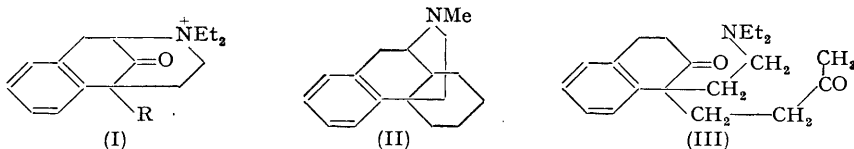


184. Syntheses in the Morphine Series. Part III.* Further Experiments with β -Tetralone.

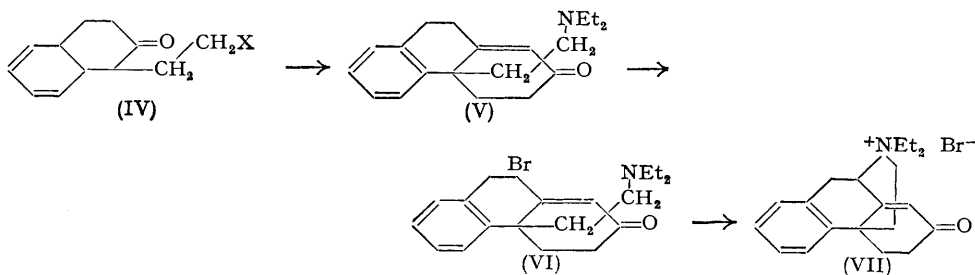
By J. A. BARLTROP and J. E. SAXTON.

β -Tetralone has been alkylated with 2-methoxyethyl chloride and with 2-dialkylaminoethyl chlorides, and the products have been transformed, by the Robinson-Mannich base ring-extension reaction, into hydrophenanthrenes substituted at C₍₁₃₎. Other experiments with β -tetralone are also described. A substance, probably (VII), possessing the morphine carbon-nitrogen skeleton has been prepared.

PART I of this series (*J.*, 1947, 399) describes methods devised for the synthesis of benzomorphan systems (I) from β -tetralone. This communication is largely concerned with attempts to extend these procedures to include the synthesis of derivatives of morphinan (II). Since substantial quantities of β -tetralone were required for these experiments, attention was directed to finding a satisfactory large-scale preparation of this substance. It soon became apparent that reduction of β -naphthol with sodium and liquid ammonia by a modification of Birch's method (*J.*, 1944, 430, and private communication) provided the best process.



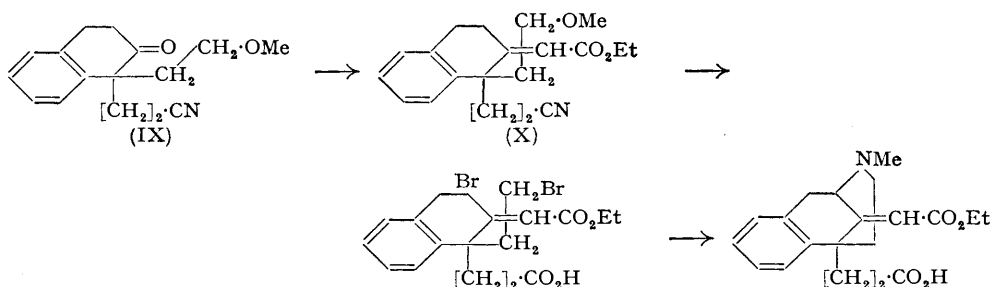
Attempts to alkylate β -tetralone with 2-dimethylaminoethyl chloride failed until it was discovered that success in this alkylation reaction was intimately connected with the quality of the sodamide employed as condensing agent. When purest sodamide was used, 1-2'-dimethylaminoethyl-1 : 2 : 3 : 4-tetrahydro-2-ketonaphthalene (IV; X = NMe₂) was obtained in 40% yield. However, the preparation of this substance was not realised until after the completion of the rest of the work described in this paper, which was, of necessity, performed on the more readily accessible diethylamino-analogue (IV; X = NEt₂). From this substance, we proposed to proceed by the reaction sequence :



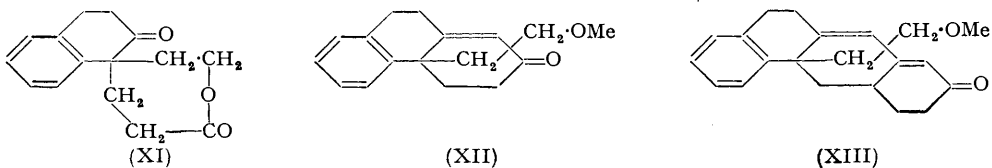
* Part II, *J.*, 1951, 2524.

The condensation of 1-alkyl-2-tetralones with diethylaminobutanone methiodide to give hydrophenanthrenes bearing angular substituents at C₍₁₃₎ has been used previously by Ghosh and Robinson (*J.*, 1944, 506) for the synthesis of substances related to morphine. We found no difficulty in applying the reaction to (IV; X = NEt₂) and obtained, in 20% yield, 13-2'-diethylaminoethyl-5:6:7:9:10:13-hexahydro-7-ketophenanthrene* (V), which has the same carbon skeleton as the methylmorphimethines, together with the uncyclised diketone (III). The exothermic reaction between (V) and *N*-bromosuccinimide gave, in addition to much polymeric material, a small quantity of a salt. Since $\alpha\beta$ -unsaturated ketones are brominated preferentially in the allyl position by this reagent (*vide Chem. Reviews*, 1948, 43, 283; Meystre and Wettstein, *Experientia*, 1946, 2, 408), it is very likely that the brominated intermediate had the structure (VI). In Part I it has been established that in similar systems cyclisation of the nitrogen ring readily occurs and, by analogy, the morphinan structure (VII) is ascribed to the reaction product. Insufficient material was obtained for a structural proof to be possible.

It was hoped that the difficulties experienced in this route and the possible ambiguity associated with the bromination by *N*-bromosuccinimide might be avoided by an alternative scheme such as the following:



The starting material 1:2:3:4-tetrahydro-2-keto-1-2'-methoxyethyl-naphthalene (IV; X = OMe) was readily prepared in a manner analogous to that of the corresponding amino-compounds, and acrylonitrile added smoothly to give (IX). The keto-group in this substance was sterically hindered, failing to react with semicarbazide or 2:4-dinitrophenylhydrazine, and this steric hindrance was responsible for the breakdown of the synthesis, for (IX) could not be caused to undergo a Reformatsky reaction. Another obstacle presented itself when (IX) was boiled with hydrobromic acid in an attempt to replace the methoxyl group by bromine. The product had the formula C₁₅H₁₆O₃. It was non-acidic but dissolved in warm sodium hydroxide solution; it did not decolourise bromine water and only slowly reacted with potassium permanganate solution. These facts can best be reconciled with the structure (XI), which contains a seven-membered lactone ring. This



formulation is supported by the infra-red absorption spectrum, which shows the absence of hydroxyl and ethylenic groups but possesses a fairly broad band of high absorption in the carbonyl region, which could be due to a carbonyl and a lactone grouping. There are very few analogies in the literature to this facile production of a monomeric ϵ -lactone.

Simultaneously with these experiments, (IV; X = OMe) was subjected to a Robinson ring-extension reaction. Two products were isolated. The main product, formed in 20% yield, was the expected 5:6:7:9:10:13-hexahydro-7-keto-13-2'-methoxyethylphen-

* This numbering is used to preserve relationship with the morphine alkaloids. Systematically, (V) should be named 12-2'-diethylaminoethyl-2:3:4:9:10:12-hexahydro-2-ketophenanthrene; similarly for other compounds in this paper.

anthrene (XII), but it was accompanied by a small amount of a substance $C_{21}H_{24}O_2$, probably the tetracyclic compound (XIII), arising from a ring extension of the primary product (XII). The formulation (XIII) is supported by the ultra-violet absorption spectrum [in ethanol; maximum at 2630 Å, $\log \epsilon = 4.1$; cf. sorbaldehyde, λ_{\max} . (in ethanol) 2630 Å, $\log \epsilon = 4.43$ (Braude, *Ann. Reports*, 1945, 115)].

EXPERIMENTAL

(M. p.s are uncorrected. Analyses are by Drs. Weiler and Strauss and Mr. F. C. Hall.)

β -Tetralone.—A suspension of β -naphthol (75 g.) in ethanol (70 c.c.) was cautiously added to liquid ammonia (800 c.c.) contained in a well-lagged 3-litre flask with a plug of cotton wool in the neck. Sodium (33 g.) was added in small pieces with occasional stirring, during 1 hour. When the blue colour of the mixture had disappeared, ammonium chloride (78 g., 2.3 mols.) was added, and the remaining ammonia allowed to evaporate. Water (300 c.c.) was then added, and the solution acidified with concentrated hydrochloric acid. The β -tetralone was extracted with ether, purified *via* the bisulphite compound, and distilled. β -Tetralone (57 g., 80%) was collected at 139°/18 mm.

1-2'-Dimethylaminoethyl-1:2:3:4-tetrahydro-2-ketonaphthalene.—Dimethylaminoethyl chloride (8.2 g.) in toluene (50 c.c.) was condensed with β -tetralone (10 g.) in the presence of finely powdered, pure sodamide (2.8 g.) under the conditions described by Bartrop (*J.*, 1946, 962) for the preparation of the diethylaminoethyl analogue. The basic fraction, b. p. 115—135°/0.1 mm., was collected and redistilled. 1-2'-Dimethylaminoethyl-1:2:3:4-tetrahydro-2-ketonaphthalene (40%), a colourless oil, n_D^{20} 1.5394, was collected at 115—118°/0.05 mm. (Found: C, 77.3; H, 9.05; N, 6.3. $C_{14}H_{19}ON$ requires C, 77.4; H, 8.75; N, 6.45%).

Condensation between 1-Diethylaminobutan-3-one and 1-2'-Diethylaminoethyl-1:2:3:4-tetrahydro-2-ketonaphthalene.—Methyl iodide (8 g.) was added in portions to 1-diethylaminobutan-3-one (8 g.), contained in a 250-c.c. flask, with swirling and cooling in ice. After 1 hour at 0°, the crystalline methiodide was washed with ether. A cotton-wool plug was placed in the neck of the flask, a stream of dry nitrogen was passed through, and a solution of 1-2'-diethylaminoethyl-1:2:3:4-tetrahydro-2-ketonaphthalene (13 g.) in dry benzene added. The mixture was cooled in ice, a solution of potassium (4 g.) in absolute alcohol (60 c.c.) added, and the flask swirled and cooled in ice until all the methiodide had reacted. After 1½ hours at 0°, and then a further hour under reflux, the mixture was cooled and extracted with dilute hydrochloric acid. The basic products were isolated in the usual way, and distilled. A very viscous oil was collected at 160—180°/0.1 mm. Fractionation of the distillate gave two fractions: A, impure 1-2'-diethylaminoethyl-1:2:3:4-tetrahydro-2-keto-1-3'-ketobutyl-naphthalene (III), a pale yellow viscous oil (2 g.), b. p. 162—165°/0.06 mm., $n_D^{15.5}$ 1.5416 (Found: C, 76.9; H, 9.4. $C_{20}H_{29}O_2N$ requires C, 76.2; H, 9.2%); B, 13-2'-diethylaminoethyl-5:6:7:9:10:13-hexahydro-7-ketophenanthrene, a pale yellow, viscous oil (3 g., 20%), b. p. 193—194°/0.2 mm., $n_D^{15.5}$ 1.5572 (Found: C, 80.4; H, 9.4; N, 5.0. $C_{20}H_{27}ON$ requires C, 80.8; H, 9.1; N, 4.7%). The picrate crystallised from ethanol in yellow prisms, m. p. 200° (decomp.).

Reaction between (V) and N-Bromosuccinimide.—The above diethylaminoethylhexahydroketophenanthrene (2.5 g.) in boiling carbon tetrachloride (25 c.c.) was treated with N-bromosuccinimide (1.5 g.), added in small portions at intervals of 1 minute. The cooled and filtered reaction mixture was set aside for 3 days during which a gum was deposited. The carbon tetrachloride was decanted from the gum, which crystallised on trituration with dry isopropanol. N-Ethyl-7-ketomorphin-8-ene ethobromide (VII) (50 mg.) separated from isopropanol-ether in colourless crystals, m. p. 182° (Found: C, 63.5; H, 6.7; N, 3.6. $C_{20}H_{26}ONBr$ requires C, 63.8; H, 6.9; N, 3.7%). The salt was readily soluble in water and gave a deep red 2:4-dinitrophenylhydrazone.

1:2:3:4-Tetrahydro-2-keto-1-2'-methoxyethyl-naphthalene.—A solution of β -tetralone (20 g.) and 2-chloroethyl methyl ether (12.3 g.) in toluene (100 c.c.) was vigorously stirred in an atmosphere of nitrogen, and finely powdered sodamide (5.2 g.) gradually added, so that the temperature of the reaction mixture remained below 35°. The temperature was then raised to 90° during 3½ hours and kept between 85° and 90° for a further 3 hours, after which the mixture was boiled under reflux for an hour. The cooled solution was washed with dilute hydrochloric acid, then twice with water, and dried and distilled. 1:2:3:4-Tetrahydro-2-keto-1-2'-methoxyethyl-naphthalene (12.9 g., 47%) was collected at 104—108°/0.1 mm., as a colourless oil, n_D^{17} 1.5390 (Found: C, 76.2; H, 7.9. $C_{13}H_{16}O_2$ requires C, 76.5; H, 7.85%). The semicarbazone,

prepared in aqueous ethanol, crystallised from ethanol in colourless prisms, m.p. 150—151° (Found : C, 64·6; H, 7·15. $C_{14}H_{19}O_2N_3$ requires C, 64·4; H, 7·3%).

1-2'-Cyanoethyl-1 : 2 : 3 : 4-tetrahydro-2-keto-1-2'-methoxyethyl-naphthalene.—A solution of acrylonitrile (3·25 g.) in dioxan (20 c.c.) was added dropwise during 20 minutes to a solution of the above ketone (12·5 g.) in dioxan (30 c.c.) to which had been added a 30% solution of potassium hydroxide in methanol (0·25 c.c.). The reaction mixture was vigorously stirred and cooled in ice. Stirring and cooling were continued for an hour, after which the solution was carefully neutralised with ethanolic hydrogen chloride, diluted with ether, and filtered. The solvent was removed, and the residual oil distilled. 1-2'-Cyanoethyl-1 : 2 : 3 : 4-tetrahydro-2-keto-1-2'-methoxyethyl-naphthalene (11 g., 75%), a colourless, viscous oil, n_D^{25} 1·5404, was collected at 176—178°/0·35 mm. (Found : N, 5·5. $C_{16}H_{19}O_2N$ requires N, 5·45%).

The Lactone of 1-2'-Carboxyethyl-1 : 2 : 3 : 4-tetrahydro-1-2'-hydroxyethyl-2-ketonaphthalene.—A solution of the above nitrile (2 g.) in concentrated hydrobromic acid (20 c.c.) and acetic acid (20 c.c.) was boiled under reflux for 8 hours. The solvents were then removed under reduced pressure, and the resulting solid was dissolved in sodium hydroxide solution. The filtered solution was acidified, and the precipitated solid was collected, dried, and crystallised from benzene (charcoal). The lactone (0·5 g., 25%) formed colourless prisms, m. p. 153—155° [Found : C, 73·5; H, 6·6; M, 245 (cryoscopic in camphor). $C_{15}H_{16}O_3$ requires C, 73·8; H, 6·6%; M, 244].

Condensation between Diethylaminobutanone and 1 : 2 : 3 : 4-Tetrahydro-2-keto-1-2'-methoxyethyl-naphthalene.—Methyl iodide (12 g.) was added in portions to 1-diethylaminobutan-3-one (12 g.), cooled in a freezing mixture. After 1 hour, the crystalline methiodide was washed with ether by decantation. A cotton-wool plug was placed in the neck of a flask, a stream of dry nitrogen was passed through, and a solution of 1 : 2 : 3 : 4-tetrahydro-2-keto-1-2'-methoxyethyl-naphthalene (15·5 g.) in dry benzene (60 c.c.) added. A solution of potassium (6·5 g.) in dry ethanol (60 c.c.) was then added, and the mixture swirled occasionally and allowed to remain in the freezing mixture until all the methiodide had reacted (*ca.* 2 hours). After a further hour, the mixture was heated under reflux for 2 hours, cooled, washed with dilute hydrochloric acid, dilute alkali, and finally with water, and dried. Distillation gave the following fractions : (i) b. p. 105—115°/0·1 mm., mainly unchanged starting material (1 g.); (ii) a colourless viscous oil (2 g.), b. p. 148—151°/0·12 mm., n_D^{25} 1·5800; (iii) a colourless viscous oil (4 g.), b. p. 151—160°/0·12 mm., n_D^{25} 1·5800; (iv) a colourless glass (2 g.), b. p. 185—195°/0·12 mm. Fractions (ii) and (iii) were impure 5 : 6 : 7 : 9 : 10 : 13-hexahydro-7-keto-13-2'-methoxyethylphenanthrene, which was purified *via* the semicarbazone, and was obtained as a colourless oil, b. p. 150—155°/0·1 mm. (Found : C, 79·2; H, 8·0. $C_{17}H_{20}O_2$ requires C, 79·7; H, 7·8%); the semicarbazone formed prisms, m.p. 200°, from ethanol (Found : C, 68·7; H, 7·6; N, 13·5. $C_{18}H_{23}O_2N_3$ requires C, 69·0; H, 7·4; N, 13·4%). Fraction (iv) solidified on trituration with ether. Crystallisation from ethanol gave 3 : 4 : 6 : 7 : 8 : 9 : 12 : 13-octahydro-6-keto-13-2'-methoxyethyl-1 : 2-benzanthracene (XIII) as colourless prisms, m. p. 122—124° (Found : C, 81·7; H, 7·6. $C_{21}H_{24}O_2$ requires C, 81·7; H, 7·8%). The 2 : 4-dinitrophenylhydrazone crystallised from acetic acid in deep red plates, m. p. 227—228° (Found : C, 66·1; H, 5·7. $C_{27}H_{28}O_8N_4$ requires C, 66·4; H, 5·7%).

We are indebted to Dr. F. B. Strauss for the light-absorption data.

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