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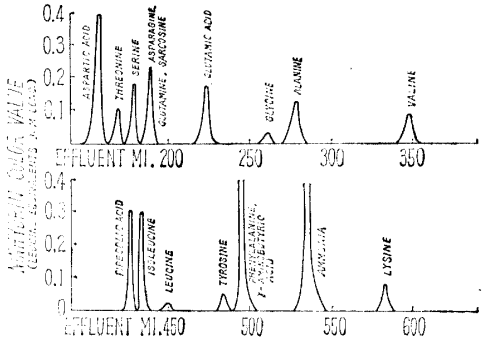

Fig. 5-Elution diagrom of amino acids in opium from India (Uttar Pradesh-UNE 605)

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DETERMINATION OF THE ORIGIN OF OPIUM BASED ON ITS CONTENT OF MECONIC ACID, SULFURIC ACID AND TOTAL ACID*

Sadaichi MIYAMOTO and Einar Brochmann-Hanssen

Meconic acid is an acid characteristic of opium, and the same perhaps also may be said of sulfuric acid. Together, these two acids acconut for about 60 to 80 per cent of the total acid content. The meconic acid content of opium is subject to considerable variation, and use is made of this fact in two of the most promising methods developed so far for the determination of the origin of opium (1, 2). It would seem reasonable to expect the content of sulfate and of total acid to be subject to the same regional variations as other constituents of opium.

Rapid and reproducible methods have been developed for quantitative determination of meconic acid, sulfuric acid and total acid in the same sample of opium. It should be noted, however, that the "total acid," as obtained in the present procedure, does not include all of the amino acids, which to a great extent are adsorbed on the ion exchange resin (3),

EXPERIMENTAL

A total fo 104 authentic opium samples were studied, representing 12 different countries. Included in this number are 45 samples from five opium-producing provinces in India.

Determination of Meconic Acid

Methods for quantitative determination of meconic acid have been described by Witte (4),

* United Nations' Secretariat, Document ST/SOA/SER-K/106 に発表

and by Asahina and Ono (5). Our method is a modification of Witte's method, differing mainly with regard to the isolation and puriffcation of the acid. When powdered opium is shaken with an aqueous suspension of a strongly acdic cationic exchange resin, the alkaloids and other basic constituents are adsorbed on the resin and can be removed by filtration. Acidic and non-ionic substances pass into the filtrate. It is interesting to note that most of the colored materials in opium are retained on the resin, resulting in a filtrate which is practically colorless. Meconic acid may be determined in this filtrate by the reaction with ferric chloride or by direct ultraviolet spectrophotometry. There is fairly good agreement between the absorption spectra of authentic meconic acid and those of the opium filtrate both before and after addition of ferric chloride (Figs. 1 and 2). It would seem, however, that a quantitative estimation based on the color reaction might be somewhat more specific than a direct spectrophotometric determination in the ultraviolet region.

Experimental conditions were studied in order to determine their effect on the results. Complete extraction of meconic acid was achieved when 100 mg. of finely powdered opium was shaken for 20 to 30 minutes with 1.0 g. of Dowex 50®-X_2 (H^+) (50–100) and 40 to 50 ml. of hot water. Increasing the extraction time and/or the amount of ion exchange resin did not cause any increase in the recoverry of meconic acid or total acid (Table I).

Table I. Effect of experimental conditions on the determination of meconic acid and total acid.

Opium	Dowex 50 g.	Shaking Time min.	Total Acidity meq.	Meconic Acid %
UN 38 L 200 mg.	5	20	191	10.2
UN 38 L 100 mg.	2	20	191	10.4
UN 38 L 100 mg.	1	20	191	10.4
UN 174 200 mg.	5	20	186	9.6
UN 174 100 mg.	2	20	186	9.6
UN 174 100 mg.	1	20	186	9.6
UN 25 A 200 mg.	5	20	196	10.6
UN 25 A 200 mg.	5	30	196	10.6

Procedure

To an extraction tube (6, 7), having a coarse filter of glass wool in the stopcock, are added 100 mg. of finely powdered opium, accurately weighed, 1 g. of Dowex 50®-X_2 (H^+) (50–100 mesh) and 40 ml. of hot water. The mixtnre is shaken mechanically for 20 minutes. The aqueous solution is then allowed to drain into a 100-ml. volumetric flask. The extraction tube and the ion exchange resin are washed with hot water to make 100 ml. filtrate. After the filtrate has been cooled to room temperature, the volume is adjusted to the mark with water and mixed well. If the filtrate is cloudy, it is centrifuged at 8,000 to 10,000 r.p.m. and the clear supernatant liquid decanted off.

The extraction can also be carried out satisfactorily in a 125-ml. Erlenmeyer flask closed with a rubber stopper. (The stopper should first be cleaned by repeated bioling with 1 *N* sodium hydroxide, then with 1 *N* hydrochloric acid and finally with distilled water until the wash water remains neutral). The meconic acid extract is filtered through a plug of cotton into a 100-ml. volumetric flask and the Erlenmyer flask and ion exchange resin washed with several portions of hot water. The filtrate is cooled to room temperature, adjusted to volume with water and centrifuged if nece-

ssary. Twenty ml. of the filtrate is pipetted into a 25-ml. volumetric flask, 0.5 ml. of 5% ferric chloride solution (in 0.1 *N* HCl) is added, and the volume is adjusted to 25 ml. with water.

The absorbance is determined in a suitable spectrophotometer at 490 mμ against a blank consisting of 20 ml. of filtrate and 5 ml. of water. A Beckman DU spectrophotometer was used in the work reported here. The amount of meconic acid in the sample is calculated on the basis of a standard curve prepared from known quantities of meconic acid trihydrate.

Results. The results obtained compare favorably with those reported by Witte (TatteII).

TableII. Determination of meconic acid

Opium	Reported by Witte %	The Authors' Method %
UN 2 A	8.8	9.2
UN 6 A	8.8	8.6
UN 9 A	9.8	9.9
UN 15	7.5	7.5
UN 25 A	10.7	10.6

Determination of Sulfate

Microquantities of sulfate are best determined by turbidimetry or nephelometry, the latter technique being the more sensitive of the two. Conditions which affect the precipitation of barium sulfate and, therefore, the reproducibility of the determination have been extensively studied by Reimers and coworkers (8, 9, 10). In our own method, sulfate is precipitated by means of crystalline barium chloride in the presence of an acid-salt solution and glycerol. Under these conditions, barium sulfate of a uniform particle size is precipitated out and held suspended by the means of glycerol. The turbidity, which is proportional to the concentration of sulfate, may be measured in a nephelometer. For reproducible results, it is important to have available a stable turbidity standard against which the instrument can be calibrated. We found a solution of methyl cellulose (ca. 0.5%) to be very satisfactory in this respect. Its turbidity did not change over a period of several weeks. Other colloids may, however, serve the same purpose equally well. A high degree of sensitivity is obtained by using a mercury lamp as the light source, in which case a visible reference beam for the instrument is produced by means of a solution of quinine sulfate. The results are somewhat dependent on experimental conditions. It is, therefore, necessary to follow a standardized procedure in order to obtain reproducible results. The method given below is a modification of the procedure described for the deteimination of sulfates in the manual accompanying the Fisher Nefluoro-Photomater (11).

Reagents

(1) **Acid-Salt Solution** : 240 g. of sodium chloride is dissolved in water, 20 ml. of concentrated hydrochloric acid (sp. gr. 1.19) is added, and the solution diluted to 1 liter with water.

(2) **Glycerol Solution** : Fifty ml. of chemically pure glycerol is dissolved in 50 ml. of water.

(3) **Barium Chloride Crystals** : Chemically pure barium chloride, 30-40 mesh is used.

(4) **Standard Potassium Sulfate Stock Solution** : Reagent grade potassium sulfate (181 mg.) is dissolved in water to make 1 liter. This solution contains 0.1 mg. of sulfate per ml.

(5) **Quinine Sulfate Generator Solution** : Twenty-five mg. of quinine sulfate is dissolved in 20 ml. of 0.1 *N* H_2SO_4 and diluted to 1 liter with water.

(6) **Turbidity Standard** : A solution of methyl cellulose (about 0.5%) is allowed to stand for a few days (or centrifuged) to precipitate insoluble, coarse impurities. The viscous, opalescent liquid is decanted into a clean container.

Standard Curve

A standard curve, which relates the amount of sulfate to the instrument reading, is obtained by preparing several standard solutions containing from 0.1 mg. to 0.4 mg. of sulfate per 10 ml. These are analyzed as described below, distilled water treated in the same manner being used as a blank in the reference cell. The results are plotted on graph paper. A Fisher Nefluoro-Photometer was used in our work, and a straight line relationship was obtained between the concentration of sulfate and "%T" in the range indicated above.

Analysis

Ten ml. of the opium filtrate, prepared as described for meconic acid, is pipetted into a 50-ml. glass-stoppered centrifuge tube (Corning Glass Works No. 8424). Next are added 2.5 ml. of acid-salt solution, 5 ml. of glycerol solution and 7.5 ml. of distilled water. After thorough mixing. 0.15 g. of barim chloride is added, the tube is shaken vigorously for 60 seconds and set aside for 4 minutes. The tube is then shaken **gently** for 15 seconds and allowed to stand for 45 seconds before the reading is taken in the nephelometer. A blank consisting of the same ingredients with the exception of barium chloride is used as a blank.

Prior to taking the reading, the instrument sensitivity is adjusted by means of the turbidity standard so as to give a sensitivity within the range of the samples analyzed. With our grade of methyl cellulose, a setting of 50% T was satisfactory. This setting must be checked for each sample.

To check the accuracy of the methop, sulfate determinations were carried out before and after addition of known amounts of sulfate to an aliquot of the opium filtrates. The recovery of sulfate was quantitative (Table Ⅲ).

Table Ⅲ. Recovery of sulfate added to opium filtrates.

Sample	Sulfate Added mg.	% T	Sulfate		
			Found mg.	Recovered mg.	Recovered %
UN 2 A	0	56.0	0.227	—	—
UN 2 A	0.05	65.0	0.277	0.050	100.0
UN 2 A	0.1	75.0	0.327	0.100	100.0
UN 15	0	55.0	0.226	—	—
UN 15	0.1	75.5	0.328	0.102	102.0
UN 177	0	71.0	0.308	—	—
UN 177	0.1	92.2	0.408	0.100	100.0

Since Dowex 50® is a sulfonated polystyrene resin, it seemed desirable to determine whether or not it would release any sulfate upon treatment with hot water. This was found not to be the case. A blank determination carried out without opium gave no sulfate in the procedure described.

Determination of Total Acid

In addition to the strongly acidic meconic and sulfuric acids, opium contains a number of weaker acids.

The total acid content is determined by titration of a 30-ml. aliquot of the opium filtrate with 0.02 *N* sodium hydroxide, phenolphthalein being used as indicator. Total acid content is expressed in terms of milliequivalents per 100 g. of opium.

RESULTS AND DISCUSSION

The results of the determinations are given in Table IV. Most of the values are averages of two or more determinations. The content of meconic acid and sulfate is expressed both in per cent and as percentages of total acidity, e.g., 100 x meq. SO_4/meq. total acid. The meconnic acid/sulfate ratio is based on milliquivalents, not on percentage values.

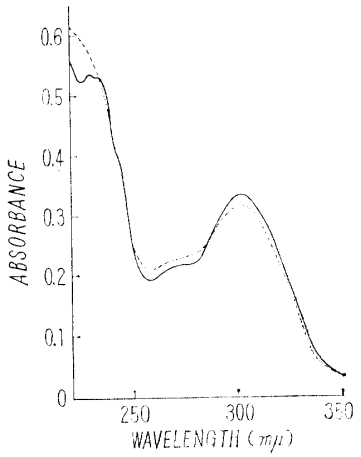

Fig. 1-U.V. absorption spectra of pure meconic acid (solid line) and of the opinm filtrate (broken line).

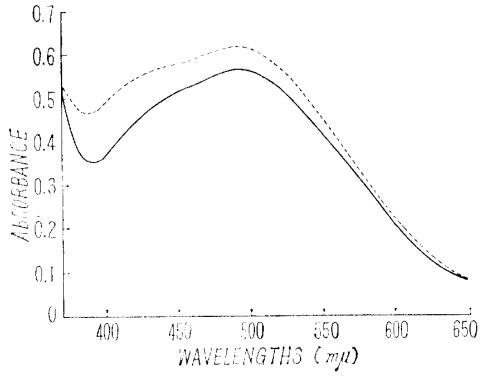

Fig.2-Absorption spectra of the ferric complexes of pure meconic acid (solid line) and of the opium filtrate (broken line).

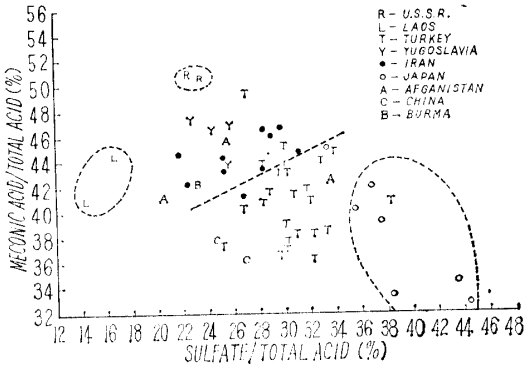

Fig. 3-Scatter diagram of meconic acid/total acid VS. sulfate/total acid for opium of different origin.

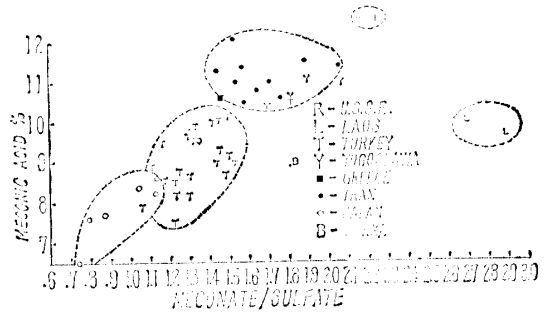

Fig. 4-Scatter diagrm of meconic acid VS. meconate/sulfate for opium of different origin.

The scatter diagrams illustrated in Figs. 3 and 4 permit fairly good differentiation between opium from Japan, Turkey, Iran, U.S.S.R. and Laos. Similarly, it is possible to distinguish between Indian samples from Uttar Pradesh and those from Madhya Bharat, Malwa and Rajasthan (Figs. 5 and 6). However, the samples from India, Pakistan and Afganistan generally overlap the regions of Japan, Turkey and Iran. Thus, a sample with a low meconic acid content and a low meconate to sulfate ratio may either be from Japan or from Uttar Pradesh.

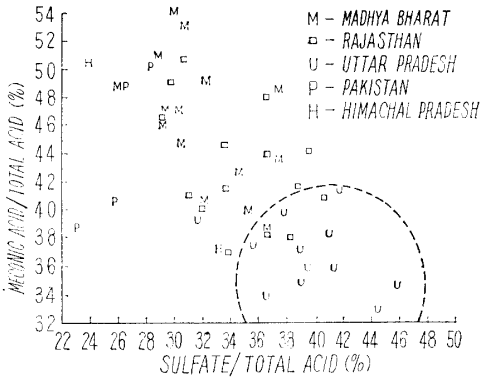

Fig. 5-Scatter diagram of meconic acid/total acid VS. sulfate/total acid for opium of different origin.

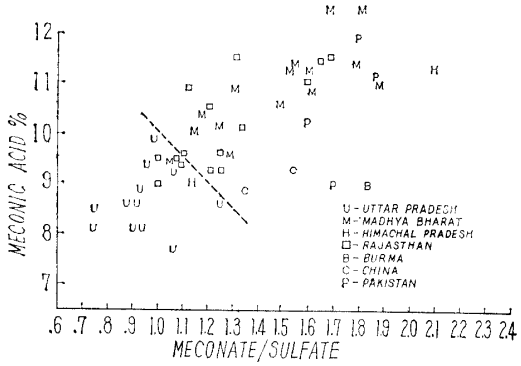

Fig. 6-Scattr diagram of meconic acid VS. meconate/sulfate for opium of different origin.

Too few samples were available from Burma, China, Greece and Yugoslavia to show definite distribution patterns.

Table IV.—Meconate, Sulfate, and total acid in opium from various geograpeic regions

Sample and Region	Other Information	Total Acid meq./100 g.	Meconic Acid		Sulfate		Meconate/Sulfate
			%	% of Total	%	% of Total	
TURKEY							
UN 2 A	Afyon. Druggist opium	179	9.2	40.4	2.3	26.8	1.51
UN 5 A	Usak. Druggist opium	183	8.7	37.4	2.2	25.1	1.49
UN 6 A	Nallihan. Druggist opium	178	8.6	38.2	2.7	32.3	1.18
UN 9 A	Kula. Druggist opium	177	9.9	44.0	2.8	33.0	1.33
UN 11 B	Aksehir. Druggist opinm	166	8.8	41.8	2.5	31.8	1.31
UN 13 A	Isparta. Druggist opium	193	8.9	36.3	3.0	32.1	1.11
UN 15	Export-standardized	159	7.5	37.1	2.3	30.2	1.23
UN 30 B	Standardized opium	166	8.2	39.1	2.4	30.1	1.30
UN 31	Standardized opium	152	7.9	40.9	2.8	38.4	1.06
UN 134 B	Amasya. Soft	185	10.1	43.0	2.6	29.7	1.45
UN 135	Erbaa. Soft	169	10.6	49.4	2.2	27.1	1.82
UN 136 D	Zile. Soft	176	10.2	45.2	2.5	30.0	1.50
UN 137 A	Balikesir. Druggist opium	183	8.8	37.8	2.6	30.3	1.25
UN 139 A	Bolvadin. Druggist opium	168	8.2	38.4	2.5	31.0	1.24
UN 140 B	Bozkir. Druggist opium	171	9.0	41.5	2.4	28.8	1.44
UN 141 B	Civril. Druggist opium	183	10.0	43.0	2.7	30.3	1.42
UN 145 A	Karaman. Druggist opium	194	9.5	38.5	3.1	33.3	1.16
UN 146 A	Sarkikaraagac. Druggist opium	168	9.3	43.8	2.4	30.1	1.46
UN 148 C	Tefenni. Druggist opium	183	8.5	36.6	2.6	29.7	1.23
UNE 689	Acipayam. Druggist opium	182	9.7	41.9	2.8	32.1	1.31
UNE 690	Acipayam. Druggist opium	182	9.6	41.5	2.7	30.8	1.33
UNE 692	Gelendost. Druggist opium	172	9.8	44.8	2.8	33.9	1.32
UNE 694	Kütahya. Druggist opium	162	9.0	43.7	2.2	28.4	1.54
IRAN							
UN 48	Isfahan	210	11.0	41.2	2.7	26.8	1.54
UN 49	Kerman	199	11.3	44.6	3.0	31.1	1.44
UN 51	Khorasan	193	11.4	46.6	2.8	29.7	1.57
UN 52	Neharand	220	12.1	43.4	3.0	28.4	1.53
UN 122	Kerman	183	10.8	46.4	2.5	28.5	1.65
UN 125	Khorasan	180	10.5	45.9	2.5	29.0	1.58

Table IV. (continued p. 50)

Sample and Region	Other Information	Total Acid meq./100g.	Meconic Acid		Sulfate		Meconate/Sulfate
			%	% of Total	%	% of Total	
IRAN							
UNE 506	Irak	198	11.0	43.2	2.4	25.3	1.71
UNE 508	Kurdistan	188	10.6	44.4	2.2	25.1	1.77
UNE 510	Burujird	202	11.4	44.7	2.1	21.7	2.06
UNE 513	Isfahan	215	11.5	42.1	2.3	22.3	1.89
PAKISTAN							
UN 100	Lahore	197	10.2	40.7	2.4	25.7	1.58
UN 269	Mardan	187	11.1	50.2	5.5	28.1	1.78
UN 270	Campbellpur	179	11.9	48.9	2.3	26.3	1.86
UN 271	Campbellpur	182	9.0	38.9	2.0	22.9	1.70
GREECE							
UN 25 A		196	10.6	43.4	2.8	29.8	1.46
JAPAN							
UN 114		176	7.9	34.3	3.6	43.4	0.79
UNE 527	Aichi	168	6.6	44.9	2.7	33.5	1.34
UNE 582	Osaka	157	6.5	32.6	3.3	44.3	0.74
UNE 529	Wakayama	182	7.7	33.3	3.3	38.3	0.87
UNE 530	Hyogo, Okayama, Nagano, Hiroshima	170	8.4	39.1	3.1	37.5	1.04
UNE 531	Hyogo, Okayama, Nagano, Hiroshima	162	8.2	40.1	2.8	35.5	1.13
UNE 672	Nagano	162	8.6	41.8	2.9	63.8	1.14
YUGOSLAVIA							
UN 38 A	Export opium	198	11.1	46.2	2.2	24.3	1.90
UN 38 H	Export opium	178	10.6	46.9	2.2	25.8	1.82
UN 38 K	Export opium	183	11.0	47.3	2.0	22.8	2.07
UN 38 L	Export opium	190	10.4	43.2	2.3	25.7	1.68
AFGANISTAN							
UNE 544		198	10.7	42.5	3.2	33.7	1.25
UNE 545		210	10.8	41.2	2.0	20.5	2.00
UNE 546		188	10.8	45.6	2.3	25.5	1.79
CHINA							
UN 37 C		194	9.3	37.7	2.3	24.7	1.53
UN 37 D		194	8.9	36.1	2.5	26.9	1.34
LAOS							
UN 26 B	Luang-Prabang	178	10.6	40.8	1.2	14.1	2.89
UN 27 B	Xieng-Khouang	177	9.0	44.5	1.4	16.5	2.70
BURMA							
UN 250	Shan States	168	9.0	42.2	1.8	23.1	1.83
UNION OF SOVIET SOCIALIST REPUBLICS							
UNE 701	Issyk Kul (Kirghiz S.S.R.)	196	2.6	50.6	2.2	23.4	2.16
UNE 702	Tienshan (Kirghiz S.S.R.)	185	2.6	50.9	2.0	22.5	2.26
INDIA Malwa							
UN 62	Excise opium	183	9.6	41.3	3.2	36.9	1.12
Himachal Pradesh							
UN 188	Nandkheri. Mixed lancings	188	9.1	38.1	3.0	33.3	1.14
UN 189	Rohru. Mixed lancings	177	11.3	50.6	2.1	23.6	2.10

Table IV. (continued p. 51)

Sample and Region	Other Information	Total Acid meq./100g.	Meconic Acid %	Meconic Acid Total % of	Sulfate %	Sulfate % of Total	Meconate/Sulfate
Madhya Bharat							
UN 100	Manasa. lst lancing Galania variety	187	10.2	42.9	3.1	34.5	1.24
UN 172	Shamgah. lst lancing Dhaturia variety	182	11.4	49.3	2.8	32.1	1.54
UN 174	Neemuch. lst lancing Gaania variety	186	9.6	40.8	2.8	32.0	1.28
UN 177	Ratlam. 2nd lancing Galania variety	188	11.3	47.2	2.8	31.1	1.52
UN 295	Neemuch. Sub-lancing	185	12.5	53.2	2.8	31.6	1.68
UN 308	Ratlam. lst lancing	182	12.5	54.1	2.6	29.8	1.81
UN 312	Neemuch. Bhatphoria seed	177	11.0	48.9	2.2	25.9	1.88
UNE 625	Neemuch. lst lancing	177	10.9	48.6	3.1	37.3	1.80
UNE 627	Neemuch. lst lancing	194	11.3	46.5	2.7	29.0	1.60
UNE 629	Neemuch. lst lancing	188	9.2	38.5	3.3	36.6	1.05
UNE 634	Mandsaur. 2nd lancing	186	10.6	44.8	2.7	30.3	1.48
UNE 639	Ratlam. 1st lancnig	188	10.4	43.7	3.3	37.2	1.17
UNE 640	Ratlam. 2 nd lancing	199	10.1	40.0	3.3	35.2	1.14
UNE 641	Ratlam. 1 st lancing	175	11.4	51.3	2.4	28.6	1.79
UNE 642	Ratlam. 2 nd lancing	183	10.9	47.0	2.5	29.2	1.61
Rajasthan							
UN 319	Chittorgarh. 1 st lancing	178	11.5	50.8	3.6	30.5	1.68
UN 328	Jhalawar. Sub-lancing	194	10.9	44.3	2.6	39.4	1.12
UN 329	Jhalawar. 1st lancing	189	11.5	48.0	3.3	36.5	1.31
UNE 643	Chittorgarh. 1 st lancing	178	9.5	41.5	2.8	33.5	1.25
INDIA Rajasthan							
UNE 644	Chittorgarh. 2 nd lancing	204	9.6	37.0	3.3	33.7	1.10
UNE 647	Kotah. 1 st ancing	183	10.4	49.0	2.6	29.6	1.65
UNE 649	Kotah. 1 st lancing	186	9.0	38.1	3.4	38.1	1.00
UNE 650	Kotah. 2 ndllancing	178	10.1	44.7	2.9	33.5	1.33
UNE 651	Jhalawar. 1 st lancing	188	10.5	44.0	3.3	36.5	1.20
UNE 652	Jhalawar. 2 nd lancing	183	9.3	40.0	2.8	31.9	1.25
UNE 653	Jhalawar. 1 st lancing	178	9.4	41.6	3.3	38.7	1.08
UNE 654	Jhalawar. 2 nd lancing	178	9.3	41.1	2.9	34.0	1.21
UNE 659	Kotah. Ghotia variety	187	11.0	46.3	2.6	29.0	1.60
UNE 660	Jhalawar. Chagia variety	194	9.5	38.5	3.4	36.5	1.09
NUE 661	Jhalawar. Teliavariety	183	9.5	40.8	3.5	40.7	1.00
Uttar Pradesh							
UN 265	Bara Banki. 1 st lancing	183	9.2	39.8	3.3	37.7	1.06
UN 289	Shahjahanpur. Sub-lancing	199	9.4	37.2	3.7	38.8	0.96
UN 291	Shahjahanpur. Sub-lancing	183	8.9	38.3	3.6	41.0	0.93
UNE 605	Bara Banki, 1 st lancing	183	8.1	34.9	3.4	39.0	0.90
UNE 606	Bara Banki .2 nd lancing	189	8.1	33.8	3.3	36.4	0.93
UNE 609	Shahjahanpur. 1 st lancing	189	8.6	35.9	3.5	39.3	0.91
UNE 611	Shahjahanpur. 1 st lancing	189	8.6	35.9	3.8	41.4	0.87
UNE 612	Shahjahanpur. 2 nd lanclng	194	8.5	34.6	4.2	45.9	1.75
UNE 614	Bareilly. 2 nd lancing	194	8.1	32.9	4.1	44.3	0.74
UNE 615	Bareilly. 1 st lancing	172	8.6	39.3	2.6	31.5	0.26
UNE 616	Bareilly. 2 nd lancing	162	7.7	37.6	2.7	35.5	1.05
UNE 617	Faizabad. Bhaku variety	188	9.9	41.4	3.8	41.7	0.99

SUMMARY

Attempts have been made to determine the origin of opium on the basis of the content of meconic acid, sulfuric acid and total acid. Simple and rapid procedures have been developed for determination of these acids. The results show that the method is capable of differentiating between opium from several geographic regions. It may find application as a means of confirming the results obtained by another independent method.

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Dissociation Constants of Certain γ-Pyrone Dicarboxylic Acids*

Meconic Acid and Chelidonic Acid

By Sadaichi MIYAMOTO and Einar Brochmann-Hanssen

Meconic acid and chelidonic acid are very strong acids having dissociation constants of the same order of magnitude as sulfuric acid. This high acidity is explained on the basis of the resonance structure of the γ-pyrone molecule.

The two main acids of opium are meconic acid and sulfuric acid, which together account for 60 to 80% of the total acid content (1). In the course of our studies of the acid composition of opium it became apparent that meconic acid is an exceptionally strong acid, from the point of view of being an organic carboxylic acid. Search of the literature failed to reveal any information about the extent of its acid strength. This led to an investigation of the dissociation constants of meconic acid and the closely related chelidonic acid.

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