Fifth SCI process development symposium

Paper presented at a meeting of the Fine Chemicals Group of the SCI, held in Birmingham on 11 November 1987

The manufacture of medicinal alkaloids from the opium poppy – a review of a traditional biotechnology

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The manufacture of purified morphine hydrochloride began in the early part of the 19th century and marks the founding of the modern pharmaceutical industry. Opium was imported from Turkey and Persia by small pharmacy businesses, specialising in what would now be called bulk pharmaceutical manufacture.

In the UK, pioneers included Thomas Morson, Luke Howard, J F Macfarlan, T & H Smith and Whiffen and Herrings. By the early part of this century Smiths and Macfarlans in Edinburgh were the only British company manufacturing opiates (drugs derived from opium), it is said mainly because the duty on alcohol was higher in England than in Scotland! The small chemists' shop soon became too cramped and larger premises were needed to keep up with the increasing demand for opiates. By the late 19th century substantial volumes of opium were being processed e.g. Smiths averaged 25 t/a then, compared with 1-200 t/a today.

The history of the manufacture of therapeutically useful products from the opium poppy is so closely interwoven with its use as a drug of abuse that separation of the commercial and political stories is difficult. Nevertheless, a relatively narrow topic has been selected.

The prime purpose of this review is to trace the technical development of opiate manufacture and perhaps throw some light onto this relatively secretive sector of the pharmaceutical industry. That it is secretive is demonstrated by the paucity of technical information in the public domain. In contrast, because of the United Nation's (UN) convention on drugs, some aspects are well collated and documented.

This review falls into three parts:

- the opium poppy, and the two raw materials (crude 'drugs') derived from it
- the conversion of the raw material to useful alkaloids
- the semi-synthetic chemistry used to produce the finished pharmaceutical bulk actives.

Illustrations of the commercial and therapeutic aspects of the business are provided throughout the review in order that the technical aspects are set in their proper context.

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The opium poppy

The morphine alkaloids are unique to the genus Papaver. Only two species, *P. somniferum.* Linnaeus (the opium poppy) and *P. bracteatum.* Lindley contain useful quantities of medicinal alkaloids. The commercialisation of the latter plant awaits political rather than commercial developments.

Early therapy

Extracts from the opium poppy have been used by man to relieve pain for at least 3,500 years. The earliest

Table 1 **Major alkaloids from opium**

Morphine	Serturner	1805
Noscapine	Derosne	1803
Codeine	Robiquet	1832
Narceine	Pelletier	1832
Thebaine	Thiboumery/Pelletier	1835
Papaverine	G Merck	1848
Cryptopine	T & H Smith	1867
Laudanosine	Hesse	1871

Table 2 **Main users of opium and poppy straw**

Manufacturing country	Opium (tonnes)	Poppy straw morphine equivalent (tonnes)
USA	350	16
UK	250	22
USSR	180	7
India	100	–
France	90	14
Japan	60	–
Australia	–	7
Others	50	34
Total	1080 (1984 Figures)	100 (1983 Figures)

Table 3 **Major manufacturers of opiates**

Area	Country	Major companies		Date of founding of opiate production
	UK	Macfarlan Smith		1837
		Boots		1940
Europe	France	Francopia		1847
	Holland	Diosynth (VPF)		1947
	Italy	Salars		–
	Hungary	Alkaloida		1928
America	USA	Mallinckrodt		1898
		Penick		–
		1st State		–
	Australia	Glaxo		1956
		Extal		1973
Rest of world	Turkey	State company	(Bolvadin)	1982
	India	State companies	Ghazipur	1820
			Neemuch	1938 (1975)
	USSR	State Company		–

authenticated sample was found in the tomb of the Egyptian Cha [15th century BC]. Also, Theophrastus in the 3rd century BC used the terms opion (for opium) and meconion (for poppy juice). Laudanum (an alcoholic extract or tincture of opium) was introduced into Britain in about 1670 by Thomas Sydenham, and Dover's powder, a mixture of opium and ipecacuanha, was sold up until the early part of this century. The inventor, Thomas Dover, was a retired buccaneer! Opium is still in use today, both as the extract (e.g. Nepenthe) and as a reconstituted mixture of the pure alkaloids – Paperveretum. Three hundred years on, the often quoted remark of Sydenham that 'without the help of opium, few would be sufficiently hard-hearted to practise medicine' continues to hold true.

What is opium?

It is the sun-dried exudate from the incised capsule of the opium poppy. It is one major source of morphine. Eighty days from planting, the petals of the flower drop, leaving the green ovary 'capsule' which contains the growing seeds. Incision of the capsule with a special tool releases a white juice which rapidly dries and darkens in the air. After collection from several 'lancings', this fresh opium is stored in large open air tanks where it dries down to

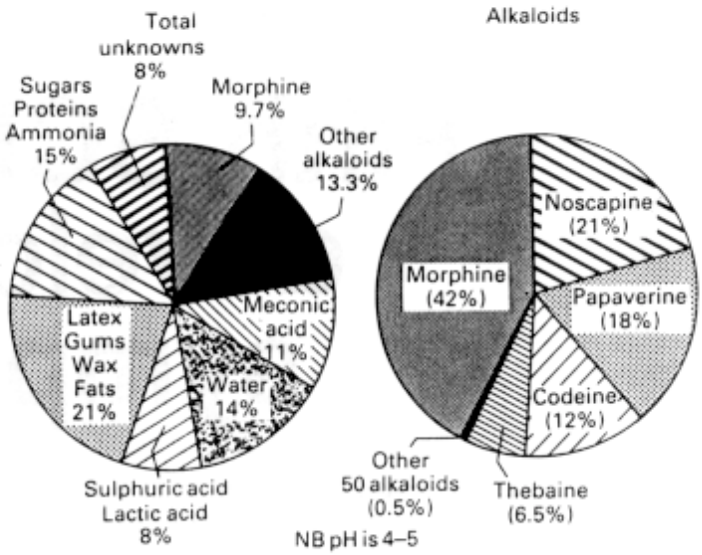


Fig 1 Composition of Indian opium

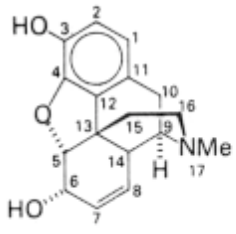
approximately 15 per cent moisture content. This black, semi-solid is the opium of commerce.

Second raw material – poppy straw

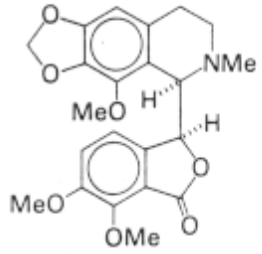
Today, morphine is derived commercially from poppy straw as well as opium. Poppy straw is the term given to the dried capsules, once freed of their seed and milled. The economics of growing opium poppies dictates that the seeds be suitable for the food industry since the value of the seed is roughly equivalent to the value of the morphine. Although higher levels of morphine can be obtained from green poppy, drying is costly and the valuable seeds are lost.

About 45 per cent of the world's morphine require-

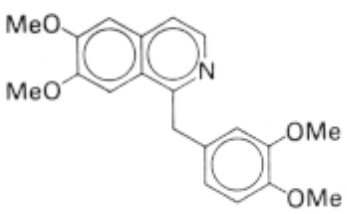
Fig 2 Structures of the major opium alkaloids



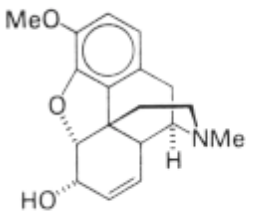
Morphine



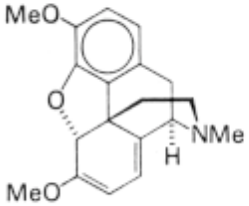
Noscapine



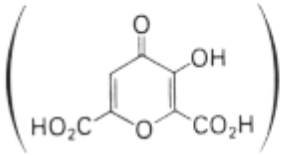
Papaverine



Codeine



Thebaine



Meconic acid

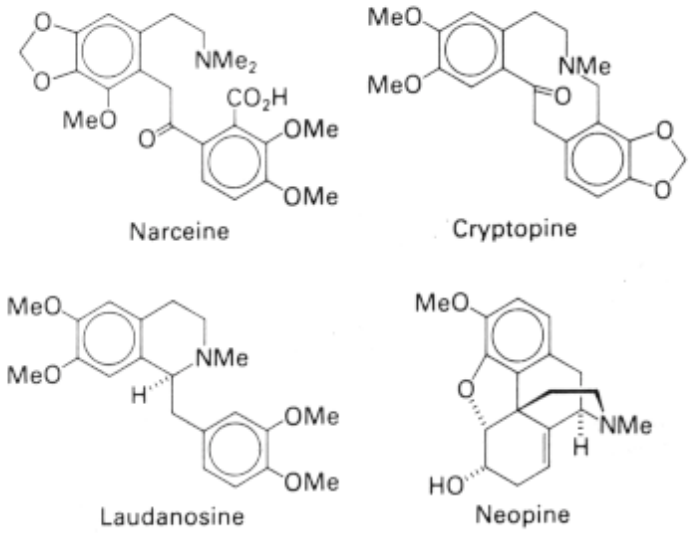


Fig 3 Minor alkaloids

ments, i.e. 80-100t is derived from the 800-1000t of Indian opium produced annually. India is the only country in which the cultivation of opium poppies for opium is still legal (licit). In earlier times Turkey, Iran and Yugoslavia were the major licit opium producers. For example, their combined production averaged 200t (morphine equivalent) in the mid-1930s. It is noteworthy that estimates made then put this figure at just 5 per cent of all production, with around 40,000 tonnes of illicit opium being produced worldwide.[1,2] Abuse is not a novel problem.

That such quantities have been produced is especially remarkable, given the extreme labour intensiveness of the operation. In India, 24,500 ha yields the 800-1000t current volume, with around 2 million people involved in poppy growing and opium collection.[1,2] In contrast, morphine derived from poppy straw is, at its most efficient, highly mechanised. In 1983, Australia produced 25 per cent of the world's morphine, with 3,500 ha yielding 4,400t of straw (equivalent to 43t morphine).

Fig 4 Schematic diagram showing the principles for separating opium alkaloids

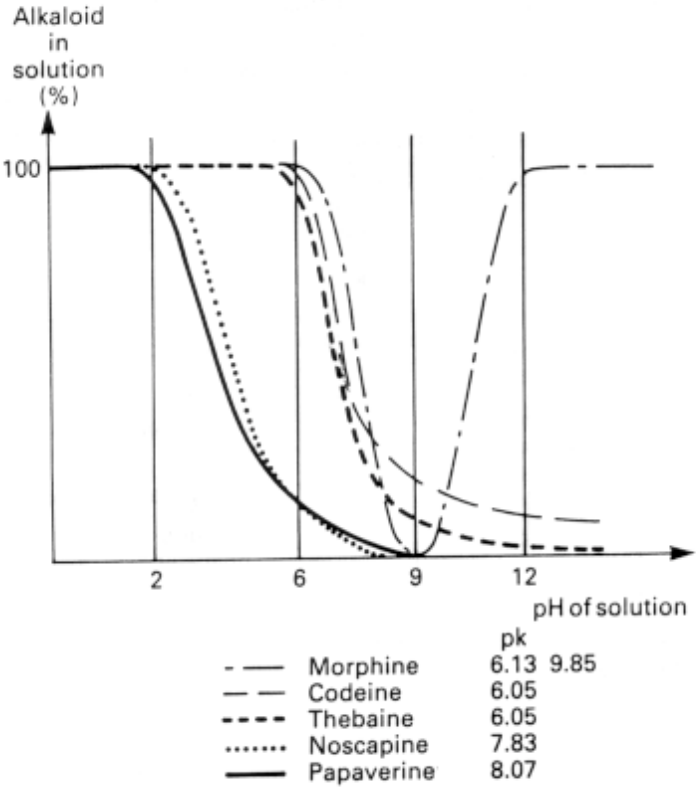


Table 4 **Important factors in opium extraction**

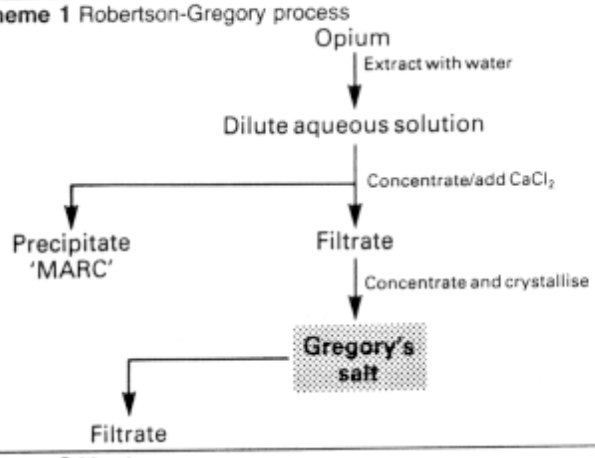
- Morphine is virtually insoluble in all solvents
- Morphine is a strong base and a weak acid
- All the alkaloid salts are moderately soluble in water
- None of the other major alkaloids are acidic
- Codeine base is fairly soluble in solvents
- Noscapine and papaverine are weak bases
- Thebaine is not stable at pH's < 3-4

Less than 1000 people are involved in growing and harvesting the crop. The third largest producer, Turkey, with 16 per cent is much less efficient, both in terms of yields and labour (30,000 ha, 130,000 people). France, Holland and Spain also produce morphine from poppy straw (Holland using imported straw).[1,2] The total world usage of morphine has remained fairly stable at around 200t/a during this century.

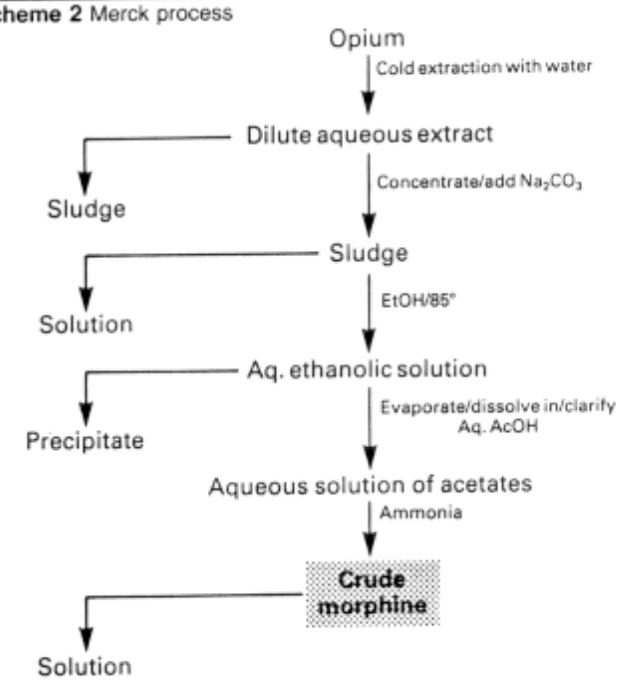
The alkaloids of opium

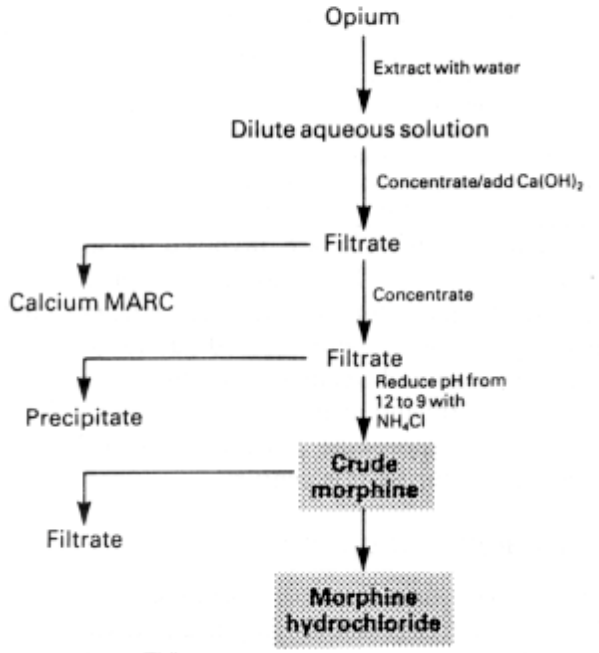
Serturner who first isolated morphine from opium in 1803 made a tremendously important discovery.[3] Not only did he isolate a pure medicinal chemical compound for the first time, he also demonstrated that it was intrinsically basic (hence ALKALOID – like an alkali). Up to that time all organic compounds were believed to be acids.[4] Table 1 highlights the major alkaloids and their discoverers. The composition of Indian opium is represented in the pie charts in Fig 1. Figures 2 and 3 show the structures of the major and some minor alkaloids, respectively.

Scheme 1 Robertson-Gregory process



Scheme 2 Merck process





Scheme 3 Pelletier-Thiboumery process

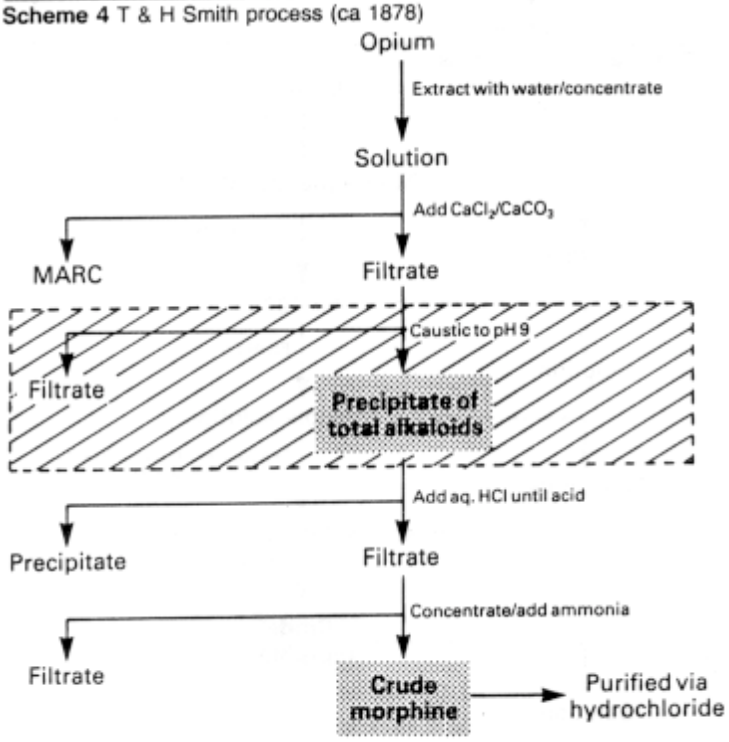
Major manufacturers

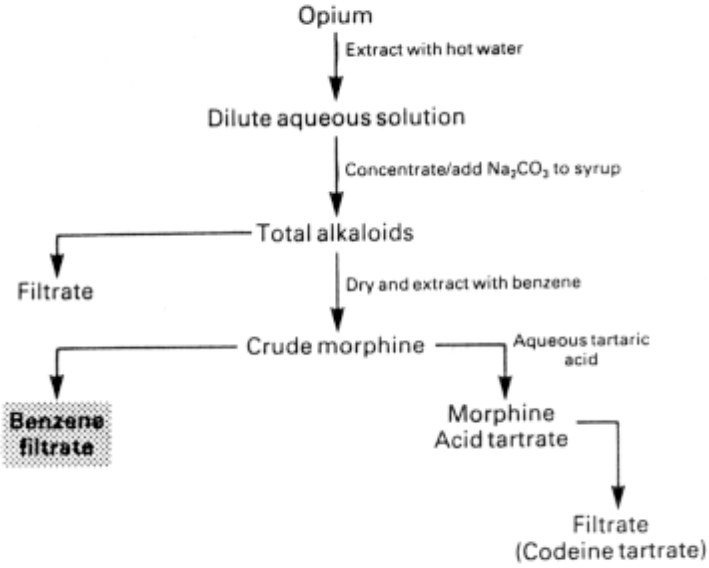
The two commercial sources of morphine are transported from the producers to the manufacturers at purities of 10 per cent opium and ca 70 per cent concentrate of poppy straw – crude morphine derived from poppy straw. Table 2 assembles the approximate tonnages of the two sources processed, by country.[1] Table 3 gives the major manufacturers now in business. The pioneers E Merck, Knoll and Boehringer in West Germany only went out of production during the past dozen years.

Finished products

Before describing the manufacture of opiates, it is useful to know the major pharmaceuticals which are currently being used. They fall into three main therapeutic categories: (note: formulations use the salts of these alkaloids in most cases, the hydrochoride, sulphate or phosphate being most popular).

Scheme 4 T & H Smith process (ca 1878)





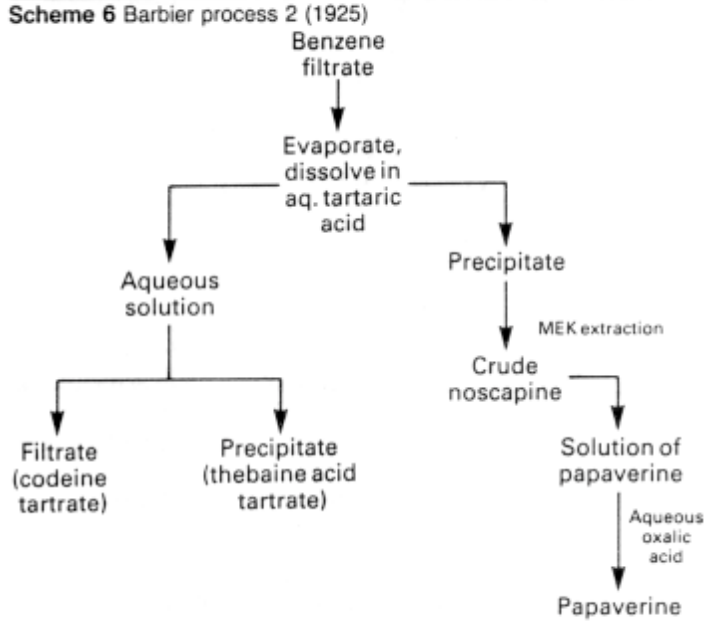
Scheme 5 Barbier process 1 (1925)

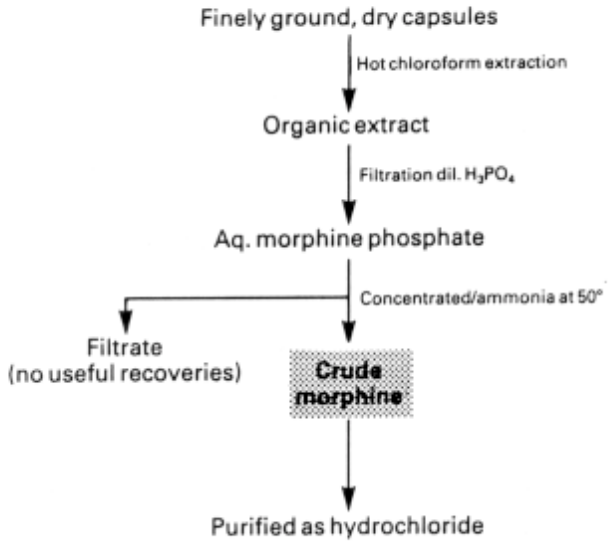
Analgesics. Morphine (relative potency, RP, =1) is used mainly in the control of severe pain, but also as an anti-diarrhoeal and sedative. Codeine (RP=0.1) is employed widely as a mild analgesic. Dihydrocodeine (RP =0.15) is finding increasing use against moderate pain, as is nalbuphine. Diamorphine or heroin (RP=2.5) and hydromorphone (RP=4.4) are used to supress severe pain, as is buprenorphine (RP=38) and to a small extent, oxymorphone (RP=10). Etorphine (RP=10,000) is used as a powerful veterinary sedative.

Antitussives. Codeine and to a lesser extent pholcodine and ethyl morphine, are the major opiate drugs used in the control of coughs. Noscapine is not strictly an opiate, an irony since its alternative name, narcotine, implies it is. The older name was coined before its true properties and structure were known. It is used as an antitussive where its lack of addictive potential makes it more acceptable. (e.g. in moslem areas) hydrocodone and oxycodone are also used in small quantities.

Narcotic antagonists (antidotes). The most undesirable side effect of the opiates, when used medicinally, is respiratory depression (sedation). The opiate antagonists naloxone and naltrexone are used as an antidote or as a co-formulation to supress this problem.

Scheme 6 Barbier process 2 (1925)





Scheme 7 Merck process (1945)

Diprenorphine, a very powerful antagonist, is used to revive animals sedated with etorphine.

Other opium-derived drugs. Apomorphine hydrochloride is a centrally acting emetic and is used in small quantities as such. More recently, it has been tested as an anti-Parkinson therapeutic. Papaverine, much of which is made synthetically, finds continuing use as a smooth muscle relaxant.

Extraction

In order to manufacture this range of bulk products, it is necessary to isolate:

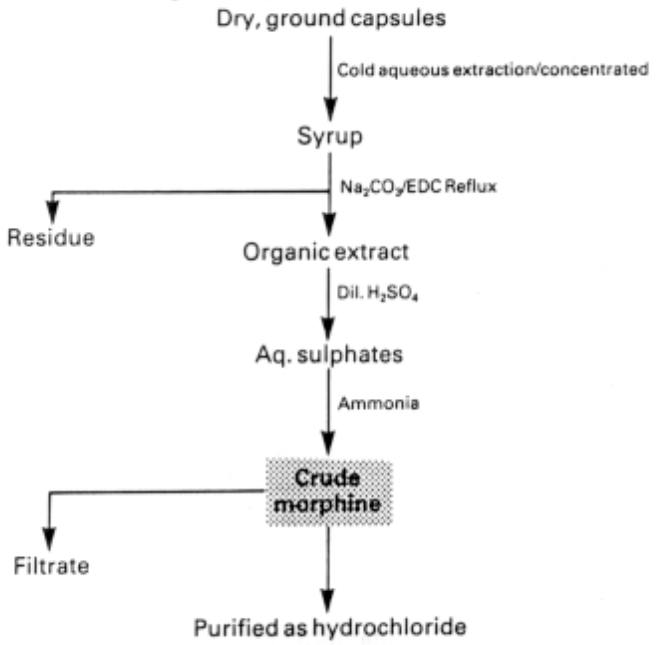
- morphine, codeine, noscapine and thebaine from opium and/or:
- morphine, codeine and thebaine from poppy straw.

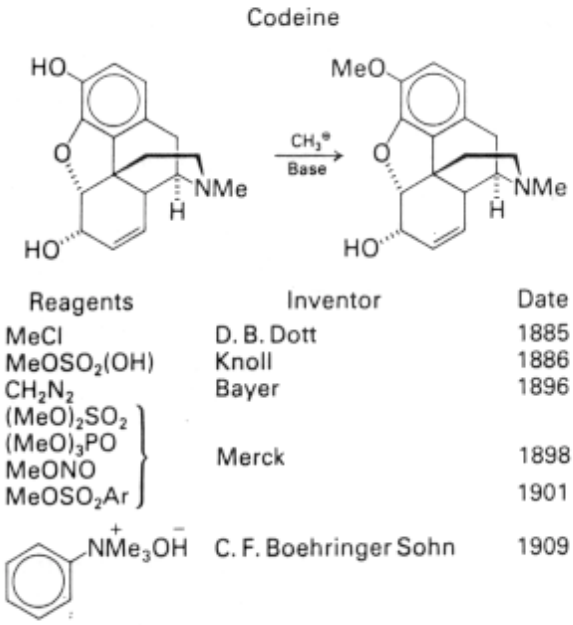
Opium

The basic principles of extraction were established in the 19th century. The factors shown in Table 4 determine the options available: they are summarised in the graphical representation in Fig 4.

Three early processes established the major strategies for the extraction of morphine. Lesser alkaloids such as

Scheme 8 Boehringer Sohn process (1945)





Reagents	Inventor	Date
MeCl	D. B. Dott	1885
$MeOSO_2(OH)$	Knoll	1886
CH_2N_2	Bayer	1896
$(MeO)_2SO_2$	Merck	1898
$(MeO)_3PO$		
MeONO		
$MeOSO_2Ar$		1901
$NMe_3^+OH^-$	C. F. Boehringer Sohn	1909

Fig 5 Codeine

codeine, narceine, papaverine and thebaine were isolated from time to time from residual tars and precipitates, but the major goal was to isolate morphine.

In Scheme 1 the Robertson-Gregory process is illustrated, the key feature of which is the removal of much of the non-alkaloidal material in the 'marc', together with the noscapine and some thebaine, and a mixture of calcium meconate, sulphate and lactate.[5,6] Purification of the codeine contaminated morphine hydrochloride (Gregory's salt) is time consuming due to the needle-shaped crystals which give serious filtration problems.[7]

In Scheme 2 the Merck process[5,6] demonstrates the principle of total alkaloid precipitation at pH 9, followed by taking up in ethanol. Crude morphine is reprecipitated from the alkaloid acetate solution. Again the morphine is purified via its hydrochloride. The Pelletier-Thiboumery process[5,6] shown in Scheme 3 is effectively a variation upon the Robertson-Gregory theme. Scheme 4 illustrates the process in use at T & H Smiths in 1878.[8] The precipitation of the total alkaloids had been inserted into the Gregory process which greatly enhanced the efficiency of the older process. Interestingly, this process was introduced by a German, Dr Delitsch, who joined the firm in 1872. During his 40 years with the company, three novel alkaloids were discovered: gnoscapine [(±)-narcotine] in 1878,[9] xanthaline (papaveraldine)[10] in 1881 and neopine in 1911.[11]

Opium processing in the 20th century

The realisation that morphine and heroin gave rise to physical addiction grew slowly over the latter part of the 19th century. Indeed heroin was originally sold as a powerful ('heroisch') pain killer free of the addictive side effects of morphine. Codeine became increasingly important in the USA, then Europe and finally in the UK. The recovery of codeine, thebaine and noscapine has become steadily more important, especially since 1960 with the rise of the semi-synthetic opiates.

Andre Barbier is generally accepted to have invented a key processing development which is illustrated in his published process, summarised in Schemes 5 and 6.[5] The key feature is the use of the acid tartrate of morphine

which crystallises even from impure solutions as an easily filtered granular solid. The solubility of the neutral tartrate salt is a bonus since it simplifies the removal of insolubles, etc. Notice too that the greater degree of clean separation of the various alkaloids is much improved in this process.

Very soon this 'acid tartrate' trick spread throughout the industry here and in Europe. However, it is interesting that although Smiths had adopted the trick by 1940, Macfarlans continued to use the Gregory Process up to the time when they amalgamated with Smiths in 1960[12] and May and Baker operated the process up to 1986.[13]

Poppy straw

As early as 1823, Tilloy in Dijon succeeded in extracting 4kg of morphine from an unspecified weight of capsules.[14,15] F L Winckler and H E Merck obtained remarkable yields of >1 per cent morphine from capsules in the early 1830s but no one commercialised such processes.[16]

In Hungary, peasants had grown poppies for their seeds and oil for centuries. One of their countrymen, Kabay set up a factory in 1928 to process the waste straw (usually fed to cattle). Although his process[17] was inefficient, with the outbreak of the Second World War many countries under German control began to process poppy straw (the supplies of opium being restricted by allied blockade).

The processing of poppy straw is quite different to processing opium. The factors shown in Table 5 mean that the scale of operations is at least 10 times as big so the logical location is close to the site of production. Two early 'concentration' processes which produce concentrate of poppy straw (CPS) are shown in Schemes 7 and 8.[18]

The yields obtained over the last 50 years have increased substantially with improved strains of poppy and agricultural methods (Table 6) The operation set up by Macfarlan Smith in the '60s in Tasmania has lead in these developments, and today the Company, now Glaxo (Australia), is a model to which the rest of the world aspires.[19] Very high recoveries of available morphine are currently achieved. Codeine and thebaine are also recovered.

Table 5 **Major factors in poppy straw processing**

- The alkaloid content varies widely, depending upon climatic conditions especially humidity
- For every tonne of morphine need to process 1-300t of dry straw
- Capsule contains approximately 10 times as much morphine as the stem
- Aqueous solvents extract large quantities of plant material
- Solvent processes extract much polyphenolic material

Table 6 **Poppy straw (20th century)**

Process	Date	Country	% Morphine extracted	(% in straw)
Kabay	1928	Hungary	0.08%	–
Heissler	1936	Czechoslovakia	0.1%	–
Roche	1935	Switzerland	?	(3-5%)
Three majors*	1940s	Germany	?	0.2%
Soc Franco Pavot (green poppy)	1945	France	0.25% (in 1962)	–
State company	1986	Turkey	0.24%	–
Glaxo	1986	Australia	1.1%	–

* E. Merck, Boehringer and Knoll

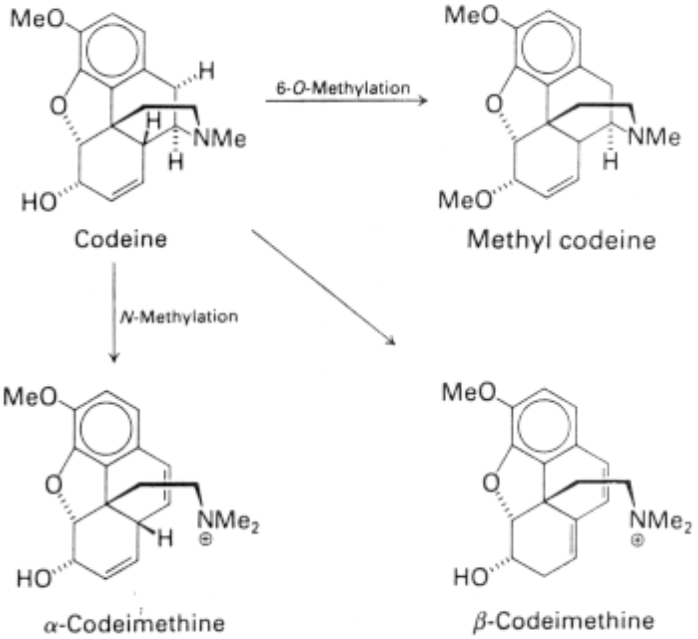


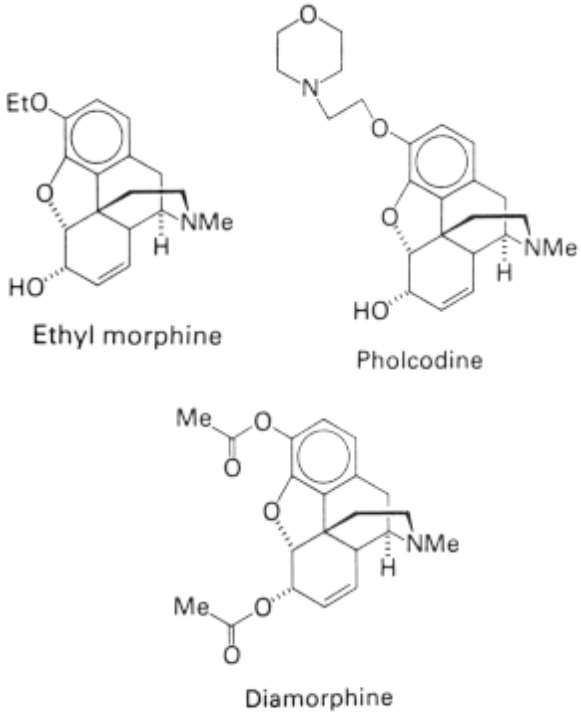
Fig 6 Side reactions in methylation

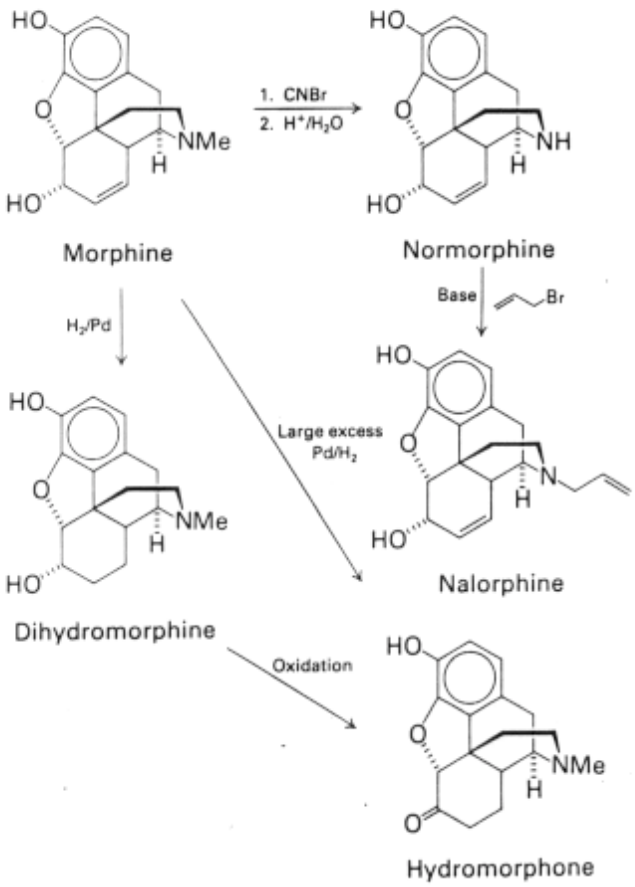
Chemistry

Morphine itself finds only limited application, although the newer slow release formulations have increased its clinical use in the 1980s.[20] Most morphine is converted to codeine (approximate world volume of 200t, as alkaloid)[1], the supply of natural alkaloid being far too small (Fig 5). The reagent of choice for this methylation continues to be phenyltrimethyl ammonium hydroxide.[21] Other cheaper methylation reagents led to low yields due to the side reactions contingent upon N- and 6-0-methylation (see Fig 6). Both morphine and codeine are elaborated into other simple products (Fig 7, Schemes 9 & 10).

The centrally acting emetic apomorphine is produced by the acid catalysed rearrangement of morphine shown in Scheme 11. It has been used in recent trials for the treatment of Parkinson's disease.[22]

Fig 7 Other simple morphine derivatives

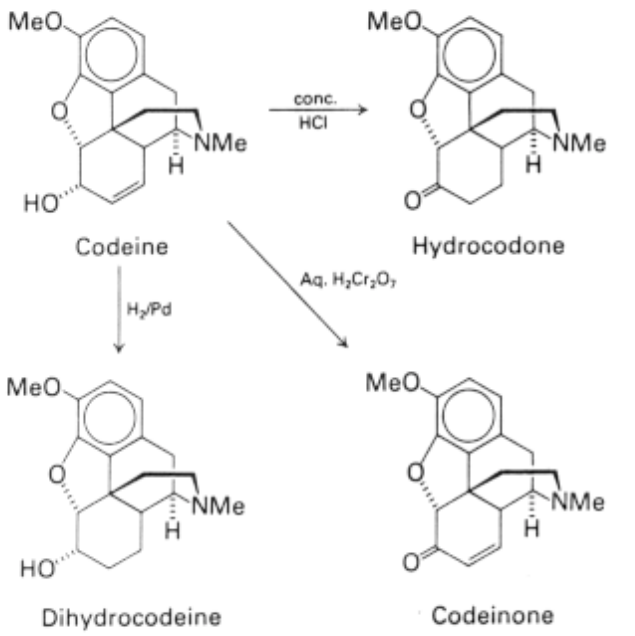




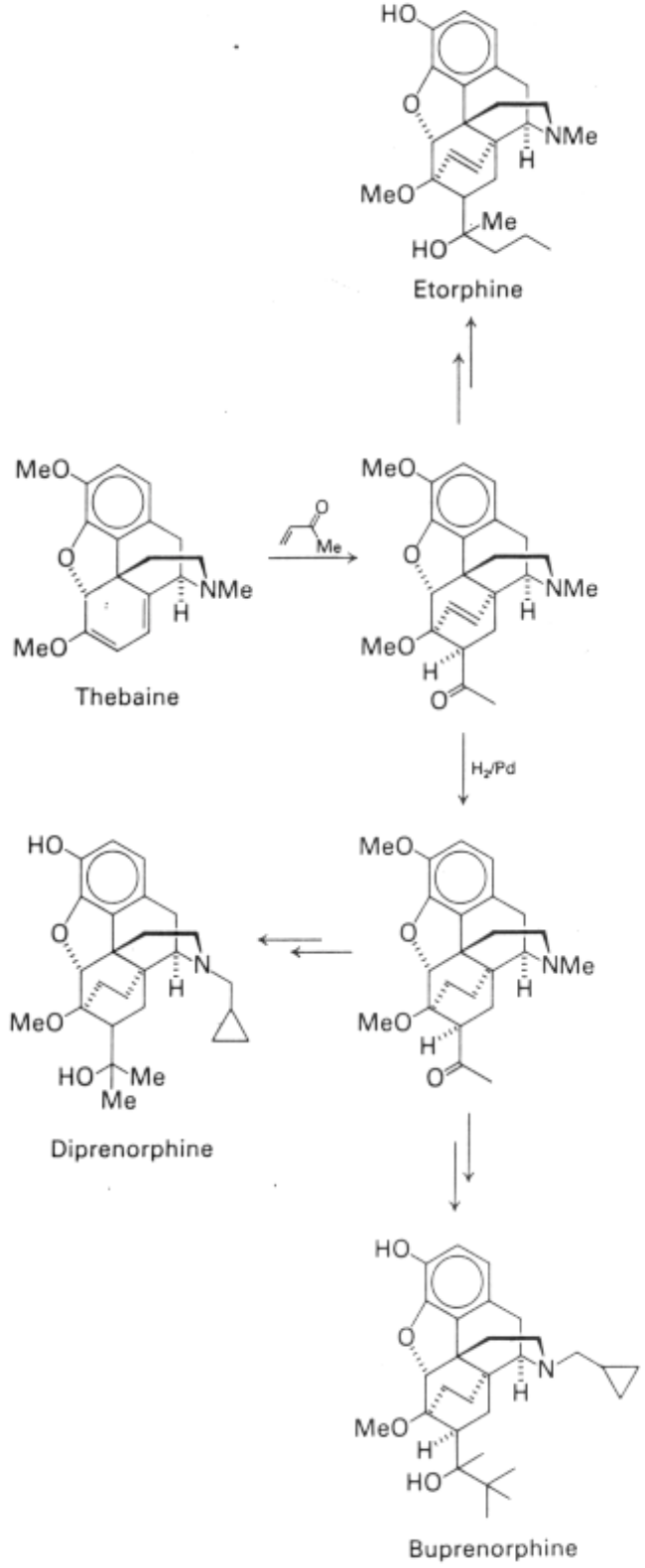
Scheme 9 Morphine as a starting material

Newer opiates

In the early 1960s, when Smiths and Macfarlans amalgamated into Edinburgh Pharmaceutical Industries the research director Dr Bentley (now Professor Bentley) was investigating a series of thebaine derivatives in the labs in Wheatfield Road. He was continuing work on thebaine derivatives which had been started in the '50s in a project jointly funded by Reckitt and Colman and Macfarlans. The remarkable narcotic power of one such derivative, was revealed when someone unknown made the coffee for the lab workers with a contaminated conical flask. Within minutes, half dozen bodies, including Professor



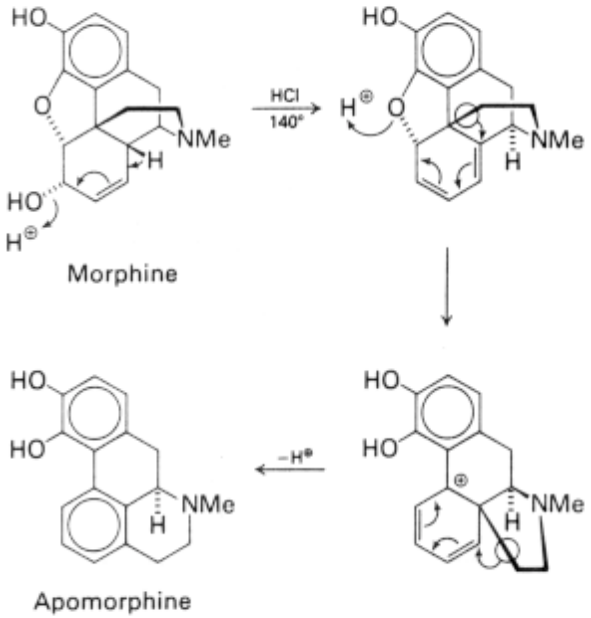
Scheme 10 Codeine as a starting material



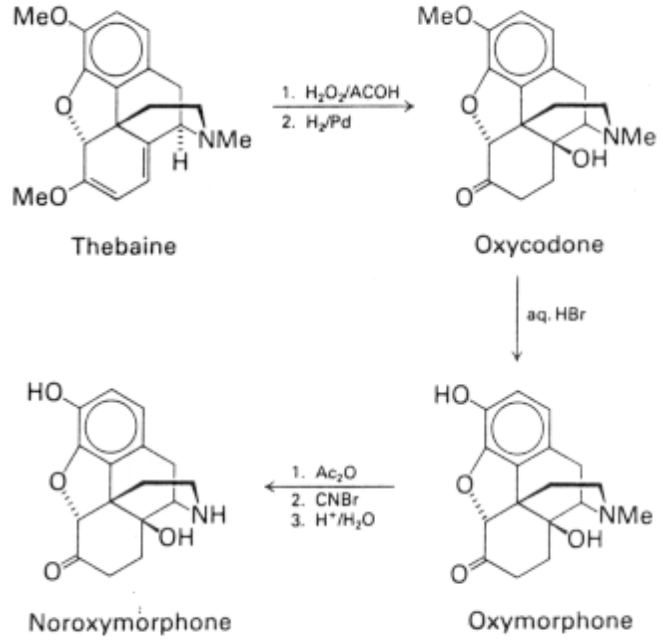
Scheme 12 Thebaine as a starting material

Bentley were lying unconscious on the lab floor. Fortunately they came round quickly, although not before the quick thinking company doctor had carried out an impromptu assessment of the clinical effects of this remarkable drug.[23]

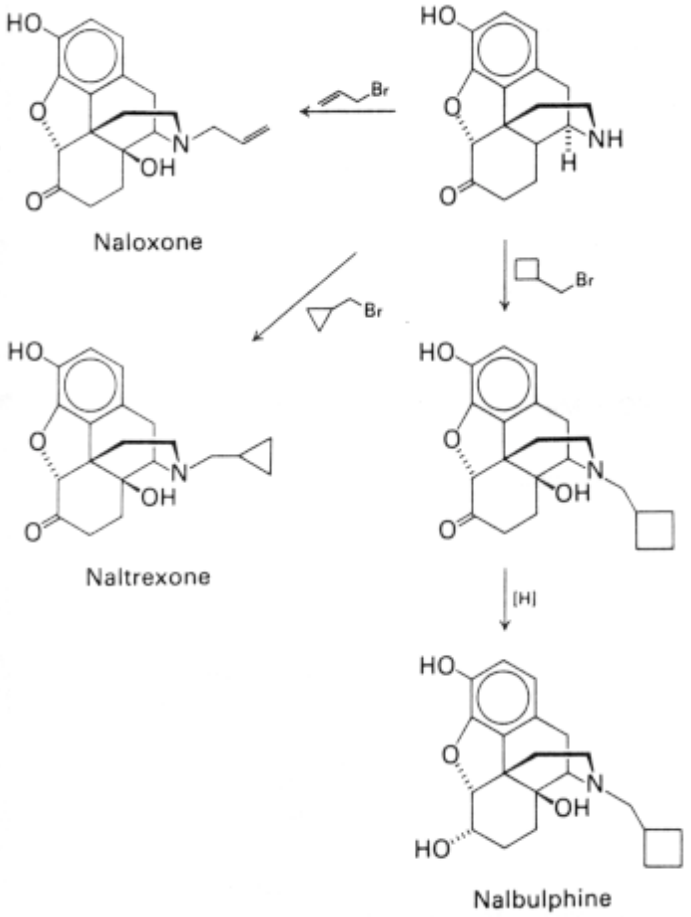
A close analogue, M99, was subsequently dubbed Etorphine and is still in use as a powerful narcotic sedative for veterinary work. It is approximately ten thousand times as powerful as morphine. The well known drug 'Temgesic' (buprenorphine HCl) was another product of this fruitful research.[25] Scheme 12 illustrates the conversion of thebaine into these M-compounds.[24] An earlier use of thebaine as a source of codeine is now of little commercial value, since another



Scheme 11 The apomorphine rearrangement



Scheme 13 Synthesis of noroxymorphone



Scheme 14 Synthesis of nal compounds

useful series of semi-synthetics, discovered by Sankyo in 1963 and developed in the USA by Dupont are derived from thebaine.[26] The key intermediate, noroxymorphone is synthesised by the route shown in Scheme 13 and the derived nal-compounds are shown in Scheme 14.

Future

A discussion of the ultimate analgesic and its properties is outside the scope of this paper, but the need for the first true pharmaceutical is likely to continue for the next couple of decades, at least.

Acknowledgements. Mr Ken Reid (discussions), Glaxo Group for permission to publish this paper and many more colleagues in Macfarlan Smith and Glaxo for their time and help. I would like to further acknowledge the help of James Lowes (Boots PLC) and John Walton (May and Baker Ltd).

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