4$, and evaporated to dryness *in vacuo*. The residue was chromatographed on SiO_2 with benzene–ethyl acetate (10 : 1) to give colorless needles (1.06 g, 85.1%), which were recrystallized from benzene–hexane. *Anal.* Calcd for $C_{17}H_{15}NO$: C, 81.90; H, 6.06; N, 5.62. Found: C, 81.72; H, 6.18; N, 5.55. IR ν_{max} cm^{-1}: 1635 (C=O). ^{1}H-NMR δ: 2.49 (3H, s, $COCH_3$), 5.30 (2H, s, NCH_2Ph), 7.00—7.50 (8H, m, arom H), 7.70 (1H, s, C_2-H), 8.20—8.53 (1H, m, C_4-H). MS *m/z* (%): 91 (100), 249 (M^+, 45).

Ethyl *N*-Acetyl-*N*-benzylanthranilate (5x) A mixture of ethyl-*N*-benzylanthranilate (**5w**) (510 mg, 2 mmol), acetic anhydride (0.462 ml, 4.2 mmol) and pyridine (5 ml) was refluxed for 9 h. After removal of the solvent *in vacuo*, the residue was dissolved in AcOEt. This solution was washed with 10% HCl, saturated $NaHCO_3$, and saturated NaCl, dried over $MgSO_4$, and evaporated to dryness *in vacuo*. The residue was chromatographed on SiO_2 with AcOEt–hexane to give yellow plates (219 mg, 37%), mp 54.5—56 °C, which were recrystallized from benzene–hexane. *Anal.* Calcd for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.82; H, 6.48; N, 4.71. IR ν_{max} cm^{-1}: 1730, 1670 (C=O). ^{1}H-NMR δ: 1.32 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 1.80 (3H, s, $COCH_3$), 4.23 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 4.17 and 5.35 (each 1H, d, J=15 Hz, $NC\underline{H}_2Ph$), 6.70—8.02 (9H, m, arom H). MS *m/z* (%): 254 (100), 297 (M^+, 5).

Spectral Data for *N*-Benzyl Derivatives 1-Benzyl-2-phenyl-1*H*-indole (**5n**): IR ν_{max} cm^{-1}: no characteristic absorption. ^{1}H-NMR δ: 5.33 (2H, s, NCH_2Ph), 6.62 (1H, s, C_3-H), 6.88—7.80 (14H, m, arom H). MS *m/z* (%): 283 (M^+, 100).

9-Benzyl-9*H*-pyrido[3,4-*b*]indole (**5e**): IR ν_{max} cm^{-1}: no characteristic absorption. ^{1}H-NMR δ: 5.48 (2H, s, NCH_2Ph), 6.89—7.57 (8H, m, arom H), 7.89 (1H, d, J=6 Hz, C_4-H), 8.10 (1H, d, J=7 Hz, C_5-H), 8.42 (1H, d, J=6 Hz, C_3-H), 8.79 (1H, s, C_1-H). MS *m/z* (%): 91 (100), 258 (M^+, 70).

Ethyl 1-(4-Methoxybenzyl)-1*H*-indole-2-carboxylate (**5l**): IR ν_{max} cm^{-1}: 1710 (C=O). ^{1}H-NMR δ: 1.34 (3H, t, J=8 Hz, $CH_2C\underline{H}_3$), 3.68 (3H, s, OCH_3), 4.30 (2H, q, J=8 Hz, $OC\underline{H}_2CH_3$), 5.72 (2H, s, NCH_2Ph), 6.50—7.75 (9H, m, arom H). MS *m/z* (%): 121 (100), 309 (M^+, 20).

Ethyl 1-(4-Nitrobenzyl)-1*H*-indole-2-carboxylate (**5m**): IR ν_{max} cm^{-1}: 1700 (C=O). ^{1}H-NMR δ: 1.35 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 4.32 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 5.91 (2H, s, NCH_2Ph), 7.09—8.20 (9H, m, arom H). MS *m/z* (%): 144 (100), 324 (M^+, 32).

Ethyl 1-Benzyl-1*H*-pyrrole-2-carboxylate (**5g**): IR ν_{max}^{neat} cm^{-1}: 1690 (C=O). ^{1}H-NMR δ: 1.25 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 4.18 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 5.50 (2H, s, NCH_2Ph), 6.05—6.25 (1H, m, arom H), 6.75—7.40 (7H, m, arom H). MS *m/z* (%): 229 (M^+, 100).

Ethyl *N*-Benzylanthranilate (**5w**): IR ν_{max}^{neat} cm^{-1}: 3340 (NH), 1670 (C=O). ^{1}H-NMR δ: 1.34 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 4.30 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 4.42 (2H, d, J=7 Hz, CH_2Ph), 6.38—8.02 (9H, m, arom H), 8.12 (1H, br s, NH). MS *m/z* (%): 208 (100), 255 (M^+, 57).

Ethyl *x*-Benzyl-1*H*-pyrrole-2-carboxylate (10) According to the general procedure for debenzylation, ethyl 1-benzyl-1*H*-pyrrole-2-carboxylate (**5g**) (0.161 g, 0.7 mmol) was treated with $AlCl_3$ (0.414 g, 3.1 mmol) in benzene (3 ml). After work-up, the residue was chromatographed on SiO_2 with benzene to give a pale brown solid (0.0294 g, 18%), mp 63—65 °C. IR ν_{max} cm^{-1}: 3280 (NH), 1680 (C=O). ^{1}H-NMR δ: 1.30 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 3.97 (2H, s, $CC\underline{H}_2Ph$), 4.25 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 6.73—6.98 (1H, br s, NH), 7.22 (7H, s, arom H). MS *m/z* (%): 229 (M^+, 100).

1-Benzyl-3,3-diphenyloxindole (11) A solution of 1-benzylisatin (**5h**) (237 mg, 1 mmol) in benzene (4 ml) was added dropwise to a suspension of $AlCl_3$ (533 mg, 4 mmol) in benzene (1 ml). The mixture was stirred at 0 °C for 30 min, then at room temperature for 30 min. The reaction mixture was poured into ice-water, and extracted with benzene. The organic layer was washed with 10% HCl, saturated $NaHCO_3$, and saturated NaCl, dried over $MgSO_4$, and evaporated to dryness *in vacuo*. The crude solid was recrystallized from hexane–$CHCl_3$ to give colorless prisms (328 mg, 88%), mp 166—168 °C. *Anal.* Calcd for $C_{27}N_{21}NO$: C, 86.37; H, 5.64; N, 3,73, Found: C, 86.13; H, 5.55; N, 3.64. IRν_{max} cm^{-1}: 1700 (C=O). ^{1}H-NMR δ: 4.95 (2H, s, NCH_2Ph), 6.63—7.45 (19H, m, arom H). MS *m/z* (%): 284 (100), 375 (M^+, 43).

References

1) Part XXV: M. Tani, T. Aoki, S. Ito, S. Matsumoto, M. Hideshima, K. Fukushima, R. Nozawa, T. Maeda, M. Tashiro, Y. Yokoyama, and Y. Murakami, *Chem. Pharm. Bull.*, **38**, 3261 (1990).
2) Y. Murakami, T. Watanabe, A. Kobayashi, and Y. Yokoyama, *Synthesis*, **1984**, 738.
3) M. Freifelder, "Practical Catalytic Hydrogenation," John Wiley and Sons, Inc., New York, 1971, p. 427.
4) Y. Murakami, Y. Yokoyama, C. Aoki, C. Miyagi, T. Watanabe, and T. Ohmoto, *Heterocycles*, **26**, 875 (1987).
5) Y. Yokoyama, N. Okuyama, S. Iwadate, T. Momoi, and Y. Murakami, *J. Chem. Soc., Perkin Trans. 1*, **1990**, 1319.
6) J. Wegmann and H. Dahn, *Helv. Chim. Acta*, **29**, 415 (1946).
7) Y. Murakami, M. Tani, M. Suzuki, K. Sudoh, M. Uesato, K. Tanaka, and Y. Yokoyama, *Chem. Pharm. Bull.*, **33**, 4707 (1985).
8) Ng. Ph. Buu-Hoi and R. Royer, *J. Org. Chem.*, **16**, 1198 (1951).
9) M. Nakazaki and Y. Isoe, *Nippon Kagaku Zasshi*, **76**, 1159 (1955).
10) N. Hirose, S. Sohda, and S. Toyoshima, *Yakugaku Zasshi*, **91**, 1323 (1971).
11) E. Beckmann, *Ber.*, **37**, 4136 (1904).
12) C. J. O'Conner and R. E. Ramage, *Aust. J. Chem.*, **30**, 527 (1977).
13) S. A. G. F. Angelino, B. H. Van Valkengoed, D. J. Buurman, H. C. Van der Plas, and F. Mueller, *J. Heterocycl. Chem.*, **21**, 107 (1984).
14) F. Feigl and H. Gleich, *Monatsh. Chem.*, **49**, 385 (1928).
15) R. H. F. Manske, "Organic Syntheses," Coll. Vol. II, ed. by A. H. Blatt, John, Wiley and Sons, Inc., New York, 1943, p. 83.
16) Yu. V. Svetkin, *Zh. Obshch. Khim.*, **26**, 1216 (1956).
17) E. F. Pratt and E. J. Frazza, *J. Am. Chem. Soc.*, **76**, 6174 (1954).
18) J. von Braun and J. Weismantel, *Ber.*, **55**, 3176 (1922).
19) P. Tavernier and M. Lamouroux, *Mem. Poudres*, **38**, 65 (1956) [*Chem. Abstr.*, **51**, 14404c (1957)].
20) Y. Kato, Japan. Kokai Tokkyo Koho, 80 06405, 80 11126 (1980)[*Chem. Abstr.*, **93**, 7860*j*, 26119*r* (1980)].
21) J. Pigulla and E. Röder, *Arch. Pharm.*, **312**, 12 (1979).