AUTOMATIC DEVICES FOR EXTRACTING ALKALOIDAL SOLUTIONS.*

II. APPLICATION TO NUX VOMICA AND BELLADONNA ALKALOIDS.

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In a previous paper[1] several automatic devices were described and their use for the extraction of alkaloidal solutions was discussed. In order to determine the optimum conditions for automatic extraction and the relative efficiency of extractors of the various types with different solvents, a detailed study was undertaken of the factors governing the use of these devices for the ordinary preparations of alkaloidal drugs. The data on nux vomica and belladonna alkaloids are given in the following pages.

It would be reasonable to suppose that the behavior with respect to solubility of alkaloids extracted at an elevated temperature (boiling point of the solvent) would differ from that of alkaloids extracted with the handshaken funnel in the cold. This difference in behavior was found to be particularly striking in the case of morphine.[2] Chloroform, although in the cold an exceedingly poor solvent for this alkaloid, becomes an excellent medium for extracting it from aqueous solutions when the automatic extractor is used.

Unless otherwise indicated, the alkaloid solutions used in this study were prepared from commercial fluidextracts by "evaporating the acidified preparation to low volume and then rediluting with water."[3] This was done in order to insure an extracted alkaloidal residue sufficiently clean to be titratable and solution of as uniform a type as possible to serve as a starting point for the experiments. It was not found practicable to prepare one large quantity of nux vomica and one of belladonna to be used for all the experiments. Smaller units uniformly prepared from various commercial fluidextracts and tinctures constitute alkaloidal solutions A, B, BX, C, D, and E. When assayed by the U. S. P. Method and Modified U. S. P. Method,[3] these solutions gave the following results:

	Alkaloid per 20 cc.	
Solution	U. S. P. method, Grams.	Modified U. S. P. method, Grams.
Nux Vomica:		
A	.....	0.2648
	.....	0.2722
B	.....	0.2417
BX	0.2402	0.236
Belladonna:		
C	0.0457	0.05031
D	0.0445	0.05020
E	0.0492	0.04454

The following factors were studied in the light of their effect on the efficiency and completeness of extraction: Variation in the ammonia concentration; variation in the solvent used; variation in the alkaloidal concentration; presence of

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[1] *Ind. Eng. Chem.*, 16, 612 (1925).

[2] *Ind. Eng. Chem.*, 16, 612 (1925), Table II.

[3] Jour. A. Ph. A., 13, 694 (1924).

ammonium sulphate; stability of the alkaloids under the conditions of extraction and variation in the type of extracting device. While the effect of a given variable was being studied all other conditions were kept as nearly constant as possible. In practically all the experiments the alkaloids were extracted for definite periods of time.

NUX VOMICA ALKALOIDS.

As was shown previously, the concentration of ammonia materially affects the speed of extraction of strychnos alkaloids, owing to their amphoteric behavior. The results of a series of experiments conducted to determine the effect of ammonia under conditions of automatic extraction (Table I, Experiments 1 to 11) fail to show a similar effect. Variation in ammonia concentration from the point just sufficient to liberate the alkaloid (approximately 2 cc. to 3 cc. of $5N$ ammonium hydroxide) made no appreciable difference in the speed of extraction or in the quantity of total alkaloids extracted.

The results of the experiments given in Table I show that under favorable conditions 95 per cent or more of the alkaloid is extracted during the first 30 minutes. As might be expected, the speed of extraction and completeness of recovery are independent of the concentration of the alkaloid in solution (Table I, Experiments 12 to 16).

Prolonged extraction at an elevated temperature is open to the criticism that ammonium sulphate may be carried over to the flask containing the alkaloid concentrate. In that event interaction between the alkaloid and the ammonium sulfate would, in effect, partially neutralize the alkaloid and cause a low titration. In order to determine this question a comparatively large excess of ammonium sulphate (0.5 gram) was added to each of the aliquots of alkaloidal solutions in Experiments 17 to 20 (Table I). This had no appreciable effect on the accuracy of the determinations.

The relative effectiveness of the more complicated forms of extractors[1] (vapor-type) is shown by the results in Table I, Experiments 21 to 26.

BELLADONNA ALKALOIDS.

The reputed instability of the belladonna alkaloids made it necessary to determine their tolerance to heat-acid treatment, incident to the process of dealcoholization[2] and partial purification of their galenical preparations, and to prolonged extraction with the various solvents at the boiling point when in contact with ammonia—conditions prevailing in continuous extraction. For this purpose known quantities of atropine and belladonna preparations of known assay were subjected to treatments and extractions under conditions that would be met in the method for belladonna preparations as described, a wider range being used for each variable than that prescribed in the method.

Atropine.—Solutions containing known quantities of atropine sulphate in 30 cc. volume were evaporated on the steam-bath with varying quantities of acid to a volume of about 10 cc. and the resulting concentrates were made alkaline and extracted in a continuous extractor for 2 hours, using chloroform. These condi-

[1] *Ind. Eng. Chem.*, 16, 612 (1925), Apparatus III and IV.

[2] *Ind. Eng. Chem.*, 16, 612 (1925), Table II.

TABLE I.—EXTRACTION EFFICIENCY OF AUTOMATIC DEVICES (NUX VOMICA ALKALOIDS).

Variant.	Exp. no.	Alkaloid used cc.	Solvent used.	Ammonia used N/2 cc.	Ammonia used 5/N cc.	Alkaloid extracted. 1st interval Gm.	1st interval %	2nd interval Gm.	2nd interval %	3rd interval Gm.	3rd interval %	4th interval Gm.	4th interval %	Total Gm.	Total %
		Sol. A				20 min.		40 min.		40 min.		40 min.			
Ammonia concentration	1	10	$CHCl_3$	2	–	0.1245	93.61	0.0036	2.70	0.0015	1.0	0.0007	0.5	0.1303	97.97
	2	10	$CHCl_3$	7	–	0.1274	95.80	0.0051	3.84	0.0015	1.0	0.0004	0.3	0.1344	101.05
	3	10	$CHCl_3$	2	2	0.1274	95.80	0.0049	3.30	0.0007	0.5	0.0004	0.3	0.1329	99.92
						30 min.		60 min.		60 min.					
	4	10	C_6H_6	2	–	0.1289	96.92	0.0022	1.65	0.0004	0.30			0.1315	98.87
	5	10	C_6H_6	7	–	0.1289	96.92	0.0025	1.88	0.0007	0.52			0.1321	99.32
	6	10	C_6H_6	2	2	0.1296	97.44	0.0015	1.12	none	—			0.1311	98.57
		Sol. B				30 min.		60 min.							
	7	20	$CHCl_3$	7.2	–	0.2205	89.63	0.0276	11.22					0.2481	100.85
	8	20	$CHCl_3$	7.2	2	0.2031	82.56	0.0422	17.15					0.2453	99.71
						30 min.		60 min.							
	9	20	C_6H_6	7.2	2.8	0.2446	99.43	0.0011	.45					0.2457	99.88
	10	20	C_6H_6	—	3.0	0.2169	88.17	0.0291	11.83					0.2460	100.00
	11	20	C_6H_6	—	–	0.2388	97.07	0.0109	4.43					0.2497	101.50
						30 min.		60 min.							
Alkaloidal concentration[1]	12	5	C_6H_6		2	0.0604	98.21	———	——					0.0604	98.21
	13	10	C_6H_6		2	0.1150	93.49	0.0073	5.94					0.1223	99.43
	14	10	C_6H_6		2	0.1186	96.43	0.0051	4.14					0.2439	99.14
	15	20	C_6H_6		4	0.2417	98.25	0.0022	0.89					0.2424	98.53
	16	20	C_6H_6		2	0.2344	95.28	0.0080	3.25						
						30 min.		60 min.							
Ammonium sulphate excess	17	20	$CHCl_3$	7.2	2	0.1922	78.13	0.0517	21.01					0.2439	99.14
	18	20	$CHCl_3$	7.2	2	0.1966	79.92	0.0473	19.22					0.2439	99.14
						30 min.		60 min.							
	19	20	C_6H_6	7.2	2	0.2468	100.03	0.0029	1.18					0.2497	101.51
	20	20	C_6H_6	7.2	2	0.2468	100.03	0.0022	0.89					0.2490	101.22
Type of extracting device															
Solvent heavier than water		Sol. A				10 min.									
Apparatus 4[2] with thimble	21	10	$CHCl_3$	7.0	–	0.1245	93.61								
Apparatus 4[2] without thimble	22	10	$CHCl_3$	7.0	–	0.0917	68.95								
		Sol. BX													
Apparatus 4[2] with thimble	23	20	$CHCl_3$	7.0	–	0.2395	101.48								
Apparatus 4[2] without thimble	24	20	$CHCl_3$	7.0	–	0.1680	71.19								
		Sol. B				20 min.									
Solvent lighter than water	25	20	C_6H_6	2.0		0.2470	100.6								
(Apparatus 3[2])	26	10	C_6H_6	2.0		0.1241	100.8								

[1] Nos. 12 to 16 diluted with water to 20 cc. volume.
[2] *Ind. Eng. Chem.*, 16, 612 (1925).

tions parallel the normal procedure for the extraction of belladonna preparations by means of the continuous extractor.

TABLE II—EFFICIENCY OF AUTOMATIC DEVICES (ATROPINE).

Variant.	Expt. no.	Alkaloid used mg.	H_2SO_4 cc.	5N NH_4OH cc.	Period of heating min.	Solvent used.	Alkaloid Extracted mg.
Heat acid treatment	1	41.0	10 cc. 0.1N		40	$CHCl_3$	41.2
	2	41.0	3 cc. N		30	$CHCl_3$	41.2
	3	41.0	10 cc. N		50	$CHCl_3$	41.2
	4	29.7	10 cc. 0.1N		35	$CHCl_3$	29.0
	5	29.7	3 cc. N		20	$CHCl_3$	29.3
	6	29.7	10 cc. N		25	$CHCl_3$	28.5
Ammonia	7	48.6		2	120	$(C_2H_5)_2O$	45.6
	8	48.6		2	120	$CHCl_3$	48.3
	9	48.6		2	120	C_6H_6	49.2

TABLE III—EXTRACTION EFFICIENCY OF AUTOMATIC DEVICES.

(Belladonna Alkaloids.)

Variant.	No.	Alkaloid used[1] Solution.	Solvent used.	Ammonia used N/2 cc.	Ammonia used 5N cc.	1st interval	mg.	2nd interval	mg.		Total mg.
Extraction period	1	C	$CHCl_3$		3						50.9
	2	C	$CHCl_3$		3					2 hr.	50.9
	3	C	C_6H_6		3						51.5
	4	C	C_6H_6		3						50.3
	5	C	$CHCl_3$		3						50.3
	6	C	$CHCl_3$		3						50.9
	7	C	C_6H_6		3					$6^2/_3$ hr.	51.5
	8	C	C_6H_6		3						51.5
	9	C	C_6H_6		2		46.9		2.3		49.2
	10	C	C_6H_6		2		46.9		2.3		49.2
	11	C	C_6H_6		2		44.5	60 min.	4.5		49.0
	12	C	C_6H_6		2		45.1		4.6		49.7
	13	C	$CHCl_3$		2	30 min.	44.0		6.8		50.8
	14	C	$CHCl_3$		2		45.1		4.5		50.1
	15	D	C_6H_6		2		53.8	30 min.	1.2		55.0
	16	D	$CHCl_3$		2		56.1		1.7		57.8
	17	D	C_6H_6		2		51.5	60 min.	3.5		55.0
	18	D	$CHCl_3$		2		55.5		1.7		57.2
Ammonia concentration	19	E	C_6H_6	5.5							45.1
	20	E	C_6H_6	5.5							45.7
	21	E	C_6H_6	5.5							45.7
	22	E	C_6H_6	10						2 hr.	47.5
	23	E	C_6H_6	10							46.9
	24	E	C_6H_6		2						49.2
	25	E	C_6H_6		4						49.2
	26	D	C_6H_6	5.5							43.4
	27	D	C_6H_6	10							49.7
	28	D	C_6H_6		2					30 min.	53.2
	29	D	$CHCl_3$	5.5							50.9
	30	D	$CHCl_3$	10							53.8
	31	D	$CHCl_3$		2						55.5

[1] 20 cc. of each solution was used.

In order to determine the stability of atropine toward ammonia, several experiments were made in which weighed quantities of atropine (representing 48.63

mgm. of the pure alkaloid) were dissolved in ether, in chloroform, and in benzene 2 cc. of 5*N* ammonia was added to each and the solutions were refluxed for 2 hours, after which they were extracted in the usual way.

As is obvious from the data in Table II, no destructive action, or at least no change in titration value, of the alkaloids occurred, either by evaporation of the solutions in the presence of acid or by hot extraction in the presence of excess ammonia, except in Experiment 1, where with ether in the presence of ammonia a measurable loss occurred. Additional experiments with the same three solvents were used for extraction. Where no acid treatment had been made and the ammonia concentration (2 cc. of 5*N* ammonium hydroxide) was the same for all, complete recovery of the atropine was easily effected with either chloroform or benzene. Consistent with previous observations, a slight loss with ether ensued.

Total or Combined Alkaloids of Belladonna.—Experiments with solutions of belladonna alkaloids (prepared from belladonna root fluidextract) showed (Table III) that complete extraction of the alkaloids can be effected by using either chloroform or benzene as the solvent. Even with prolonged extraction ($6^2/_8$ hours in Experiments 5 to 8), there was no evidence of destruction or loss, so far as is indicated by titration. Experiments were made to determine the effect of varying ammonia concentration on the accuracy of assay or completeness of extraction (Experiments 19 to 25) and on the relative speed of extraction (Experiments 26 to 31, Table III). A slightly more rapid extraction of alkaloids is obtained with higher concentrations of ammonia (Experiments 26 to 31). Under optimum conditions nearly all the alkaloid is extracted within 30 minutes. This fact is brought out more conclusively in the results of Experiments 9 to 18 (Table III), in which the effect of time variations was studied while other conditions were constant.

A series of experiments was conducted to determine the completeness of automatic continuous extraction for belladonna alkaloidal preparations as compared with that of the hand-shaken separatory funnel extraction. When extracted with benzene for 2 hours, using the automatic device, 20 cc. of the solution (E) yielded 47.43 mgm. of alkaloid. After titration the resulting solution of the alkaloids was re-extracted by hand, using the separatory funnel with chloroform until a negative test with Mayer's reagent indicated completeness of extraction. Only 45.7 mgm. of alkaloid was obtained. A second 20 cc. aliquot of the same belladonna preparation when extracted by means of the hand-shaken separatory funnel yielded 44.54 mgm. of alkaloids. The residual aqueous layer, from which no more alkaloid could be extracted by hand, as evidenced by negative tests with Mayer's reagent, was then subjected to continuous extraction in the automatic device for 2 hours in the usual way. A yield of 3.18 mgm. of alkaloid was obtained. Physiological tests showed that this additional alkaloid was mydriatic.

SUMMARY.

A detailed study was made of the application of automatic devices to liquid preparations of nux vomica and belladonna. The results of the experiments showed that under conditions of dealcoholization and subsequent prolonged hot extraction, no ammonium sulphate is carried over to the alkaloid concentrate; that almost all of the alkaloid is extracted in the first 30 minutes; that, even with a decided variation in the conditions of experiment, the quantity of titratable alka-

loids extracted is not affected; that, in the case of belladonna, at least, a slightly greater quantity of alkaloid can be extracted by means of the automatic devices than by means of a separatory funnel and that in view of the high efficiency already obtainable with the simple types (reported for nux vomica and belladonna), there would appear to be no practical advantage in using the more complicated apparatus for extracting nux vomica and belladonna alkaloids.

THE COMPOSITION OF THE BISMUTH SALT IN GLYCERITE OF BISMUTH.

BY C. C. GLOVER AND THEODORE F. THORSBERG. (1)

An attempt has here been made to determine the chemical composition of the bismuth salt in solution in the glycerite of bismuth of the "National Formulary IV." In the examination of the literature for previous work done on the subject of bismuth salts and chiefly that of bismuth tartrate, we found that a great deal of work had been done, but that few definite results had been recorded. Dr. Ruddiman in his "Whys in Pharmacy" gives the following chemical equation for the reaction taking place when the preparation is made up.

$$BiONO_3 + 2HNO_3 \longrightarrow Bi(NO_3)_3 + H_2O$$
$$2Bi(NO_3)_3 + 3H_2C_4H_4O_6 + 6NaHCO_3 \longrightarrow$$
$$Bi_2(C_4H_4O_6)_3 + 6NaCO_3 + 6CO_2 + 6H_2O$$

The first one to write about a bismuth tartrate was Schwarzenberg, (2) who obtained a white crystalline substance from Bi_2O_3 by digesting $Bi(NO_3)_3$ with $NaC_2H_3O_2$ and $KHC_4H_4O_6$. By this manipulation the bismuth went into solution. He concentrated the filtrate on the water-bath and obtained a white crystalline powder which he spoke of as bismuth potassium tartrate, giving it the formula $C_4H_4O_6KBiO$. R. Schneider (3) made a hot mixture of a moderately concentrated solution of five parts Bi_2O_3 in nitric acid with a concentrated solution of four parts $KHC_4H_4O_6$ in water. On cooling, small crystals formed which he gave the formula $Bi_2(C_4H_4O_6)_3.6H_2O$, which he called a neutral bismuth tartrate. Later, Baudran (8) prepared salts of tartaric acid and a potassium salt with bismuth from freshly prepared $Bi(OH)_3$, which was prepared by treating a bismuth solution with alkali at ordinary temperature. He added to this, tartaric acid and obtained a bismuth tartrate which he gave the formula $BiOC_4H_5O_6.H_2O$. This precipitate was soluble in two hundred twenty eight parts of water. It was in the form of small needles and was decomposed by alkalies. If the alkaline solution is treated with a large amount of potash lye, the bismuth potassium tartrate will crystallize out. He gave it the formula $K(BiO)C_4H_4O_6.H_2O$.

Later, A. Rosenheim and W. Vogelsang (9) worked on the bismuth and alkali bismuth tartrate, since those previously engaged in the work had not come to any definite results. In order to make a nitric acid free bismuth tartrate, the Schneider salt was added in small portions to a boiling concentrated solution of tartaric acid. When the salt had all gone into solution, upon cooling, a nitric acid free bismuth tartrate was formed in beautiful, glazy, crystals. The crystals dissolved in alkali, giving a clear solution, and produced a basic salt when added to water. Its formula was given as $Bi(C_4H_4O_6)C_4H_5O_6.2H_2O$. Rosenheim and Vogelsang could not