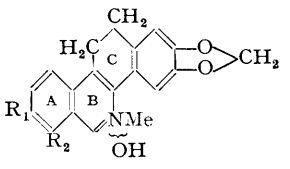
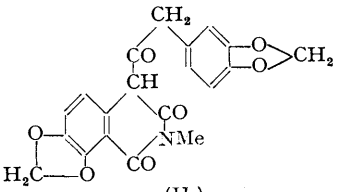
285. *Experiments on the Synthesis of the* Chelidonium *Alkaloids.*

By H. S. Forrest, R. D. Haworth, A. R. Pinder, and T. S. Stevens.

Several synthetic routes to the benzphenanthridine system have been explored, using initial materials derived from (*a*) homophthalic acid, (*b*) benzyl-1-naphthylamine. A new synthesis is described of the methylenedioxymethylphenanthridone which Kondo obtained in the degradation of lycorine. By the action of sodium, ethyl homophthalate affords, probably, a naphthalene derivative.

Degradative studies by Gadamer and Späth (*Ber.*, 1931, **64**, 370, 1123, 2034) and their co-workers have shown that the *Chelidonium* alkaloids, *e.g.*, chelerythrine (I, $R_1 = R_2 = MeO$) and sanguinarine (I, $R_1R_2 = CH_2O_2$), are derivatives of 1 : 2-benzphenanthridine. Noller, Denyes, Gates, and Wasley (*J. Amer. Chem. Soc.*, 1937, **59**, 2079) report preliminary synthetic experiments, including some, based on Pschorr's phenanthrene synthesis, which are complementary to work described below. The synthesis of the tetracyclic system by Richardson, Robinson, and Seijo (*J.*, 1937, 835) is not readily adaptable to the production of a molecule vicinally substituted in ring A. In view of the availability of suitably oriented dimethoxy- and methylenedioxy-homophthalic acids, Haworth (*ibid.*, p. 1312) attempted, unsuccessfully, to effect ring-closure in the homophthalimide derivative (II).


(I.)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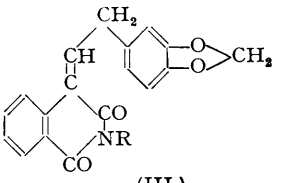
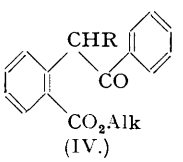

(III.)

Homophthalimide and its *N*-methyl derivative have now been condensed with homopiperonal; the *products*, presumably (III), were unstable and numerous attempts at ring-closure failed.

The potentially serviceable ester (IV, $R = CO_2Et$) should be obtainable by condensation of ethyl homophthalate with ethyl benzoate, but the sole definable *product*, $C_{20}H_{14}O_5$, was also formed by treating ethyl homophthalate alone with sodium. This substance was a monohydric phenol, yielding a *methyl ether* and a p-*nitrobenzoate*; it behaved as a lactone and is believed to be one of the two isomers derivable from the acid (V).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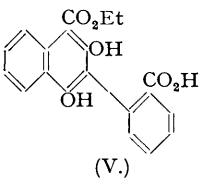
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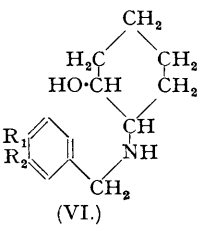
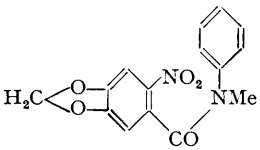

(VI.)

Methyl o-*phenacylbenzoate*, $Ph{\cdot}CO{\cdot}CH_2{\cdot}C_6H_4{\cdot}CO_2Me$, obtained from homophthalic anhydride through the Friedel–Crafts reaction, was treated with ethyl bromoacetate and sodium ethoxide in order to prepare (IV, $R = CH_2{\cdot}CO_2Et$), which contains the complete carbon skeleton of benzphenanthridine. This could not be effected, and similar attempts to condense o-*carbomethoxybenzyl cyanide* with ethyl bromoacetate and with ω-bromoacetophenone failed.

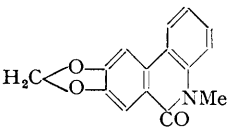
In another method of approach, 2 : 3-methylenedioxy- or 2 : 3-dimethoxy-benzaldehyde could contribute ring A, and ring B be closed by establishing the bond between rings A and C. This ring-closure was first attempted in the *compounds* (VI, $R_1R_2 = 2MeO$ or CH_2O_2), readily obtained from the appropriate primary amines and *cyclo*hexene oxide, and in their *N*-methyl derivatives. In no case could cyclo-dehydration be effected [compare Staub's generalisations as to the scope of the Pomeranz–Fritzsch synthesis of simple *iso*quinolines (*Helv. Chim. Acta*, 1922, **5**, 888)].

Pictet and Gonset (*Arch. Sci. phys. nat.*, 1897, **3**, 37) applied the Pschorr phenanthrene synthesis to the preparation of *N*-methylphenanthridone from *o*-nitrobenzoylmethylaniline. Similarly, by reduction and diazotisation, 2′-*nitro*-4′ : 5′-*methylenedioxybenzomethylanilide* (VII) gave in fairly good yield 6 : 7-methylenedioxy-10-methylphenanthridone (VIII), which Kondo and Uyeo (*Ber.*, 1935, **68**, 1756) encountered in the degradation of lycorine and synthesised by a less effective method. 2′-*Nitro*-4′ : 5′-*methylenedioxybenzomethyl*-1-*naphthalide* was prepared

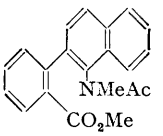
and reduced, but numerous attempts to effect ring-closure to a benzphenanthridone failed. The acid-sensitive *amine* obtained by reducing *2'-nitro-4'* : *5'-methylenedioxybenzyl*-N-*methylaniline* (VII; CH_2 for CO) gave no identifiable product on diazotisation and warming. *Nitromethylenedioxybenzylmethylnaphthylamine* was resinified on attempted reduction.



(VII.)



(VIII.)



(IX.)

With a view to a Pschorr synthesis in which the diazo-group should be attached to ring c, 2-nitro-1-naphthylamine was heated with piperonal, but like many other *o*-nitroamines it failed to give a Schiff base.

Elks and Hey (*J.*, 1943, 441) have shown that the triazen $NMe_2 \cdot N{:}N \cdot C_6H_4 \cdot CO_2Me$ yields an *o*-arylbenzoic ester when treated with an aromatic compound under acid conditions. The reaction was applied unsuccessfully to *N*-methylacetnaphthalide in the hope of obtaining the substance (IX) as one product.

Experimental.

Homopiperonylidene-N-*methylhomophthalimide* (III, R = Me).—In preparing homopiperonal from safrole *via* safrole glycol (Erdtman and Robinson, *J.*, 1933, 1530), the safrole was advantageously dissolved in acetone (15 parts) before adding cooled permanganate solution. Homopiperonal (1·8 g.) and piperidine (1 c.c.) were added to *N*-methylhomophthalimide (2 g.) in alcohol (20 c.c.), and solution completed by warming. After 30 minutes the yellow solid (80%) was collected, and its benzene solution passed through a column of alumina. By elution with alcohol, pale yellow *homopiperonylidene*-N-*methylhomophthalimide* was obtained, m. p. 119—130° (Found: C, 70·9; H, 4·9. $C_{19}H_{15}O_4N$ requires C, 71·0; H, 4·7%). Recrystallisation from alcohol or aqueous acetic acid led to great loss, with production of gum. The substance was recovered unchanged after standing for 5 days in chloroform with excess of phosphorus oxychloride; the same reagent undiluted or in boiling toluene, phosphorus pentachloride in chloroform, and phosphoric oxide in benzene failed to cause ring-closure. The double bond was not reduced by hydrogen over palladium or the Adams platinum catalyst in acetic acid or ethyl acetate, even in an all-glass apparatus. Homopiperonylidenehomophthalimide (III, R = H), from homopiperonal (0·5 g.) and homophthalimide (0·5 g.) in alcohol (50 c.c.) with piperidine (6 drops), crystallised from alcohol, had m. p. 195—198°. Purification was difficult, and the crude material could not be cyclised.

Lactone of 1 : 3-*Dihydroxy*-4-*carbethoxy*-2-2'-*carboxyphenylnaphthalene* (V).—Sodium wire (1·3 g.) was added to ethyl homophthalate (5 g.) in ether (25 c.c.) containing alcohol (1 drop), and after 2 days the mixture was heated under reflux for 24 hours. The resulting acidic fraction, treated with a little ether and kept at 0°, afforded the crystalline *lactone* (0·5 g.) which formed colourless needles from acetone, m. p. 181° [Found: C, 71·8, 72·4; H, 3·9, 4·3; *M* (Rast), 315. $C_{20}H_{14}O_5$ requires C, 71·9; H, 4·2%; *M*, 334]. The p-*nitrobenzoate*, prepared in benzene–pyridine, crystallised from acetone in clusters of needles, m. p. 284° (Found: C, 67·2; H, 4·0; N, 3·1. $C_{27}H_{17}O_8N$ requires C, 67·1; H, 3·5; N, 2·9%). The *methyl ether* from the lactone (0·2 g.) in acetone (20 c.c.) with ethereal diazomethane from 4·5 c.c. of nitrosomethylurethane, crystallised from methanol in clusters of needles, m. p. 150° (Found: C, 72·0, 72·7; H, 5·0, 5·0. $C_{21}H_{16}O_5$ requires C, 72·4; H, 4·6%), which dissolved only slowly in warm alkali. The lactone (V), little soluble in cold alkali, dissolved readily on warming to a yellow solution which turned dark red; acidification then afforded a product, orange-brown prisms from alcohol, decomp. above 300° (Found: C, 74·0; H, 4·4%).

Distilled in a stream of hydrogen over zinc dust, the lactone gave a brown gum, which was exhaustively distilled in steam. The volatile *solid* crystallised from methanol–chloroform in leaflets, m. p. 173° (Found: C, 93·8; H, 5·8. $C_{16}H_{12}$ requires C, 94·1; H, 5·9%); although approximating in composition to, it was distinct from, the expected 2-phenylnaphthalene, m. p. 102°. The stable *trinitrobenzene adduct* crystallised from alcohol in light orange leaflets, m. p. 138—140° (Found: C, 53·6; H, 2·9; N, 13·8. $C_{16}H_{12},2C_6H_3O_6N_3$ requires C, 53·3; H, 2·9; N, 13·3%); the unstable *picrate* formed orange microscopic leaflets from alcohol, m. p. 104—114° (Found: C, 52·7; H, 3·0. $C_{16}H_{12},2C_6H_3O_7N_3$ requires C, 50·8; H, 2·7%).

o-Phenacylbenzoic acid (Graebe and Trümpy, *Ber.*, 1898, **31**, 377) melted at 160° (previous softening); 2 : 4-*dinitrophenylhydrazone*, orange-red prisms from ethyl acetate, m. p. 224—225° (Found: N, 13·0. $C_{21}H_{16}O_6N_4$ requires N, 13·3%); *oxime*, colourless needles from ligroin, m. p. 132°, soluble in cold alkali (Found: N, 5·4. $C_{15}H_{13}O_3N$ requires N, 5·5%). The *methyl* ester, prepared by refluxing the dry silver salt with methyl iodide in ether for 1 hour, formed colourless needles, m. p. 114°, from methanol (Found: C, 75·3; H, 5·6. $C_{16}H_{14}O_3$ requires C, 75·6; H, 5·5%); treated with potassium ethoxide (2 mols.) in cold ether–benzene, it afforded a substance, long prisms from much alcohol, decomp. 300°, which gave red solutions in alkali (Found: C, 76·7; H, 3·4%).

The *methyl* ester of *o*-carboxyphenylacetonitrile (Wislicenus, *Annalen*, 1886, **233**, 102), prepared *via* the silver salt, crystallised from ligroin in felted needles, m. p. 47—48° (Found: C, 68·2; H, 5·4. $C_{10}H_9O_2N$ requires C, 68·6; H, 5·1%).

2-(3' : 4'-*Methylenedioxybenzyl*)*amino*cyclo*hexanol* (VI, $R_1R_2 = CH_2O_2$).—Methylenedioxybenzylamine (Mannich and Kuphal, *Ber.*, 1912, **45**, 318), b. p. 130—132°/10 mm. (1 g.), and *cyclo*hexene oxide

(*Org. Synth.*, 1925, **5**, 35; 0·65 g.) were heated at 160° (bath-temp.) for 45 minutes and then at 210—220° for 30 minutes. The cyclo*hexanol*, b. p. 175—180°/0·3 mm. (1·5 g.), crystallised from ligroin in long prisms, m. p. 66—67° (Found: C, 67·5; H, 7·7. $C_{14}H_{19}O_3N$ requires C, 67·5; H, 7·6%); *hydrochloride*, rhombic prisms, m. p. 200—201° (previous softening) from 2N-hydrochloric acid (Found: Cl, 12·4; equiv., 284·6. $C_{14}H_{20}O_3NCl$ requires Cl, 12·4%; equiv., 285·5). Boiling for 20 minutes with acetic anhydride containing a drop of sulphuric acid gave the ON-*diacetyl* derivative, hexagonal prisms, m. p. 120°, from ligroin (Found: Ac, 25·7; $C_{14}H_{17}O_3NAc_2$ requires Ac, 25·8%).

A mixture of the base (VI, $R_1R_2 = CH_2O_2$) (5 g.), 90% formic acid (2·2 c.c.), and 35% formalin (2 c.c.) was heated at 100° for 3 hours. The basic fraction, isolated in ether, was dried over potassium hydroxide and distilled; 2-(3′ : 4′-*methylenedioxybenzyl*)*methylamino*cyclo*hexanol*, b. p. 190—200°/0·4 mm., crystallised from ligroin in hexagonal prisms, m. p. 63° (Found: C, 68·3; H, 8·0. $C_{15}H_{21}O_3N$ requires C, 68·3; H, 8·0%); *hydrochloride*, clusters of needles from alcohol–ether, m. p. 160—161° (Found: Cl, 11·7; $C_{15}H_{22}O_3NCl$ requires Cl, 11·8%). Attempted ring-closure with phosphorus oxychloride gave 2-(3′ : 4′-*methylenedioxybenzyl*)*methylamino*cyclo*hexyl chloride hydrochloride*, prisms from alcohol–ether, m. p. 124—125° (Found: Cl′, 11·2; $C_{15}H_{21}O_2NCl{\cdot}Cl'$ requires Cl′, 11·2%).

2-(3′ : 4′-*Dimethoxybenzyl*)*amino*cyclo*hexanol* (VI, $R_1 = R_2 =$ OMe), from dimethoxybenzylamine (Juliusberg, *Ber.*, 1907, **40**, 120) and *cyclo*hexene oxide at 200°, formed rosettes of needles, b. p. 185—192°/0·2 mm., m. p. 90° (Found: C, 68·1; H, 8·6. $C_{15}H_{23}O_3N$ requires C, 67·9; H, 8·7%); *hydrochloride*, prisms from alcohol, m. p. 166° (Found: Cl, 11·8. $C_{15}H_{24}O_3NCl$ requires Cl, 11·8%). The N-*methyl* derivative, prepared like its analogue, stout prisms from ligroin, had b. p. 215—220°/0·3 mm., m. p. 66° (Found: C, 68·8; H, 8·9. $C_{16}H_{25}O_3N$ requires C, 68·8; H, 9·0%); *hydrochloride*, prisms from alcohol, m. p. 186—187° (Found: Cl, 11·2. $C_{16}H_{26}O_3NCl$ requires Cl, 11·3%). Treated with acetic anhydride and pyridine at 100°, the secondary base gave the glassy *diacetyl* derivative, b. p. (bath temp.) 180—220°/0·005 mm. (Found: Ac, 24·0. $C_{15}H_{21}O_3NAc_2$ requires Ac, 24·6%); it (1 g.) was kept at room temperature for 2½ hours in a solution of sodium (0·075 g.) in methanol, the exactly neutralised solution evaporated, and the oil taken up in methylene chloride and distilled; this N-*monoacetyl* derivative (0·8 g.) was a gum, b. p. (bath-temp.) 180—190°/0·005 mm. (Found: Ac, 13·9. $C_{15}H_{22}O_3NAc$ requires Ac, 14·0%).

Neither the monoacetyl compound just described nor the secondary and tertiary bases mentioned in the last three paragraphs could be cyclised by treatment with sulphuric acid, phosphoric oxide, phosphorus oxychloride, or phosphorus pentachloride.

6 : 7-*Methylenedioxy*-10-*methylphenanthridone* (VIII).—2-Nitro-4 : 5-methylenedioxybenzoyl chloride (Bedi and Narang, *J. Indian Chem. Soc.*, 1936, **13**, 253) (2·25 g.) was added to methylaniline (1·1 g.) and potassium carbonate (2·2 g.) in ether, and the mixture heated under reflux for 2 hours. 2′-*Nitro*-4′ : 5′-*methylenedioxybenzomethylanilide* (VII) crystallised from alcohol in needles or rhombs, m. p. 145° (Found: C, 60·4; H, 4·2. $C_{15}H_{12}O_5N_2$ requires C, 60·0; H, 4·0%). It absorbed 3 mols. of hydrogen in alcohol over palladium–strontium carbonate; 2′-*amino*-4′ : 5′-*methylenedioxybenzomethylanilide*, which separated from the filtered and concentrated solution, had m. p. 166° after crystallisation from benzene–ligroin (Found: C, 66·4; H, 5·4. $C_{15}H_{14}O_3N_2$ requires C, 66·6; H, 5·2%). Sodium nitrite (0·3 g. in 1·5 c.c. of water) was added to a cooled solution of the base (0·6 g.) in 0·7N-sulphuric acid (10 c.c.), and the mixture heated slowly to 100° until it gave no diazo-reaction. The resulting tar, washed with alkali, crystallised from 80% alcohol in fine needles (0·3 g.), m. p. 238°, as found by Kondo and Uyeo (*loc. cit.*) (Found: C, 71·1; H, 4·4. Calc. for $C_{15}H_{11}O_3N$: C, 71·1; H, 4·3%).

2′-*Nitro*-4′ : 5′-*methylenedioxybenzomethyl*-1-*naphthalide*, prepared like its analogue, formed needles, m. p. 186° (Found: C, 65·3; H, 4·1. $C_{19}H_{14}O_5N_2$ requires C, 65·1; H, 4·0%); hydrogenated in acetone, it gave the *amino*-analogue as needles, m. p. 170° (Found: C, 70·7; H, 5·0. $C_{19}H_{16}O_3N_2$ requires C, 71·2; H, 5·0%). Ring-closure was attempted by diazotisation in aqueous sulphuric, hydrochloric, or acetic acid, or, owing to the low water-solubility of the salts with mineral acids, acetic acid or methanol was used as solvent; decomposition was effected by heating, by treatment with copper powder, or by warming with sodium carbonate or acetate. The acetyl derivative of the amine, m. p. 196°, was treated with " nitrous fumes " in acetic acid, and the crude product heated in benzene or ligroin (cf. Grieve and Hey, *J.*, 1934, 1966). These processes gave brown, amorphous materials, not purifiable by crystallisation, sublimation or chromatography.

2′-*Nitro*-4′ : 5′-*methylenedioxybenzylmethylaniline* was prepared by heating nitromethylenedioxybenzyl chloride (Robinson and Robinson, *J.*, 1915, **107**, 1758) with methylaniline (2 mols.) in benzene for 7½ hours; it was extracted with ligroin from the residue after evaporation of benzene, and crystallised from methanol in yellow plates (70%), m. p. 94° (Found: C, 62·4; H, 5·0. $C_{15}H_{14}O_4N_2$ requires C, 62·9; H, 4·9%). Reduced over palladium–strontium carbonate in acetone, it gave 2′-*amino*-4′ : 5′-*methylenedioxybenzylmethylaniline* (90%), needles from ligroin, m. p. 118° (Found: C, 70·2; H, 6·1. $C_{15}H_{16}O_2N_2$ requires C, 70·3; H, 6·3%); in mineral acids the base turned red and decomposed. With methyl-1-naphthylamine, nitromethylenedioxybenzyl chloride afforded 2′-*nitro*-4′ : 5′-*methylenedioxybenzylmethyl*-1-*naphthylamine*, yellow needles from alcohol, m. p. 133° (Found: C, 67·8; H, 4·7. $C_{19}H_{16}O_4N_2$ requires C, 67·9; H, 4·8%). Attempted reduction gave only brown basic tars.

Piperonal and 2-nitro-1-naphthylamine failed to react in boiling acetic acid, or alone at 140—160°; a higher temperature caused decomposition.

Acetomethyl-1-naphthalide (8 g.) and 1-*o*-carbomethoxyphenyl-3 : 3-dimethyltriazen (Elks and Hey, *loc. cit.*; 4 g.) were heated at 100° and dry hydrogen chloride passed in; the dark red mixture afforded only acetomethylnaphthalide. Heating the same reactants in acetic acid for 20 hours gave no useful result.

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