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## MORPHINE, CODEINE, AND NARCOTINE IN INDIAN OPIUM.

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THE chemistry of Indian opium naturally differs somewhat from that of Turkish opium on account of variation in soil, climate, seeds, method of cultivation, of lancing the poppy capsules, and in the collection of opium. It would be beyond the scope of the subject to dwell more fully on the question of how the constituents of opium vary with the variations in the above conditions. It has been found, however, in the case of crops of poppy grown by Mr. G. O. B. Power, of the Government Opium Department, that healthy plants, at the first lancements of their capsules, yield opium with higher morphine content than that from weaker plants, or than the drug otherwise collected by subsequent lancements of the same capsules.

MORPHINE.—The author has been estimating morphine in no fewer than 3,000 samples of opium a year by the British Pharmacopœia and by the polarimetric methods (Rakshit, *ANALYST*, 1918, **43**, 321), but has never met with a sample of opium which could justify the remark in “Allen’s Commercial Organic Analysis” (Vol. VI., fourth edition, p. 408): “East Indian opium is, as a rule, remarkably

weak in morphine, the proportion being sometimes as low as 2·5 per cent., more commonly 3·5 and 5, and occasionally as high as 8 or 9 per cent." During this last half century there has been no such change as would produce any improvement in Indian opium in respect of its morphine content. As a matter of fact, not a single bag of opium has been received from the districts during the last seven years which gave less than 7 per cent. of morphine. The bulk of them gave 8·5 to 10·5 per cent., whilst a good quantity showed 10·5 to 12·5 per cent. Obviously, then, the former analysts must have adopted grossly erroneous methods to obtain such low results.

The British Pharmacopœia process has been well criticised by quite a number of authors, but the way in which results obtained by this process are vitiated by the tropical climate of India has not been noted to any extent. In Upper India the humidity during the summer months becomes often as low as 4 and 5, and under such conditions evaporation during the trituration in the mortar and the filtration is quite rapid, and effectively concentrates the solution. The filtered lime solution of the opium often does not amount to 51 c.c. in the case of Indian opium, as required by the B.P. process; whilst when the ether is transferred to the filter-papers, a part of it rapidly evaporates during filtration, leaving a yellowish resinous deposit of alkaloids on the top portion of the upper filter-paper, and seldom any on the counterpoised lower one. The 10 c.c. of ether recommended in the process for washing the filter-paper does not completely wash this deposit, nor does it act uniformly on the two papers. In addition to this, a small quantity of ether left on the filter-paper, after the aqueous mother liquor has passed through, always leaves a residue on the upper filter-paper only. The deposit left on the evaporation of the ether is never removed by the recommended subsequent washing with morphinated water. Such residues, however, are always found to be soluble in ether or acid.

In some laboratories methods of the United States Pharmacopœia are adopted, and since these are purely gravimetric methods, the errors due to the evaporation during the preparation of the solution and the filtration are not introduced. The prescribed washings with alcohol and ether completely remove the residue left on evaporation of the ether which escapes filtration. It must not be assumed, however, that this method is free from defects. The substance dissolved by the lime water has been taken to be pure morphine, which, however, is not the case, as is shown below. Moreover, no correction is made for the retention of morphine by the mother-liquor.

Several experiments have been made to compare the results obtained by the polarimetric process with those of the U.S.P. process, and a few typical results are given below :

Sample.	Polarimeter				Morphine
	Result.				Strength,
			Per Cent.		U.S.P.
					Per Cent.
Ghazipur	...	...	10·2	...	9·8
Lucknow	...	...	10·1	...	9·7
Cawnpore	...	...	9·8	...	9·6

To ascertain the amount of morphine left in solution after the precipitation of the base in the U.S.P. process, the aqueous mother liquor was thrice extracted with

ether, 100 c.c. being used each time to get rid of any codeine which might still be present in solution, evaporated to a small bulk, acidified with 1 c.c. of hydrochloric acid, made up to 100 c.c., decolorised with 20 grms. of animal charcoal, and polarised in a 200 mm. tube.

Sample.	Reading on Ventzke Scale.	Total Mor- phine in 100 c.c. gm.
1 gm. of morphine hydrochloride (dry) instead of extract from 10 grms. of opium	... -1.3 ...	0.18
Karmansa ... ..	-1.7 ...	0.23
Ghazipur ... ..	-1.8 ...	0.24
Gwalior ... ..	-2.6 ...	0.36

A quantity of 0.5 gm. of morphine, obtained by the U.S.P. process, was titrated with  $\frac{N}{10}$  sulphuric acid, with litmus as indicator, and the neutral or slightly acid solution was made up to 50 c.c., filtered, and polarised in a 200 mm. tube. The specific rotation was calculated by assuming the gross weight to be entirely due to morphine, and by regarding as morphine everything which neutralised acid.

Sample.	Morphine as Obtained by Titration.	Reading on Ventzke Scale.	Specific Rotation based on—	
			Gross Weight.	Titration Value.
Ghazipur ... ..	Per Cent. 98.34	-6.72	-116.5°	-119.5°
" ... ..	97.34	-6.80	-118.5°	-121.2°
" ... ..	96.80	-6.72	-116.5°	-120.2°
Pure morphine ... ..	—	—	-127.5°	-127.5°

Morphine (0.5 gm.), obtained by the U.S.P. process, was shaken with 50 c.c. of freshly made lime water in a 250 c.c. Erlenmeyer flask, the liquid filtered through counterpoised double filter-papers, and the residue washed with lime water until the filtrate, on acidification, ceased to give any precipitate with Mayer's reagent. The substances dissolved and undissolved by the lime water were usually determined gravimetrically. The lime-water solution was made up to 250 c.c. with lime water, and polarised in a 200 mm. tube, and the specific rotation was calculated by taking the weight of morphine to be that of the substances dissolved by lime water. The following results, however, show that the substances dissolved by the lime water are not all morphine :

Sample.	Morphine as Obtained by Solution in Lime Water.	Reading on Ventzke Scale.	Specific Rot- ation of Sub- stance Accepted as Morphine.
Pure morphine ... ..	Per Cent. 100.0	-1.4°	-60.68°
Cawnpore opium ... ..	92.4	-1.2°	-56.3°
Ballia opium... ..	95.8	-1.2°	-53.5°

CODEINE.—Next in importance to morphine among the opium alkaloids is codeine; so its study requires some consideration. Since only very unsatisfactory determinations of its solubility were available, a fresh series of determinations has been made with all the solvents generally used for practical purposes. An excess of pure, well-powdered, dry codeine was shaken in conical flasks, at intervals, during two hours with the different solvents at different temperatures (varying not more than 2° C.), and 20 c.c. of the clear solution then withdrawn by means of a hot pipette.

SOLUBILITY OF CODEINE IN GRMS. PER 100 C.C. OF SOLUTION AT DIFFERENT TEMPERATURES.

Solvents.				20° C.	30° C.	40° C.	50° C.	60° C.	70° C.	80° C.	90° C.	100° C.
Ether	...	...	...	2.5	2.8	—	—	—	—	—	—	—
Acetone	...	...	...	16.3	18.0	21.1	29.1	—	—	—	—	—
Chloroform	...	...	...	34.6	52.3	53.8	72.1	—	—	—	—	—
Benzene	...	...	...	7.3	9.3	15.5	23.4	38.4	58.8	63.8	—	—
Toluene	...	...	...	5.5	6.8	10.4	19.9	32.4	44.8	56.4	73.6	—
Alcohol	90 per cent.	V/V	...	22.2	34.3	50.0	—	—	—	—	—	—
"	60	"	"	20.4	48.6	59.4	65.9	—	77.0	—	84.1	—
"	50	"	"	20.0	41.9	50.6	64.7	—	75.0	—	81.4	—
"	40	"	"	19.5	26.4	40.0	51.5	—	64.0	—	78.8	—
"	30	"	"	7.8	11.6	21.6	36.0	47.1	49.2	63.7	77.4	—
"	20	"	"	3.0	3.8	7.0	11.1	18.0	26.4	47.7	61.4	—
"	10	"	"	1.5	1.8	2.4	3.1	4.1	5.2	9.9	15.8	25.0
Ammonia	10	"	W/V	0.9	1.2	1.5	1.8	2.3	2.3	3.2	—	—
"	5	"	"	1.1	1.2	1.4	1.7	2.0	2.1	2.6	—	—
"	1	"	"	1.0	1.2	1.5	1.8	2.0	2.1	2.3	2.6	3.2
Water	...	...	...	0.9	1.0	1.1	1.3	1.5	1.8	1.9	2.4	3.2

For the estimation of codeine in opium the method described by Andrews (ANALYST, 1911, 36, 489) has often been adopted. It is not only very lengthy, but has also several defects, more particularly when applied to Indian opium. The resinous mass which separates on the addition of sodium salicylate solution has been said to contain thebaine, but, in reality, is practically free from any alkaloid, and consists chiefly of salicylic acid and colouring matter. The results thus obtainable are hardly concordant, and the codeine isolated is seldom free from other alkaloids; the latter fact was ascertained by polarimetric examination. Codeine obtained by this process was titrated with  $\frac{N}{10}$  sulphuric acid, the solution made up to 50 c.c. and polarised, and the specific rotation calculated upon the corrected weight obtained from the titration.

The figures clearly show that the codeine obtained by titration does not represent either the actual amount of codeine present or that contained in opium. Annett and Sen (ANALYST, 1920, 45, 321) have described a method for the extraction of codeine with toluene from the lime solution of opium. Attempts have been made to estimate codeine by this process in the case of twenty samples from different places, thoroughly representative of the total poppy cultivation in India, but unfortunately

in every case, the toluene emulsion could not be broken up, and hence the estimations were found to be impracticable. Moreover, the authors appear to have taken no precaution to remove porphyroxine, which is always extracted to some extent by almost all immiscible solvents from the lime solution of opium and in a moderate degree by toluene (Rakshit, *J. Chem. Soc.*, 1919, 457).

Sample.	Weight of Codeine obtained—		Specific Rotation.
	Gross.	Corrected by Titration.	
Codeine, pure ... ..	Grm. 0·200	Grm. 0·200	-137·5°
Ghazipur opium ... ..	0·200	0·167	-124·8°
Lucknow „ ... ..	0·180	0·142	-130·0°
Gwalior „ ... ..	0·108	0·100	-130·0°
Simla „ ... ..	0·104	0·88	-132·0°
Cawnpore „ ... ..	0·089	0·068	-128·0°
Azamgarh „ ... ..	0·160	0·120	-128·0°

A method for the estimation of codeine has been worked out. The opium alkaloids more or less soluble in ammonia solution which require consideration are: Morphine, pseudo-morphine, thebaine, meconidine, codamine, laudanine, laudanidine, protopine, narceine, and porphyroxine, whilst the rest may be disregarded, being thrown out of solution by ammonia. Morphine, pseudo-morphine, laudanine, and narceine, are practically insoluble in ether, and the others—viz., thebaine, meconidine, codamine, laudanine, protopine, and porphyroxine—are much less soluble in ether than codeine; but, with the exception of porphyroxine, these are only nominally present in Indian opium. Hence, the alkaloid last mentioned is the only one which would cause much difficulty if an attempt were made to isolate codeine by a method based on the above differences in properties.

An aqueous extract of opium was treated with strong ammonia (sp. gr. 0·880) and filtered, the filtrate shaken with three successive portions of ether to eliminate narcotine, the ethereal extract shaken with a 1 per cent. solution of acetic acid, and the acid solution of alkaloids separated and neutralised with calcium carbonate. When the alkaloid was re-extracted with ether by making the filtered solution alkaline with sodium hydroxide the residue, left on evaporation of the ether, did not crystallise like codeine, and, on warming with a little dilute hydrochloric acid, gave the usual red coloration of porphyroxine, which was thus proved not to have been eliminated by this process.

It was then observed that when porphyroxine was heated with dilute hydrochloric acid on a steam bath it was rapidly changed into a red colouring matter, which, when treated with caustic alkalis, gave a precipitate insoluble in ether. Codeine, under such conditions, did not undergo any change. After numerous trial experiments with this process of eliminating porphyroxine from codeine, the following scheme was ultimately found to give satisfactory results:

Twenty grms. of powdered opium and 200 c.c. of water are shaken for three

hours or more in an Erlenmeyer flask and filtered, and 100 c.c. of the filtrate are added to 20 c.c. of strong ammonia solution contained in a similar conical flask, and the mixture shaken for an hour and then filtered. One hundred c.c. of this filtrate are thrice extracted with ether in a 500 c.c. stoppered separator, 100 c.c. being used each time. The ethereal extracts are filtered into another 500 c.c. separator, and the filter-paper rinsed with 20 c.c. of ether. The extract and washings are twice shaken for ten minutes with a 10 per cent. W/V solution of hydrochloric acid, 25 c.c. being used at a time. The two acid extracts are evaporated to dryness in a basin on the steam bath. The residue thus obtained, which is generally of a dark pink colour, is dissolved in 30 c.c. of water, slightly warmed on the steam bath, the solution filtered if necessary and transferred to a separator, 50 c.c. of ether and 10 c.c. of a 10 per cent. solution of pure sodium hydroxide added, and the mixture shaken for ten minutes. The aqueous layer is transferred to another separator, and the extraction repeated twice more with similar quantities of ether. The ethereal extracts are dried over two or three lumps of calcium chloride and filtered, the separator and the filter-paper washed with 20 c.c. of ether, the filtrate and washings evaporated to dryness, the residue dissolved in 10 c.c. of  $\frac{N}{10}$  sulphuric acid, and the solution titrated back with  $\frac{N}{10}$  alkali with litmus indicator. The codeine present is calculated from the results, or, if suitable, the acid solution is filtered, made up to 50 c.c., and polarised in a 200 mm. tube :

$$\text{Per cent. of codeine in opium} = \frac{\text{Vantzke reading} \times 100 \times 0.3468 \times 1.2 \times 10}{-137.5 \times 2 \times 2}$$

The following are the results of the estimation of codeine in some typical samples by the above process :

Sample.	Codeine.
1. Two grms. of codeine (instead of 20 grms. of opium)	99.6 per cent.
2. Ghazipur opium	1.63 "
3. " (duplicate)	1.84 "
4. Gwalior	1.52 "
5. Lucknow	0.88 "
6. " (duplicate)	0.79 "
7. Simla	0.89 "
8. Karmusa	0.60 "

**NARCOTINE.**—Narcotine, having practically no medicinal value, has hitherto not been made the subject of much chemical investigation. Now, however, that cotarnine, one of its oxidation products, has been finding a ready market, the parent alkaloid is also receiving attention. Statements about its solubility, recorded in several places, are neither correct nor complete. Its solubility has therefore been studied in the same way as that of codeine in certain cases, and is considered to be of some practical importance.

Few methods of estimating narcotine have been described, and these are not only incomplete but decidedly erroneous. Henry ("Plant Alkaloids," p. 205) states that "narcotine is usually estimated by extracting the dried opium with dry ether or benzene, and shaking the solution with ammonia, which removes narceine. The narcotine left on distilling off the ether or benzene is dried and weighed." "Allen's

Commercial Organic Analysis" (Fourth Ed., Vol. VI., p. 401) states that "narcotine may be extracted from dried opium by ether or benzene." The narcotine thus obtained will not only contain small quantities of other alkaloids, but also the bulk of the opium wax (*cf.* Rakshit, ANALYST, 1918, 43, 321); Plugge's method (ANALYST, 1887, 12, 197) for the quantitative separation of narcotine from its hydrochloric acid solution by the addition of a concentrated solution of sodium acetate can hardly be considered as correct, as the alkaloid is appreciably soluble in the dilute acetic acid (see table above) liberated in the solution.

SOLUBILITY OF NARCOTINE IN GRMS. PER 100 C.C. OF SOLUTION AT DIFFERENT TEMPERATURES.

Solvents.				20° C.	30° C.	40° C.	50° C.	60° C.	70° C.	80° C.	90° C.	100° C.
Acetone	...	...	...	4.9	6.3	7.5	9.4	—	—	—	—	—
Benzene	...	...	...	3.4	5.0	6.0	7.5	10.6	14.3	19.3	—	—
Toluene	...	...	...	2.2	2.5	4.0	4.8	7.2	9.4	12.1	17.9	20.8
Ether	...	...	...	0.4	0.6	—	—	—	—	—	—	—
Chloroform	...	...	...	45.9	48.1	50.9	53.4	—	—	—	—	—
Petroleum spirit (b.-pt. 82° C.)				0.02	0.02	0.06	0.07	0.16	0.18	—	—	—
Petroleum spirit (b.-pt. 93° C. to 127° C.)				0.01	0.05	0.09	0.13	0.15	0.21	0.29	0.51	0.64
Alcohol	100 per cent.	...	...	0.40	0.60	0.90	1.20	2.20	3.20	5.10	—	—
"	95	"	V/V	0.45	0.65	0.97	1.70	2.10	3.30	4.60	—	—
"	90	"	"	0.43	0.60	0.90	1.7	2.1	3.3	4.3	—	—
"	80	"	"	0.32	0.48	0.67	1.29	1.6	2.3	4.2	—	—
"	70	"	"	—	0.32	0.55	0.79	1.3	2.0	4.1	—	—
"	60	"	"	—	0.22	0.29	0.49	0.74	1.35	1.8	—	—
"	50	"	"	—	0.18	0.25	0.32	0.49	0.78	1.06	—	—
"	20	"	"	—	0.07	0.10	0.08	0.09	0.10	0.17	—	—
Ammonia	10	"	W/V	—	—	0.01	0.03	0.04	0.06	0.10	—	—
"	5	"	"	—	0.05	0.02	0.04	0.04	0.04	0.04	0.05	0.05
"	1	"	"	—	—	0.01	0.01	—	—	—	—	—
Acetic acid	20	"	"	—	—	7.35	8.10	9.80	10.7	11.0	—	—
"	10	"	"	—	—	3.10	3.5	3.9	4.0	4.0	—	—
"	5	"	"	—	—	1.50	1.50	1.60	1.70	1.80	—	—
"	1	"	"	—	—	0.40	0.44	0.45	0.52	0.59	—	—
Water	...	...	...	—	0.03	0.07	0.10	0.10	0.10	0.10	0.15	0.20

A method has been worked out and has given satisfactory results during the last four years in this laboratory: Ten grms. of dry opium powder and 5 grms. of fresh slaked lime are triturated in a mortar for half an hour and then transferred to a conical flask, the mortar being rinsed with about 10 c.c. of benzene, and the mixture is shaken well with 100 c.c. of benzene during half an hour. The clear benzene is decanted into a separator, and the residue in the flask twice more extracted with benzene, 50 c.c. being used each time. The total benzene extract is vigorously shaken with 100 c.c. of strong ammonia solution for half an hour, which results in the formation of a permanent white emulsion. This is transferred to a basin and

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heated on the steam bath until the benzene has completely evaporated, leaving a soft yellowish residue on the surface of the aqueous ammonia layer. This residue is filtered off and washed until the filtrate ceases to give any odour of ammonia, and is then treated, together with the filter-paper, with 100 c.c. of 1 per cent. hydrochloric acid on the steam bath, when a pinkish solution is obtained. This acid solution is filtered into a separator, the residue washed with a small quantity of water, 100 c.c. of benzene introduced, the solution then made alkaline with ammonia and again very faintly acid with dilute acetic acid, and well shaken for ten minutes. After separation of the benzene the extraction is once more repeated, this time with 50 c.c. of benzene. The benzene extract is filtered and evaporated, and the residue dried and weighed as narcotine. The alkaloid thus obtained has been proved to be practically pure narcotine. The following are typical results of analyses by this process :

Sample.	Narcotine.
Benares opium ... ..	... 6.4 per cent.
Ghazipur ,, ... ..	... 3.6 ,,
Karmansa opium (received in 1920) ... ..	... 1.4 ,,
Gwalior ,, ... ..	... 2.8 ,,

The author desires to express his best thanks to Mr. F. D'Costa for analysing many samples by the above process.

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