428. *The Chemistry of Bacteria. Part V.*[1] *Some Acylindoles.*

By J. A. Ballantine, C. B. Barrett, R. J. S. Beer, B. G. Boggiano, Stephen Eardley, B. E. Jennings, and Alexander Robertson.

In connection with an investigation on the constitution of a C_{20}-acid (I) derived from violacein the ultraviolet and infrared absorption spectra of a number of acylindoles of types (II), (III), and (IV) have been examined.

The assignment of structure (I) to the C_{20}-acid [1] derived from violacein depends partly on a spectroscopic comparison of the compound with various acylindoles which have been prepared as models. The present paper collects the available data on these compounds which include (*a*) simple 3-acylindoles, 3-acyl-5-methoxyindoles, and 1 : 2 : 3 : 4-tetrahydro-4-oxocarbazole, all represented by the generalised expression (II), (*b*) 2-acetyl-3-methylindole and some 1 : 2 : 3 : 4-tetrahydro-1-oxocarbazoles (III), and (*c*) a group of compounds represented by (IV). Since they contain the γ-keto-acid system the compounds in the latter group are close models of the C_{20}-acid.

Ultraviolet absorption data for the acylindoles are given in Table 1. Compounds of type (II) each have three absorption maxima of roughly equal intensity. When the 5-position is unsubstituted (II; R = H) the maxima appear at *ca.* 240, 265, and 300 mμ, whilst the 5-methoxyindoles (II; R = OMe) have maxima at *ca.* 255, 280, and 300 mμ. The indolyl-oxobutyric acid group (type IV) shows essentially the same characteristics,

[1] Part IV, Ballantine, Barrett, Beer, Boggiano, Clarke, Eardley, Jennings, and Robertson, preceding paper.

although in one example the central maximum is missing and in two other cases it appears as a shoulder. The 2-acylindoles (type III), on the other hand, have quite different absorption curves, with two high-intensity maxima at *ca.* 235 and 310 mμ and a pronounced minimum at *ca.* 265 mμ.

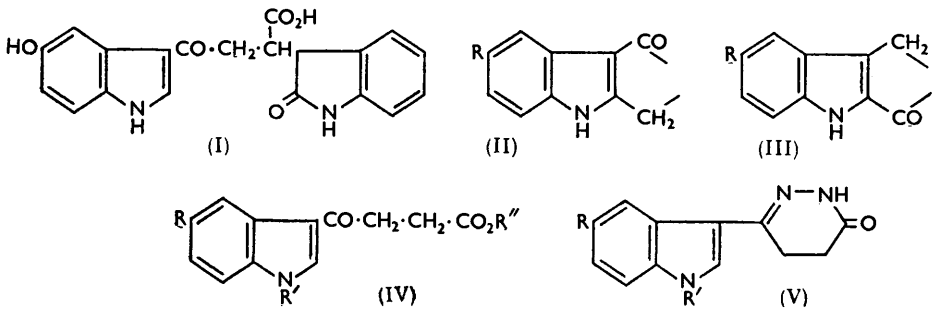

Table 2 lists the important peaks in the infrared absorption spectra of some of the acylindoles. It will be observed that the absorption maxima due to the ketone groups in the 3-acylindoles which have a free NH group fall within the range 1590—1620 cm.$^{-1}$, whilst the 3-acyl-1-methylindoles have peaks between 1620 and 1640 cm.$^{-1}$. The two α-acylindoles for which data are available have a carbonyl gand at 1630 cm.$^{-1}$. The NH (stretching) peaks in 3-acylindoles appear between 3130 and 3220 cm.$^{-1}$, at rather lower frequencies than the characteristic range for simple indoles [2] (3330—3500 cm.$^{-1}$). The two 2-acylindoles have peaks at 3247 and 3311 cm.$^{-1}$ respectively.

The acylindoles required for this study were prepared either by methods already described or by suitable modifications of conventional procedures. It has become clear

TABLE 1. *Ultraviolet absorption spectra of acylindoles.*

Type	Compound	$\lambda_{max.}$ (mμ) (log ε)	$\lambda_{min.}$ (mμ) (log ε)
3-Acyl	3-Acetyl-2-methylindole	240 (4·02), 266 (3·92), 300 (3·98)	225 (3·77), 254 (3·79), 279 (3·83)
	2-Methyl-3-phenylacetylindole	244 (4·17), 268 (4·07), 303 (4·13)	229 (3·95), 255 (3·95), 281 (3·96)
	1 : 2 : 3 : 4-Tetrahydro-4-oxocarbazole	242 (4·26), 265 (4·16), 295 (4·10)	224 (3·85), 251 (3·98), 279 (3·97)
	3-Acetyl-5-methoxy-2-methylindole	254 (4·07), 278 (4·00), 301 (4·00)	234 (3·88), 263 (3·94), 292 (3·96)
	5-Methoxy-2-methyl-3-phenylacetylindole	255 (4·23), 278 (4·14), 303 (4·12)	234 (3·77), 265 (4·03), 289 (4·06)
	γ-(3-Indolyl)-γ-oxobutyric acid	242 (4·01), 298 (4·10), shoulder, 259 (3·95)	271 (3·78)
	γ-(1-Methyl-3-indolyl)-γ-oxobutyric acid	245 (4·15), 304 (4·14)	272 (3·65)
	γ-(5-Methoxy-3-indolyl)-γ-oxobutyric acid	252 (4·20), 268 (4·03), 303 (4·02)	263 (4·02), 283 (3·89)
	γ-(5-Methoxy-1-methyl-3-indolyl)-γ-oxobutyric acid	255 (4·25), 307 (4·04), shoulder, 273 (3·99)	235 (3·69), 284 (3·82)
2-Acyl	2-Acetyl-3-methylindole	238 (4·17), 312 (4·33)	265 (2·98)
	1 : 2 : 3 : 4-Tetrahydro-1-oxocarbazole	236 (4·31), 307 (4·46)	263 (3·03)
	1 : 2 : 3 : 4-Tetrahydro-6-methoxy-1-oxocarbazole	232 (4·22), 314 (4·44)	265 (3·13)
	1 : 2 : 3 : 4-Tetrahydro-6 : 7-dimethoxy-1-oxocarbazole	231 (4·21), 334 (4·43)	267 (3·04)

that 3-acylindoles are readily methylated at the NH group with methyl sulphate and alkali and this method has normally been used for the preparation of 3-acyl-1-methylindoles. The methyl esters of the γ-indolyl-γ-oxobutyric acids (type IV) were condensed with hydrazine, yielding indolylpyridazinones (V) which served as models for a product [1]

[2] Bellamy, " The Infra-red Spectra of Complex Molecules," Methuen, London, 1954, p. 215.

of similar structure prepared from the trimethyl and tetramethyl derivatives of the C_{20}-acid. Details of the ultraviolet absorption spectra of these pyridazinones are collected in Table 3.

TABLE 2. *Infrared absorption spectra.*

Type	Compound	NH region ($cm.^{-1}$)	Carbonyl region ($cm.^{-1}$)
3-Acyl	3-Acetyl-2-methylindole	3135	1597
	3-Acetyl-5-methoxy-2-methylindole	3134	1601, 1618
	1 : 2 : 3 : 4-Tetrahydro-4-oxocarbazole	3165	1592
	1 : 2 : 3 : 4-Tetrahydro-9-methyl-4-oxocarbazole	—	1626
	γ-(3-Indolyl)-γ-oxobutyric acid	3220	1684 (CO_2H), 1621
	Methyl γ-(3-indolyl)-γ-oxobutyrate	3155	1742 (CO_2Me), 1618
	γ-(1-Methyl-3-indolyl)-γ-oxobutyric acid	—	1690 (CO_2H), 1621
	Methyl γ-(1-methyl-3-indolyl)-γ-oxobutyrate	—	1710 (CO_2Me), 1627
	γ-(5-Methoxy-3-indolyl)-γ-oxobutyric acid	3155	1733 (CO_2H), 1613
	γ-(5-Methoxy-1-methyl-3-indolyl)-γ-oxobutyric acid	—	1712 (CO_2H), 1639
2-Acyl	2-Acetyl-3-methylindole	3311	1631
	1 : 2 : 3 : 4-Tetrahydro-1-oxocarbazole	3247	1629

TABLE 3. *Ultraviolet absorption spectra of indolylpyridazinones.*

Compound	$\lambda_{max.}$ (mμ) (log ε)	$\lambda_{min.}$ (mμ) (log ε)
3-3′-Indolylpyridazin-6-one	274 (4·06), 314 (4·34)	245 (3·86), 280 (4·02)
3-(1-Methyl-3-indolyl)pyridazin-6-one	274 (4·02), 322 (4·32)	247 (3·84), 283 (3·87)
3-(5′-Methoxy-1′-methyl-3′-indolyl)pyridazin-6-one	279 (4·21), 326 (4·29), shoulders, 272 (4·15), 313 (4·22)	247 (3·81), 290 (3·88)

EXPERIMENTAL

Unless otherwise stated, the light petroleum used had b. p. 60—80°. Spectroscopic measurements were made as described in Part IV.[1]

3-Acylindoles.—The 3-acetyl, 3-phenylacetyl, and 3-benzoyl derivatives of 2-methylindole were prepared by Seka's method.[3]

3-Acetyl-5-methoxy-2-methylindole was prepared from 5-methoxy-2-methylindole[4] (1·0 g.), with acetonitrile (3 ml.), and hydrogen chloride in ether and subsequent hydrolysis of the resulting ketimine hydrochloride with hot aqueous-alcoholic sulphuric acid. The compound separated from aqueous alcohol in colourless prisms (0·33 g.), m. p. 228—230° (Found: N, 6·9. $C_{13}H_{13}O_2N$ requires N, 6·9%). Similarly prepared, *5-methoxy-2-methyl-3-phenylacetylindole* (yield, 60%) crystallised from benzene in colourless slender needles, m. p. 180—181° (Found: C, 77·2; H, 6·15. $C_{18}H_{17}O_2N$ requires C, 77·4; H, 6·1%), and *3-benzoyl-5-methoxy-2-methylindole* (yield, 50%) from aqueous alcohol in colourless needles, m. p. 171—172° (Found: N, 5·3. $C_{17}H_{15}O_2N$ requires N, 5·3%).

1 : 2 : 3 : 4-Tetrahydro-4-oxocarbazole.—This was best prepared by the method of Clemo and Felton,[5] but was also obtained by cyclisation of *cyclo*hexane-1 : 3-dione monophenylhydrazone with boron trifluoride–ether complex in boiling acetic acid and formed colourless rhombs, m. p. 221°, from aqueous methanol (Found: C, 78·1; H, 5·7; N, 7·5. Calc. for $C_{12}H_{11}ON$: C, 77·8; H, 6·0; N, 7·6%).

1 : 2 : 3 : 4-Tetrahydro-9-methyl-4-oxocarbazole.—The solution obtained by heating *cyclo*hexane-1 : 3-dione *N*-methyl-*N*-phenylhydrazone (5·4 g.) on the steam-bath for 30 min. with concentrated sulphuric acid (20 ml.) and water (50 ml.) was filtered and diluted with water (200 ml.). The resulting *1 : 2 : 3 : 4-tetrahydro-9-methyl-4-oxocarbazole* separated from aqueous acetone in colourless plates (3·0 g.), m. p. 198—199° (Found: C, 78·5; H, 6·6; N, 7·1. $C_{13}H_{13}ON$ requires C, 78·4; H, 6·5; N, 7·0%). This compound was also obtained by the action of methyl sulphate on 1 : 2 : 3 : 4-tetrahydro-4-oxocarbazole dissolved in a mixture of acetone and aqueous potassium hydroxide. The *2 : 4-dinitrophenylhydrazone* crystallised from acetic acid in deep red rectangular prisms, m. p. 297—298° (decomp.) (Found: N, 18·3. $C_{19}H_{17}O_4N_5$ requires N, 18·5%).

[3] Seka, *Ber.*, 1923, **56**, 2058.
[4] Beer, Clarke, Davenport, and Robertson, *J.*, 1951, 2031.
[5] Clemo and Felton, *ibid.*, p. 700.

2-Acylindoles.—2-Acetyl-3-methylindole was prepared by Oddo's method.[6] 1 : 2 : 3 : 4-Tetrahydro-1-oxocarbazole was prepared by Kent's method [7] and an analogous preparation yielded 1 : 2 : 3 : 4-*tetrahydro-6-methoxy-1-oxocarbazole* which formed colourless prisms, m. p. 213—214°, from 50% acetone (Found : C, 72·5; H, 5·9; N, 6·8. $C_{13}H_{13}O_2N$ requires C, 72·6; H, 6·0; N, 6·5%). The 2 : 4-*dinitrophenylhydrazone* separated from acetic acid in deep red prisms, m. p. 297° (decomp.) (Found : N, 17·6. $C_{19}H_{17}O_5N_5$ requires N, 17·7%), and the *picrate* crystallised from alcohol in red needles, m. p. 166—167° (Found : C, 51·8; H, 3·6; N, 12·3. $C_{13}H_{13}O_2N,C_6H_3O_7N_3$ requires C, 51·4; H, 3·6; N, 12·6%).

1 : 2 : 3 : 4-*Tetrahydro-6* : 7-*dimethoxy-1-oxocarbazole* formed pale brown needles, m. p. 198°, from alcohol (Found : C, 69·0; H, 5·9; N, 6·0. $C_{14}H_{15}O_3N$ requires C, 68·6; H, 6·1; N, 5·7%) and gave a 2 : 4-*dinitrophenylhydrazone* in dark red prisms, m. p. 293° (decomp.) (from acetic acid) (Found : N, 16·4. $C_{20}H_{19}O_6N_5$ requires N, 16·5%), and a *picrate* in dark red needles, m. p. 193—194° (from alcohol) (Found : C, 50·9; H, 3·4; N, 11·6. $C_{14}H_{15}O_3N,C_6H_3O_7N_3$ requires C, 50·6; H, 3·8; N, 11·8%).

γ-3-Indolyl-γ-oxobutyric Acid.[8]—Indole (17·5 g.), in ether (50 ml.), was added to ethereal ethylmagnesium iodide [from ethyl iodide (23·4 g.) and magnesium (3·6 g.)] at such a rate as to maintain gentle boiling. The mixture was then heated on the steam-bath for 15 min. and diluted with sufficient ether to redissolve the green oil which separated. The solution was decanted from a little residual magnesium and added dropwise during 1 hr. to a stirred solution of β-methoxycarbonylpropionyl chloride [9] (22·5 g.) in ether (40 ml.) at about −10°. The yellow complex was decomposed with ice and ammonium chloride, the ether layer separated, and the aqueous layer extracted with ether (2 × 50 ml.); the combined ether extracts were dried and evaporated. The residual oil was extracted repeatedly with hot light petroleum (b. p. 40—60°) to remove indole, leaving a solid which on crystallisation from benzene–light petroleum gave *methyl γ-3-indolyl-γ-oxobutyrate* in colourless needles (11·0 g.), m. p. 116° (Found : C, 67·2; H, 5·3; N, 5·9. $C_{13}H_{13}O_3N$ requires C, 67·5; H, 5·6; N, 6·1%).

This ester (100 mg.) was heated under reflux with 2N-aqueous sodium hydroxide (7 ml.) until it had dissolved. Acidification of the cooled solution with dilute hydrochloric acid gave γ-3-indolyl-γ-oxobutyric acid, which separated from ethyl acetate in white plates (90 mg.), m. p. 235° (Found : C, 66·2; H, 5·0; N, 6·3. Calc. for $C_{12}H_{11}O_3N$: C, 66·4; H, 5·1; N, 6·1%).

γ-(1-Methyl-3-indolyl)-γ-oxobutyric Acid.—Methyl sulphate (1·5 ml.) was added gradually to an agitated solution of γ-3-indolyl-γ-oxobutyric acid (200 mg.) in acetone (20 ml.) and water (5 ml.), containing potassium hydroxide (1 g.). 15 Min. later the acetone was evaporated, the residual solution acidified with dilute hydrochloric acid, and the precipitate isolated and crystallised from ethyl acetate, giving *γ-(1-methyl-3-indolyl)-γ-oxobutyric acid* in colourless leaflets (190 mg.), m. p. 176° (Found : C, 67·9; H, 5·5; N, 5·8. $C_{13}H_{13}O_3N$ requires C, 67·5; H, 5·6; N, 6·1%). With excess of methyl sulphate, so that the reaction mixture became acid, the major product was the corresponding *methyl ester* which formed colourless needles, m. p. 118°, from benzene–light petroleum (Found : C, 68·9; H, 6·3; N, 5·8. $C_{14}H_{15}O_3N$ requires C, 68·6; H, 6·1; N, 5·7%). On hydrolysis with hot aqueous sodium hydroxide this ester gave γ-(1-methyl-3-indolyl)-γ-oxobutyric acid, m. p. and mixed m. p. 176°.

γ-(5-Methoxy-3-indolyl)-γ-oxobutyric Acid.—Prepared by the method used for the indole derivative, the Grignard compound from 5-methoxyindole [10] (4·0 g.), dissolved in ether–benzene, was added to a solution of β-methoxycarbonylpropionyl chloride (5·6 g.) in ether at −10°. After decomposition of the yellow complex with ice and ammonium chloride, the solid product was collected and recrystallised from methanol, giving *methyl γ-(5-methoxy-3-indolyl)-γ-oxobutyrate* (3·0 g.) in colourless needles, m. p. 188° (Found : C, 64·3; H, 5·8; N, 5·1. $C_{14}H_{15}O_4N$ requires C, 64·4; H, 5·8; N, 5·4%). The ether–benzene layer from the reaction mixture contained only a trace of the ester. Formed in quantitative yield by hydrolysis with 2N-sodium hydroxide, *γ-(5-methoxy-3-indolyl)-γ-oxobutyric acid* separated from acetone–light petroleum in colourless prisms, m. p. 237° (Found : C, 62·6; H, 5·3; N, 5·8. $C_{13}H_{13}O_4N$ requires C, 63·2; H, 5·3; N, 5·7%).

γ-(5-Methoxy-1-methyl-3-indolyl)-γ-oxobutyric Acid.—With methyl sulphate (8 ml.) and

[6] Oddo, *Gazzetta*, 1913, **43**, II, 202.
[7] Kent, *J.*, 1935, 97.
[8] Majima, Shigematsu, and Robkaku, *Ber.*, 1924, **57**, 1453.
[9] *Org. Synth.*, Coll. Vol. III, p. 169.
[10] Blaikie and Perkin, *J.*, 1924, **125**, 296; Hughes and Lions, *J. Proc. Roy. Soc. New South Wales*, 1937—8, **71**, 475.

potassium hydroxide (5 g.) in aqueous acetone methyl γ-(5-methoxy-3-indolyl)-γ-oxobutyrate (1·0 g.) yielded *methyl γ-(5-methoxy-1-methyl-3-indolyl)-γ-oxobutyrate* which crystallised from benzene–light petroleum in colourless prisms (0·8 g.), m. p. 111° (Found : N, 5·1. $C_{15}H_{17}O_4N$ requires N, 5·1%). The corresponding *acid*, obtained as a by-product in this reaction and formed in quantitative yield by alkaline hydrolysis of the ester, separated from ethyl acetate in colourless needles, m. p. 178° (Found : C, 64·1; H, 5·7; N, 5·1. $C_{14}H_{15}O_4N$ requires C, 64·4; H, 5·8; N, 5·4%).

3-3′-*Indolylpyridazin-6-one*.—After concentration, the solution obtained by heating under reflux for 12 hr. methyl γ-3-indolyl-γ-oxobutyrate (1·0 g.), alcohol (15 ml.), and hydrazine hydrate (5 ml.; 98%) deposited the *pyridazinone*. Recrystallised from alcohol, it formed colourless prisms (0·85 g.), m. p. 215° (Found : C, 67·8; H, 5·1; N, 19·5. $C_{12}H_{11}ON_3$ requires C, 67·6; H, 5·2; N, 19·7%).

3-(1-*Methyl-3-indolyl*)*pyridazin-6-one* was similarly prepared from methyl γ-(1-methyl-3-indolyl)-γ-oxobutyrate (0·8 g.) and crystallised from alcohol in pale yellow leaflets (0·7 g.), m. p. 210° (softens 205°) (Found : C, 68·8; H, 5·7; N, 18·4. $C_{13}H_{13}ON_3$ requires C, 68·7; H, 5·7; N, 18·5%).

3-(5-*Methoxy*-1-*methyl*-3-*indolyl*)*pyridazin-6-one* (0·45 g.), from methyl γ-(5-methoxy-1-methyl-3-indolyl)-γ-oxobutyrate (0·65 g.) and hydrazine hydrate (3·7 ml.) in alcohol, formed pale yellow prisms, m. p. 232°, from methanol (Found : C, 64·9; H, 5·8; N, 16·6. $C_{14}H_{15}O_2N_3$ requires C, 65·4; H, 5·8; N, 16·3%).

UNIVERSITY OF LIVERPOOL. [*Received, November 26th*, 1956.]