Studies in the Echinulin Series. Part I. Synthesis of 3-(Indol-2-yl)-3-methylbut-1-ene

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Some preliminary model experiments directed towards the synthesis of echinulin are described, including the synthesis of 3-(indol-2-yl)-3-methylbut-1-ene.

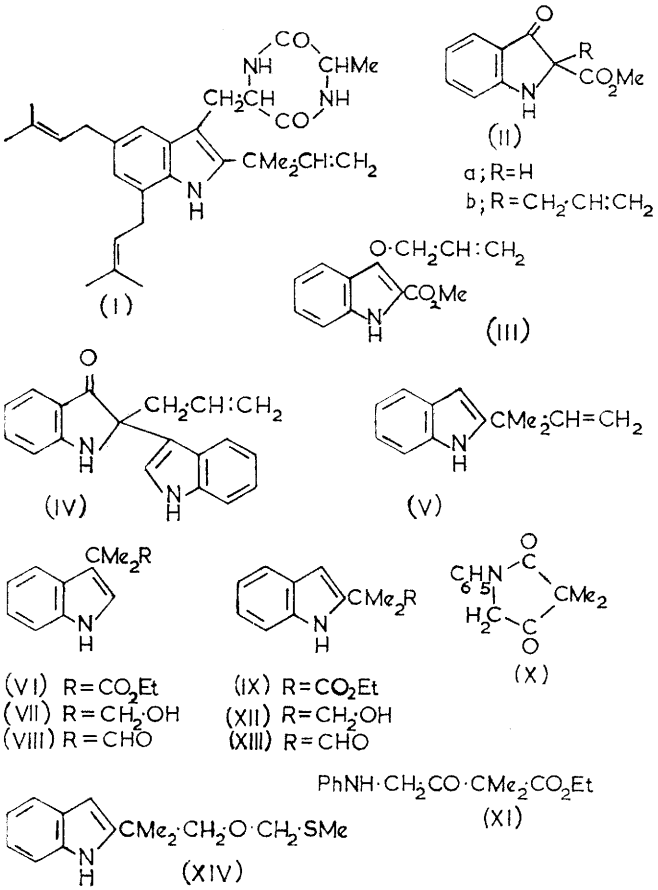
At the outset of our studies no investigations directed towards the total synthesis of echinulin (I) had been published, and the only ones available to date are those of Jackson and Smith [1] and Plieninger and Herzog.[2]

In common with the latter group we initially hoped to introduce the dimethylallyl side-chain into position 2 of the indole ring by means of a Claisen rearrangement; accordingly we first studied the behaviour of 3-allyloxyindole. 3-Allyloxyindole appears not to have been previously prepared; our first attempt to prepare it required as intermediate 3-allyloxy-2-methoxycarbonylindole (III), which we hoped to prepare by *O*-alkylation of 2-methoxycarbonylindoxyl (IIa). This reaction parallels that reported by Plieninger and Herzog,[2] who alkylated the corresponding ethyl ester, but obtained only the *C*-alkylated product. In our hands the alkylation of 2-methoxycarbonylindoxyl [3] with allyl bromide and potassium hydroxide in acetone afforded the *O*-allyl derivative (III), but in only 5% yield; the major product (65%) was the product of *C*-alkylation (IIb). Alkylation with allyl bromide and potassium carbonate in dimethyl sulphoxide [4] gave a similar mixture of *O*-alkylation (6·5%) and *C*-alkylation (48%) products. As expected the *C*-allyl derivative was the only product obtained from the alkylation with allyl bromide and sodium methoxide in methanol.

In confirmation of its structure 3-allyloxy-2-methoxycarbonylindole exhibits u.v. maxima at 231 (ε 22,100) and 298 (16,800) mμ, which correspond closely with those of 3-methoxy-2-methoxycarbonylindole [2]

[1] A. H. Jackson and A. E. Smith, *Tetrahedron*, 1965, **21**, 989.
[2] H. Plieninger and H. Herzog, *Monatsh.*, 1967, **98**, 807.
[3] A. Robertson, *J. Chem. Soc.*, 1927, 1939; D. Vorländer and R. von Schilling, *Annalen*, 1898, **301**, 349.
[4] G. Brieger and W. M. Pelletier, *Tetrahedron Letters*, 1965, 3555.

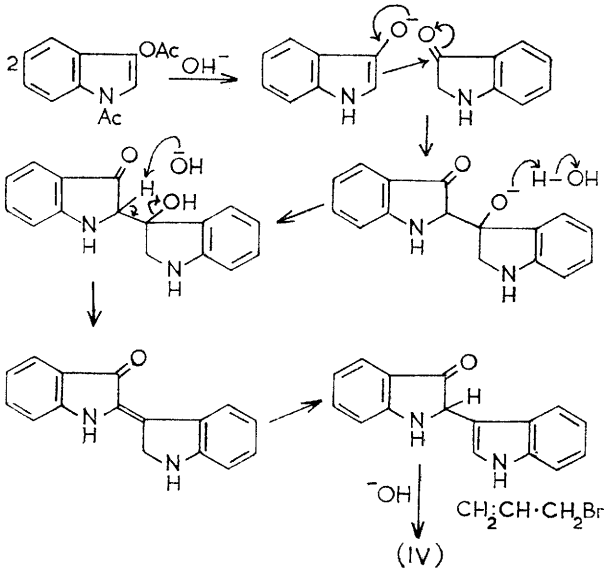
($\lambda_{max.}$ 230 and 297 mμ). It does not exhibit the characteristic indoxyl absorptions at 1680 and 1615 cm.$^{-1}$ in the i.r. In the n.m.r. spectrum of (III) the methylene group attached to oxygen gives rise to a double triplet signal with centre at τ 5·2, coupled with the adjacent olefinic proton (J 5·5) and with the protons of the terminal



methylene group (J 1·5 c./sec.). This terminal methylene group gives a multiplet at τ 4·4—4·9 and the olefinic –CH= gives a twelve-peak signal at τ 3·48—4·15. This last results from coupling with the adjacent olefinic protons (J_{cis} 0, J_{trans} 17 c./sec.) and with the –O–CH_2– protons (J 5·5 c./sec.). In contrast the yellow C-alkylation product (IIb) exhibits typical indoxyl spectra ($\lambda_{max.}$ 232, 256infl, and 394 mμ; $\nu_{max.}$ 1680 and 1615 cm.$^{-1}$). The C-2 methylene group gives rise to a multiplet at τ 6·7—7·7, *i.e.* at considerably higher field, as expected, than that due to the oxygen-bound methylene group of (III).

It was hoped next to hydrolyse 3-allyloxy-2-methoxycarbonylindole to the corresponding acid, which could then be decarboxylated to 3-allyloxyindole or utilised immediately in an attempted Claisen rearrangement. However, alkaline hydrolysis of (III) gave a complex mixture which, in view of the uneconomic preparation of the starting material, was not further investigated. We subsequently attempted to prepare 3-allyloxyindole directly from 3-acetoxy-N-acetylindole,[5] by treatment with aqueous sodium hydroxide followed by allyl bromide, thus avoiding the isolation of the intermediate indoxyl. However, the only isolable product was a yellow solid, $C_{19}H_{16}N_2O$, the u.v. spectrum of which ($\lambda_{max.}$ 221, 258, 280, 288, and 400 mμ) was a summation of indole and indoxyl chromophores. We formulate this product as 2-allyl-2-(indol-3-yl)indoxyl (IV), a constitution which agrees with its chemical and physical properties. It is insoluble in alkali and gives no colour with ferric chloride, but gives an orange-red colouration with the Ehrlich reagent. Its i.r. spectrum contains imino- (3350 and 3260 cm.$^{-1}$) and indoxyl (1670 and 1610 cm.$^{-1}$) absorptions, and its n.m.r. spectrum shows, in addition to the aromatic protons and the indole α-proton, the general pattern of absorptions of a C-allyl group, although in this case the multiplets are not very well resolved.

The compound (IV) is presumably formed from 3-acetoxy-N-acetylindole by hydrolysis to indoxyl, aldol condensation of the latter in the presence of base, and C-2 alkylation of the product. The Scheme shows a possible mechanism for the reactions.



We also attempted to obtain 2-allylindole by Claisen rearrangement of N-allylindole, but the latter was recovered unchanged after being heated at 250° for 8 hr. This result is in accord with Jackson and Smith's failure to rearrange N-allyl-3-methylindole.[1]

We next attempted a more conventional preparation of 3-(indol-2-yl)-3-methylbut-1-ene (V). As a model we first studied the corresponding indol-3-yl series, since this enabled us to utilise as starting material ethyl α-indol-3-ylisobutyrate (VI), which is readily available from the reaction of indole, acetone, and chloroform in the presence of sodium hydroxide.[6] Lithium aluminium hydride reduction of (VI) gave the correspond-

[5] S. J. Holt and P. W. Sadler, *Proc. Roy. Soc.*, 1958, *B*, **148**, 481.

[6] H. Erdtman and A. Jönsson, *Acta Chem. Scand.*, 1954, **8**, 119.

ing primary alcohol (VII), which we then intended to oxidise to the aldehyde (VIII), prior to introducing the terminal methylene group by the Wittig reaction. However, oxidation of (VII) by a modified Oppenauer reaction (*p*-benzoquinone and aluminium t-butoxide) gave a disappointingly low yield (10%) of aldehyde [contrast the oxidation of the *N*-methyl derivative of (VII) by the same process [7]]. Attempts to oxidise the alcohol (VII) with lead tetra-acetate in pyridine [8] or with phosphoric acid and dicyclohexylcarbodi-imide in dimethyl sulphoxide [9] also failed. Oxidation with acetic anhydride and dimethyl sulphoxide [10] afforded a product which exhibited intense absorption at 1710 cm.$^{-1}$ and a sharp peak at 3400 cm.$^{-1}$ (NH), but no hydroxy-absorption. It proved to be a mixture of two compounds (t.l.c.) with closely similar R_F values, presumably (in the light of later experience) the desired aldehyde (VIII) and the methylthiomethyl ether of the starting material. However, repeated attempts to separate this mixture by chromatography on Kieselgel G or alumina failed, and in view of more promising results in the 2-substituted series this model sequence was not further investigated.

Ethyl α-indol-2-ylisobutyrate (IX) has previously been prepared by Jönsson,[11] who obtained it as a colourless, crystalline solid, m.p. 83·5—84·5°, from the Bischler reaction of crude ethyl 4-bromo-2,2-dimethylacetoacetate with aniline at 140—150°. Repetition of Jönsson's experiment gave a low yield of a colourless, crystalline solid of m.p. 82—84°, together with a crystalline compound of m.p. 101—103°. The latter was identified from its spectrographic properties as 3,3-dimethyl-1-phenylpyrrolidine-2,4-dione (X), and is presumably formed by intramolecular loss of ethanol from the α-arylamino-ketone (XI), a known intermediate in the Bischler reaction. The material of m.p. 82—84° was shown to be a mixture of (X) with the desired ester (IX), which was obtained as colourless needles, m.p. 120—122°. By use of purified ethyl 4-bromo-2,2-dimethylacetoacetate and an excess of aniline the yield of (IX) was increased to 50%.

Reduction of (IX) with lithium aluminium hydride afforded the alcohol (XII), m.p. 90—92°, which was then oxidised to the aldehyde (XIII) by acetic anhydride and dimethyl sulphoxide. Chromatography of the product on Kieselgel G gave 2-(indol-2-yl)-2-methylpropyl methylthiomethyl ether (XIV), m.p. 50—52°, and the aldehyde (XIII), m.p. 68—70°. Wittig reaction of the aldehyde (XIII) with methylenetriphenylphosphorane afforded 3-(indol-2-yl)-3-methylbut-1-ene (V) as an oil, which was purified by chromatography on Kieselgel G. The constitution of (V) was confirmed by the spectral data; in particular the C-2 substituent was responsible for n.m.r. signals at τ 8·58 (6H, s, CMe_2), 4·8—5·2 (2H, octet, J_{AB} 18, J_{AC} 10, J_{BC} 2 c./sec., $-CH_A{=}CH_BH_C$), and 3·67—4·2 (1H, q, J_{AB} 18, J_{AC} 10 c./sec., $-CH_A{=}CH_BH_C$). The indole 3-proton was observed as a doublet at τ 3·72 (J 2·5 c./sec.).

Further reactions of this product will be described in a subsequent communication.

EXPERIMENTAL

Ultraviolet absorption spectra were measured in ethanol solution with a Unicam SP 200 spectrometer. I.r. spectra were determined with a Perkin-Elmer 125 spectrometer and n.m.r. spectra with a Varian A 60 spectrometer.

3-Allyloxy-2-methoxycarbonylindole and 2-Allyl-2-methoxycarbonylindoxyl.—(*a*) A solution of 2-methoxycarbonylindoxyl (1·91 g.) and allyl bromide (1·21 g.) in acetone (40 ml.) was stirred and cooled to 0° and potassium hydroxide (0·6 g.) in water (3 ml.) was added dropwise. The mixture was stirred for 10 hr. at 0°, then set aside overnight in the refrigerator. The acetone was evaporated under reduced pressure and the residue was taken up in water and ether. The combined ethereal layers were washed with water, dried (Na_2SO_4), and evaporated to yield a yellow oil, which was chromatographed on Kieselgel G with benzene as eluant. 3-Allyloxy-2-methoxycarbonylindole (0·12 g., 5·2%) was eluted first, followed by fractions containing both the *O*- and the *C*-allyl derivatives; finally pure 2-allyl-2-methoxycarbonylindoxyl (1·5 g., 65·5%) was obtained. *3-Allyloxy-2-methoxycarbonylindole* was obtained from light petroleum (b.p. 40—60°) as colourless needles, m.p. 86—88° (Found: C, 67·4; H, 5·5; N, 6·3. $C_{13}H_{13}NO_3$ requires C, 67·5; H, 5·65; N, 6·05%), $\nu_{max.}$ (KCl) 3330 (NH), 1675 (CO_2Me), and 1265 (aryl alkyl ether) cm.$^{-1}$, $\lambda_{max.}$ 231 (ε 22,100) and 298 (16,800) mμ, τ ($CDCl_3$) 6·05 (3H, s, CO_2Me), 5·2 (2H, d t, J 5·5 and 1·5 c./sec., $-O{\cdot}CH_2-$), 4·4—4·9 (2H, m, $-CH{=}CH_2$), 2·15—3·1 (4H, m, aromatic), and 1·25br (1H, NH). *2-Allyl-2-methoxycarbonylindoxyl* was obtained from light petroleum (b.p. 60—80°) as yellow prisms, m.p. 71—73° (Found: C, 67·4; H, 5·65; N, 6·15. $C_{13}H_{13}NO_3$ requires C, 67·5; H, 5·65; N, 6·05%), $\nu_{max.}$ (KCl) 3340 (NH), 1740 (CO_2Me), and 1680 and 1615 (indoxyl) cm.$^{-1}$, $\lambda_{max.}$ 232 (ε 24,800), 256infl (5950), and 394 (3630) mμ, τ ($CDCl_3$) 6·7—7·7 (2H, m, $-CH_2-CH{=}CH_2$), 6·25 (3H, s, CO_2Me), 4—5·1 (4H, m, $-CH{=}CH_2$ and NH), and 2·3—3·3 (4H, m, aromatic).

(*b*) 2-Methoxycarbonylindoxyl (0·191 g.), allyl bromide (0·121 g.), and potassium carbonate (0·145 g.) were added to dimethyl sulphoxide (10 ml.) and the mixture was heated at 70° for 2 hr. When cold, it was poured into water and the aqueous layer was extracted with ether. The extract was washed with water, dried ($MgSO_4$), and evaporated to yield a yellow oil, which was chromatographed on Kieselgel G with benzene as eluant. 3-Allyloxy-2-methoxycarbonylindole (0·015 g., 6·5%) and 2-allyl-2-methoxycarbonylindoxyl (0·11 g., 47·5%) were obtained, and were identified by comparison of spectral data with those of authentic material prepared as described above.

2-Allyl-2-methoxycarbonylindoxyl.—2-Methoxycarbonylindoxyl (2 g.) was added to a solution of sodium (0·24 g.) in methanol (25 ml.), and the solution was warmed and stirred. Allyl bromide (1·4 g.) was added dropwise and the solution was stirred and heated under reflux for 8 hr., then cooled. The methanol was removed under reduced pressure and the residue was taken up in water and ether.

[7] D. A. Cockerill, Sir Robert Robinson, and J. E. Saxton, *J. Chem. Soc.*, 1955, 4369.
[8] R. E. Partch, *Tetrahedron Letters*, 1964, 3071.
[9] K. E. Pfitzner and J. G. Moffatt, *J. Amer. Chem. Soc.*, 1963, **85**, 3027.
[10] J. D. Albright and L. Goldman, *J. Amer. Chem. Soc.*, 1965, **87**, 4214.
[11] A. Jönsson, *Svensk. kem. Tidskr.*, 1955, **67**, 188.

The aqueous layer was separated and extracted twice with ether. The combined ethereal layers were dried ($MgSO_4$) and the ether was evaporated to yield a yellow oil which slowly crystallised. The latter was chromatographed on Kieselgel G with benzene as eluant to give 2-allyl-2-methoxycarbonylindoxyl (1·2 g., 52%), which was obtained from light petroleum (b.p. 60—80°) as yellow prisms, m.p. 71—73°, identified by comparison of spectral data with those of authentic material prepared as in (*a*).

Attempted Alkaline Hydrolysis of 3-*Allyloxy*-2-*methoxycarbonylindole*.—3-Allyloxy-2-methoxycarbonylindole (75 mg.) was added to sodium hydroxide (75 mg.) in water (5 ml.) and the mixture was heated under reflux for 4 hr. in an atmosphere of nitrogen, then cooled. The aqueous layer was extracted with ether, acidified with dilute hydrochloric acid, and extracted again with ether, and the combined ether extracts were dried (Na_2SO_4). Evaporation of the ether left an oily mixture of several products (t.l.c. with benzene–5% ether as eluant).

Attempted O-*Alkylation of Indoxyl*.—(This reaction was carried out in an atmosphere of oxygen-free nitrogen.) 3-Acetoxy-*N*-acetylindole (1 g.) was added to sodium hydroxide (0·37 g.) in water (15 ml.) and the mixture was stirred at room temperature for 15 min. It was then stirred and heated under reflux until the diacetylindoxyl had dissolved. The solution was then cooled to room temperature and allyl bromide (0·56 g.) was added slowly. The yellow precipitate obtained was chromatographed on Kieselgel G with benzene–2% ethanol as eluant. 2-*Allyl*-2-(*indol*-3-*yl*)-*indoxyl* (0·31 g., 46%) was obtained from ethanol–water as yellow plates, m.p. 207—210° (Found: C, 78·8; H, 5·35; N, 9·9. $C_{19}H_{16}N_2O$ requires C, 79·15; H, 5·6; N, 9·7%), $\nu_{max.}$ (KCl) 3350 (NH), 3260 (NH), and 1670 and 1610 (indoxyl) cm.$^{-1}$ $\lambda_{max.}$ 221 (ε 49,300), 258 (11,000), 280 (7580), 288 (6060), and 400 (3790) mμ, τ (deuteriopyridine) 6·5—7·2 (2H, m, $-CH_2-CH=CH_2$), 4·6—5·1 (2H, d, $-CH=CH_2$), 3·7—4·5 (1H, m, $-CH=CH_2$), 1·7—3·5 (10H, m, aromatic protons, indole α-proton, and NH), and —1·6br (1H, s, NH).

N-*Allylindole*.—Sodium (3 g.) was added in small pieces to liquid ammonia (300 ml.) containing ferric nitrate (0·1 g.). When dissolution was complete, indole (10 g.) in ether (25 ml.) was added to the stirred mixture. After 10 min., allyl bromide (10 ml.) was added dropwise and stirring was continued for a further 2 hr. The ammonia was allowed to evaporate, water (100 ml.) and ether (100 ml.) were added, the ethereal layer was separated and dried ($MgSO_4$), and the solvent was removed. The residual oil distilled at 122—128°/12 mm. and was shown to be a mixture of indole and *N*-allylindole (i.r. spectrum and t.l.c.). It was chromatographed on Kieselgel G with benzene as eluant. *N*-Allylindole (6 g., 45%) was obtained as a colourless oil, b.p. 130—132°/13 mm., n_D^{23} 1·5867, $\nu_{max.}$ (film) 920 and 990 ($-CH=CH_2$) cm.$^{-1}$, $\lambda_{max.}$ 220 (ε 34,000), 280 (6000), and 292 (4500) mμ, τ (neat) 6·1 (2H, d t, *J* 5 and 1·5 c./sec., $-N-CH_2-CH=CH_2$), 5·1—5·6 (2H, m, $-CH_2-CH=CH_2$), 4·2—4·9 (1H, 10-peak signal, $-CH_2-CH=CH_2$), 3·57 (1H, d, *J* 3 c./sec., indole β-proton), 3·38 (1H, d, *J* 3 c./sec.; indole α-proton), and 2·2—3·1 (4H, m, aromatic) (lit.,[12] b.p. 114—116°/6 mm.).

2-(*Indol*-3-*yl*)-2-*methylpropan*-1-*ol*.—Ethyl α-indol-3-ylisobutyrate [6] (3 g.) in dry ether (50 ml.) was added dropwise to a stirred suspension of lithium aluminium hydride (6 g.) in dry ether (75 ml.) during 30 min., and the mixture was then heated under reflux for 1 hr. The excess of lithium aluminium hydride was destroyed with ice–water, an excess of water was added, and the ethereal layer was separated and dried ($MgSO_4$). The residue, after evaporation of the ether, crystallised from benzene–light petroleum (b.p. 60—80°). 2-(*Indol*-3-*yl*)-2-*methylpropan*-1-*ol* (2 g., 81%) was obtained from pentane–benzene as colourless plates, m.p. 71—72° (Found: C, 76·1; H, 7·6; N, 7·45. $C_{12}H_{15}NO$ requires C, 76·15; H, 8·0; N, 7·4%), $\nu_{max.}$ (KCl) 3470 (NH) and 3310 (OH) cm.$^{-1}$, $\lambda_{max.}$ 222 (ε 35,900), 282 (6100), and 290 (5270) mμ, τ ($CDCl_3$) 8·62 (6H, s, CMe_2), 8·43br (1H, s, OH), 6·29 (2H, s, $-CH_2-OH$), 3·21 (1H, d, *J* 2·5 c./sec., indole α-proton), 2·67—3·1 (3H, m,) and 2·1—2·4 (1H, m) (aromatic protons), and 1·85br (1H, NH).

α-(*Indol*-3-*yl*)*isobutyraldehyde*.—A mixture of 2-(indol-3-yl)-2-methylpropan-1-ol (1·5 g.), *p*-benzoquinone (3 g.), aluminium t-butoxide (3·75 g.), and dry benzene (50 ml.) was heated under reflux for 1 hr. The cooled solution was filtered, the solid was washed well with ether, and the combined organic extracts were washed with dilute sulphuric acid and then with aqueous sodium hydroxide until the aqueous extracts were colourless. At this stage emulsification was troublesome; the alkali was therefore added in portions of 25 ml. and the liquids were merely swirled until most of the quinone had been removed. The ether–benzene solution was then dried ($MgSO_4$), and the solvent was removed to yield a red semi-solid residue, which was crystallised from light petroleum (b.p. 60—80°) (charcoal) to give α-(*indol*-3-*yl*)*isobutyraldehyde* (0·15 g., 10%) as colourless needles, m.p. 48—49° (Found: C, 77·1; H, 6·7; N, 7·45. $C_{12}H_{13}NO$ requires C, 76·95; H, 7·0; N, 7·5%), $\nu_{max.}$ (KCl) 3380 (NH) and 2700 and 1710 (CHO) cm.$^{-1}$, $\lambda_{max.}$ 220 (ε 32,900), 280 (6350), and 289 (5100) mμ, τ ($CDCl_3$) 8·49 (6H, s, CMe_2), 3·01 (1H, d, *J* 2·5 c./sec.; indole α-proton), 2·3—3·0 (4H, m, aromatic), 1·7br (1H, NH), and 0·5 (1H, s, CHO).

Ethyl α-*Indol*-2-*ylisobutyrate*.—(*a*) Bromine (16 g.) in chloroform (50 ml.) was added dropwise, with stirring, to ethyl 2,2-dimethylacetoacetate [13] (16 g.) in chloroform (50 ml.). When bromination was complete the solvent was removed *in vacuo* (maximum bath temperature 40°). Aniline (20 g.) was then added in small portions with cooling and shaking and the resulting mixture was heated at 140—150° for 4 hr. When cold, the semi-solid mass was brought into solution by treatment with ether and N-hydrochloric acid. The ethereal extracts were washed with N-hydrochloric acid, water, and sodium hydrogen carbonate solution, and then dried (Na_2SO_4). The ether was removed and the residual oil was distilled *in vacuo*; a yellowish oil was obtained which solidified in the receiver. The product gave a colourless crystalline solid (2·5 g.), m.p. 82—84° (from ethanol) (Found: C, 71·3; H, 6·8; N, 7·2. Calc. for $C_{14}H_{17}NO_2$: C, 72·7; H, 7·4; N, 6·05%), $\nu_{max.}$ (KCl) 3400 (NH) and 1700 and 1770 cm.$^{-1}$, $\lambda_{max.}$ 221 (ε 35,000) and 264 (17,600) mμ, τ (CCl_4) 8·8 (3H, t, *J* 8 c./sec., $CO_2{\cdot}CH_2{\cdot}CH_3$), 8·75 (s), 8·4 (s), 5·95 (2H, q, *J* 8 c./sec., $CO_2{\cdot}CH_2{\cdot}CH_3$), 5·9 (s), 3·83 (1H, d, *J* 3 c./sec., indole β-proton), and 2·3—3·3 (aromatic protons).

The mother-liquor gradually deposited more colourless crystalline material (320 mg.), m.p. 101—103°, identified as 3,3-dimethyl-1-phenylpyrrolidine-2,4-dione [see preparation (*c*) for analytical data].

[12] M. Nakazaki and S. Isoe, *J. Chem. Soc. Japan*, 1955, **76**, 1159.

[13] K. Folkers and H. Adkins, *J. Amer. Chem. Soc.*, 1931, **53**, 1417.

From comparison of these n.m.r. spectra with that of ethyl α-indol-3-ylisobutyrate it was concluded that the product of m.p. 82—84° was a mixture of ethyl α-indol-2-yl-isobutyrate and the product of m.p. 101—103°. This mixture was converted into 2-isopropylindole by the method of Jönsson.[11] Attempts at separation of this mixture by chromatography on silica or alumina failed.

(*b*) When ethyl 4-bromo-2,2-dimethylacetoacetate and aniline were boiled under reflux in Cellosolve for either (i) 1 hr. or (ii) 4 hr. a similar mixture to that described above was obtained. The use of zinc chloride as a catalyst in boiling Cellosolve also gave this mixture of products.

(*c*) Freshly distilled aniline (40 g.) was added in small portions to redistilled ethyl 4-bromo-2,2-dimethylaceto-acetate (32 g.) with cooling and shaking, and the mixture was heated at 140—150° for 4 hr. It was worked up as described in (*a*) and the product was chromatographed on Kieselgel G (300 g.; column diam. 3 in.) with benzene as eluant. Ethyl α-indol-2-ylisobutyrate (12 g., 26%) was eluted first, then benzene–10% ether eluted 3,3-dimethyl-1-phenylpyrrolidine-2,4-dione, m.p. 101—103° (6·5 g.).

Ethyl α-indol-2-ylisobutyrate was obtained from light petroleum (b.p. 60—80°) as colourless needles, m.p. 120—122° (Found: C, 72·8; H, 7·1; N, 6·2. $C_{14}H_{17}NO_2$ requires C, 72·7; H, 7·4; N, 6·05%), $\nu_{max.}$ ($CHCl_3$) 3460 (NH) and 1720 (CO_2Et) cm.$^{-1}$, $\lambda_{max.}$ 220 (ε 30,600), 284 (7850), and 290 (6320) mμ, τ (CCl_4) 8·78 (3H, t, *J* 8 c./sec., $CO_2{\cdot}CH_2{\cdot}CH_3$), 8·35 (6H, s, CMe_2), 5·85 (2H, q, *J* 8 c./sec., $CO_2{\cdot}CH_2{\cdot}CH_3$), 3·73 (1H, d, *J* 2·5 c./sec., indole β-proton), 2·4—3·2 (4H, m, aromatic), and 1·3br (1H, NH).

3,3-Dimethyl-1-phenylpyrrolidine-2,4-dione was obtained from light petroleum (b.p. 60—80°) as colourless prisms, m.p. 101—103° (Found: C, 70·55; H, 6·5; N, 7·4. $C_{12}H_{13}NO_2$ requires C, 70·9; H, 6·45; N, 6·9%), $\nu_{max.}$ 1700 (γ-lactam) and 1770 (C=O) cm.$^{-1}$, $\lambda_{max.}$ 207 (ε 16,500) and 250 (8250) mμ, τ (CCl_4) 8·72 (6H, s, CMe_2), 5·82 (2H, s, $-CO-CH_2-N$), and 2·15—3·0 (5H, m, aromatic).

Use of a molar ratio of ethyl 4-bromo-2,2-dimethyl-acetoacetate to aniline of 1 : 4 gave ethyl α-indol-2-yliso-butyrate in 50% yield.

2-(Indol-2-yl)-2-methylpropan-1-ol.—A solution of ethyl α-indol-2-ylisobutyrate (23 g.) in sodium-dried ether (300 ml.) was added dropwise to a stirred suspension of lithium aluminium hydride (12 g.) in sodium-dried ether (500 ml.) and the mixture was boiled under reflux for 2 hr. The mixture was then cooled in ice and the excess of lithium aluminium hydride was destroyed with water. The residue, after evaporation of the dried ($MgSO_4$) ethereal layer, was crystallised from light petroleum (b.p. 60—80°). *2-(Indol-2-yl)-2-methylpropan-1-ol* (18 g., 95%) was obtained as colourless plates, m.p. 90—92° (Found: C, 75·8; H, 8·35; N, 7·6. $C_{12}H_{15}NO$ requires C, 76·15; H, 8·0; N, 7·4%), $\nu_{max.}$ (KCl) 3530 (OH), 3340 (NH), and 1035 (OH) cm.$^{-1}$, $\lambda_{max.}$ 222 (ε 30,200), 280 (7100), and 290 (5900) mμ, τ (CCl_4) 8·8 (6H, s, CMe_2), 7·83br (1H, OH), 6·67 (2H, s, CH_2-OH), 3·85 (1H, d, *J* 2·5 c./sec., indole β-proton), 2·4—3·2 (4H, m, aromatic), and 1·6br (1H, NH).

α-(Indol-2-yl)isobutyraldehyde.— 2-(Indol-2-yl)-2-methyl-propan-1-ol (9 g.) was dissolved in dimethyl sulphoxide (150 ml.), acetic anhydride (100 ml.) was added, and the mixture was set aside overnight. After extraction with water and ether, the ethereal layer was separated and washed with sodium hydrogen carbonate solution until free from acid, then with water. The residue, after evaporation of the dried (Na_2SO_4) ethereal layer, was shown by t.l.c., with benzene as eluant, to be a mixture of two components. It was chromatographed on Kieselgel G (175 g., column diam. 3 in.) with benzene as eluant. The chromatography was followed by t.l.c. and the fractions containing pure components were combined; those still containing the mixture were rechromatographed on Kieselgel G (125 g., column diam. 3 in.), with benzene as eluant. 2-(Indol-2-yl)-2-methylpropyl methylthiomethyl ether was eluted from the column first, followed by α-(indol-2-yl)isobutyr-aldehyde.

2-(Indol-2-yl)-2-methylpropyl methylthiomethyl ether (2·88 g., 24·3%) was obtained from pentane as colourless prisms, m.p. 50—52° (Found: C, 67·1; H, 7·4; N, 5·65. $C_{14}H_{19}NOS$ requires C, 67·45; H, 7·65; N, 5·65%), $\nu_{max.}$ ($CHCl_3$) 3440 (NH) and 1065 ($-CH_2-O-CH_2-$) cm.$^{-1}$, $\lambda_{max.}$ 223 (ε 25,600), 280 (6750), and 290 (5700) mμ, τ 8·65 (6H, s, CMe_2), 7·98 (3H, s, $S-CH_3$), 6·53 (2H, s, $C-CH_2-O-$), 5·43 (2H, s, $-O-CH_2-S-$), 3·88 (1H, d, *J* 2·5 c./sec., indole β-proton), 2·5—3·2 (4H, m, aromatic), and 1·6br (1H, NH).

α-(Indol-2-yl)isobutyraldehyde (5·4 g., 60·4%) was obtained from light petroleum (b.p. 40—60°) as colourless needles, m.p. 68—70° (Found: C, 77·15; H, 7·05; N, 7·65. $C_{12}H_{13}NO$ requires C, 76·95; H, 7·0; N, 7·5%), $\nu_{max.}$ ($CHCl_3$) 3480 (NH) and 2810, 2710, and 1720 (CHO) cm.$^{-1}$, $\lambda_{max.}$ 222 (ε 20,500), 282 (8000), and 290 (6230) mμ, τ ($CDCl_3$) 8·45 (6H, s, CMe_2), 3·58 (1H, d, *J* 2·5 c./sec., indole β-proton), 2·3—3·1 (4H, m, aromatic), 1·75br (1H, NH), and 0·5 (1H, s, CHO).

3-(Indol-2-yl)-2-methylbut-1-ene.—(Tetrahydrofuran was distilled from lithium aluminium hydride and then passed down a Grade 1 alumina column. The phosphonium salt was powdered and dried under vacuum at 100°. This reaction was carried out in oxygen-free nitrogen.) Butyl-lithium (0·029 mole) in ether was added to a stirred sus-pension of triphenylmethylphosphonium bromide (8·1 g., 0·029 mole) in tetrahydrofuran (150 ml.). The mixture was stirred for 30 min., then α-(indol-2-yl)isobutyraldehyde (5·4 g.) in tetrahydrofuran (250 ml.) was added dropwise and the mixture was heated under reflux overnight. After evaporation of the tetrahydrofuran, the residue was dis-solved in water and ether. The ethereal layer was washed with water, and then dried (Na_2SO_4). Evaporation of the ether yielded an oil which was chromatographed on Kiesel-gel G with benzene as eluant. *3-(Indol-2-yl)-3-methylbut-1-ene* (3·2 g., 60%) was obtained as a colourless oil which was shown to be virtually pure by t.l.c. and its n.m.r. spectrum; $\nu_{max.}$ ($CHCl_3$) 3470 (NH) and 920 and 1000 ($-CH=CH_2$) cm.$^{-1}$, $\lambda_{max.}$ 225 (ε 19,800), 280 (7230), and 291 (5830) mμ, τ ($CDCl_3$) 8·58 (6H, s, CMe_2), 4·8—5·2 (2H, ABC octet, J_{AB} 18, J_{AC} 10, J_{BC} 2 c./sec., $-CH_A=CH_BH_C$), 3·67—4·2 (1H, ABC quartet, J_{AB} 18, J_{AC} 10 c./sec., $-CH_A=CH_BH_C$), 3·72 (1H, d, *J* 2·5 c./sec., indole β-proton), and 2—3·1 (5H, m, aromatic protons and NH).

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