The Reaction of Indolylmagnesium Iodide with Enol-lactones of γ-Keto-acids.

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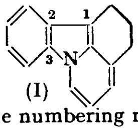
[Reprint Order No. 6184.]

Indolylmagnesium iodide has been shown to react with 4 : 5-dihydro-5-oxo-2-phenylfuran, α-angelicalactone and γ-oxopimelic anhydride to give 1-acylated indoles. 1-Lævuloylindole has been cyclised to 3-methyl-1 : 2-(2′ : 7′)-benzylenepyrid-6-one, the action of alcoholic alkali on which supports an explanation previously advanced for the yellow colour and green fluorescence frequently encountered in alcoholic alkaline solution of certain strychnine derivatives.

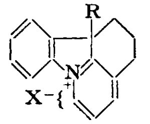
It has been shown that 2 : 3-benzopyrrocolines are alkylated in the 1-position (Robinson and Saxton, *J.*, 1952, 976); thus the derivative (I) should yield the pyridinium salt (II) which is of interest in simulating a portion of the strychnine molecule.

A possible route to the tetracyclic skeleton (I) would be the condensation of indole with the readily available γ-oxopimelic acid in three positions as shown in (III). However this could not be done directly, for indole shows maximum activity towards cationoid reagents at the 3 (or sometimes 1-position) whereas the cationoid activity of the keto-group in pimelic acid, which it is desired to condense with position 2 of the indole, is greater than that of the carboxyl groups. It is, however, possible to reverse this order of reactivity by the use of enol-lactones (or a dilactone) instead of the keto-acids.

Although in general γ- and δ-keto-acids and their esters are attacked by Grignard reagents at the carbon atom of the keto-group, yet in the enol-lactones derived from them the carbon atom of the carboxyl group would be expected to become the centre for attack by anionoid reagents. This type of reaction has recently been used with enol-δ-lactones to introduce $C_{(4)}$ of the steroid nucleus (Fujimoto, *J. Amer. Chem. Soc.*, 1951, **73**, 1856; Woodward, Sondheimer, Taub, Heuster, and McLamore, *ibid.*, 1952, **74**, 4223; Wieland, Weberwasser, Anner, and Miescher, *Helv. Chim. Acta*, 1953, **36**, 1231), but no example of the reaction of an enol-γ-lactone with a Grignard reagent appears to have been recorded.



(I)
(The numbering refers to pyrrocoline itself.)



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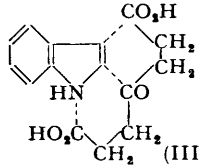

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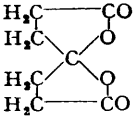

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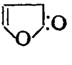

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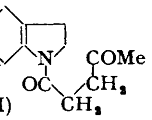


(VI)

γ-Oxopimelic acid does not form an enol-lactone, but the above considerations apply also to the dilactone (IV). As a preliminary to work with this dilactone, it was decided to investigate the reaction of indolymagnesium iodide with the simpler α-angelicalactone (V; R = Me) and 4 : 5-dihydro-5-oxo-2-phenylfuran (V; R = Ph), *i.e.*, the enol-lactones of lævulic acid and β-benzoylpropionic acid.

The reactions of indolylmagnesium halides have been extensively investigated and, in accordance with the hybrid nature of the indole anion, although in the majority of cases the 3-substituted indole is produced, it is sometimes accompanied by the 1-substituted or the 1 : 3-disubstituted indole (*e.g.*, Oddo, *Gazzetta*, 1911, **41**, 221, 234). The dependence of the orientation on solvent and temperature has been reported in special cases : Alexandri (*Atti R. Accad. Lincei*, 1915, **24**, II, 194) obtained 1-formylindole with only small amounts of 3-formylindole from ethyl formate in ether; Majima and Kotake (*Ber.*, 1922, **55**, 3859) used anisole as a solvent and isolated mainly 3-formylindole. The latter authors found (*ibid.*, p.3865) that the yield of 3-substituted products was in general higher with this solvent except in reactions with acid chlorides. Potokhin (*J. Russ. Phys. Chem. Soc.*, 1927, **59**, 761; *Chem. Abs.*, 1928, **22**, 3409) used benzene as solvent and found that, with ethyl formate at 0° the 1-derivative was formed, but at 85° 3-formylindole.

When 4 : 5-dihydro-5-oxo-2-phenylfuran (V; R = Ph) was allowed to react with preformed indolylmagnesium iodide in ether, only one product was isolated, which analysed correctly for a mono-(β-benzoylpropionyl)indole and could have been either the 1- or the 3-substituted product. A distinction could easily be made, for it is known that 1-acylindoles are readily hydrolysed by warm dilute alkali whereas 3-acylindoles are unaffected (*e.g.*, Saxton, *J.*, 1952, 3592); under these conditions the compound underwent cleavage to β-benzoylpropionic acid and indole and was thus shown to be 1-β-benzoylpropionylindole. This conclusion was supported by the infrared spectrum which showed no band at 2·90—2·94 μ; this band is given by all indoles which are not 1-substituted (Brown, Henbest, and Jones, *J.*, 1952, 3174). 1-β-Benzoylpropionylindole was characterised as the 2 : 4-dinitrophenylhydrazone and semicarbazone. The reaction between indolylmagnesium iodide and 4 : 5-dihydro-5-oxo-2-phenylfuran was carried out eight times under different conditions, ether and anisole being used as solvent and temperature and duration of the reaction varied. Under those conditions that appear to favour 3-substitution (see above), small amounts of by-products were formed, but 1-β-benzoylpropionylindole was the only pure substance isolated.

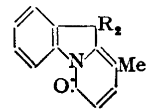
When α-angelicalactone (V; R = Me) was caused to react with indolylmagnesium iodide in ether (or in anisole) the product was a viscous red oil which did not crystallise even on being seeded with material from an earlier run. However, a homogeneous lævuloylindole semicarbazone could be prepared which, on being refluxed with pyruvic acid in dilute acetic acid (cf. Hershberg, *J. Org. Chem.*, 1948, **13**, 542), was reconverted into the parent compound. Ready alkaline hydrolysis to lævulic acid and indole showed this compound to be 1-lævuloylindole (VI), and this was confirmed by the absence of an N–H band in the infrared spectrum. 1-Lævuloylindole was further characterised as the 2 : 4-dinitrophenylhydrazone and oxime.

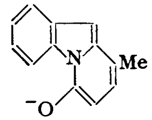
The reaction of the dilactone (IV) with indolylmagnesium iodide gave very similar results to those recorded above for α-angelicalactone. An oil was formed affording a semicarbazone which was decomposed with pyruvic acid, and the product was proved to be 1-(6-carboxy-4-oxohexanoyl)indole by reason of its sensivity to alkali and its infrared spectrum. The methyl ester was prepared with the aid of diazomethane; it afforded a 2 : 4-dinitrophenylhydrazone.

Many attempts were made to cyclise the foregoing 1-oxoacylindoles using (i) phosphoric anhydride in boiling toluene, (ii) phosphoryl chloride alone or with chloroform, cold or at the b. p., (iii) polyphosphoric acid at 150°, (iv) boron trifluoride in chloroform, (v) sulphuric acid, (vi) hydrogen chloride in ethyl acetate, and (vii) refluxing acetic anhydride, with or without zinc chloride. After many trials a crystalline perchlorate was isolated from the product of 1-lævuloylindole and sulphuric acid, from which the cyclised base was obtained with ammonia. This was shown to be 3-methyl-1 : 2(2′ : 7′)-benzylenepyrid-6-one (VII; R = H), and not a double bond isomer of this, by comparison of the infrared spectrum with that of 3 : 7′ : 7′-trimethyl-1′ : 7′(1 : 2)-benzylenepyrid-6-one (VII; R = R = Me) (Robinson and Saxton, *loc. cit.*). Unfortunately all efforts to cyclise the other 1-oxoacylindoles failed and this led to the abandonment of that line of research.

In work involving the treatment of strychnine derivatives with alcoholic alkali, it has been frequently observed that a brownish-yellow solution exhibiting characteristic green fluorescence is produced. This is formed, for example, from strychnine in warm alcoholic potassium hydroxide in presence of air. Woodward, Brehm, and Nelson recognised strychnone as an aromatic-type indole derivative (*J. Amer. Chem. Soc.*, 1947, **69**, 2250), and Bailey and Robinson in expressing similar views about bruzone (*Nature*, 1948, **161**, 433) took the opportunity to attribute the above-mentioned colour and fluorescence to the formation of a hydroxybenzopyrrocoline system.

(VII)





(VIII)

The substance (VII; R = H) (but not R = Me) develops a brownish-yellow solution with green fluorescence in warm alcoholic potassium hydroxide and this is probably due to the anion (VIII). The exhibition of this property strongly supports the suggestion of Bailey and Robinson.

EXPERIMENTAL

1-β-*Benzoylpropionylindole*.—A solution of indole (3·51 g.) in ether (15 c.c.) was gradually added, at 0°, with stirring, to one of methylmagnesium iodide (magnesium 0·87 g.; methyl iodide, 4·8 g.; ether, 50 c.c.). After the solution had been refluxed for 15 min. and cooled again to 0°, 4 : 5-dihydro-5-oxo-2-phenylfuran (4·5 g.) (Kugel, *Annalen*, 1898, **299**, 54) in ether (70 c.c.) was added. The mixture was refluxed for 15 min. and the complex decomposed at 0° by water (50 c.c.) and 2N-acetic acid (46 c.c.). A part of the *product* gradually crystallised and a further quantity was obtained from the ethereal layer (total yield, 2·8 g., 37%). Two recrystallisations from ethanol gave colourless needles, m. p. 147—149° (Found: C, 78·2; H, 5·6; N, 5·1. $C_{18}H_{15}O_2N$ requires C, 78·0; H, 5·4; N, 5·1%). The Ehrlich reaction was a cherry-red coloration. The 2 : 4-*dinitrophenylhydrazone* was prepared in alcoholic solution containing hydrochloric acid, and after chromatographic purification (alumina–benzene) crystallised from acetic acid as yellow needles, m. p. 231—232° (Found: C, 62·7; H, 4·2. $C_{24}H_{19}O_5N_5$ requires C, 63·0; H, 4·2%). The *semicarbazone*, prepared in pyridine, crystallised from ethanol in prisms, m. p. 178—180° (Found : C, 68·4; H, 5·6. $C_{19}H_{18}O_2N_4$ requires C, 68·2; H, 5·4%).

1-β-Benzoylpropionylindole (0·2 g.) was heated with aqueous 5% sodium hydroxide (6 c.c.) and ethanol (1·5 c.c.) for 4 hr. at 60°. The whole was extracted with benzene, and indole picrate, m. p. and mixed m. p. 180—183° (decomp.), was isolated from the hydrocarbon layer with picric acid. The semicarbazone of β-benzoylpropionic acid was obtained from the aqueous layer. It had m. p. 207—208° (decomp.), undepressed on admixture with an authentic specimen [Attwood, Stevens, and Thorpe, *J.*, 1923, **123**, 1762, give m. p. 206° (decomp.)].

Indole picrate separated from benzene as red needles, m. p. 181—185° (decomp.) (Found : C, 48·7; H, 3·2. Calc. for $C_{14}H_{10}O_7N_4$: C, 48·6; H, 2·9%). Baeyer and Caro (*Ber.*, 1877, **10**, 1263; 1879, **12**, 1314) quote an analysis for this compound, but no m. p. seems to have been recorded.

1-*Lævuloylindole* (VI).—A solution of α-angelicalactone (19·6 g.) (prepared by the method of Thiele, Tischbein, and Lossow, *Annalen*, 1902, **319**, 184) in ether (50 c.c.) was added, gradually, with stirring, at 0°, to one of indolylmagnesium iodide, prepared from indole (23·4 g.) as above, and the solution was stirred at room temperature for 30 min. and refluxed for 15 min. Water (260 c.c.) and acetic acid (36 c.c.) were added at 0°. The ethereal layer was separated and the ether removed. The residual red oil was warmed to 70—80° with pyridine (150 c.c.), and semicarbazide hydrochloride (18 g.) in water (18 c.c.) was added; 1-*lævuloylindole semicarbazone* (22·3 g., 41%) began to separate in prisms almost immediately. After a few hours it was collected and washed eight times with cold ethanol; the m. p. was 210—212°, raised by two crystallisations from a large volume of ethanol to 216° (Found : C, 62·3; H, 6·0. $C_{14}H_{16}O_2N_4$ requires C, 61·8; H, 5·9%). A mixture of this semicarbazone (22·3 g.), acetic acid (300 c.c.), and pyruvic acid (13 g.) was refluxed for 15 min. and, while it was still boiling, water (300 c.c.) was added gradually during 10 min., followed by more water (500 c.c.) added all at once. On cooling slowly, 1-*lævuloylindole* (14 g., 79%) separated in needles; after recrystallisation from ethanol–water (1 : 1) these had m. p. 78—79° (Found : C, 72·4; H, 6·1. $C_{13}H_{13}O_2N$ requires C, 72·6; H, 6·0%). The substance gave a deep purple-red Ehrlich reaction. The 2 : 4-*dinitrophenylhydrazone*, prepared in acid ethanol and purified by chromatography (alumina–benzene) separated from toluene in yellow prisms, m. p. 214—215° (Found : C, 57·3; H, 4·3. $C_{19}H_{17}O_5N_5$ requires C, 57·7; H, 4·3%). The *oxime*, prepared in pyridine, separated from ethanol–water (1 : 1) as plates, m. p. 138° (Found : C, 67·4; H, 6·2. $C_{13}H_{14}O_2N_2$ requires C, 67·8; H,6·1%). Treatment of lævuloylindole overnight with aqueous 2N-sodium hydroxide, followed by extraction with benzene, led to the isolation of indole (picrate, m. p. and mixed m. p. 180—183°) from the benzene layer, and lævulic acid (2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 203—205° with an authentic specimen of m. p. 204—206°; Strain, *J. Amer. Chem. Soc.*, 1935, **57**, 758, gives m. p. 206°) from the aqueous solution.

γ-*Oxopimelic Dilactone* (2 : 2′-spiro*Tetrahydropyran*-5-*one*) (IV).—γ-Oxopimelic acid (40 g.) (U.S.P. 2,436,532; *Chem. Abs.*, 1948, **42**, 5048) and acetic anhydride (60 c.c.) were refluxed for 2½ hr., and volatile compounds removed at 100°/13 mm. Addition of a little chloroform–ethanol (1 : 10) to the residue gave the anhydride (32·4 g., 90%) which after crystallisation from the same solvent had m. p. 60—61°, unchanged by further recrystallisation (Found : C, 54·0; H, 4·9. Calc. for $C_7H_8O_4$: C, 53·8; H, 5·1%). Volhard (*Annalen*, 1889, **253**, 221) gives m. p. 75°, and later (*ibid.*, 1892, **267**, 105), m. p. 69°; Michael (*J. prakt. Chem.*, 1891, **44**, 118) gives m. p. 64—65°.

1-(6-*Carboxy*-4-*oxohexanoyl*)*indole*.—γ-Oxopimelic dilactone (30·8 g.) in anisole (30 c.c.) was brought into reaction with indolylmagnesium iodide (from indole, 23·2 g.) in a similar manner to that described above for the preparation of 1-lævulylindole. 1-(6-*Carboxy*-4-*oxohexanoyl*)-*indole semicarbazone* (17 g., 26%) separated from pentyl alcohol in prisms, m. p. 189—190° (Found : C, 58·2; H, 5·9. $C_{16}H_{18}O_4N_4$ requires C, 58·2; H, 5·5%). This derivative (17 g.) was decomposed with pyruvic acid essentially as before, to give the parent *indole* (10·8 g., 77%), which crystallised from aqueous ethanol (1 : 1) in needles, m. p. 126—126·5° (Found : C, 66·1; H, 5·4. $C_{15}H_{15}O_4N$ requires C, 65·9; H, 5·5%). The Ehrlich test gave a cherry-red colour. The *methyl ester*, prepared in 95% yield by means of ethereal diazomethane, crystallised from methanol in needles, m. p. 73—73·5° (Found : C, 66·5; H, 5·9. $C_{16}H_{17}O_4N$ requires C, 66·9; H, 5·9%) The methyl ester gave a 2 : 4-*dinitrophenylhydrazone* which, after chromatographic purification (alumina–benzene–ether), separated from ethanol in yellow needles, m. p. 144—146° (Found : C, 56·5; H, 4·5. $C_{22}H_{21}O_7N_5$ requires C, 56·5; H, 4·5%). 1-(6-Carboxy-4-oxohexanoyl)indole was hydrolysed as described above for 1-lævuloylindole, to give indole picrate, m. p. and mixed m. p. 181—185°, and γ-oxopimelic acid semicarbazone, m. p. and mixed m. p.

196° (decomp.) (Asahina and Fujita, *Acta Phytochim.*, 1922, **1**, 33; Beilstein's "Handbuch," Suppl. II, Vols. III/IV, p. 487, give m. p. 204°).

3-*Methyl*-1 : 2(2′ : 7′)*benzylenepyrid*-6-*one* (VII; R = H).—Concentrated sulphuric acid (15 c.c.) was poured on 1-lævuloylindole (15 g.). The mixture became hot and the solid dissolved to a red solution which was kept an hour and then added to a mixture of acetic acid (25 c.c.) and perchloric acid (32 c.c. of 60%). The *perchlorate* (7·3 g., 36%) which separated recrystallised from acetic acid as needles, m. p. 275° (explosive decomp.) (Found: C, 52·9; H, 3·9. $C_{13}H_{12}O_5NCl$ requires C, 52·5; H, 4·0%). The perchlorate (12 g.) was shaken with chloroform (60 c.c.), water (30 c.c.), and aqueous ammonia (*d* 0·88; 40 c.c.) for a few minutes, all the solid dissolving. Solvent was removed from the dried chloroform layer, and the product crystallised from acetic acid. The *pyridone* separated in colourless needles, m. p. 154—155·5° (Found: C, 79·2; H, 5·6; N, 7·1. $C_{13}H_{11}ON$ requires C, 79·2; H, 5·6; N, 7·1%). The substance does not give a colour with Ehrlich's reagent. When the pyridone was boiled with ethanol and solid potassium hydroxide added, a brown-yellow solution was formed and this exhibited an intense green fluorescence; it soon faded when shaken in air.

The authors are grateful to the Ministry of Education for a F.E.T.S. grant awarded to one of them (A. R. K.).

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