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Review Articles

Papaver bracteatum — a Summary of Current Knowledge

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Abstract

Increasing abuse of opiates has made it necessary to obtain alternative sources to *Papaver somniferum* as raw material for the pharmaceutical industry. One suitable source is *Papaver bracteatum* Lindl. which has been closely investigated for 15 years. A review of recent investigations in the fields of botany, genetics, cytology, biochemistry and pharmacognosy is given in this summary. The closely related *P. orientale* and *P. pseudo-orientale* are briefly reviewed. Other alternative sources to *P. somniferum* are also discussed.

Introduction

Plants of the genus *Papaver* have many different uses [1]. The most important species, *Papaver somniferum* L., is an outstanding medicinal plant which has been associated with man for thousands of years. The products of *P. somniferum*, opium, morphine and codeine, are indispensable medicinals, used for their analgesic and hypnotic effects [2]. The seeds are also used as a flavour in baking and for oil production in some countries.

But opium, morphine, and especially the semi-synthetic derivative heroin, also have narcotic and addicting effects, which have led to a substantial worldwide social problem. Today, the major part of the illicit morphine of the world goes into the production of heroin. Legal production of morphine from opium and poppy straw amounted to 170 tons in 1972 [3] and has continued to rise since then. About 90 per cent of this morphine was converted into other bases, mainly codeine, which is the medicinally most important opiate with a very low abuse potential.

In spite of the enormous efforts to find a superior synthetic codeine substitute, this has not yet been achieved. In their extensive survey of this whole field EDDY et al. [4] reached the following conclusions: "... *there are other substances available that could be used as alternates for codeine, ... but the use of these other substances would result in no particular gain and probably no particular loss.*"

As long as codeine has not been surpassed by cheaper and better synthetic compounds (the total synthesis of codeine has been reported by GATES and TSCHUDI [5] but is not economically feasible), there is an obvious need for additional and better sources of raw material, sources that eliminate the risky opium and morphine production. One such source is the alkaloid thebaine which is a minor component of opium (2 to 5 per cent) [6] and which has been used for many years in the production of additional codeine.

The reports of some varieties of *Papaver bracteatum* LINDLEY where thebaine constitutes 98 per cent of the total alkaloids [7] with a content of 0.7 to 1.3 per cent in the roots, 26 per cent in the dry latex [8] or 3.5 per cent in the dry, ripe capsules [9], have made this species most interesting as a potential new raw material for opiate production [3, 10, 11].

The last 15 years have seen an increasing number of studies concerning *P. bracteatum*. In 1972 the U.N. Division of Narcotic Drugs initiated a special project called "Scientific Research on Papaver bracteatum" and since then international conferences have been held regularly. This coordination of botanical and phytochemical research has proven most important, and one of the major sources of information on *P. bracteatum* today is the series of papers published by the U.N. (United Nations. Division of Narcotic Drugs. "Scientific Research on *Papaver bracteatum*." ST/SOA/SER.J./ 1–23, Geneva, 1973–1976; "Scientific research on *Papaver* Species as Sources of Codeine, Morphine and Thebaine." ST/SOA/SER.J/ 24–28, Geneva, 1976–1977).

This accumulation of information and the now greatly increased knowledge of the taxonomy of *P. bracteatum* and alkaloid production from this species induced us to prepare the following summary of what is currently known about this plant.

Botanical investigations

Taxonomy of section Oxytona BERNH.

Papaver bracteatum was first accepted by LINDLEY [12] as an independent species, and it belongs together with the closely related *P. orientale* L. and *P. pseudo-orientale* FEDDE to section *Oxytona* BERNH. (= *Macrantha* FEDDE). The natural habitat of this section covers the mountainous regions of Iran, eastern Turkey and the Transcaucasian USSR (Fig. 1).

The species in section *Oxytona* are very much alike, and incorrect botanical identifications resulted in much confusion in earlier literature with regards to their alkaloid contents and chromosome numbers. A close investigation of the species in their natural habitats [13] has revealed important characteristics for the identification of the species and a reevaluation of the taxonomy.

All species in section *Oxytona* are perennial and are easily distinguished from other *Papaver* species, with the exception of *Papaver monanthum* sect. *Pilosa*. In earlier taxonomic treatments of this section [14–18] four to five spe-

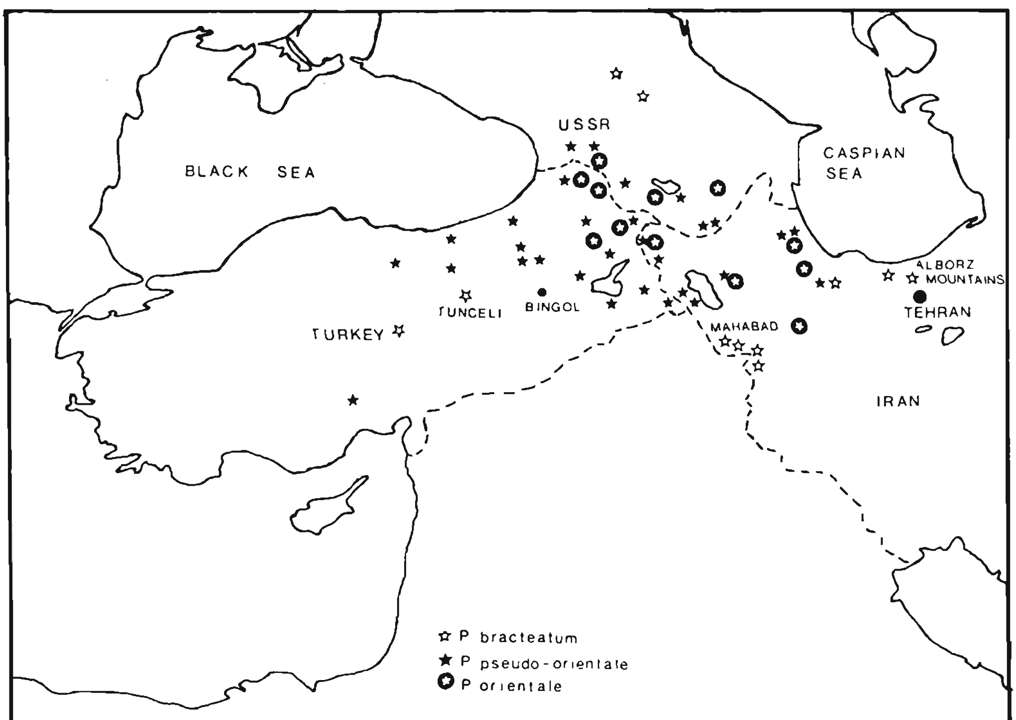


Fig. 1. Distribution of species of section *Oxytona*.

cies have been recognized. MEDWEDEV [19] recognized only three species: *Papaver orientale*, *P. pseudo-orientale* and *P. bracteatum*, and later work [13] confirms the existence of only three species. A complete review of older taxonomic treatments is given by GOLDBLATT [13]. The varieties of *P. bracteatum* studied up till now originate mostly from two separate areas in Iran, the Alborz mountains and the Mahabad region.

The following characters are considered typical of the different species: 1) the position of the insertion of leaves, 2) the bracts, 3) the flower buds, and 4) the petals.

The uppermost leaf is found on the upper third of the stalk in *P. bracteatum* and *P. pseudo-orientale*, while in *P. orientale* it is situated around the midline and often as three leaves grouped together.

Bracts are found only in *P. bracteatum* and in some individuals of *P. pseudo-orientale*, but those found in *P. bracteatum* are larger and more numerous (3 to 8).

The flower buds of *P. bracteatum* and *P. pseudo-orientale* are erect throughout their growth, but the calyx bristles of *P. pseudo-orientale* are more sparsely spread compared to the broad based bristles of *P. bracteatum*. The bud of *P. orientale* is pendulous during development, and straightens just before the flower opens.

The petals of *P. bracteatum* are deeply red-coloured with square or long blackish stripes from the base to midline. *P. pseudo-orientale* and *P. orientale* have orange-red petals, but *P. orientale* is without basal spot. *P. pseudo-orientale* has a dark rectangular blotch above the base, but as this can be absent in some individuals, other characters must be used for identification. The pigments of the petal do not fade on storage in *P. bracteatum* whereas the petals of *P. orientale* and *P. pseudo-orientale* fade [20]. Some of the taxonomic characters mentioned are summarized in Fig. 2.

Paper chromatography of the petals can be used to distinguish the species [21], since *P. bracteatum* petals contain pelargonidin-3-glucoside while *P. orientale* petals contain pelargonidin-3-sophoriside-7-glucoside [22, 23].

For species identification in the seedling stage chromosome numbers can be utilized, but this procedure is time consuming and another way for identification has been developed [24]. Cellophane impressions of the true leaves from

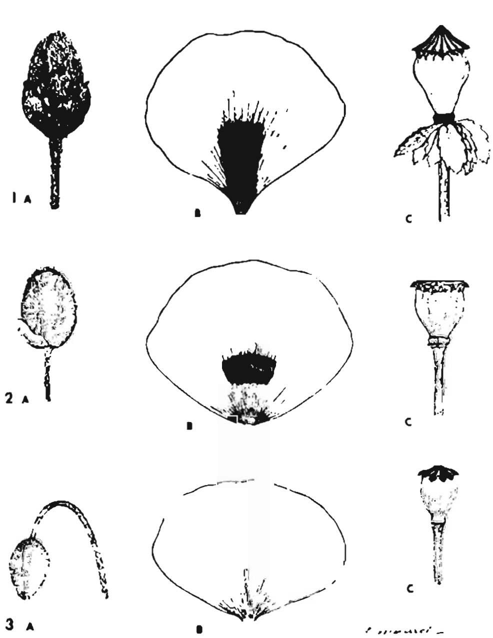


Fig. 2. Taxonomic characters of *Papaver bracteatum* [1], *P. pseudo-orientale* [2] and *P. orientale* [3]. (A = bud; B = petals; C = mature capsules). After GOLDBLATT [13].

seedlings are taken and the size of the epidermal cells, particularly the stomata, is measured under a microscope. FAIRBAIRN and WILLIAMSON [25, 26] have developed a similar method using the stomata of the cotyledons at a definite stage of seedling development.

Growth and vegetative propagation of Papaver bracteatum.

The plant develops from a rosette stage very similar to other perennial *Papaver* species. The rosette consists of long, pinnately dissected, deeply incised leaves [13]. Reproductive stages are rarely reached until the second year, when a flowering stem begins to elongate shortly after full development of the leaves. The stem is unbranched and covered with white bristles. The plant enters dormancy in that the flowering stem and other plant parts die out [27]. After fruit ripening innovation shoots, covered with leaves, are formed below the soil level. Only tissues connecting innovation shoots and root parts survive. Independently growing individuals arise from each innovation shoot and new rosettes are formed shortly after dormancy. These remain during the following winter and a flowering stem is produced from each rosette in the spring. A schematic growth model of the plant is given in Fig. 3.

The most suitable time for vegetative propagation is when the plants are dormant. The root is then cut in 15 to 20 cm pieces as in Fig. 4 and the root parts are placed upright 5 to 10 cm below soil level [28, 29].

GREPPIN et al. [30] have cultivated *P. bracteatum* in controlled environments. The best developments up to the age of 78 days was found with a 20 h photoperiod and light intensities of 8000

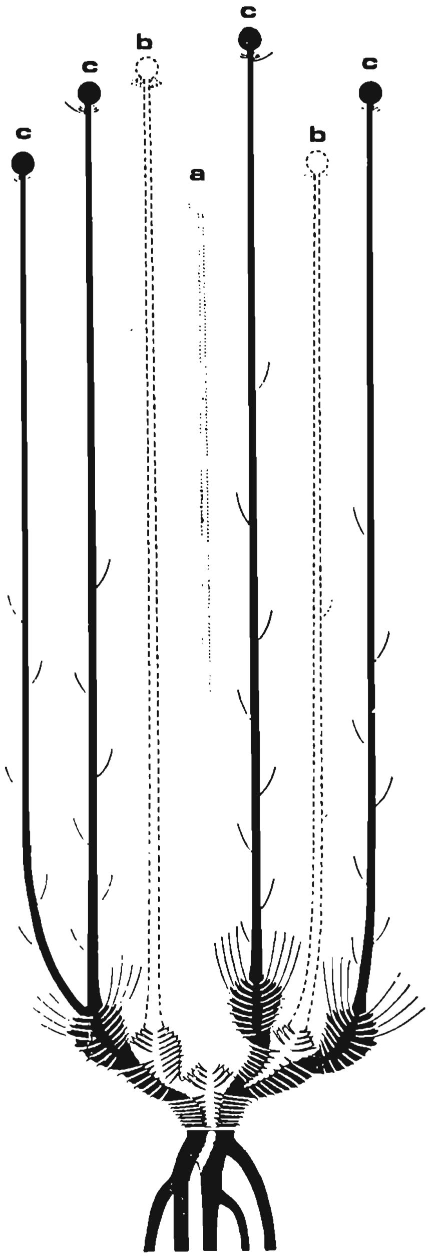


Fig. 3. Habit of *Papaver bracteatum*, a) 2nd year flower, b) 3rd year flower and c) 4th year flowers.

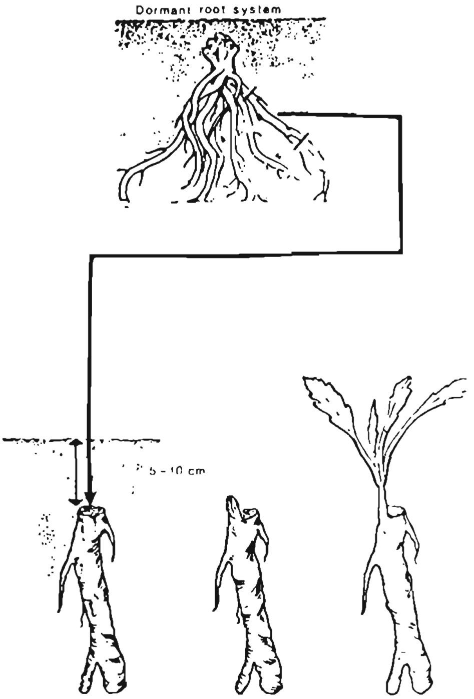


Fig. 4. Vegetative propagation of *Papaver bracteatum.*

lux or above. At a photoperiod of 24 h an inhibiting effect appeared.

Characteristics of the seeds

The seeds of *Papaver bracteatum* have a dark brown to black colour and the thousand seed weight varies between 0.20 to 0.41 grams [31] compared to 0.40 to 0.64 grams for *P. somniferum* [32]. The lipid content, obtained as an ether extract, varies between 18 and 43.3 per cent [33, 34] but the lower figure was obtained from not quite ripe seeds raised in Norway. The fatty acid composition given in Table I [33, 36] shows great similarity with that of *P. somniferum* [35]. The protein content is reported to be 26 to 27.3 per cent [34] and amino acid analysis has shown that *P. bracteatum* contains twice the amount of methionine found in seeds of *P. somniferum* [37]. Carbohydrates are present in amounts between 40.4 to 49.9 per cent [34]. The seeds have thus a favourable composition, in regards to the oil and protein, and in Central Anatolia the seeds are used as food [38].

Maximum germination of the seeds occurs with a constant temperature of 10 to 25° C, and seedlings emerge from soil depths of 0.5 cm or less. Good germination and seedling growth is obtained within a wide pH range (5.1 to 10) but the salts affecting the pH are of great importance as some of them e.g. sodium salts, inhibit germination. The best establishment and growth are however obtained with a pH of 6.5 to 7.0. The germination period can be decreased by soaking the seeds in water for 24 hours at room temperature prior to sowing [33].

Irradiation experiments with seeds, utilizing γ-rays, have shown that above 40 Rad germination is inhibited, but flowering plants have been obtained with doses of 20 to 40 Rad [34].

Cytology, cytogenetics and reproduction

Cytological studies have shown that the chromosomal base number in section *Oxytona* is 7 and the chromosomes show a close resemblance to those of other *Papaver* species [13, 39, 40]. Characteristics of the chromosomes from *P. bracteatum* are given in Table II and idiograms of *P. bracteatum, P. rhoeas* and *P. somniferum* are given in Fig. 5.

Table I
Fatty acid composition of seed oils of *Papaver bracteatum* [33, 36] and *P. somniferum* [35].

Fatty acid	Per cent of total fatty acids in *P. bracteatum*	*P. somniferum*
Palmitic	7.1 — 12.5	4.8 — 11.1
Palmito-oleic	0.3 — 0.5	0.8 — 1.6
Stearic	1.4 — 2.5	1.2 — 4.2
Oleic	8.7 — 12.5	11.0 — 30.1
Linoleic	76.1 — 80.8	62.2 — 73.0
Arachidic	0.5 — 0.7	0.1 — 0.4

Table II
Chromosome characteristics of *Papaver bracteatum,* after SAIDABADI and GORENFLOT [39].

Chromosome pair	Long arm (μm)	Short arm (μm)	Total length (μm)	Relative length	Ratio long/short	Type of chromosome
I	2.53 ± 0.42	1.23 ± 0.26	3.76	15.9	2.1	Submetacentric
II	2.56 ± 0.46	1.06 ± 0.40	3.62	15.3	2.4	Submetacentric, satellite
III	2.50 ± 0.43	1.08 ± 0.28	3.58	15.1	2.3	Submetacentric
IV	2.67 ± 0.44	0.89 ± 0.18	3.56	15.1	3.0	Subtelocentric
V	1.80 ± 0.41	1.44 ± 0.30	3.24	13.7	1.2	Metacentric
VI	2.09 ± 0.30	1.02 ± 0.19	3.11	13.1	2.0	Submetacentric
VII	1.93 ± 0.35	0.87 ± 0.17	2.80	11.8	2.2	Submetacentric
I — VII	—	—	23.67	100.0	—	—

P. bracteatum (diploid) has the chromosome number 2n = 14 (= 2 ×), *P. orientale* (tetraploid) 2n = 28 (= 4×), and *P. pseudo-orientale* (hexaploid) 2n = 42 (= 6 ×). In some of the natural habitats hybrids between the species occur, but these are mostly sterile, due to the different ploidy levels. *Papaver pseudo-orientale* is intermediate in many features between *P. bracteatum* and *P. orientale,* and the chromosome number suggests that *P. pseudo-orientale* may have arisen as an allohexaploid from these two species.

Artificial production of hybrids between *P. somniferum* and both *P. bracteatum* and *P. orientale* have been reported. LJUNGDAHL [41] obtained a hybrid with 32 chromosomes, 11 from the *somniferum* mother and 21 from the *orientale* father, which indicates that in the cross *P. orientale* had been confused with *P. pseudo-orientale.* KAWATANI and ASAHINA [42] also used *P. pseudo-orientale,* described as *P. orientale,* as the chromosome number was 42, and the petals were scarlet with purple-black spots at the base. The hybrid obtained had 32 chromosomes, was perennial and had stems, peduncles, flower buds and petals like the female parent, *P. pseudo-orientale.* In the early stages

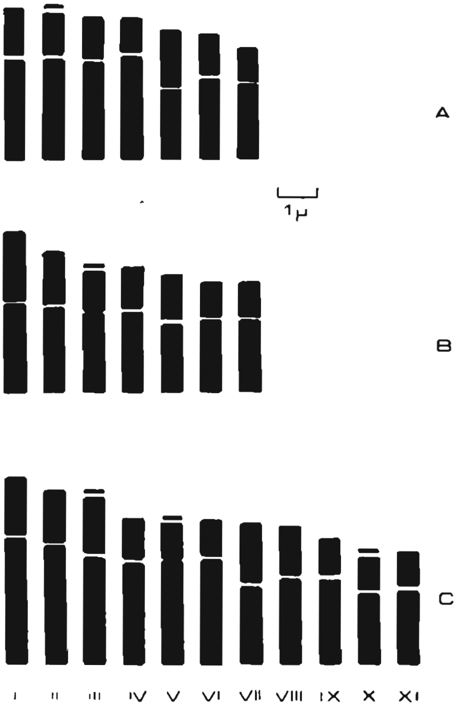


Fig. 5. Idiograms of *Papaver bracteatum* (A), *P. rhoeas* (B) and *P. somniferum* (C).

of growth the leaves varied in their resemblance to the parents. Yasui [43] found in the offspring from the cross *P. somniferum* × *P. bracteatum* that no homologous chromosomes existed between the two species. The hybrid obtained had 18 chromosomes and in studies of the pollen mother cell 4 bivalents and 10 univalents were observed. The bivalents were ascribed to the haploid constitution of $4_{II}+3_{I}$ in *P. somniferum* [44, 45].

Hybrids between *P. bracteatum* and *P. somniferum* have also been reported by Pirovano [46], unfortunately without any botanical descriptions of the parents used in the study. Kasaeva [47] obtained no seeds when *P. somniferum* was the pollen donor, but the reciprocal cross was succesful, and fertile hybrids were obtained. Fertile hybrids have also been described by Vilmorin [48]. Böhm [49] made a reciprocal cross between *P. somniferum* and *P. bracteatum*. With *somniferum* as mother plant an average of 530 seeds/capsule was obtained and the reciprocal cross yielded 760 seeds/capsule. No differences in the offsprings from the reciprocal crosses could be observed. The hybrid was sterile, and polyploidisation failed in so far as fully developed polyploid plants were never obtained. Crosses with tetraploid *P. somniferum* and tetraploid *P. bracteatum* are probably necessary to obtain fertile hybrids [50].

With regard to sexual reproduction, Böhm [50] considers *P. bracteatum* to be self-incompatible as 394 self-pollinated plants resulted in 64 capsules containing on an average 314 seeds over a 3 year period. Twelve plants gave on self-pollination 57, pollination with a neighbouring flower from the same plant 80, and cross-pollination 4360 seeds/capsule. Yasui [44] found a high sterility when the plants were selfed, but intercrossing yielded a good seed set.

Alkaloid production in Papaver bracteatum

Biosynthesis and structure.

In *Papaver bracteatum* thebaine predominates and only small amounts of alpinigenine, orientalidine and isothebaine seem to be present in certain strains like Halle III [51] and material from the Polour region of Iran [52]. In material from Tunceli (Turkey) 0.225 per cent of salutaridine and 0.3 per cent of thebaine is reported from the dry capsules [53]. Biosynthetically thebaine has been demonstrated to be derived exactly in the same way as in *P. somniferum* [54] i.e. via 3,4-dihydroxyphenylalanine and (–)-reticuline. As precursors of thebaine NORDAL et al. [55] also found phenylalanine, tyrosine, glycine and urea. Isothebaine has been demonstrated to be derived from (+)-orientaline via (–)-orientalinone [56, 57] and no significant conversion of isothebaine into thebaine occurs. Alpinigenine and the rhoeadine type alkaloids are derived from (+)-reticuline via tetrahydropalmatine [58–61] An outline of the alkaloid biosynthesis in *P. bracteatum* is given in Fig. 6 and for comparison *P. orientale* and *P. pseudo-orientale* are included. Species names within parenthesis denote that the alkaloid is a minor one in this species. The outline is partly hypothetical as some of the intermediates, e.g. norreticuline and reticuline, have not yet been isolated.

The alkaloids are present mainly in the latex, and vesicles, similar to those in *P. somniferum* [62, 63], have been found [64]. Whether these are the site of biosynthesis, as in *P. somniferum*, or not, is however not yet known but they represent the major component of the exuded latex.

A total of 27 alkaloids, belonging to 10 of the 14 alkaloid groups described for the genus *Papaver* [57], have been found in *P. bracteatum*, and besides thebaine, alpinigenine and isothebaine, the following have been reported:

(Pro-) Morphinanes:
Oripavine [65], salutaridine [66], co-

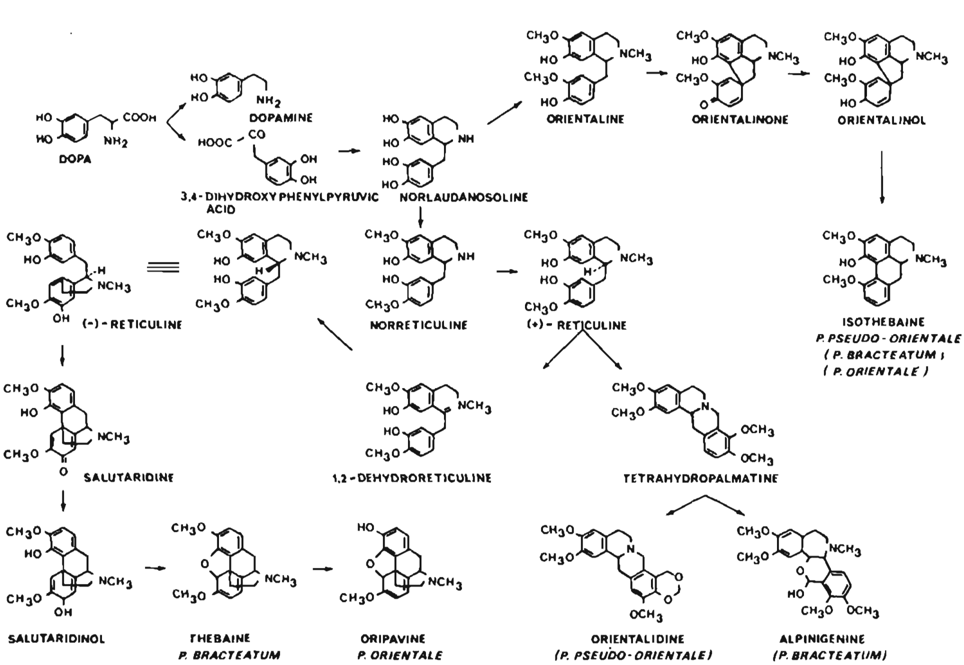


Fig. 6. Biosynthesis of some major alkaloids of section *Oxytona*.

deine, neopine [67], α- and β-thebaine-N-oxide [68], 14-β-hydroxycodeinone, and 14-β-codeine [69].
(Pro-) Aporphines:
Bracteine [65], bracteoline [70], orientalinone [66], and nuciferine [71].
Protoberberines:
Mecambridine (oreophiline) [66], orientalidine (bractavine) [72], and coptisine [57].
Protopines:
Protopine [49].
Benzophenanthridines:
Oxysanguinarine [71].
Rhoeadine/papaverrubines:
Alpinine [67], epialpinine [73], papaverrubine B, D, and E [74], and papaverrubine C [75].
Isoquinolines:
N-methylcorydaldine [69].
Unknown structure:
Bractamine [65].

The alkaloid earlier described as alkaloid E has been found to be identical with alpinigenine [76]. Fairly high amounts (0.053 per cent in the dry capsules) of a non-alkaloidal compound, α-thebaol, closely related to thebaine [77] have been found in certain strains of *P. bracteatum* [67].

As discussed by GOLDBLATT [13], it is possible that plants used in some of the cited alkaloid studies were incorrectly identified. Until plants from all natural habitats of *P. bracteatum* (especially Turkey and USSR) have been more thoroughly investigated with respect to their alkaloid content, a more critical survey of the cited studies is, although probably justified, impossible to make.

Alkaloid content and production.

In *Papaver bracteatum* several races, based on alkaloid content and accumulation sites for thebaine, seem to exist. The German strain, Halle III, consists of two different alkaloid races: the thebaine race, with only thebaine present, and the alpinigenine race, with thebaine and small amounts of alpinigenine (alkaloid E) [51]. The Halle III strain is further characterized by a high thebaine content in the roots, 0.7 to 1.3 per cent, compared with 0.05 to 0.3 per cent in the vegetative parts [7, 78]. Ontogenetic studies revealed that 2 week old plants, of the thebaine race, contained 6 to 8 alkaloids with alpinigenine as the major one. During the following two weeks isothebaine appeared and the thebaine and alpinigenine amounts increased. In the following month the alkaloids remained unchanged, but afterwards alpinigenine decreased and disappeared after 3 months. At a very characteristic stage (at most 4 months after germination) isothebaine also completely disappeared, and the time between its presence and absence may be as short as 3 days (Fig. 7). Feeding of the direct precursor to alpinigenine, tetrahydropalmatine, to old plants resulted in formation of alpinigenine in the leaves [79]. The alpinigenine race differs from the thebaine race in that alpinigenine remains and isothebaine slowly disappears and is totally absent in the second vegetation year.

Another spectrum of alkaloids was observed by CHENG [31] in an Iranian wild type of *P. bracteatum* where orientalidine was the major alkaloid up till the age of 3 months (Fig. 7). Thebaine showed a steady increase during growth

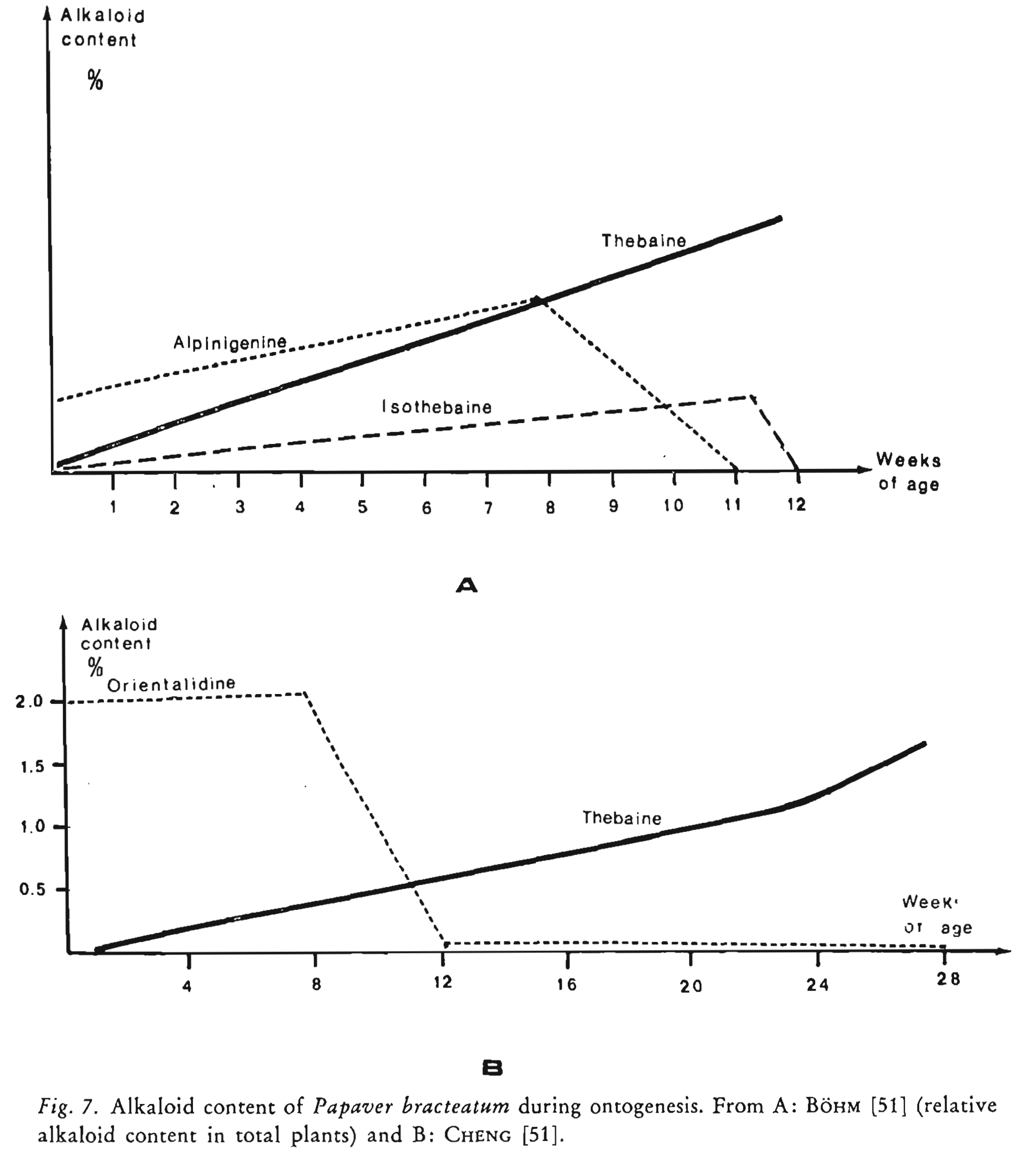


Fig. 7. Alkaloid content of *Papaver bracteatum* during ontogenesis. From A: BÖHM [51] (relative alkaloid content in total plants) and B: CHENG [51].

and reached a peak just before the onset of dormancy. Isothebaine was never detected. In plants derived from 8 different seed sources CHENG [31] observed a wide variation of thebaine, isothebaine and orientalidine contents in the roots and vegetative parts (Table III) of 7-month-old plants.

Orientalidine and alpinigenine are both derived from (+)-reticuline and their presence as major alkaloids during the first months indicate that the conversion of (+)-reticuline to (–)-reticuline has not reached full efficiency during this period.

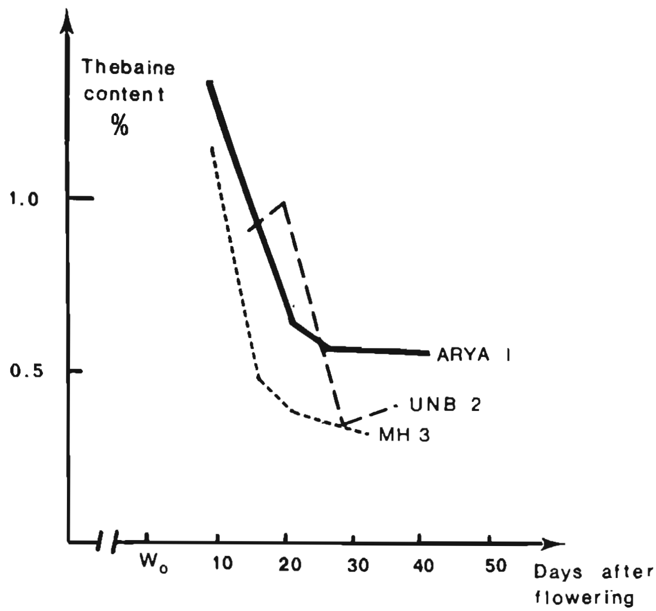
Thebaine contents in young plants

Table III
Alkaloid content in 7-month-old plants of ***Papaver bracteatum*** from different seed samples, after CHENG [31].

Seed samples	Thebaine content per cent Roots	Leaves	Orientalidine content per cent Roots	Leaves	Isothebaine content per cent Roots	Leaves
Norway	0.16	trace	0.28	trace	0.20	0.05
Denmark	0.15	0.02	0.18	trace	0.10	0.13
Poland	0.20	0.02	0.34	—	0.21	0.01
Leningrad	0.18	0.004	0.40	trace	—	0.08
Moscow	0.13	0.07	0.12	—	0.12	—
Halle III	1.30	0.32	—	—	—	—
Wild type (Iran)	0.61	0.27	0.09	0.04	—	—
Liverpool	trace	trace	0.02	0.06	0.02	trace

from different germplasm sources have also been studied by COFFMAN et al. [80], and they found a thebaine content of 0.48 per cent in the roots from 18-week-old plants, the vegetative parts containing 0.05 per cent. In 37-week-old plants the roots contained 0.47 per cent and the vegetative parts 0.1 per cent.

Cultivation in controlled environ-



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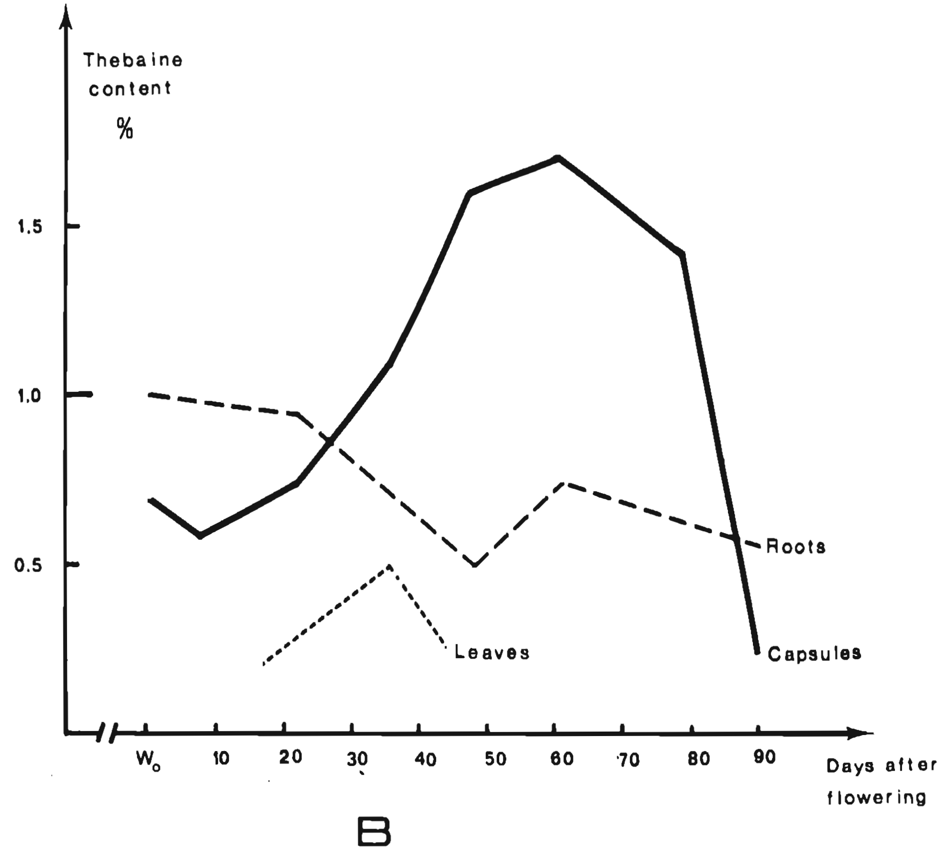

Fig. 8. Thebaine in different plant parts after flowering in *Papaver bracteatum.* From A: FAIRBAIRN and HELLIWELL [82] (fruiting tops) and B: AYNECHI and JAFFARIAN [81].

ment has revealed a maximum in the thebaine content (0.55 per cent in dry matter) from the leaves of 120-days-old plants cultivated with 20 h photoperiod and a light intensity of 6000 lux [30]. A broader maximum (from 120 to 180 days) was found with a photoperiod of 24 h. A minimum in the thebaine content (around 0.1 per cent) was found in 170-days-old plants with photo-periods of 12, 16 and 20 h.

In investigations of wild material from Iran the new types "Arya I" (from the Alborz mountains) and "Arya II" (from the Mahabad region) have been found. The thebaine content in the dry, ripe capsules from plants of Arya II, in their natural habitat, is as high as 3.5 to 5.8 per cent [9, 33]. Other aerial parts contain thebaine in large amounts e.g. the stems have a content of 1.6 to 2.1 per cent prior to flowering. AYNEHCHI and JAFFARIAN [81] have investigated different parts of plants, from Polure in Iran, at some stages after flower initiation. Their results are summarized in Fig. 8. The thebaine content in the leaves was too low for determination, with the method used in the study, except for 8 weeks after flower initiation when they contained 0.09 per cent. The thebaine content in the capsules shows a remarkable decrease during the month prior to dormancy. A similar, but less pronounced pattern was obtained by FAIRBAIRN and HELLIWELL [82] in a comparative trial with some different races in England (Fig. 8) when capsules and 15 to 20 cm attached pedicel were analysed.

Latex samples were drawn at different intervals after flowering, and the thebaine content was found to increase rapidly (from 8 to 15 per cent in fresh latex) during the first two weeks after flowering. A peak of around 18 per cent thebaine was reached 4 weeks after flowering. One of the investigated strains differed however in that maximum content of thebaine was found during the first week and then a continuous decrease followed. This strain behaved similarly in an earlier investigation [20]. Latex samples were also taken at 2 hourly intervals during a 24 hour period. Maximum content of thebaine was found to occur around 15.00 h. The morphine variation in *P. somniferum* has been investigated in a similar manner [83] and a distinct peak before noon was found, but the thebaine content in *P. somniferum* reached a peak in the afternoon. The diurnal variation in the thebaine content found in *P. bracteatum* was much smaller (± 20 per cent of the daily mean value) compared to the morphine variation found in *P. somniferum* (± 90 per cent).

To investigate the possibilities of collecting an equivalent to opium, called *bractium*, latex samples were drawn 2 to 4 weeks after flowering between 14.00 and 15.30 h. As an average 49.4 mg/capsule of dry latex was obtained at the first lancing and 38.1 mg/capsule at the second lancing. Between 32.7 and 54.5 per cent thebaine was found in *bractium* and in all cases a higher thebaine content was found in the samples from the second lancing [82]. In earlier investigations of the thebaine content in the dry latex values between 26 and 45 per cent have been reported [8, 31, 52]. Storage of *bractium* led to losses of thebaine varying between 0 and 8 per cent after six months and 12 to 20 per cent after one year.

From an agricultural point of view the collection of aerial parts is to be preferred especially as some experience can be gained from straw collection of *P. somniferum*. After combined harvesting capsules with 20 to 30 cm adhering stem probably will be obtained. FAIRBAIRN and HELLIWELL [82] investigated the thebaine content in this product from 3 different varieties at different intervals after petal opening. A peak in the thebaine content occurred during the first three weeks, but in some varieties a second peak was found 5 to 6 weeks after petal opening. Maximum values for the thebaine content of the fruiting tops, when unthreshed (including seeds), varied between 1.0 to 1.35 per cent (Fig. 8).

FAIRBAIRN and HELLIWELL [84] found in some samples that after extraction with ammoniacal methanol, further thebaine could be extracted if dilute acetic acid was used. These results indicated that thebaine is present in two forms, a normal thebaine salt and a "bound" form. Some of the thebaine salt present in the latex appears to be meconate as meconic acid has been identified in *P. bracteatum* and *P. pseudo-orientale* [85]. Both forms are not always present and mostly the bound form is found in the capsule. On closer investigation FAIRBAIRN and HELLIWELL [82] found 30 to 70 per cent bound thebaine (of total thebaine content) in bled capsules and 18 to 36 per cent bound thebaine in the whole capsules .In fully ripe capsules practically no bound forms were present.

The most suitable material for commercial production seem to be the "fruiting tops" of the plants, harvested 5 to 7 weeks after petal opening. FAIRBAIRN et al. [20, 82] have found with a plant spacing of 625 plants/100 m^2, 50 kg of thebaine/ha can be produced if each capsule yields 40 mg thebaine and 20 capsules/plant is obtained. If strains with high thebaine content in the roots, like Halle III, are used, an additional 25 kg/hectare can be obtained if the roots are harvested as well. Roots from normal strains would yield around 8 kg/ha. The figures given are theoretical and must be considered optimal, but even with losses around 50 to 65 per cent in practical agriculture the yield of around 20 kg thebaine/ha is quite interesting.

Collection of *bractium* would yield 58 kg of dry latex/ha if the capsules are scarified twice. From *P. somniferum* the opium yield varies from 1.5 to 26.5 kg/hectare [86].

Analysis of the alkaloid composition in *P. orientale* and *P. pseudo-orientale* has been performed on well identified plants from their natural habitats [87].

Dried latex from *P. orientale* contained 20 per cent oripavine and 9 per cent thebaine. Traces of isothebaine were found in plants from Khalkhal (northwest Iran). Analysis of dry, ripe capsules from *P. orientale* has revealed the existence of 5 different chemotypes [88]: A. oripavine; B. oripavine and thebaine; C. oripavine and isothebaine; D. oripavine and alpinigenine; E. oripavine, thebaine and alpinigenine. Oripavine was the major alkaloid in all chemotypes; dry capsules (without seeds) contain 0.5 to 1.25 per cent oripavine.

The alkaloids present in the dry latex of *P. pseudo-orientale* were [87] 11.7 per cent isothebaine, 0.5 per cent orientalidine and small amounts of bracteoline, salutaridine, Or 1 and 2 [72], PO 4 [89], and 11-demethylmecambridine (aryapavine).

In a Turkish sample of *P. pseudo-orientale*, salutaridine and macrantaline were found to be major alkaloids and macrantoridine was found in minor amounts [90, 91].

Spontaneous hybrids between *P. bracteatum* and *P. orientale*, occuring in natural habitats, contain both thebaine and oripavine as dominant alkaloids [13]. Hybrids between *P. orientale* and *P. pseudo-orientale* had an analogous composition with isothebaine as major alkaloid and oripavine in significant amounts.

BÖHM [49] produced the hybrid between *P. somniferum* and *P. bracteatum* to study the alkaloid production in the progeny. The hybrid contained 1.5 per cent morphine, 0.1 per cent thebaine and traces of alpinigenine in the dry capsules. The extra thebaine produced by the *bracteatum* genome was thus converted into morphine by the demethylating-reducing system of the *somniferum* genome. The presence of alpinigenine suggested that all *bracteatum* alkaloids were formed in the hybrid.

GREPPIN et al. [30] found a high thebaine content in some hybrids between *P. somniferum* and *P. bracteatum*.

Tissue culture of Papaver bracteatum

Callus cells derived from sterile seedlings have been cultured on agar medium [92] containing 3 per cent sucrose, 1 mg/litre NAA, 0.1 mg/litre kinetin and 10 per cent coconut milk. Thebaine was found at the early stages of growth in these cells (0.002 to 0.006 per cent in dry matter) but was almost absent at the later stages of development. Addition of some amino acid precursors (tyrosine, DOPA) stimulated thebaine formation to some extent [93]. Stylopine and protopine were produced in amounts of 0.01 to 0.02 per cent in dry matter [94] and their formation was more stimulated than that of thebaine by the addition of some amino acid precursors.

Thebaine in tissue cultures of plants from the Arya II population has been reported [95] but no amounts are given.

IKUTA et al. [96] investigated 11 representative species of Papaveraceae for their alkaloid contents in the callus cells. All were similar to each other and the alkaloids found were benzophenanthridines, protopines, and aporphines. Morphinanes were not produced in any of the callus cells derived from the *Papaver* species investigated. *P. bracteatum* contained norsanguinarine, oxysanguinarine, dihydrosanguinarine, sanguinarine, chelirubine, protopine and magnoflorine.

The occurrence of thebaine in other Papaver species

Recent investigations have shown that thebaine is the major alkaloid in other *Papaver* species. PHILLIPSON et al. [97] investigated material of *Papaver fugax* POIR. collected in mountain regions near Bingöl (Turkey) and found thebaine as the major alkaloid. *P. fugax* belongs to section *Miltantha*, and some confusion exists regarding the taxonomy of the three closely related species *P. fugax*, *P. caucasicum*, and *P. floribundum*. FEDDE [14] considers them to be distinct species but according to CULLEN [17] *P. caucasicum* and *P. floribundum* are synonyms to *P. fugax*.

In a perennial plant, morphologically very similar to *P. fugax* and *P. caucasicum*, thebaine is reported to constitute 95 per cent of total alkaloids [64]. All parts of the plant contain approximately 1% thebaine, with small amounts of fugapavine and two or three additional minor alkaloids. In a herbarium material of *P. armeniacum* (L.) DC. thebaine has also been found to be the major alkaloid, as confirmed by thin layer chromatography and gas chromatography-mass spectrometry [98].

Section *Miltantha* apparently contains some members with high thebaine content, but the absence of a concise taxonomy of this section has resulted in confusion in the literature, with regards to the alkaloid content of the species

[71, 99–103]. The situation is comparable to that in section *Oxytona* before 1974.

In *P. somniferum* thebaine is normally present in small amounts (1/10 of the morphine content). By individual plant selection, a strain has been obtained, that contains thebaine as major alkaloid and only minor amounts of morphine [6]. Further selections have resulted in a breeding line with 90 per cent plants with high thebaine/low morphine content [104]. The fresh latex from plants with high thebaine content shows a reddish colour.

Environmental factors have a great influence on the alkaloid content in *P. somniferum*. Tookey et al. [105] observed an increased production of codeine (0.26 per cent in the dry capsules) and a codeine:morphine ratio of 0.42 when the plants were grown in a controlled environment. Normally the codeine:morphine ratio varies between 0.032 and 0.077 in *P. somniferum* but, after selection, high ratio values up to 0.98 were achieved in controlled environments.

Thebaine is also found, as mentioned above, in some of the chemotypes of *P. orientale*.

Thebaine as a raw material for drugs

Most of the interest in thebaine centers on its potential as an additional and alternative raw material for the manufacture of codeine. Already, 10 tons of thebaine annually are being pro-

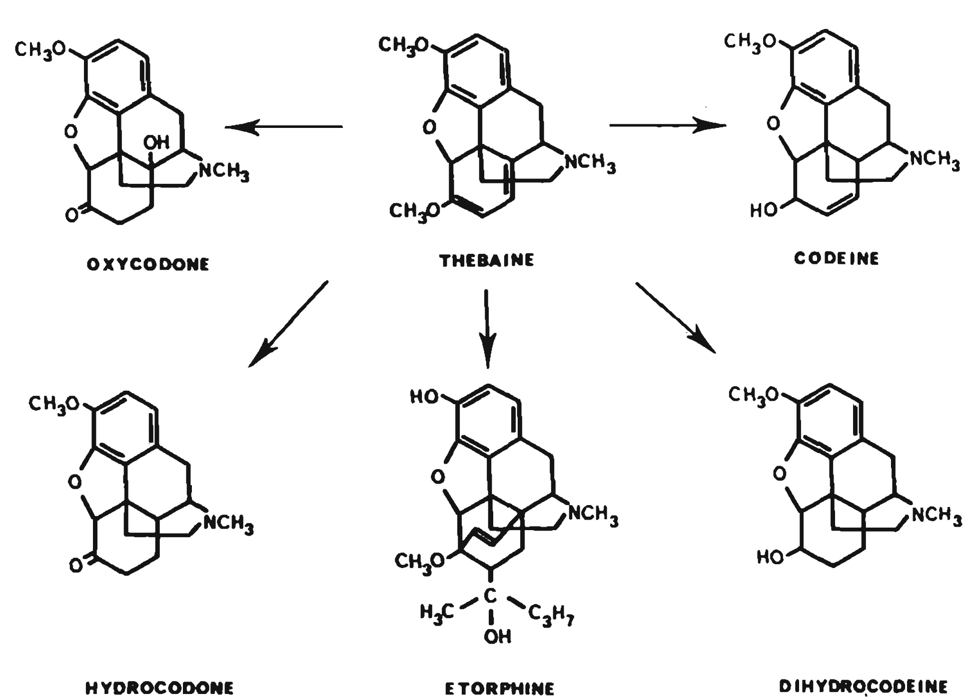

Fig. 9. Drugs currently produced by conversion of thebaine.

duced from *P. somniferum* and mainly converted into codeine [106]. This conversion is a simple two-step process which does not involve morphine [64].

Also manufactured currently from thebaine are the antitussive and analgesic derivatives oxycodone, hydrocodone, and dihydrocodeine (Fig. 9). An interesting product obtained from thebaine is the highly potent analgesic etorphine [107–108] (one of the "Bentley compounds"), which is used as a sedative to assist in the control of large animals. The total world production of etorphine amounts to 3 to 4 kg annually [86].

In contrast to morphine, there is no medical use and no abuse of thebaine. Heroin and morphine may be prepared from thebaine (via codeine), but this is a low yielding, difficult, and consequently very unlikely method. However, because of the abuse potential of several of its derivatives, thebaine has been placed under international control.

A U.N. expert group has also concluded [106]:

1) As long as the supply of illicit morphine is available, the choice of drug for abuse is heroin.
2) Should heroin cease to be available, it would be most likely to be replaced by wholly synthetic materials whose potency, pharmacological effects and ease of preparation from uncontrolled materials would make them more attractive to illicit operators than compounds preparable from thebaine.
3) Nevertheless, any cultivation of *P. bracteatum* and other plants producing thebaine should be controlled in such a way as to avoid leakage of thebaine into the illicit traffic.

Addendum

During the preparation of this review the following additional information has appeared.

Feeding of labelled precursors (1,2-dehydroreticuline and (±)-reticuline) to *P. bracteatum* established a biosynthetic route for the formation of thebaine, similar to that in *P. somniferum*. Further feeding experiments revealed the ability of *P. bracteatum* to reduce codeinone into codeine, but the plant was unable to demethylate codeine into morphine. Further metabolism of thebaine was observed but not by demethylation to oripavine or northebaine [109].

In *P. orientale* demethylation of oripavine into oripavidine (nororipavine) occurs to some extent, as indicated by the isolation of this later alkaloid from the species [110].

Several of the alkaloids earlier described from *P. bracteatum* have been isolated and characterized in Russian material of the species [111].

Further studies of various strains of *P. bracteatum* for their thebaine content in roots and aboveground portions during ontogenesis have been performed [112]. In selecting *P. bracteatum* for high thebaine yield, total thebaine content should be considered rather than high thebaine concentrations in various parts. It was thus shown, at the prevailing climatic conditions of Beltsville, USA, that Arya I produced, as an average in mature plants ,for all plant parts (root, leaf, stem, capsule) 161 150 µg thebaine and Arya II 97 540 µg. The thebaine distribution within the plant was for Arya I: root – 60 %, leaf – 13 %, stem – 12 %, and capsule – 15 %, for Arya II: root – 47 %, leaf – 14 %, stem – 13 %, and capsule – 26 %.

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