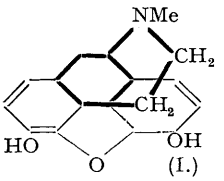
81. *Syntheses in the Morphine Series. Part I. Derivatives of* bicyclo[3 : 3 : 1]-2-*Azanonane.*

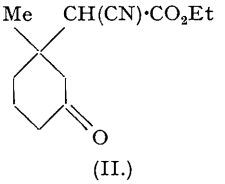
By J. A. Barltrop.

The synthesis of certain bi- and tri-cyclic ring-systems occurring in the morphine molecule has been effected by cyclisation of the β-diethylaminoethyl derivatives of ethyl *cyclo*hexanone-carboxylate and of 1-alkyl-β-tetralones to the corresponding *bicyclo*[3 : 3 : 1]-2-azanonanes.

This paper is the first of a series embodying the results of preliminary experiments directed toward the synthesis of members of the morphine sub-group of alkaloids. Previous work in this field has been executed largely by Robinson *et al.* (*J.*, 1931, 3163, 3173; 1932, 785, 789), Robinson and Ghosh (*J.*, 1944, 506), Manske (*J. Amer. Chem. Soc.*, 1931, **53**, 1104), Fieser and Holmes (*ibid.*, 1938, **60**, 2548), Koelsch (*ibid.*, 1945, **67**, 569), Holmes and Trevoy (*Canad. J. Res.*, 1944, *B*, **22**, 56, 109), and Grewe (*Ber.*, 1939, **72**, 426, 785, 1314; 1943, **76**, 1072, 1076). There are two possible approaches to the problem of the synthesis of morphine; first by a step-by-step synthesis in the classical tradition, and secondly by methods depending on theories as to the probable course of the phytochemical synthesis. Researches are being pursued along both channels, but herein are reported only the results of investigations along the first. Examination of the Gulland and Robinson structure of the morphine molecule suggests that one of the most difficult stages is likely to be the formation of the nitrogen-containing *meta*-bridged system (I, heavy lines), and this paper describes the synthesis of such a system in model substances.



(I.)



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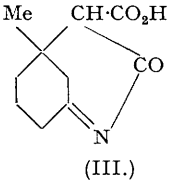
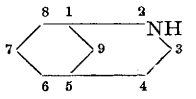
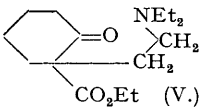


(III.)

The literature reveals only one " synthesis " of such a ring system. Farmer and Ross (*J.*, 1926, 3235) obtained (II) by Michael addition of ethyl cyanoacetate to 3-methyl-Δ^2-*cyclo*hexenone, and on boiling it with 15% hydrochloric acid obtained in quantitative yield an acidic substance giving an intense ferric chloride colour to which they ascribe the structure (III). This structure is most improbable for the following reasons : (*a*) it violates Bredt's rule, which states that the carbon atom at the bridge head of a bridged ring system cannot bear a double bond; (*b*) it is a derivative of malonic semi-amide and should thus not give a ferric chloride reaction; and (*c*) it is difficult to believe that a compound of such structure would be stable to boiling mineral acid. There is thus no evidence that the ring system (IV) has ever been synthesised heretofore, and, to save difficulties with the cumbrous and obscure *bicyclo*aza nomenclature, it is suggested that it be given the trivial name " morphan " (a suggestion for which I am indebted to Sir Robert Robinson) and be numbered as shown.



(IV.)



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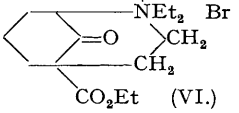
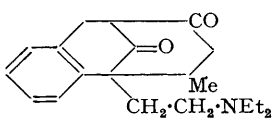


(VI.)

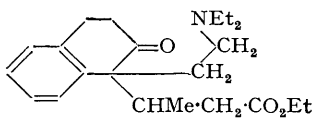
Ethyl sodio*cyclo*hexanone-2-carboxylate refluxed with diethyl-β-chloroethylamine in toluene solution gave *ethyl* 2-β-*diethylaminoethyl*cyclo*hexanone*-2-*carboxylate* (V), which was converted by bromine in the cold into the hydrobromide of the 6-bromo-derivative. This was not isolated, but immediately treated with sodium bicarbonate solution to give the free base which on heating in toluene afforded *ethyl* 9-*keto*-2-*ethylmorphan*-5-*carboxylate ethobromide* (VI) in small yield. The ultra-violet absorption spectrum of the substance (examined by Dr. F. Strauss) showed no αβ-unsaturated carbonyl absorption, indicating that it was not the isomeric hydrobromide of ethyl 2-β-diethylaminoethyl-Δ^5-*cyclo*hexenone-2-carboxylate.

The synthesis of the morphan ring system having been shown to be practicable along these lines it was decided to perform similar operations on β-tetralones in the hope of obtaining the benzmorphan system occurring in morphine. 2-Keto-1-β-diethylaminoethyl-1 : 2 : 3 : 4-tetrahydronaphthalene (Barltrop, *J.*, 1946, 958) and ethyl crotonate in the presence of sodium ethoxide yielded a mixture of 2 : 9-*diketo*-4-*methyl*-5-β-*diethylaminoethyl*-6 : 7-*benzo*bicyclo[3 : 3 : 1]*nonane*

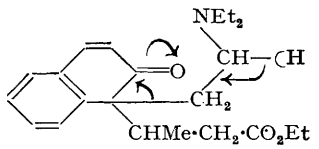
(VII) and 2-*keto*-1-β-*diethylaminoethyl*-1-β-*carbethoxy*iso*propyl*-1 : 2 : 3 : 4-*tetrahydronaphthalene* (VIII). The latter substance when brominated and treated with alkali as in the *cyclo*hexanone series gave a small yield of a salt which appeared to be *diethylvinylamine hydrobromide*. This presumably arose by loss of hydrogen bromide from the bromo-β-tetralone to give (IX) in which



(VII.)



(VIII.)

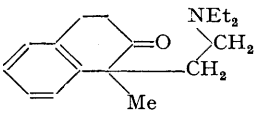


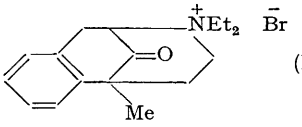
(IX.)

the tendency to become aromatic is so great as to cause extrusion of the basic side-chain, a phenomenon closely parallel to the well-known elimination of the ethanamine side-chain in the morphine group of alkaloids when they assume an aromatic structure. At this stage it seemed that further work was called for on the process of cyclisation and more accessible materials were chosen.

2-Keto-1-methyl-1 : 2 : 3 : 4-tetrahydronaphthalene (Cornforth, Cornforth, and Robinson, *J.*, 1942, 690) was alkylated with diethyl-β-chloroethylamine and sodamide giving 2-*keto*-1-*methyl*-1-β-*diethylaminoethyl*-1 : 2 : 3 : 4-*tetrahydronaphthalene* (X). In the previously described experiments, the amino-ketone free base had been brominated, but as a variant (X) was converted into its hydrobromide, and this, without further purification, was brominated in chloroform solution. On washing with sodium bicarbonate solution, the free base was liberated and rapidly cyclised in the cold to 9-*keto*-5-*methyl*-2-*ethyl*-6 : 7-*benzomorphan ethobromide* (XI).

(X.)





(XI.)

The substance did not decolorise potassium permanganate solution and thus cannot be the isomeric β-naphthol derivative.

Experiments are in progress having as their object the synthesis of the tertiary amine analogues of (XI) and the cyclisation of the third carbon ring of the morphine molecule.

Experimental.

Ethyl 2-β-*Diethylaminoethyl*cyclo*hexanone*-2-*carboxylate* (V).—Ethyl *cyclo*hexanone-2-carboxylate (34·3 g.; Kötz and Hesse, *Annalen*, 1906, **350**, 210; 1907, **358**, 198) was added with agitation and cooling to powdered sodium (4·6 g.) under toluene (100 c.c.). When reaction had ceased the sodio-derivative was refluxed for 6 hours with a toluene solution of diethyl-β-chloroethylamine [prepared by basifying the hydrochloride (54 g.) with potassium carbonate, extracting several times with toluene, and drying over potassium carbonate]. The reaction mixture was extracted with hydrochloric acid, the aqueous layer basified with sodium hydroxide, and the liberated amine isolated with ether and distilled. The *keto-ester* (33 g.) was collected at 164°/11 mm. (Found: C, 66·5; H, 10·3; N, 5·4. $C_{15}H_{27}O_3N$ requires C, 66·9; H, 10·0; N, 5·2%).

9-*Keto*-5-*carbethoxy*-2-*ethylmorphan Ethobromide* (VI).—The above amine (1·1 g.) dissolved in ligroin (5 c.c.) was cooled to 0° and treated gradually with a cooled solution of bromine (0·65 g.) in ligroin (3 c.c.). Ice-water (3 c.c.) was added to dissolve the oily hydrobromide, and separated from the ligroin which was washed with ice-water (3 c.c.). The combined aqueous extracts were immediately treated with a solution of sodium bicarbonate (1 mol.) and rapidly extracted with toluene. The extract was dried and heated on the steam-bath for 16 hours. A brown oil was deposited, followed after several hours by plate-like crystals. The *ethobromide* (*ca.* 10 mg.), m. p. 201°, was collected and washed with ether (Found: C, 51·4; H, 7·5; Br, 22·9. $C_{15}H_{26}O_3NBr$ requires C, 51·7; H, 7·5; Br, 23·0%).

2-*Keto*-1-β-*diethylaminoethyl*-1-β-*carbethoxy*iso*propyl*-1 : 2 : 3 : 4-*tetrahydronaphthalene* (VIII).—2-Keto-1-β-diethylaminoethyl-1 : 2 : 3 : 4-tetrahydronaphthalene (14·2 g., Barltrop, *loc. cit.*) and ethyl crotonate (7·1 g.) were added to a solution of sodium (1·33 g.) in dry ethanol (25 c.c.). The mixture was refluxed for 4 hours and left overnight; water (120 c.c.) and glacial acetic acid (3·0 g.) were then added and the products isolated with ether and distilled. The following fractions were obtained: (*a*) b. p. 140°/0·04 mm.; (*b*) b. p. 140—165°/0·04 mm. (mainly 150°); (*c*) b. p. 165—190°/0·04 mm. On refractionation, (*a*) and (*b*) gave unchanged 2-keto-1-β-diethylaminoethyl-1 : 2 : 3 : 4-tetrahydronaphthalene and 2 : 9-*diketo*-4-*methyl*-5-β-*diethylaminoethyl*-6 : 7-*benzo*bicyclo[3 : 3 : 1]*nonane* (VII), a yellow oil, b. p. 160° (bath)/0·01 mm. (Found: C, 76·1; H, 8·9. $C_{20}H_{27}O_2N$ requires C, 76·7; H, 8·6%), and a high boiling residue, which was added to (*c*) and refractioned. 2-*Keto*-1-β-*diethylaminoethyl*-1-β-*carbethoxyisopropyl*-1 : 2 : 3 : 4-*tetrahydronaphthalene* (VIII) (6 g.), a viscous yellow oil, was collected at 175°/0·1 mm. (Found: C, 73·6; H, 9·1. $C_{22}H_{33}O_3N$ requires C, 73·5; H, 9·2%).

Attempted Cyclisation of (VIII).—Bromine (0·32 g., 0·002 mol.) dissolved in toluene (5 c.c.) was added

to a cooled solution of the above amino-keto-ester (0·72 g., 0·002 mol.) in toluene (5 c.c.). Sodium carbonate solution was added, the mixture shaken, and the toluene layer separated and combined with the toluene extract of the aqueous layer. After being dried ($MgSO_4$), the toluene solution (*ca.* 50 c.c.) was dried azeotropically by distilling a few c.c. under reduced pressure and then heated on the steam-bath. A few colourless plate-like crystals separated and were collected and crystallised from ethanol–ether (Found : Br, 44·4. $C_6H_{13}N,HBr$ requires Br, 44·4%). The substance decolorises acidified potassium permanganate solution instantaneously.

2-*Keto*-1-*methyl*-1-β-*diethylaminoethyl*-1 : 2 : 3 : 4-*tetrahydronaphthalene* (X).—2-Keto-1-methyl-1 : 2 : 3 : 4-tetrahydronaphthalene (16 g., Cornforth, Cornforth, and Robinson, *loc. cit.*), diethyl-β-chloroethylamine (14·3 g.), and toluene (80 c.c.) were stirred in an atmosphere of nitrogen, and powdered sodamide (4·3 g.) was added gradually with external cooling. When the initial exothermic reaction had ceased, the temperature of the reaction mixture was slowly raised to 90° during 2 hours, maintained there for 5 hours, and finally refluxed for 1 hour. After cooling, the mixture was extracted with hydrochloric acid, the acid extract was washed with ether and basified, and the liberated amines were isolated with ether and distilled. The *amino-ketone* (10 g.), a viscous yellow oil, was collected at 120°/0·18 mm. (Found : C, 78·8, 78·2; H, 9·8, 9·6; N, 5·55, 5·4. $C_{17}H_{25}ON$ requires C, 78·8; H, 9·65; N, 5·4%). The picrate, picrolonate, oxalate, and flavianate were all oils.

9-*Keto*-5-*methyl*-2-*ethyl*-6 : 7-*benzomorphan Ethobromide* (XI).—The above amino-ketone (2·6 g., 0·01 mol.) dissolved in dry ether was converted into the gummy hydrobromide which was washed thrice with ether and dissolved in chloroform (10 c.c.). After cooling to 0° a cooled solution of bromine (1·6 g.) in chloroform (5 c.c.) was added dropwise with cooling. A cooled solution of sodium bicarbonate (3 g.) was added, and the mixture was shaken and separated. The chloroform layer was dried and then evaporated at room temperature under reduced pressure giving an orange gum insoluble in ether. This was dissolved in chloroform and concentrated under reduced pressure. On keeping, crystals (*ca.* 0·3 g.), m. p. 203° (decomp.), separated and were collected. The *ethobromide* crystallised from much *iso*propanol in colourless microscopic needles, m. p. 212° (decomp.) (Found : C, 60·0; H, 7·25; Br, 24·2. $C_{17}H_{24}ONBr$ requires C, 60·3; H, 7·1; Br, 23·7%). The substance is soluble in water and does not decolorise potassium permanganate solution.

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