The Synthesis of Emetine and Related Compounds. Part VI.[1] Improvements in the Synthesis of 3-Alkyl-1,3,4,6,7,11b-hexahydro-9,10-dimethoxybenzo[*a*]quinolizin-2-ones and 3-Alkyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizin-2-ones. Formation of Some Related Diazabicyclo[3,3,1]nonanes

By **Norman Whittaker**, The Wellcome Research Laboratories, Beckenham, Kent, BR3 3BS

A simplified procedure is reported for the almost quantitative conversion of the dihydroisoquinoline (II) into the benzo[*a*]quinolizines (I; R = alkyl). A by-product formed in the preparation of the 3-unsubstituted compound (Ic) is assigned the pentacyclic structure (VII). 3,4-Dihydro-β-carboline condenses with Mannich bases in the presence of carbon dioxide to give the indolo[2,3-*a*]quinolizines (XII; R = alkyl) in good yield. The unsymmetrical di-Mannich base (XIII) condenses with two molecules of the dihydroisoquinoline (II) to give the 9,18-methanodi-isoquino[2,1-*a* : 1′,2′-*d*][1,5]diazocine (XV); the symmetrical di-Mannich base (XVI), or the 4-oxopiperidinium salt (XIX), gives the substituted 9,18-methanodi-isoquino[2,1-*a* : 2′,1′-*e*][1,5]diazocine (XVIII), together with a trace of the dipentacyclic ketone (XXII).

THE hexahydrobenzo[*a*]quinolizinone (Ia) is the key intermediate in commercial syntheses of emetine [1] and 2-dehydroemetine,[2,3] and the related octahydroindolo-[2,3-*a*]quinolizinone (XIIa) has found application in the syntheses of (±)- and (−)-corynantheidine,[4,5] (±)-dihydrocorynantheine,[4] and flavopereirine.[6] Continued interest in these two intermediates and homologues led to a closer study of their one-step synthesis [7] to see if the already good yield of (Ia) and the indifferent yield of (XIIa) could be improved.

In the original procedure,[7] reaction of 3,4-dihydro-6,7-dimethoxyisoquinoline (II) with the protonated Mannich base (IIIa) in ethanol under reflux gave only a 28% yield of the benzo[*a*]quinolizine (Ia), whereas reaction with the methiodide gave a 75% yield. Experiments in which the decreasing concentration of the dihydroisoquinoline in the reaction solution was followed spectroscopically have now revealed that the lower yield simply represents a slow reaction. The pK_a values of the dihydroisoquinoline (II) and the Mannich base (IIIa) are 7·8 and 8·6 respectively, and it has been demonstrated spectroscopically that proton transfer from (IIIa) to (II) occurs to the extent of 33% in ethanolic solution. Thus the effective concentrations of the reacting species, the un-ionised dihydroisoquinoline (II) and the cationic form (IIIa) of the Mannich base, are lower than in analogous reactions with the quaternary Mannich base, and this results in a smaller rate of formation of the benzo[*a*]quinolizine (Ia). The yield of the latter could be raised by increasing the concentration and the reaction time. However, if the reaction was carried out in aqueous solution at room temperature for 24 hr., the analytically pure product (Ia) crystallised as the free base, the form required for further synthetic work, in almost quantitative yield. The 3-butylbenzo[*a*]quinolizine (Ib) was obtained quantitatively in a similar manner. The success of this procedure is probably a consequence of the sparing solubility of the bases (I) in water, enabling their reversible formation from the intermediate quaternary dihydroisoquinolinium ion (IV) to proceed to completion. Reaction of the protonated acetone Mannich base (IIIc) with the dihydroisoquinoline (II) gave the 3-unsubstituted benzo-[*a*]quinolizine (Ic) in only 67% yield, owing to the simultaneous formation of two other compounds, one of which has been studied in detail and assigned the pentacyclic structure (VII).* Its molecular formula was not established unequivocally by micro-analysis but the mass spectrum contained a peak at *m/e* 452, corresponding to $C_{26}H_{32}N_2O_5$, indicating that the compound had been formed from two molecules of the dihydroisoquinoline (II) and one of the Mannich base (IIIc). Intense peaks at *m/e* 191 and 261 were due to extensive fragmentation of the molecular ion to the dihydroisoquinoline (II) and an M − 191 species. Absorption at 1706 cm.$^{-1}$ was attributed to ketonic carbonyl, shown to be present as MeCO· by the three-proton signal at δ 1·98 in the ^{1}H n.m.r. spectrum, and the absence of N–D stretching after treatment with deuterium oxide pointed to the absence of N–H, so that the alternative structure (VIII) was clearly excluded in favour of structure (VII). The ^{1}H n.m.r. spectrum fully supported this structure; the one-proton singlet at δ 4·36 and the one-proton doublet with centre at δ 4·27 (J 10 c./sec.) were assigned to the hydrogens H_A and H_B; the doublet was decoupled on irradiation at the frequency of H_C. In ethanolic sodium hydroxide, compound (VII) exhibits only substituted veratrole absorption at 282—291 mμ but in 0·1N-ethanolic hydrochloric acid there is strong

* Dr. Cs. Szántay (Budapest) has also assigned this structure to a compound obtained from a vinyl ketone and the dihydroisoquinoline (II). The author thanks him for notification of his results before publication.[8]

[1] Part V, H. T. Openshaw and N. Whittaker, *J. Chem. Soc.*, 1963, 1461.

[2] A. Brossi, M. Baumann, L. H. Chopard-dit-Jean, J. Würsch, F. Schneider, and O. Schnider, *Helv. Chim. Acta*, 1959, **42**, 772.

[3] N. Whittaker, *J. Chem. Soc.* (*C*), 1968,

[4] J. A. Weisbach, J. L. Kirkpatrick, K. R. Williams, E. L. Anderson, N. C. Yim, and B. Douglas, *Tetrahedron Letters*, 1965, 3457.

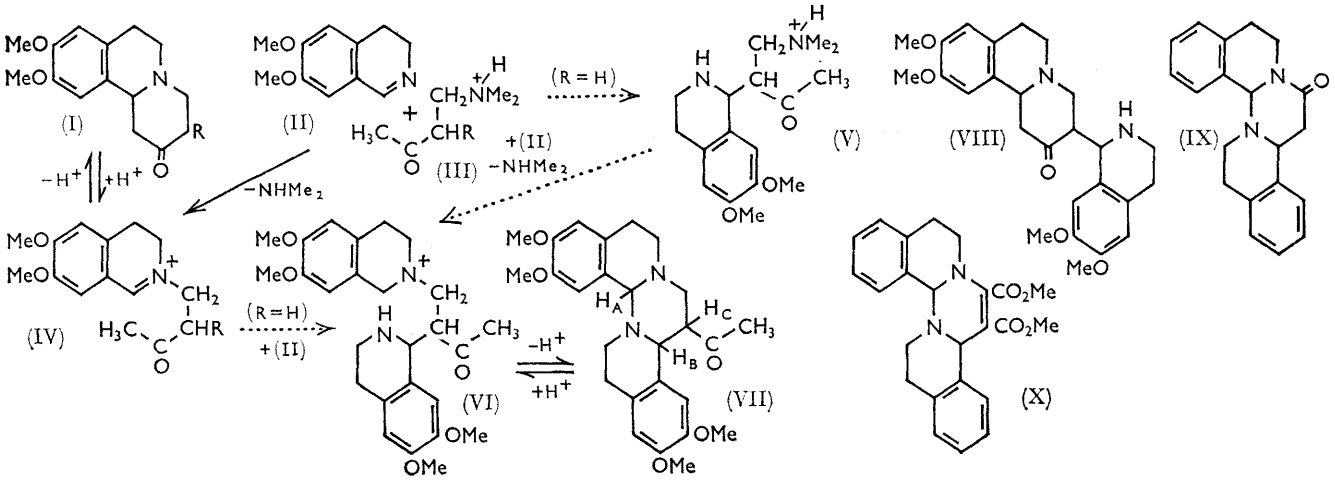
[5] Cs. Szántay and M. Bárczai-Beke, *Tetrahedron Letters*, 1968, 1405.

[6] Cs. Szántay and L. Töke, *Acta Chim. Acad. Sci. Hung.*, 1963, **39**, 249.

[7] H. T. Openshaw and N. Whittaker, *J. Chem. Soc.*, 1963, 1449.

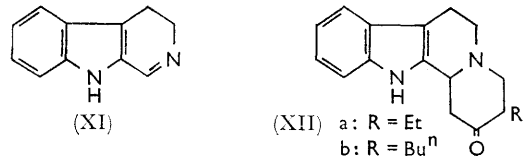
[8] Cs. Szántay and L. Novák, *Chem. Ber.*, 1967, **100**, 2038.

absorption at 376 mμ, ascribed to ring-opening to the quaternary dihydroisoquinolinium ion (VI) and not to elimination of the protonated dihydroisoquinoline (II), which has $\lambda_{max.}$ 363 mμ. This is a substantially reversible process; the spectrum reverts almost completely to that of the starting material on basification of the acid solution. Two reaction mechanisms which could account for the formation of the pentacyclic ketone (VII) are indicated by dotted arrows in the Scheme. The diisoquinopyrimidine ring-system of (VII) is present in the lactam (IX), obtained by Thesing and Hofmann [9] from the reaction of 3,4-dihydroisoquinoline with keten, and in the di-ester (X), obtained by Huisgen and Herbig [10] by an analogous reaction with dimethyl acetylenedicarboxylate.



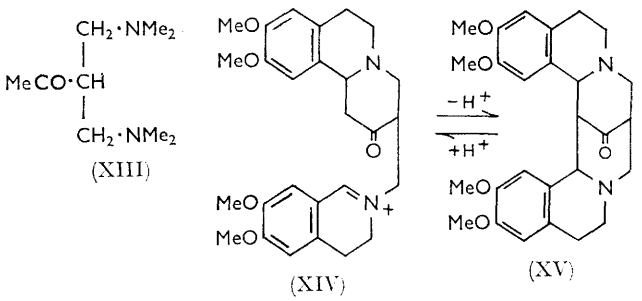
SCHEME

a, R = Et; b, R = Bu^n; c, R = H



In order to re-examine the synthesis [7] of indolo[2,3-*a*]quinolizin-2-ones (XII), a substantial quantity of 3,4-dihydro-β-carboline (XI) was required. It was found that cyclisation of *N*-formyltryptamine to 3,4-dihydro-β-carboline proceeds spontaneously and exothermically in phosphoryl chloride at room temperature, an unexpected result in view of the vigorous conditions employed by other workers.[11] By this means 3,4-dihydro-β-carboline was obtained in 94% overall yield from tryptamine. When the dihydrocarboline was heated with 3-dimethylaminomethylpentan-2-one in ethanol in the absence of acid, the indoloquinolizine (XIIa) was obtained (35%). This indicated that there is significant protonation of the Mannich base by the solvent alone and, further, that the dihydrocarboline is more reactive than the dihydroisoquinoline (II) which, under comparable conditions, gave only 7% of the benzo[*a*]quinolizine (Ia). The dihydrocarboline also reacted with the hydrochloride (IIIa) of the Mannich base at room temperature but the yield of product (XIIa) was only 30%, owing to the formation of dark-coloured by-products. These side reactions were less apparent when benzoic acid was the means of protonation of the Mannich base, and the yield of product increased to 47%. Carbonic acid in ethanol at 60° proved even more satisfactory, however, and gave a 73% yield of the indoloquinolizine (XIIa), and it was applied with similar success to the synthesis of the n-butyl homologue (XIIb).

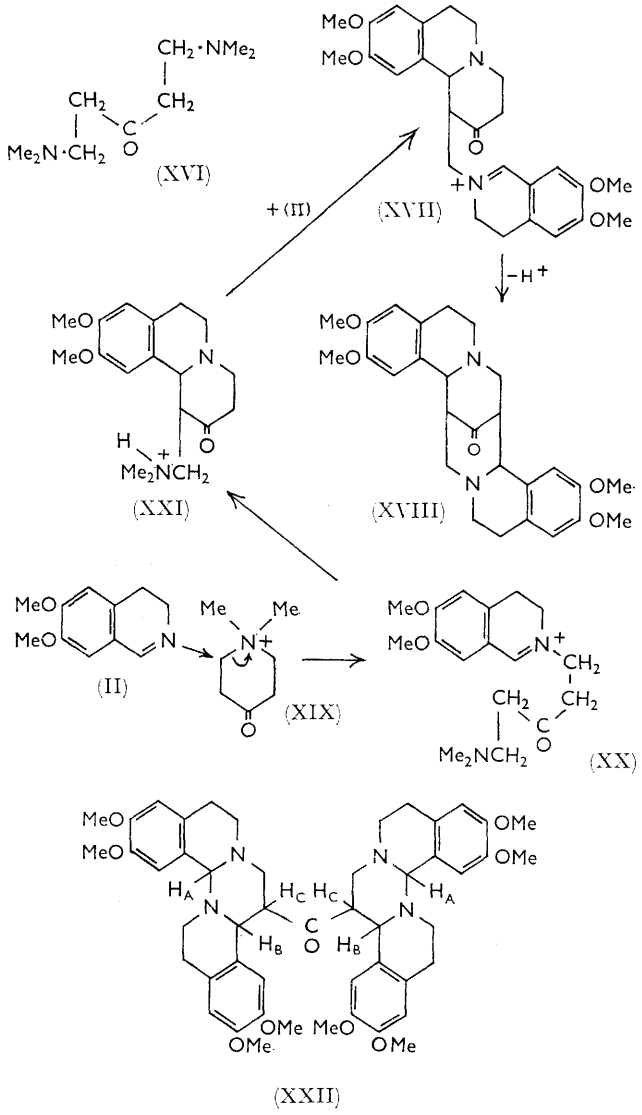
When the above annelation reaction of mono-Mannich bases was applied to the dihydrochloride of the unsymmetrical di-Mannich base (XIII), concurrent reaction with two molecules of the dihydroisoquinoline (II) produced the methanodi-isoquinodiazocinone derivative (XV) directly. The final step leading to its formation was shown to be reversible; treatment of the product with acid gave absorption at 370 mμ due to the presence



of (XIV) and of some dihydroisoquinoline (II) formed by fragmentation of (XIV).

[9] J. Thesing and K. Hofmann, *Chem. Ber.*, 1957, **90**, 229.
[10] R. Huisgen and K. Herbig, *Annalen*, 1965, **688**, 98.
[11] (*a*) E. Späth and E. Lederer, *Ber.*, 1930, **63**, 2102; (*b*) C. Schöpf and H. Steuer, *Annalen*, 1947, **558**, 124; (*c*) M. Onda and M. Sasamoto, *Pharm. Bull. (Japan)*, 1957, **5**, 305; (*d*) R. N. Gupta and J. D. Spenser, *Canad. J. Chem.*, 1962, **40**, 2049; (*e*) Cs. Szántay, L. Töke, M. B. Bárczai, and Gy. Kalaus, *Periodica Polytech.*, 1965, **9**, 231.

The symmetrical di-Mannich base (XVI) dihydrochloride also reacted with the dihydroisoquinoline (II) and the resulting methanodi-isoquinodiazocinone derivative (XVIII)* crystallised from the reaction solution in high yield. The parent compound (XVIII; H for MeO) was obtained from 3,4-dihydroisoquinoline, but in substantially lower yield. Since the *N*-dimethyl-4-oxopiperidinium ion (XIX) is essentially a quaternary Mannich base, it was considered likely to undergo heterolytic fission comparable to that effected by dimethylamine,[12] on treatment with the dihydroisoquinoline (II), and so serve as an alternative source of the five-carbon



(XXII)

fragment needed for the formation of the sparteine derivative (XVIII). This expectation was fulfilled and a good yield of product was again obtained. Here it is possible to formulate the course of the reaction for, in the absence of an external proton source, the intermediate ion (XX) must cyclise to the benzo[*a*]quinolizine (XXI) before further reaction with the dihydroisoquinoline (II) can take place. Unlike its isomer (XV), compound (XVIII) does not readily undergo ring-opening in acid solution at room temperature. A sparingly soluble by-product was obtained in trace quantities in the synthesis of the sparteine derivative (XVIII) and is assigned the dipentacyclic ketone structure (XXII) on the basis of its i.r. absorption, which strikingly resembles that of compound (VII) in the region 700—1650 cm.$^{-1}$, and its ^{1}H n.m.r. spectrum.

Since the foregoing account was written, Szántay and collaborators have announced [13] the synthesis of compound (XV) by a somewhat different route and compound (XVIII) by substantially the same procedure as that reported here.

* The stereochemistry of compounds (XV) and (XVIII) has not been determined but it appears that in each compound at least one of the two quinolizidine ring systems is *trans*-fused, in view of Bohlmann absorption at 2700—2800 cm.$^{-1}$.

EXPERIMENTAL

I.r. spectra were measured for potassium chloride dispersions. The ^{1}H n.m.r. spectra were determined for solutions in deuteriochloroform, with tetramethylsilane as internal reference, by use of a Varian HA 100 instrument.

1,3,4,6,7,11b-*Hexahydro*-9,10-*dimethoxybenzo*[a]*quinolizin*-2-*ones* (I).—The extent of reaction of 3,4-dihydro-6,7-dimethoxyisoquinoline (II) with the Mannich base hydrochlorides (III) in ethanolic or aqueous solution was determined by treatment of a measured quantity of the reaction mixture with 0·1N-ethanolic hydrogen chloride and measuring the absorption of the unreacted protonated dihydroisoquinoline (II), $\lambda_{max.}$ 363 mμ (ε 8320). The following represent the best reaction conditions found in each case.

(a) *The* 3-*ethyl compound* (Ia). 3,4-Dihydro-6,7-dimethoxyisoquinoline hydrochloride trihydrate (10 g.), dissolved in cold water (30 ml.), was treated with 3-dimethylaminomethylpentan-2-one (5·6 g., 1·1 mol.) and set aside at room temperature. Crystallisation began after *ca.* 40 min. and after 29 hr. the mass of colourless needles was triturated under water (50 ml.) and collected, to yield 3-ethyl-1,3,4,6,7,11b-hexahydro-9,10-dimethoxybenzo[*a*]-quinolizin-2-one (9·66 g., 94%), m.p. 109—110° (lit.,[7] 109·5—110·5°).

(b) *The* 3-*n-butyl compound* (Ib). Addition of 3-dimethylaminomethylheptan-2-one to an aqueous solution of 3,4-dihydro-6,7-dimethoxyisoquinoline hydrochloride gave, after 3 days at room temperature, a quantitative yield of 3-n-butyl-1,3,4,6,7,11b-hexahydro-9,10-dimethoxybenzo[*a*]-quinolizin-2-one, m.p. 111—113° (lit.,[7] 112—113°).

(c) *The* 3-*unsubstituted compound* (Ic). A cooled solution of 3,4-dihydro-6,7-dimethoxyisoquinoline (20·4 g.) in water (90 ml.) was neutralised with concentrated hydrochloric acid (9·33 ml.), treated with 1-dimethylaminobutan-3-one (13·5 g., 1·1 mol.), and set aside at room temperature for 2 days. The resulting crystals (23·7 g.) were collected and a red impurity was removed by extraction into water from a solution in benzene. The product recovered from the benzene gave 1,3,4,6,7,11b-hexahydro-9,10-dimethoxybenzo[*a*]quinolizin-2-one (18·6 g., 67%), m.p. 150·5—152° (from ethanol) (lit.,[7] 152—153°). Concentration of the

[12] H. M. E. Cardwell, *J. Chem. Soc.*, 1950, 1056.

[13] Cs. Szántay, L. Novak, and A. Buzas, *Tetrahedron*, 1968, 24 4713.

alcoholic liquors gave a mixture (3·5 g.) of the benzo[*a*]-quinolizine with the by-product (VII) which was chromatographed (alumina; 170 g.) in methylene chloride. The by-product was eluted first and was crystallised by concentration of a solution in hot ethanol, to yield colourless needles (1·3 g.), m.p. 235—236°, of the *di-isoquinopyrimidine* (VII) [Found: C, 68·95; H, 7·05; N, 6·1%; *M* (mass spectrometer), 452. $C_{26}H_{32}N_2O_5$ requires C, 69·0; H, 7·15; N, 6·2%; *M*, 452), $\nu_{max.}$ 2790 and 2760 (Bohlmann bands) and 1706 (C=O) cm.$^{-1}$, $\lambda_{max.}$ (0·015N-EtOH–NaOH) 224, 282infl, 286, and 291infl mμ (ε 19,800, 7450, 7770, and 7280). In 0·1N-alcoholic hydrogen chloride the spectrum showed, after 10 min., $\lambda_{max.}$ 249, 296, 316, and 376 mμ (ε 20,800, 7500, 12,000, and 11,900) owing to the formation of the quaternary ion (VI). Heating with 0·1N-hydrochloric acid or with 5% aqueous acetic acid at 100° for 2 hr. gave 3,4-dihydro-6,7-dimethoxyisoquinoline, the benzo[*a*]quinolizine (Ic), and traces of unidentified products.

3,4-*Dihydro*-β-*carboline* (XI).—When crude *N*-formyltryptamine (6·95 g.) [from tryptamine [11b] (5·48 g.)] cooled in ice–water was treated with phosphoryl chloride (25 ml.) the temperature of the mixture rose to 67°. After 1·5 hr. at room temperature, the excess of phosphoryl chloride was removed *in vacuo*, the residue was stirred with water (500 ml.), and the aqueous solution was filtered and basified with concentrated aqueous ammonia. 3,4-Dihydro-β-carboline separated as a pale yellow micro-crystalline solid (5·48 g., 94%) which was recrystallised by concentration of a filtered solution in ether (200 ml.) to *ca.* 20 ml., and afforded almost colourless needles (4·5 g.), m.p. 87° [with evolution of ether (7·5%)] and then 175—176° (Found, on dried material: C, 77·8; H, 6·2; N, 16·35. Calc. for $C_{11}H_{10}N_2$: C, 77·6; H, 5·9; N, 16·45%). Its u.v. absorption in alkaline and in acid solution agreed closely with that recorded by Fleming and Harley-Mason [14] for pure 3,4-dihydro-β-carboline. In other experiments the recrystallised product contained 1—2% of ether. Crystallisation of 3,4-dihydro-β-carboline from benzene also gave solvated crystals [*cf.* ref. 11*e*], m.p. 84° [with evolution of benzene (20%)] and then 175—176°.

3-*Ethyl*-1,2,3,4,6,7,12,12b-*octahydroindolo*[2,3-a]*quinolizin*-2-*one* (XIIa).—Each of the following experiments relates to the reaction of 3,4-dihydro-β-carboline (1 g.) with 3-dimethylaminomethylpentan-2-one (0·93 g., 1·1 mol.).

(*a*) The reactants were heated together in ethanol (1·5 ml.) under nitrogen on a steam-bath for 8 hr. and the resulting suspension of crystals was cooled and filtered to yield 3-ethyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizin-2-one (XIIa) (0·56 g., 35%), m.p. 203—205° (lit.,[7] 206—207°). Similar reaction at 60° (bath) for 7 hr. gave the same product (0·25 g.).

(*b*) The carboline, suspended in water (2·5 ml.), was treated with 5N-hydrochloric acid to give pH 5, then with ethanol (1·5 ml.) and the Mannich base, and set aside overnight. The resulting suspension of crystals was shaken with chloroform and aqueous potassium hydroxide and the base obtained from the chloroform solution gave the indoloquinolizine (XIIa) (0·48 g., 30%), m.p. 198—200° (from ethanol). When the reaction was carried out in ethanol (4 ml.) alone, a dark red colour developed and a lower yield of compound (XIIa), contaminated with a substantial quantity of alcohol-insoluble resin, was obtained.

(*c*) Treatment of a solution of the reactants in ethanol (1·75 ml.) with benzoic acid (0·72 g., 1 mol.) at room temperature gave the indoloquinolizine (XIIa) base (0·74 g., 47%), m.p. 203—205°, directly.

(*d*) A stream of carbon dioxide was passed through a heated (60°) solution of the reactants in ethanol–water (6 : 1) (1·75 ml.) for 7 hr. The resulting suspension of colourless crystals was set aside at room temperature overnight, then at 0° for 7 hr., and filtered, to yield the indoloquinolizine (XIIa) (1·08 g., 68·5%), m.p. 205·5—207°, $\lambda_{max.}$ (EtOH) 207infl, 225, 275infl, 283, and 291 mμ (ε 19,200, 37,200, 7300, 7700, and 6510). Concentration of the alcoholic liquors and refrigeration gave more product (80 mg., 5%).

3-*n-Butyl*-1,2,3,4,6,7,12,12b-*octahydroindolo*[2,3-a]*quinolizin*-2-*one* (XIIb).—Reaction of 3,4-dihydro-β-carboline (1 g.) with 3-dimethylaminomethylheptan-2-one [7] (1·11 g.) as in (*d*) above gave the *indoloquinolizine* (XIIb) (1·2 g., 69%), m.p. 177—179°. A recrystallised (ethanol) specimen had m.p. 180—181° (Found: C, 76·85; H, 7·9; N, 9·35. $C_{19}H_{24}N_2O$ requires C, 77·0; H, 8·15; N, 9·45%).

5,6,8,9,10,12,13,17b,18,18a-*Decahydro*-2,3,15,16-*tetramethoxy*-9,18-*methanodi-isoquino*[2,1-a : 1′,2′-d][1,5]*diazocin*-19-*one* (XV).—3,4-Dihydro-6,7-dimethoxyisoquinoline hydrochloride trihydrate (1 g.), dissolved in water (3 ml.), was treated with 4-dimethylamino-3-dimethylaminomethylbutan-2-one [15] (XIII) (0·31 g., 0·5 mol.) and set aside at room temperature. The gum which began to separate after a few min. gradually crystallised and, after 24 hr., the pinkish crystals were collected and washed with water. A filtered solution of the crystals in benzene (60 ml.) was washed with water (3 × 25 ml.), dried (Na_2SO_4), and evaporated, and the residue was crystallised from ethanol (8 ml.) to give colourless needles (0·285 g.), m.p. 192—194°, raised by two further recrystallisations to 194—196°, of the *methanodi-isoquinodiazocinone* (XV) (Found: C, 69·65; H, 7·0; N, 6·0. $C_{27}H_{32}N_2O_5$ requires C, 69·8; H, 6·95; N, 6·05%), *m/e* 464 (M^+) and 232 (M^{++}), $\nu_{max.}$ 2765 (*trans*-fused quinolizidine) and 1725 (C=O) cm.$^{-1}$, $\lambda_{max.}$ (0·015N-EtOH–NaOH) 222, 284, and 288infl mμ (ε 19,300, 7330, and 7000), $\lambda_{max.}$ (0·1N-EtOH–HCl, after 10 min.) 238, 289, 314, and 370 mμ (ε 14,900, 6640, 5940, and 6300); basification of the acid solution, after 30 min., with sodium hydroxide gave absorption at 311 mμ due to some 3,4-dihydro-6,7-dimethoxyisoquinoline.

1,5-*Bisdimethylaminopentan*-3-*one* (XVI).—This intermediate was obtained by Cardwell's reaction [12] but with modification of his isolation procedure, and distillation of the free base, as follows.

A solution of *N*-methyl-4-piperidone methiodide (44 g.) in aqueous dimethylamine (32% w/v; 400 ml.) was set aside at room temperature for 5 days and the excess of dimethylamine was removed at room temperature under reduced pressure through a Vigreux column into a cooled (CO_2) trap. The residual aqueous solution was treated with potassium hydroxide pellets (200 g.), with cooling, and the liberated base was extracted into ether (2 × 300 ml.). The dried (K_2CO_3) extract was evaporated and the residual oil was distilled, to yield the pure *di-Mannich base* (27 g., 91%), b.p. 47°/0·15 mm., n_D^{22} 1·4448 (Found: C, 62·65; H, 11·2; N, 16·45. $C_9H_{20}N_2O$ requires C, 62·75; H, 11·7; N, 16·25%). This compound was obtained in only 8% yield by reaction of acetonedicarboxylic acid with formaldehyde and dimethylamine in aqueous solution at 10°.

5,6,8,9,9a,14,15,17,18,18a-*Decahydro*-2,3,11,12-*tetramethoxy*-9,18-*methanodi-isoquino*[2,1-a : 2′,1′-e][1,5]*diazo*-

[14] I. Fleming and J. Harley-Mason, *J. Chem. Soc.*, 1966, 425.
[15] C. Mannich and O. Salzmann, *Ber.*, 1939, **72**, 506.

cin-19-*one* (XVIII).—(*a*) An ice-cooled solution of 3,4-dihydro-6,7-dimethoxyisoquinoline (18 g.) in water (80 ml.) was treated with concentrated hydrochloric acid (8·2 ml.) followed by 1,5-bisdimethylaminopentan-3-one (8·1 g., 0·5 mol.) and stirred at room temperature. Seeding with crystals of the product after 1 hr. initiated crystallisation and, after 3 days, the crystals (20·2 g.) were collected. A solution of the crystals in chloroform (200 ml.) was washed with dilute aqueous potassium hydroxide (200 ml.) and with water, dried (Na_2SO_4), and evaporated, and the residual syrup was treated with hot ethanol (200 ml.). The resulting suspension of colourless prisms was cooled and filtered, to yield the *methanodi-isoquinodiazocinone* (XVIII) (14·5 g., 67%), double m.p. 218—220° and 226—228° (evac. cap.) (Found: C, 69·7; H, 6·9; N, 6·1. $C_{27}H_{32}N_2O_5$ requires C, 69·8; H, 6·95; N, 6·05%), $\nu_{max.}$ 2760 (*trans*-fused quinolizidine) and 1728 (C=O) cm.$^{-1}$. The compound is dimorphous; crystallisation from ethanol on two occasions gave prisms, m.p. 231—232° (evac. cap.). When the ethanolic liquors from the above 14·5 g. of crystals were set aside for several days, mixed crystals (50 mg.), m.p. 254—256° (evac. cap.), separated. Recrystallisation, by addition of hot ethanol (30 ml.) to a solution of the crystals in chloroform (1 ml.) afforded colourless needles (35 mg.), m.p. 295° (decomp.; evac. cap.), of the *di-pentacyclic ketone* (XXII) (Found: C, 69·2; H, 6·95; N, 6·9. $C_{49}H_{58}N_4O_9$ requires C, 69·5; H, 6·9; N, 6·6%), $\nu_{max.}$ 2790 and 2750 (Bohlmann bands) and 1688 (C=O) cm.$^{-1}$, δ 4·27 (s, $2H_A$) and 4·37 (d, J 10 c./sec., $2H_B$ decoupled on irradiation at frequency of H_C).

(*b*) Reaction of 3,4-dihydro-6,7-dimethoxyisoquinoline (2·5 g.) with *N*-methyl-4-piperidone methochloride (XIX) (1·07 g., 0·5 mol.) in water (11·5 ml.) at room temperature for 3 days gave crystals (2·41 g.), m.p. 223—227° (evac. cap.), purified as in (*a*) to give the same product (XVIII) (2·06 g., 68%), m.p. 230—231° (evac. cap.). The by-product (XXII) crystallised slowly from the ethanolic liquors.

5,6,8,9,9a,14,15,17,18,18a-*Decahydro*-9,18-*methanodi-isoquino*[2,1-a : 2′,1′-e][1,5]*diazocin*-19-*one* (XVIII; H for MeO).—A mixture of 3,4-dihydroisoquinoline (2 g.), ethanol–water (5 : 2; 13 ml.), concentrated hydrochloric acid (1·32 ml.), and 1,5-bisdimethylaminopentan-3-one (1·32 g., 0·5 mol.) was seeded with crystals of the product and shaken at room temperature for 4 days. Treatment of the resulting crystals (1·95 g.), as described for the analogue (XVIII), gave colourless prisms (1·18 g.), m.p. 212—215°, shown by t.l.c. (silica, 40 : 1 $CHCl_3$–MeOH) to contain traces of a by-product, presumed to be (XXII; H for MeO). The by-product alone was decomposed when a solution of the crystals in N-hydrochloric acid (10 ml.) was set aside for 4 hr., and the base recovered from the acid solution was recrystallised from ethanol, to yield the pure *methanodi-isoquinodiazocinone* (XVIII; H for MeO) (1·05 g.), m.p. 216—217° (Found: C, 80·45; H, 7·0; N, 8·25. $C_{23}H_{24}N_2O$ requires C, 80·2; H, 7·0; N, 8·15%), $\nu_{max.}$ 2760 (*trans*-fused quinolizidine) and 1733 (C=O) cm.$^{-1}$.

The author thanks Dr. A. J. Everett and Mr. A. Ferrige for measuring and interpreting the n.m.r. spectra, Dr. J. M. Wilson (Manchester) for the mass spectra, and Dr. H. T. Openshaw for his interest and encouragement.

[8/1035 *Received, July 22nd,* 1968]