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FISCHER IONDOLIZATION AND ITS RELATED COMPOUNDS—X[1]

APPLICATION OF THE ADVANCED FISCHER INDOLIZATION OF A 2-METHOXYPHENYLHYDRAZONE DERIVATIVE TO SYNTHESES OF SOME NATURALLY OCCURRING 6-SUBSTITUTED INDOLES

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Abstract—Two naturally occurring 6-substituted indoles, 6-(3-methylbuta-1,3-dienyl)indole (2) and 6-(3-methyl-2-butenyl)indole (5), were synthesized by using an advanced Fischer indolization of a 2-methoxyphenylhydrazone derivative.

In the preceeding paper,[2] we showed that Fischer indolization of ethyl pyruvate 2-methoxyphenylhydrazone (1) in the presence of an excess amount of an enolizable dicarbonyl compound gave ethyl indole-2-carboxylate possessing an active methine group at the C_6 position of the indole nucleus. And also, in a preliminary communication,[1] we reported the synthesis of naturally occurring 6-(3-methylbuta-1,3-dienyl)indole[3] (2) from ethyl α - acetyl - 2 - ethoxycarbonylindole - 6 - acetate (3). In the present paper, we present the synthesis of this natural product and another naturally occurring 6-substituted indole, 6 - (3 - methyl - 2 - butenyl)indole[4] (5).

In 1969, Šorm *et al.*[4] isolated two indole alkaloids from *Riccardia sinuata* (Hook.) Trev. (Hepaticae) and showed that one of these alkaloids was 6- (3 - methyl - 2 - butenyl)indole (5). Furthermore, in 1972, Taylor *et al.*[3] isolated 6 - (3 - methylbuta - 1,3 - dienyl)indole (2) from *Monodora tenuifolia* (Annonaceae). It seemed to us that both of these two indole alkaloids having an isoprene unit at the C_6 position could suitably be synthesized from ethyl α - acetyl - 2 - ethoxycarbonylindole - 6 - acetate (3), which can be easily prepared by the advanced Fischer indolization of a 2-methoxyphenylhydrazone.

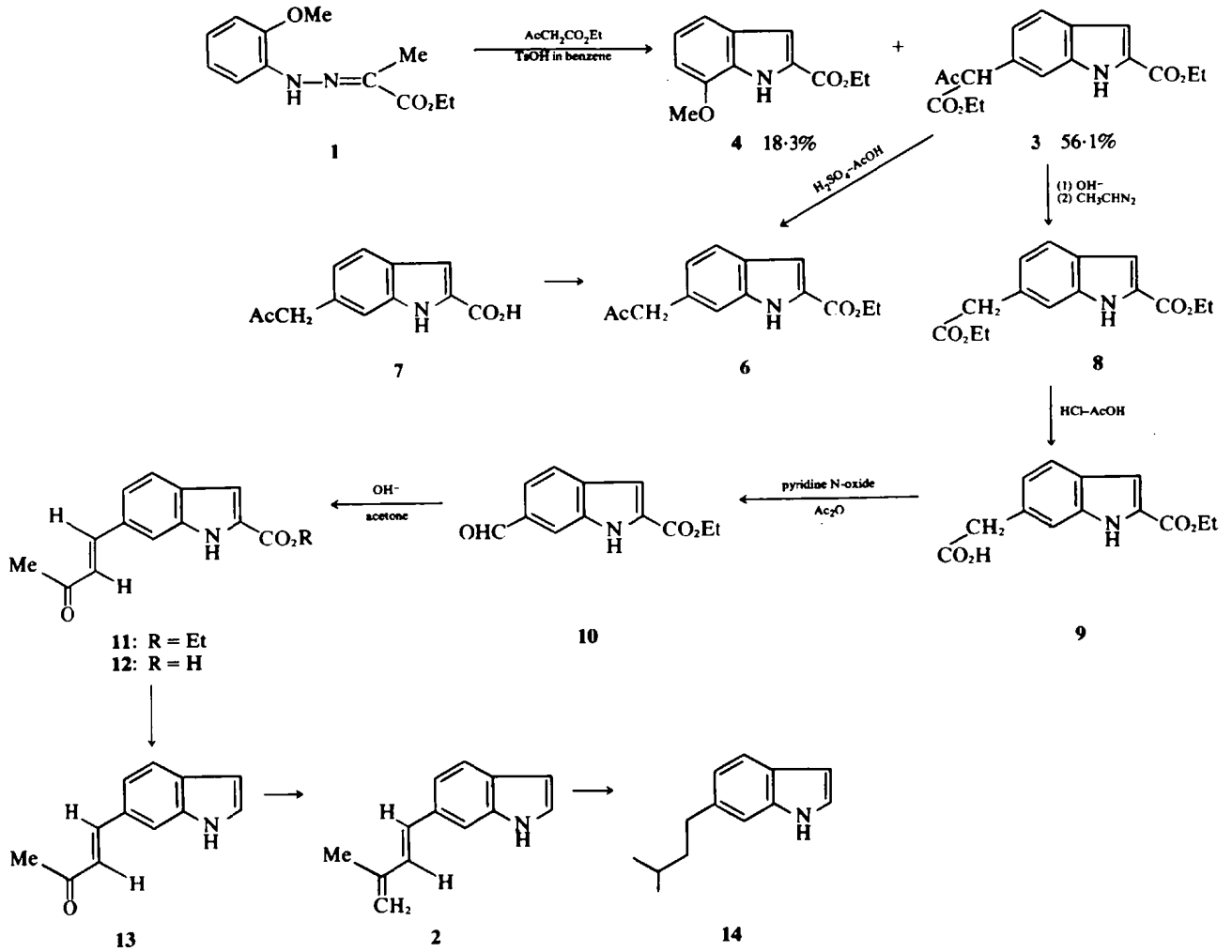
As described,[2] ethyl pyruvate 2 - methoxyphenylhydrazone (1) gave an indole product (3) having an ethyl acetoacetate group in its molecule in 56·1% yield by treatment with *p*-toluenesulfonic acid. Treatment of the indoleacetoacetate (3) with mixed sulfuric and acetic acids gave ethyl 6 - (2 - oxopropyl)indole - 2 - carboxylate (6), which has also been prepared from 6 - (2 - oxopropyl)indole - 2 - carboxylic acid[2] (7) by esterification. As the structure of the free acid (7) had been correlated with that of ethyl 6 - n - propylindole - 2 - carboxylate prepared by the Reissert method, the location of the acetoacetate group of the indole derivative (3) was directly confirmed to be the C_6 position (Scheme 1), and this had been indirectly proved by the non-identity of the indole-acetate compound (8) derived from indole-acetoacetate (3) with ethyl 2 - ethoxycarbonylindole - 5 - acetate prepared via an alternative route in the previous paper.[2]

2 - Ethoxycarbonylindole - 6 - acetic acid (9) seemed to be a likely common intermediate for our synthetic approach to both 6-substituted indoles. Degradation of the above acetoacetate derivative (3) with base followed by esterification with diazoethane gave ethyl 2 - ethyloxycarbonylindole - 6 -acetate (8). The required acid (9) was obtained from this acetate (8) by partial hydrolysis with conc. HCl in AcOH. The presence of an ethyl ester and a carboxyl group in the molecule was indicated by examination of its properties as an acid and because signals due to one ethyl ester only were observed (Experimental). The consideration that an aliphatic ester is, as a rule, more easily hydrolysed than an aromatic ester allows us to assign the structure to this acid (9).

We first aimed at synthesizing Taylor's base[3] (3). In 1965, Rüchardt *et al.*[5] and Cohen *et al.*[6] independently reported that oxidation of derivatives of phenylacetic acid with pyridine N-oxide gave the corresponding benzaldehyde derivatives in good yields. Application of this method to the above indole - 6 - acetic acid (9) gave ethyl 6 - formylindole - 2 - carboxylate (10) which shows an aldehydic proton at 10·02 δ as a singlet in the NMR spectrum.

Treatment of this aldehyde (10) with acetone furnished two aldol condensation products, ethyl 6 - (3 - oxo - 1 - butenyl)indole - 2 - carboxylate (11) and its free acid (12) in 24·6% and 64·7% yields respectively. Hydrolysis of the ester (11) provided the free acid (12) quantitatively.

The acid (12) was decarboxylated to 4 - (6 - indolyl) - 3 - buten - 2 - one (13) in 60·7% yield by treatment with copper chromite.[7] Treatment of the α,β-unsaturated ketone (13) with methylenetriphenylphosphorane gave colourless leaflets, m.p. 126–130° (lit.[3] m.p. 124–127°), in 76·9% yield. The product was so labile that a part of it was immediately hydrogenated with Pd–C to give a tetrahydro


OMe
Me
N–N=C
H
CO2Et
1
AcCH2CO2Et
TsOH in benzene
MeO
4 18·3%
+
AcCH
CO2Et
3 56·1%
H2SO4-AcOH
(1) OH⁻
(2) CH3CHN2
AcCH2
7
6
CH2
8
HCl-AcOH
pyridine N-oxide
Ac2O
OHC
10
CO2H
9
OH⁻
acetone
H
Me
O
11: R = Et
12: R = H
13
2
14

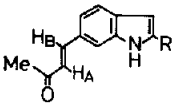
Scheme 1.

derivative (**14**), m.p. 36–38°. Each of these products was identified with an authentic sample of the natural product, 6 - (3 - methylbuta - 1,3 - dienyl)indole (**2**), and its tetrahydro derivative (**14**), respectively.

In connection with our synthetic study, we could establish the geometrical configuration of the double bond of Taylor's base (**2**), which had not been mentioned in the report[3] on the structural elucidation of the natural product. Decoupling experiments on the above two aldol condensation products and the decarboxylated derivative (**11, 12** and **13**) permitted us to discriminate the signals due to their olefinic protons from those due to aromatic protons. As all of these olefinic protons have a fairly large coupling constant (*ca* 16·0 Hz) as shown in Table 1, we may safely assign an E-configuration to the 3 - methylbuta - 1,3 - dienyl side chain of the natural product (**2**).

In 1971, Plieninger *et al.*[8] reported the synthesis of Šorm's base[4] (**5**) by treatment of 6-bromoindole with π - (3,3 - dimethylallyl)nickel bromide. As, however, preparation of the starting 6-bromoindole is not simple, we aimed at synthesizing this compound (**5**) from 2 - ethoxycarbonylindole - 6 - acetic acid (**9**). For this purpose, the carboxyl group of the acid (**9**) must be converted to an aldehyde group without reduction of the ester group at C_2 position. Brown *et al.*[9] reported that an acid group was subject to reduction with diborane more easily than an ester to give a primary alcohol. We applied this method to the acid (**9**). Treatment of **9** with an equimolecular amount of diborane using an internal system gave ethyl 6 - (2 - hydroxyethyl)indole - 2 - carboxylate (**15**) in 76·2% yield. The structure of this product was confirmed by NMR spectroscopy: two 2H triplets (J = 6·3 Hz) at 2·95 and 3·90 δ due to a sequence of $PhCH_2CH_2OH$; and a 3H triplet (J = 7·2 Hz) at 1·42 δ and a 2H quartet (J = 7·2 Hz) at 4·40 δ due to an ethyl ester group.

Table 1



	R	H_A	H_B
11	CO_2Et	6.75(d, J=16.0 Hz)	7.61(d, J=16.0 Hz)
12	CO_2H	6.70(d, J=16.0 Hz)	7.67(d, J=16.0 Hz)
13	H	6.73(d, J=16.0 Hz)	7.63(d, J=16.0 Hz)
Taylor's base (2)		6.65(d, J=16.2 Hz)	6.94(d, J=16.2 Hz)

Subsequent oxidation of this alcohol to the corresponding acetaldehyde derivative (**16**) was found to be rather troublesome. We attempted it with several reagents (Collins,[10] Jones,[11] etc). Although all reagents examined afforded some amount of the indole-aldehyde type compound (**10**) as a by-product, Collins reagent[10] provided the desired ethyl 6 - formylmethylindole - 2 - carboxylate (**16**) with least amount of contaminant in reasonable yield. Furthermore, because the desired aldehyde (**16**) itself readily polymerized during purification, it was characterized as the 2,4-dinitrophenylhydrazone. The crude product obtained with Collins reagent was suitable for the following step, Wittig reaction.

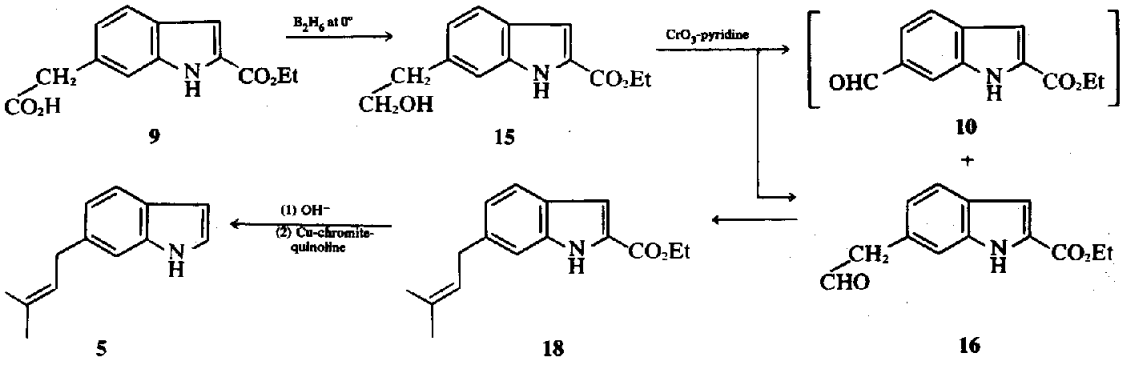
Treatment of the above acetaldehyde (**16**) with isopropylidenetriphenylphosphorane[12] gave ethyl 6 - (3 - methyl - 2 - butenyl)indole - 2 - carboxylate (**18**), the structure of which was confirmed by the presence of signals due to a 3,3-dimethylallyl group in its NMR spectrum [Experimental].

Hydrolysis of this allyl product (**18**) with base followed by decarboxylation with copper chromite[7] gave 6 - (3 - methyl - 2 - butenyl)indole (**5**) as an oily substance. This product formed a complex with 1,3,5 - trinitrobenzene as light-orange fine needles, m.p. 111·5–113°, [lit.[4] m.p. 106°], which were identified with an authentic sample of the 1,3,5-trinitrobenzenate obtained from the natural product.

The completion of our synthetic projects indicates the usefulness of the advanced Fischer indolization for the preparation of 6-substituted indoles.

EXPERIMENTAL

All m.ps were measured on a micro-melting hot-stage (Yanagimoto) and are uncorrected. IR, NMR and mass spectra were obtained with Hitachi EPI-G3, JEOL JMN-4H-100, and Hitachi RMU-6-E spectrometers, respectively. Assignments of all



Scheme 2.

NH and C_3–H signals were confirmed by disappearance of the NH signal and change of shape of the C_3–H signal from doublet to singlet after addition of D_2O. For column chromatography, silicic acid (100 mesh, Mallinckrodt Chemical Works) was used. For preparative TLC, Kieselgel GF_{254} nach Stahl (Merck) was used.

Ethyl α - acetyl - 2 - ethoxycarbonylindole - 6 - acetate (**3**). A soln of 42·8 g $TsOH·H_2O$ in 350 ml benzene was refluxed for 1 hr using a Dean–Stark water collecting trap. To the soln was added a mixture of 146·5 g ethyl acetoacetate and 17·7 g ethyl pyruvate 2-methoxyphenylhydrazone (**1**). The mixture was refluxed for 30 min, poured into ice-water, and extracted with ether. The organic layer was washed with $NaHCO_3$ aq, dried over $MgSO_4$ and evaporated *in vacuo*. The excess ethyl acetoacetate was removed by distillation under reduced pressure. The residue (23·4 g) was dissolved in benzene and chromatographed on silicic acid. Elution with benzene gave 3·01 g of **4**,[12] colourless needles, m.p. 116–117°. Subsequent elution with 15% AcOEt in benzene gave 13·55 g (56·1%) of **3**, colourless needles, m.p. 116–118°, which was identified with an authentic sample described in the previous report.[13]

Ethyl 6 - (2 - oxopropyl)indole - 2 - carboxylate (**6**). To a mixture of 2·1 ml AcOH, 0·28 ml H_2SO_4 and 1·4 ml water was added 350 mg of **3**. The mixture was refluxed for 30 min, poured into water and extracted with ether. The ethereal soln was washed with 5% $NaHCO_3$, dried over $MgSO_4$, and evaporated to dryness *in vacuo*. Preparative TLC (benzene:AcOEt = 19:1) of the residue (213 mg) gave 157 mg (52·5%) of colourless plates, m.p. 78·5–80·5°, which were recrystallized from benzene–hexane. This material was identified with an authentic sample of **6** prepared by esterification of **7**; IR ν_{max}^{Nujol} cm^{-1}: 3313 (NH), 1708sh, 1690 (C=O). NMR (CCl_4) δ: 1·42 (3H, t, J = 7·0 Hz, $CH_2\underline{CH_3}$), 2·08 (3H, s, $COCH_3$), 3·68 (2H, s, $\phi\underline{CH_2}CO$), 4·41 (2H, q, J = 7·0 Hz, OCH_2CH_3), 6·87 (1H, dd, J = 8·5 and 2·0 Hz, C_5–H), 7·07 (1H, d, J = 2·0 Hz, C_3–H), 7·25 (1H, d, J = 2·0 Hz, C_7–H), 7·52 (1H, d, J = 8·5 Hz, C_4–H), 9·79 (1H, br. s, NH). Mass spectrum *m/e*: 245 (M^+) (Found: C, 68·73; H, 6·21; N, 5·65. $C_{14}H_{15}O_3N$ requires: C, 68·55; H, 6·16; N, 5·71%).

Esterification of 6 - (2 - oxopropyl)indole - 2 - carboxylic acid[2] (**7**). To a suspension of **7**[2] (131 mg) in 10 ml ether was added a soln of diazoethane in ether (prepared from 500 mg nitrosoethylurea). The mixture was left to stand at room temp. overnight, then diluted with 50 ml ether, washed with dil $NaHCO_3$ aq, dried over $MgSO_4$, and evaporated to dryness *in vacuo*. The residue (153 mg) was dissolved in $CHCl_3$ and purified by column chromatography on silicic acid to give 75 mg of **6**. Recrystallization of the product from benzene–hexane gave colourless plates, m.p. 77·5–79·5°. This compound was found to be identical with a sample obtained from **3**.

Ethyl 2 - ethoxycabonyl indole - 6 - acetate (**8**). A soln of **3** (12·257 g) in 120 ml EtOH containing KOH (9·75 g) was refluxed for 1 h. After removal of the solvent by distillation under reduced pressure, the mixture was dissolved in water, made acidic with conc. HCl and extracted with ether. The ethereal soln was dried over $MgSO_4$ and evaporated to dryness to give the crude dicarboxylic acid (7·00 g).

To a soln of the above crude dicarboxylic acid (1·00 g) in 30 ml ether was added a soln of diazoethane in 80 ml ether, which was prepared from 3·0 g nitrosoethylurea. The mixture was allowed to stand at room temp. overnight then evaporated to dryness. The residue (1·358 g) was dissolved in benzene and chromatographed on silicic acid. Elution with benzene containing 5% AcOEt gave colourless needles (1·081 g), m.p. 92–94°, which were recrystallized from benzene–hexane. This material was identified with a sample prepared by the method described in the previous paper.[2]

2-Ethoxycarbonylindole - 6 - acetic acid (**9**). To a mixed soln of 3 ml conc. HCl and 15 ml AcOH was added 500 mg of **8**. The mixture was heated at 70° for 3 hr and evaporated to dryness *in vacuo*. Recrystallization of the residue from EtOH–benzene gave 335 mg (74·6%) of colourless needles, m.p. 178·5–179·5°. IR ν_{max}^{Nujol} cm^{-1}: 3240 (NH), 1712, 1669 (C=O). NMR (DMSO-d_6) δ: 1·36 (3H, t, J = 7·5 Hz, $CH_2\underline{CH_3}$), 3·60 (2H, s, $\phi\underline{CH_2}CO_2H$), 4·32 (2H, q, J = 7·5 Hz, $OC\underline{H_2}CH_3$), 6·93 (1H, dd, J = 8·0 and 1·8 Hz, C_5–H), 7·03 (1H, d, J = 2·5 Hz, C_3–H), 7·32 (1H, d, J = 1·8 Hz, C_7–H), 7·51 (1H, d, J = 8·0 Hz, C_4–H), 11·65 (1H, br. s, NH). Mass spectrum *m/e*: 247 (M^+) (Found: C, 63·46; H, 5·30; N, 5·66. $C_{13}H_{13}O_4N$ requires: C, 63·15; H, 5·30; N, 5·67%).

Ethyl 6-Formylindole - 2 - carboxylate (**10**). To a suspension of **9** (1·00 g) in a mixed soln of 15 ml abs benzene and 1·25 g Ac_2O was added pyridine N-oxide (3·08 g), the mixture thereby becoming clear. After being refluxed for 3 hr, the mixture was diluted with ether, washed with dil. HCl and dil. $NaHCO_3$ aq, dried over $MgSO_4$, and evaporated to dryness *in vacuo*. The residue (744 mg) was dissolved in $CHCl_3$ and chromatographed on silicic acid. Elution with $CHCl_3$ gave 422 mg of pale yellow needles, m.p. 180–181·5°, which were recrystallized from benzene. IR ν_{max}^{Nujol} cm^{-1}: 3321 (NH), 1694, 1683 (C=O). NMR (DMSO-d_6) δ: 1·39 (3H, t, J = 7·3 Hz, $CH_2\underline{CH_3}$), 4·38 (2H, q, J = 7·3 Hz, $OC\underline{H_2}CH_3$), 7·18 (1H, d, J = 2·3 Hz, C_3–H), 7·55 (1H, dd, J = 8·0 and 2·0 Hz, C_5–H), 7·78 (1H, d, J = 8·0 Hz, C_4–H), 8·01 (1H, d, J = 2·0 Hz, C_7–H), 10·02 (1H, s, CHO), 12·32 (1H, br. s, NH). Mass spectrum *m/e*: 217 (M^+) (Found: C, 66·41; H, 5·04; N, 6·46. $C_{12}H_{11}O_3N$ requires: C, 66·35; H, 5·10; N, 6·45%).

Aldol condensation of ethyl 6 - formylindole - 2 - carboxylate **10** *with acetone.* To a suspension of **10** (120 mg) in 12 ml of dil. acetone (acetone:H_2O = 1:1) was added 0·5 ml of 2% NaOH aq. The mixture was stirred for 2·5 hr at room temp., poured into a large amount of water, made acidic with conc. HCl, and extracted with ether. The ethereal soln was extracted with 5% $NaHCO_3$ aq.

Ethyl 6 - (3 - oxo - 1 - butenyl)indole - 2 - carboxylate (**11**). The organic layer was dried over $MgSO_4$ and evaporated to dryness *in vacuo*. Preparative TLC (hexane:ether = 1:1) gave 35 mg of colourless leaflets, m.p. 148–149°, which were recrystallized from benzene. IR ν_{max}^{Nujol} cm^{-1}: 3308 (NH), 1690, 1669 (C=O). NMR ($CDCl_3$) δ: 1·43 (3H, t, J = 7·2 Hz, $CH_2\underline{CH_3}$), 2·38, (3H, S, $COCH_3$), 4·43 (2H, q, J = 7·2 Hz, $OC\underline{H_2}CH_3$), 6·75 (1H, d, J = 16·0 Hz, $COC\underline{H}$ = $CH\phi$), 7·18 (1H, diffused s, C_3–H), 7·33 (1H, dd, J = 8·0 and 2·0 Hz, C_5–H), 7·58 (1H, d, J = 2·0 Hz, C_7–H), 7·61 (1H, d, J = 16·0 Hz, $COCH$=$C\underline{H}\phi$), 7·65 (1H, d, J = 8·0 Hz, C_4–H), 9·49 (1H, br. s, NH). Mass spectrum *m/e*: 257 (M^+) (Found: C, 70·00; H, 5·91; N, 5·39. $C_{15}H_{15}O_3N$ requires: C, 70·02; H, 5·88; N, 5·44%).

6 - (3 - Oxo - 1 - butenyl)indole - 2 - carboxylic acid (**12**). The soln in 5% $NAHCO_3$ aq. mentioned above was made acidic with conc. HCl and extracted with ether. The ethereal soln was dried over $MgSO_4$, evaporated to dryness *in vacuo*. Recrystallization of the residue from dioxane·H_2O gave 82 mg (64·7%) of pale yellow fine prisms, m.p. 283–285° (dec). IR ν_{max}^{Nujol} cm^{-1}: 3310 (NH), 1688 (C=O). NMR (DMSO-d_6) δ: 2·34 (3H, s, $COCH_3$), 6·70 (1H, d, J = 16·0 Hz, $COC\underline{H}$=$CH\phi$), 7·05 (1H, d, J = 2·0 Hz, C_3–H), 7·38 (1H, diffused d, J = 8·5 Hz, C_5–H), 7·64 (1H, d, J = 8·5 Hz, C_4–H), 7·67 (1H, d, J = 16·0 Hz, $COCH$=$C\underline{H}\phi$), 7·68 (1H, diffsued s, C_7–H), 11·88 (1H, br. s, NH). Mass spectrum *m/e*: 229 (M^+) (Found: C, 67·81; H, 4·83; N, 6·02. $C_{13}H_{11}O_3N$ requires: C, 68·11; H, 4·84; N, 6·11%).

Hydrolysis of ethyl 6 - (3 - oxo - 1 - butenyl)indole - 2 - carboxylate (**11**). To a soln of **11** (100 mg) in 4 ml acetone was added 1 ml of 5% NaOH aq. The mixture was stirred for 2 hr at room temp., poured into a large amount of water, made acidic with conc. HCl, and extracted with ether. The ethereal soln was dried over $MgSO_4$ and evaporated to dryness *in vacuo* to give **12** quantitatively.

4 - (6 - Indolyl) - 3 - buten - 2 - one (**13**). To a soln of **12** (100 mg) in 1·5 ml quinoline was added 20 mg copper chromite.[7] The mixture was heated at 210° under argon for 1 hr. After cooling, the

mixture was diluted with ether and filtered off. The filtrate was washed with dil. HCl and 5% $NaHCO_3$ aq, dried over $MgSO_4$, and evaporated to dryness *in vacuo*. Recrystallization of the residue gave 47 mg of pale yellow leaflets, m.p. 135–137°, which were recrystallized from cyclohexane–benzene. IR ν_{max}^{Nujol} cm^{-1}: 3325 (NH), 1675 (C=O). NMR ($CDCl_3$) δ: 2·37 (3H, s, $COCH_3$), 6·54 (1H, m, C_3–H), 6·73 (1H, d, J = 16·0 Hz, $COCH{=}CH\phi$), 7·28 (1H, m, C_2–H), 7·30 (1H, dd, J = 8·2 and 2·0 Hz, C_5–H), 7·57 (1H, d, J = 2·0 Hz, C_7–H), 7·61 (1H, d, J = 8·2 Hz, C_4–H), 7·63 (1H, d, J = 16·0 Hz, $COCH{=}CH\phi$), 8·71 (1H, br. s, NH). NMR ($CDCl_3$ + D_2O) δ: 6·54 (1H, d, J = 3·7 Hz, C_3–H), 7·28 (1H, d, J = 3·7 Hz, C_2–H). Mass spectrum *m/e*: 185 (M^+) (Found: C, 77·69; H, 5·96; N, 7·41. $C_{12}H_{11}ON$ requires: C, 77·81; H, 5·99; N, 7·56%).

6 - (3 - *Methyl* - 1,3 - *butadienyl*)*indole* (**2**). To a suspension of triphenylmethyl phosphonium bromide (480 mg)[14] in 1·5 ml THF was added 0·43 ml of a 20% soln of n-BuLi (Merck) in hexane with cooling under argon. A soln of **13** (125 mg) in 2 ml THF was added to the above mixed soln. The mixture was refluxed for 1 hr under argon, poured into water, and extracted with ether. The ethereal soln was washed with water, dried over $MgSO_4$, and evaporated to dryness *in vacuo*. Preparative TLC (ether:hexane = 1:1) of the oily residue (315 mg) gave 95 mg of colourless leaflets, m.p. 126–130°, which were purified by distillation under reduced pressure, b.p. 140° (2 mmHg). IR ν_{max}^{Nujol} cm^{-1}: 3382 (NH). Mass spectrum *m/e*: 183 (M^+). This material was identified with a sample of naturally occurring 6 - (3 - methyl - 1,3 - butadienyl) - indole by IR, UV and TLC.

6-*Isopentylindole* (**14**)

(a) *Synthetic specimen.* A soln of **2** (84 mg) in 20 ml EtOH was hydrogenated over 5% Pd-C (100 mg) under atom pressure at room temp. and the catalyst was filtered off. The filtrate was evaporated to dryness *in vacuo*. Preparative TLC (ether:hexane = 1:1) of the oily residue (60 mg) gave **14** (30 mg) as colourless needles, m.p. 36–38°, which were purified by distillation under reduced pressure, b.p. 150–160° (2 mmHg). IR ν_{max}^{Nujol} cm^{-1}: 3395 (NH). Mass spectrum *m/e*: 187 (M^+) (Found: C, 82·93; H, 9·23; N, 7·01. $C_{13}H_{17}N$ requires: C, 83·37; H, 9·15; N, 7·48%). This material was identified with a sample of the tetrahydro derivative of the natural product.

(b) *From the natural product.* The natural product, a gift from Prof. Taylor, was purified by preparative TLC. A soln of 50 mg of the freshly purified natural product was hydrogenated over 100 mg 5% Pd–C at atom pressure. After removal of the catalyst by filtration, the filtrate was evaporated *in vacuo*. Purification of the residue (31 mg) by preparative TLC and distillation under reduced pressure, b.p. 130° (1 mmHg) gave 13 mg of colourless needles, m.p. 38–41°.

Ethyl 6 - (2 - *hydroxyethyl*)*indole* - 2 - *carboxylate* (**15**). A soln of **9** (267 mg) in 2 ml diglyme was added to 64 mg $NaBH_4$ at 0° under argon. To the mixture was added 224 mg $BF_3{\cdot}Et_2O$ dropwise for 20 min. After being stirred for 1·5 hr under cooling, the mixture was poured into a large amount of water and extracted with ether. The ethereal soln was washed with dil. $NaHCO_3$ aq and H_2O several times, dried over anhyd. K_2CO_3, and evaporated to dryness *in vacuo*. Recrystallization of the residue (297 mg) from benzene–cyclohexane gave 192 mg of colourless prisms, m.p. 119–120·5°. IR ν_{max}^{Nujol} cm^{-1}: 3465 (NH), 3175 (OH), 1694 (C=O). NMR ($CDCl_3$) δ: 1·42 (3H, t, J = 7·2 Hz, CH_2CH_3), 1·80 (1H, s, OH), 2·95 (2H, t, J = 6·3 Hz, ϕCH_2CH_2), 3·90 (2H, t, J = 6·3 Hz, CH_2CH_2OH), 4·40 (2H, q, J = 7·2 Hz, OCH_2CH_3), 7·00 (1H, dd, J = 8·2 and 1·8 Hz, C_5–H), 7·17 (1H, d, J = 2·0 Hz, C_3–H), 7·22 (1H, d, J = 1·8 Hz, C_7–H), 7·58 (1H, d, J = 8·2 Hz, C_4–H), 9·15 (1H, br. s, NH). Mass spectrum *m/e*: 233 (M^+) (Found: C, 67·10; H, 6·66; N, 5·91. $C_{13}H_{15}O_3N$ requires: C, 66·93; H, 6·48; N, 6·01%).

Ethyl 6 - *Formylmethylindole* - 2 - *carboxylate* (**16**). To a soln of 2·81 ml pyridine in 85 ml anhyd. CH_2Cl_2 was added CrO_3 (1·89 g) with stirring under cooling. After 30 min, a soln of 15 (537 mg) in 25 ml anhyd. CH_2Cl_2 was added to the above soln in one lot. The mixture was stirred at 0° for 30 min then filtered. The ppt was washed with CH_2Cl_2. The filtrate combined with washings was washed with 1% NaOH aq dried over $MgSO_4$, and evaporated to dryness *in vacuo*. The residue (357 mg) was dissolved in a mixed soln of ether and hexane (2:3), and chromatographed on silicic acid. First elution with the above mixed solvent gave 40 mg of pale yellow needles, m.p. 180–181·5°, which were identified with a sample of **10**.

Subsequent elution with the same mixed solvent afforded 212 mg of colourless needles, m.p. 99·5°. NMR ($CDCl_3$) δ: 1·45 (3H, t, J = 7·0 Hz, CH_2CH_3), 3·79 (2H, d, J = 2·5 Hz, ϕCH_2CHO), 4·43 (2H, q, J = 7·0 Hz, OCH_2CH_3), 6·98 (1H, dd, J = 8·0 and 2·0 Hz, C_5–H), 7·17–7·30 (2H, m, C_3–H and C_7–H overlapped with the signal of $CHCl_3$), 7·65 (1H, d, J = 8·0 Hz, C_4–H), 9·21 (1H, br. s, NH), 9·78 (1H, t, J = 2·5 Hz, CH_2CHO). Mass spectrum *m/e*: 231 (M^+). This material was so labile that it was characterized as its 2,4-dinitrophenylhydrazone (**17**).

Ethyl 6 - *formylmethylindole* - 2 - *carboxylate* 2,4 - *dinitrophenylhydrazone* (**17**) A soln of **16** (86 mg) in 1·5 ml EtOH was added to a mixed soln of 81 mg 2,4 - dinitrophenylhydrazine and 0·5 ml H_2SO_4 in dil. EtOH (EtOH:H_2O = 2·0 ml:0·6 ml). The ppt was collected by filtration and washed with EtOH. Recrystallization from dioxane–EtOH·H_2O gave 115 mg of yellow fine needles, m.p. 202–204°. IR ν_{max}^{Nujol} cm^{-1}: 3342, 3294 (NH), 1695 (C=O). NMR (DMSO-d_6) δ: 1·35 (3H, t, J = 7·0 Hz, CH_2CH_3), 3·77 (2H, d, J = 5·8 Hz, $\phi CH_2CH{=}C$), 4·32 (2H, q, J = 7·0 Hz, OCH_2CH_3), 6·99 (1H, dd, J = 8·2 and 2·0 Hz, C_5–H), 7·08 (1H, diffused s, C_3–H), 7·35 (1H, d, J = 2·0 Hz, C_7–H), 7·59 (1H, d, J = 8·2 Hz, C_4–H), 7·91 (1H, d, J = 9·1 Hz, C_6–H), 8·14 (1H, t, J = 5·8 Hz, $CH_2CH{=}N$), 8·32 (1H, dd, J = 9·1 and 2·5 Hz, C_5–H), 8·84 (1H, d, J = 2·5 Hz, C_3–H), 11·38 (1H, s, $\phi NHN{=}C$), 11·76 (1H, diffused s, NH) (Found: C, 55·51; H, 4·21; N, 16·95. $C_{19}H_{17}O_6N_5$ requires: C, 55·47; H, 4·17; N, 17·03%).

Ethyl 6 - (3 - *methyl* - 2 - *butenyl*)*indole* - 2 - *carboxylate* (**18**). To a suspension of isopropyltriphenylphosphonium iodide (620 mg)[14] in 4 ml anhyd. THF was added 0·42 ml of a 20% soln of n-BuLi in hexane (Merck) at 0° under argon. To this soln was added a soln of **16** (220 mg) in 2 ml anhyd. THF. After being stirred at room temp. for 15 min, the mixture was diluted with ether and filtered. The filtrate was washed with water, dried over anhyd. K_2CO_3, and evaporated to dryness *in vacuo*. The oily residue was dissolved in benzene and purified by column chromatography on silicic acid. Elution with benzene gave 191 mg of a crude product. Preparative TLC (benzene) of this product gave 169 mg of colourless needles, m.p. 119–121°, which were recrystallized from hexane. IR ν_{max}^{Nujol} cm^{-1}: 3330 (NH), 1693 (C=O). NMR (CCl_4) δ: 1·45 (3H, t, J = 7·0 Hz, CH_2CH_3), 1·77 (6H, diffused s, $C{=}C(CH_3)_2$), 3·42 (2H, d, J = 7·5 Hz, $\phi CH_2CH{=}C$), 4·42 (2H, q, J = 7·0 Hz, OCH_2CH_3), 5·36 (1H, diffused t, J = 7·5 Hz, $CH_2CH{=}C$), 6·85 (1H, dd, J = 8·7 and 1·8 Hz, C_5–H), 7·06 (1H, d, J = 2·0 Hz, C_3–H), 7·11 (1H, diffused s, C_7–H), 7·46 (1H, d, J = 8·7 Hz, C_4–H), 9·36 (1H, br. s, NH). Mass spectrum *m/e*: 257 (M^+) (Found: C, 74·76; H, 7·53; N, 5·36. $C_{16}H_{19}O_2N$ requires: C, 74·68; H, 7·44; N, 5·44%).

6 - (3 - *Methyl* - 2 - *butenyl*)*indole* - 2 - *carboxylic acid* (**19**). A soln of **18** (80 mg) in 2·5 ml EtOH was added to a soln of KOH (100 mg) in 1·5 ml EtOH. The mixed soln was refluxed for 30 min, cooled and poured into a large amount of water. The mixture was made acidic with conc. HCl and extracted with ether. The ethereal soln was dried over $MgSO_4$ and evaporated to dryness. Recrystallization of the residue from benzene gave 63 mg of colourless fine prisms, m.p. 164–166°. IR ν_{max}^{Nujol} cm^{-1}: 3392 (NH), 1684 (COOH). NMR (DMSO-d_6) δ: 1·71 (6H, s, $C{=}C(CH_3)_2$), 3·36 (2H, d, J = 7·5 Hz, $\phi CH_2CH{=}C$), 5·31 (1H, diffused t, J = 7·5 Hz, $CH_2CH{=}C$), 6·84 (1H, dd, J = 8·3 and 1·5 Hz, C_5–H), 6·98 (1H, d, J = 2·5 Hz, C_3–H), 7·18 (1H, d, J = 1·5 Hz, C_7–H), 7·49 (1H, d,

$J = 8{\cdot}3$ Hz, C_4–H), 11·47 (1H, diffused s, NH). Mass spectrum *m/e*: (M^+) (Found: C, 73·49; H, 6·63; N, 5·84. $C_{14}H_{15}O_2N$ requires: C, 73·34; H, 6·59; N, 6·11%).

6 - (3 - *Methyl* - 2 - *butenyl*)*indole* (**5**). A mixture of **19** (48 mg) and copper chromite[7] (12 mg) in 1·5 ml quinoline was heated at 205–210° for 45 min under argon. The mixture was diluted with ether, extracted with 5% HCl aq dried over anhyd. K_2CO_3, then evaporated to dryness *in vacuo*. Preparative TLC (benzene) of the residue (45 mg) gave 25 mg of an oily product which was purified by distillation at 120–130° at reduced pressure (2 mmHg). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3488 (NH). NMR ($CDCl_3$) δ: 1·74 (6H, s, $C{=}C(CH_3)_2$), 3·41 (2H, d, $J = 7{\cdot}5$ Hz, $\phi CH_2CH{=}C$), 5·38 (1H, diffused t, $J = 7{\cdot}5$ Hz, $\phi CH_2CH{=}C$), 6·46 (1H, m, C_3–H), 6·93 (1H, dd, $J = 8{\cdot}3$ and 1·5 Hz, C_5–H), 7·07 (1H, m, C_2–H), 7·13 (1H, diffused s, C_7–H), 7·52 (1H, d, $J = 8{\cdot}3$ Hz, C_4–H), 7·90 (1H, br. s, NH). Irradiation at 7·90 δ changed the C_3 and C_2–H signals from multiplets to doublets ($J = 3{\cdot}0$ Hz), respectively. UV λ_{max}^{EtOH} nm (log ϵ): 222 (4·61), 271 (3·78), 275 *sh* (3·77), 281 (3·77), 285 *sh* (3·69). Mass spectrum *m/e*: 185 (M^+).

6 - (3 - *Methyl* - 2 - *butenyl*)*indole* 1,3,5 - *trinitrobenzenate* (**21**). A soln of **20** (16 mg) and 1,3,5-trinitrobenzene (18·5 mg) in EtOH was evaporated to dryness. Recrystallization of the residue from 70% EtOH aq gave light-orange fine needles, m.p. 111·5–113° (Found: C, 57·46; H, 4·58; N, 14·00. $C_{13}H_{15}N{\cdot}C_6H_3N_3O_6$ requires: C, 57·28; H, 4·55; N, 14·07%). This material was identified by its IR spectrum with an authentic sample prepared from the natural product.

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