

soda lime at elevated temperatures and subsequently absorbing the gaseous products in bromine.

2. The use of crotyl chloride for this purpose represents a more convenient procedure. Its use in preference to 2,3-dibromobutane is recommended because less charring occurs, the yields of 1,2,3,4-tetrabromobutane are better, and the temperature required for reaction is lower.

WILMINGTON, DELAWARE

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

THE SURFACE TENSION OF VARIOUS ALIPHATIC ACIDS PREVIOUSLY STUDIED FOR BACTERICIDAL ACTION TO MYCOBACTERIUM LEPRAE. XX¹

BY W. M. STANLEY AND ROGER ADAMS

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During a research on compounds possessing antileprocidal properties, a large number of aliphatic acids were prepared, many of which were found to be bactericidal *in vitro* toward *Mycobacterium leprae*. Since the effective acids differed from each other rather widely in chemical structure, it was concluded that their bactericidal effectiveness was due to a certain combination of physical properties common to all of these acids, rather than to any specific chemical structure as was at first thought probable. A study of the physical properties was undertaken to determine whether any correlation could be found between one or more of these and the bactericidal effectiveness of the acids.

During the bacteriological work the acids were usually tested for their effectiveness in the form of their soluble salts. It was noticed that, in general, the aqueous solutions of the sodium salts of the most effective acids were very soapy, whereas those of the ineffective acids were not. This suggested that the ability to form soapy solutions might be one of the important properties related to the bactericidal action of the acids, and hence that a correlation might exist between the bactericidal action and the surface tension of solutions of the acids in the form of their salts. A further indication of such a correlation was the fact that the acids were bactericidally effective *in vitro* only in a form in which the surface tension reducing action became effective, that is, in the form of the soluble salts. The free acids appeared to be effective only in so far as they were able to form soluble salts with the buffer of the media. The ethyl esters unable to form sodium salts were entirely ineffective *in vitro*.

¹ For the last papers in this field see Stanley, Jay and Adams, *THIS JOURNAL*, 51, 1261 (1929); Ford and Adams, *ibid.*, 52, 1259 (1930); Browning, Woodrow and Adams, *ibid.*, 52, 1281 (1930); Armentt and Adams, *ibid.*, 52, 1289 (1930); Greer and Adams, *ibid.*, 52, 2540 (1930). In these and in previous papers the bactericidal action of these compounds may be found.

The relationship of surface tension depressants, usually the sodium salts of castor oil acids,² and bacteriological growth has been the subject of some study during recent years. It was found that in most cases lowering the surface tension of the media decreased the growth of the organism. Larson³ found that all pellicle forming organisms ceased to grow at the surface when the surface tension of the medium was below 45 dynes per cm. Berczeller⁴ has discussed the effect of surface tension on pharmacological action and Traube⁵ and Somogyi believe that bacteriological activity is correlated with the surface tension of the medium. It therefore appeared quite probable that the bactericidal effectiveness of these aliphatic acids might be closely related to their surface tension depressant action.

In this investigation the surface tensions of aqueous and media solutions of the sodium salts of one hundred and twenty different aliphatic acids in several different dilutions have been determined. Acids having a cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl and one or more cyclohexyl groups, as well as hydroxy acids, unsaturated acids and certain naturally occurring acids such as hydnocarpic, chaulmoogric and ricinoleic acids were included among those tested. It was found that without exception all of the bactericidally effective aliphatic acids were marked surface tension depressants. However, while the surface tension depressant action is closely allied with the bactericidal action, it must not be regarded as the sole criterion of bactericidal effectiveness, for α -bromopalmitic acid (Table VI), the total acids of cod liver oil and some of the acids having approximately nineteen or more carbon atoms were found to be good surface tension depressants and yet were relatively non-effective as bactericides. With the exception of these acids the surface tension paralleled the bactericidal effectiveness.

The present data indicate that a bactericidally effective acid must be a good surface tension depressant and must also have a molecular weight of approximately 256, that is, one which corresponds to an acid of sixteen carbon atoms. Decreasing the molecular weight of the acid below 256 caused a drop in bactericidal effectiveness and a parallel drop in surface tension effect while increasing the molecular weight above 256 caused a drop in bactericidal effectiveness usually without the corresponding drop in surface tension effect. Thus while one physical property, namely, surface tension depressant action, can be correlated directly with the bactericidal effectiveness of the acids, it is but one of two or more factors which are responsible for the bactericidal action of these aliphatic acids.

Several general qualitative correlations between chemical structure

² Wolf, *Biochem. J.*, **17**, 813 (1923).

³ Larson, *J. Infectious Diseases*, **25**, 41 (1919).

⁴ Berczeller, *Biochem. Z.*, **66**, 202 (1914).

⁵ Traube, *ibid.*, **120**, 90 (1921).

and surface tension were revealed in this investigation. Regardless of the structure, the surface tension of solutions of the sodium salts of the acids, which is high for the low molecular weight acids, decreased with an increase in molecular weight and then began to increase slightly when the acid contained about nineteen carbon atoms (Fig. 1). A similar action was found in a normal fatty acid series of fourteen acids studied by Lascaray,⁶ and of other similar acids studied by Dubrisay,⁷ and by Walker.⁸ The behavior of certain α -hydroxy fatty acids was just the reverse, an increase in molecular weight causing an increase in the surface tension (Table I, No. 8). A ring structure caused slight increase in surface tension over the

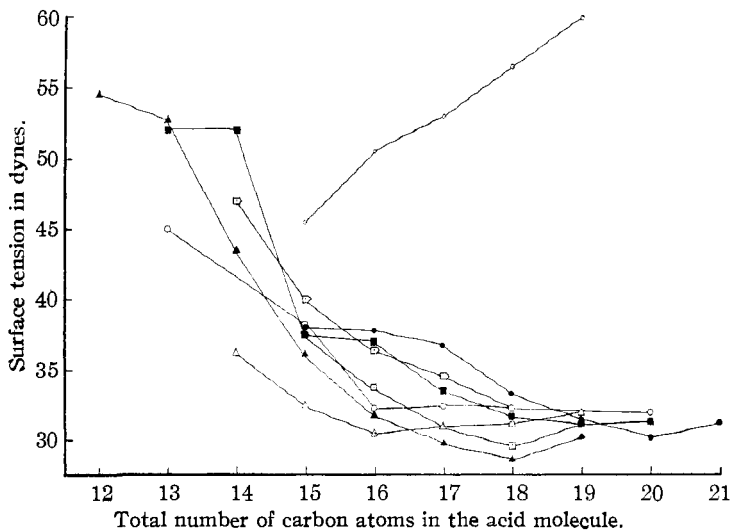


Fig. 1.—Change in surface tension with molecular weight: 1 : 500. ○, hydroxy acids; ○, allyl acids; ●, cyclopentenyl acids; △, cyclopropyl acids; □, cyclobutyl acids; ◻, cyclopentyl acids; ■, cyclohexyl acids; ▲, aliphatic (averaged).

corresponding straight-chained acids with the carboxyl group other than at the end of the chain (compare isomers in Table I, No. 1 to 4, Tables III and IV, with isomers in Table I, Nos. 9 to 17). The rather marked effect of a ring structure upon the properties of the acids with the carboxyl group at the end of the chain is especially to be noted (Table III). The introduction of an iso group caused a slight increase in the surface tension (Table I, Nos. 18 to 21, Tables II and V). The introduction of a double bond into the ring or carbon chain of the acids had no appreciable effect on the surface tension (compare Table I, Nos. 4 to 7 with Table I, No. 3 and Nos. 9 to 17). The

⁶ Lascaray, *Kolloid Z.*, **34**, 73 (1924).

⁷ Dubrisay, *Compt. rend.*, **178**, 1976 (1924).

⁸ Walker, *J. Chem. Soc.*, **119**, 1521 (1921).

concentration at which an acid had the minimum surface tension varied in an indefinite manner with the structure of the acid.

The position of the carboxyl group in the higher fatty acids is of especial interest. The sodium salts of palmitic and stearic acids formed a semi-solid gelatinous mass when present one part in 500 parts of water at 25°, whereas all the isomers with the carboxyl group at any other position than on the end carbon atom were quite soluble under the same conditions. The isomeric acids were even readily soluble in 10 to 20% solutions, forming perfectly fluid liquids. This great change in solubility

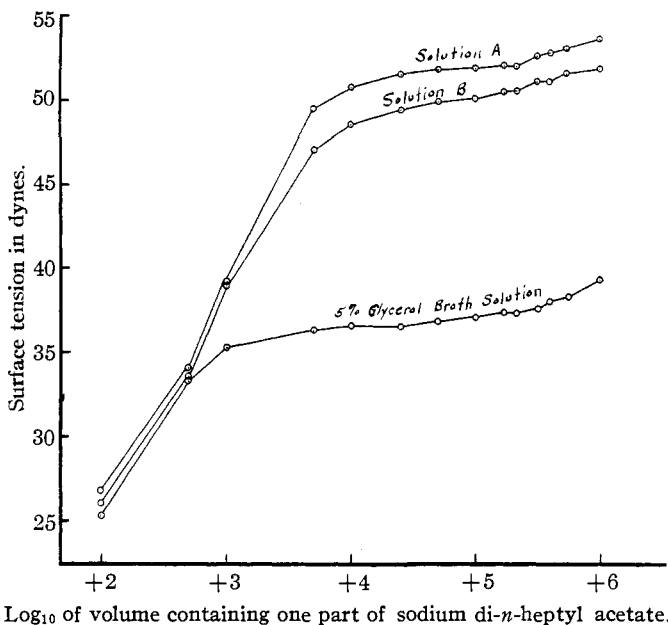


Fig. 2.—Changes of surface tension on dilution of sodium di-*n*-heptyl acetate: Tensiometer method.

caused by moving the carboxyl group from the end carbon atom to any other carbon atom, is especially interesting since palmitic and stearic acid have no bactericidal properties, while the isomers, especially of palmitic acid, possess a high bactericidal action. The shift of the carboxyl group to the second carbon atom caused a very large drop in the surface tension. The sodium salt of di-*n*-heptylacetic acid, an isomer of palmitic acid, the ethyl and glyceryl esters of which have been tested clinically, lowers the surface tension of water approximately 50 dynes per cm. in 0.1 molar solution and even 20 dynes per cm. in so dilute a solution as one part in one million parts of water (Fig. 2). As the carboxyl was moved farther down the chain, the surface tension increased slightly and then again de-

TABLE I
SURFACE TENSION IN DYNES PER CM. DILUTION, 1:500

R =		C ₄ H ₈	C ₆ H ₁₂	C ₈ H ₁₆	C ₁₀ H ₂₀	C ₁₂ H ₂₄	C ₁₄ H ₂₈	C ₁₆ H ₃₂	C ₁₈ H ₃₆	C ₂₀ H ₄₀	C ₂₂ H ₄₄	C ₂₄ H ₄₈	C ₂₆ H ₅₂	C ₂₈ H ₅₆	
1	Cyclopropylmethyl alkyl acetic acids C ₃ H ₅ CH ₂ CH(COONa)R	T 25°	49.7	45.1		38.8	32.2	32.5	32.3						
2	Cyclobutylmethyl alkyl acetic acids C ₄ H ₇ CH ₂ CH(COONa)R	D 20°				37.5	33.8	31.1	29.7	31.2					
3	Cyclopentyl alkyl acetic acids C ₅ H ₉ CH(COONa)R	T 25°			47.0	40.1	36.6	34.7	32.2						
4	Cyclopentenylethyl alkyl acetic acids C ₅ H ₇ (CH ₂) ₂ CH(COONa)R	T 25°		38.2	37.9	36.7	33.2	31.5	30.4	31.2					
5	Allyl alkyl acetic acids C ₃ H ₅ CH(COONa)R	T 25°					36.3	32.8	30.6	31.1	31.2	33.0			
6	Undecylenyl alkyl acetic acids CH ₂ =CH(CH ₂) ₉ CH(COONa)R	T 25°	35.7	33.3	30.0	28.2									
7	α,β-Unsaturated acids C ₈ H ₇ CH=C(COONa)R	T 25°	47.0		33.5	26.0									
8	α-Hydroxy acids R(CH ₂) ₈ CH(OH)COONa	D 20°		45.5	50.6	53.0	56.5	60.0							
9	CH ₃ CH(COONa)R	D 20°										28.2	25.8	25.0	
		T 25°										31.5	28.3	27.8	26.2
10	C ₂ H ₅ CH(COONa)R	D 20°											29.3	27.4	29.6
		T 25°										33.5	30.3	29.9	29.5
11	C ₃ H ₇ CH(COONa)R	D 20°											29.8	27.5	29.3
		T 25°							35.8	31.8	30.1	29.0	33.5		
12	<i>iso</i> -C ₃ H ₇ CH(COONa)R	D 20°				54.7									
		T 25°				54.6									
13	C ₄ H ₉ CH(COONa)R	D 20°			54.6	51.4	38.8			30.8	28.0	28.2			
		T 25°			55.4	52.3	44.2			31.7	30.8	29.3			

TABLE I (Concluded)

R =	C ₄ H ₉	C ₅ H ₁₁	C ₆ H ₁₃	C ₇ H ₁₅	C ₈ H ₁₇	C ₉ H ₁₉	C ₁₀ H ₂₁	C ₁₁ H ₂₃	C ₁₂ H ₂₅	C ₁₃ H ₂₇	C ₁₄ H ₂₉	C ₁₅ H ₃₁
14 C ₅ H ₁₁ CH(COONa)R	D 20°	55.0		43.4		32.5	28.4	28.3				
	T 25°	54.5	53.4	43.9	38.7	34.4	30.5	30.0	31.2			
15 C ₆ H ₁₃ CH(COONa)R	D 20°				31.9	27.2	26.7					
	T 25°		42.4	38.0	33.8	28.1	27.9					
16 C ₇ H ₁₅ CH(COONa)R	D 20°			31.7	27.6	25.6						
	T 25°			33.7	28.0	26.8	26.1					
17 C ₈ H ₁₇ CH(COONa)R	D 20°				25.6							
	T 25°				26.5							
18 CH ₃ CH(CH ₃)CH ₂ CH(COONa)R	D 20°						34.1		29.0			
	T 25°						32.6		30.4			
19 CH ₃ CH(CH ₃)CH(COONa)R	D 20°						33.2			30.0		
	T 25°						32.3			30.8		
20 C ₂ H ₅ CH(CH ₃)CH(COONa)R	D 20°								28.7			
	T 25°								29.5			
21 C ₃ H ₇ CH(CH ₃)CH(COONa)R	D 20°							28.4				
	T 25°							28.6				

T, Tensiometer method; D, Drop-weight method

creased slightly as it reached the middle carbon atom (Fig. 3). The change in surface tension caused by moving the carboxyl group from the end carbon atom to any other carbon atom is not nearly so pronounced in the lower fatty acids. Another interesting phenomenon is that the introduction of an α -hydroxyl group into palmitic acid caused the acid to be perfectly soluble in 1:500, yet the solution had a high surface tension, whereas the introduction of an α -bromine atom caused the acid to be perfectly soluble in 1:500 and the solution had a low surface tension, yet possessed no appreciable bactericidal action (Table I, No. 8, Table VI).

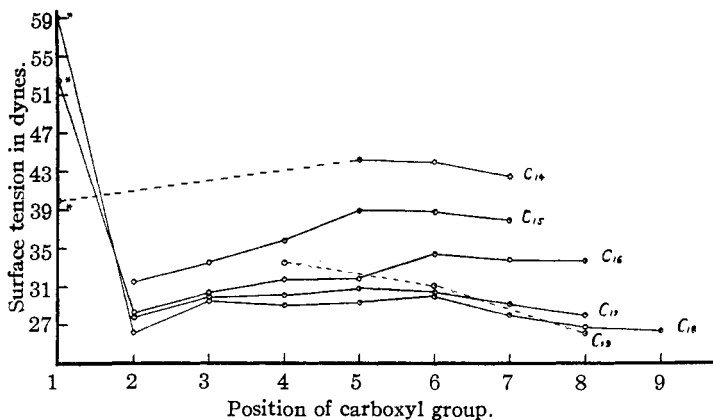


Fig. 3.—Change in surface tension with position of carboxyl group in a number of isomeric fatty acids. * — Values by Lascaray, *Kolloid. Z.*, **34**, 73 (1924); dilution, 1:500.

The surface tension of solutions of the salts of hydnocarpic and chaulmoogric acids, the acids which constitute the major portion of oils which have been used in the treatment of leprosy, was determined and found to be fairly low (Table II).

Procedure

The solutions of the sodium salts of the acids for surface tension determinations were prepared in the same manner as the solutions for bacteriological testing. A sample of 0.100 g. of acid was dissolved in ethyl alcohol and neutralized to phenolphthalein with 0.5 *N* sodium hydroxide solution. The solution was then evaporated to dryness and taken up in either 10 or 50 cc. of distilled water. This solution was then diluted and rediluted to the desired concentrations. The media solutions were prepared in the same manner except that 5% glycerol broth was used as a solvent.

The surface tensions of the solutions were determined by the drop-weight method, using the Harkins procedure and corrections and also by means of a du Noüy tensiometer. Duplicate determinations by both

methods on several solutions gave practically identical results. Since the tensiometer method was more rapid it was used for most of the determinations. The tensiometer was especially valuable since it enabled surface tensions on an entire series of acids or dilutions to be determined rapidly and it is believed that the values so obtained are very accurate from a comparative standpoint. Duplicate determinations on the same solution never varied over 0.2 dynes per cm., and duplicate determinations on the same acid at a given concentration seldom varied over 1.5 dynes per cm. The latter includes the experimental error in weighing, diluting and determining the surface tension of duplicate samples of an acid. The values given in the tables are, therefore, accurate to approximately 5% or less. The dilutions of the solutions are indicated at the top of the columns in the tables by notations such as 1:500, which means one part of the sodium salt of the acid in 500 parts of water.

TABLE II
 CHANGE OF SURFACE TENSION ON DILUTION
 Surface tension in dynes per cm. by tensiometer at 25°

	1:100	1:500	1:1000	1:10000	1:100000
$C_3H_5CH_2CH(COONa)C_{10}H_{21}$	34.7	32.2	35.0	42.4	45.5
$C_8H_9CH(COONa)C_{10}H_{21}$	33.6	34.7	40.4	46.3	48.0
$C_8H_7CH_2CH(COONa)C_8H_{19}$	33.7	33.2	37.1	48.4	53.5
$C_6H_{11}(CH_2)_{10}COONa$	36.8	32.2	32.6	36.2	51.7
$C_6H_{11}(CH_2)_2CH(COONa)(CH_2)_2C_6H_{11}$	34.8	42.8	47.6	53.6	57.6
<i>iso</i> - $C_8H_7CH(COONa)C_7H_{15}$	42.7	54.6	57.7	64.5	69.6
$C_8H_{11}CH(COONa)C_8H_{11}$	43.7	54.5	56.8	60.7	71.1
$CH_3CH(COONa)C_{13}H_{27}$	33.4	28.3	24.6	28.6	41.3
$C_7H_{15}CH(COONa)C_7H_{15}$	26.8	33.7	38.8	49.2	50.7
$CH_3CH(CH_3)CH_2CH(COONa)C_{10}H_{21}$	33.3	32.6	35.0	42.8	46.7
$C_7H_{15}CH(COONa)C_8H_{17}$	25.7	28.0	35.0	44.5	49.2
$C_7H_{15}CH(COONa)C_8H_{19}$	26.0	26.8	31.8	45.8	51.6
$C_8H_7CH(COONa)C_{14}H_{29}$		33.5	32.2	42.9	
$C_8H_{11}CH(COONa)C_{12}H_{25}$		31.2	30.2	37.0	
$C_7H_{15}CH(COONa)C_{10}H_{21}$		26.1	26.4	40.8	
$C_3H_5CH(COONa)C_{12}H_{25}$	35.0	31.1	29.0	36.0	45.0
$CH_2=CH(CH_2)_9CH(COONa)C_8H_{11}$	32.7	33.3	35.7	48.9	53.8
$CH_3(CH_2)_8CH=C(COONa)C_7H_{15}$	26.3	33.5	38.9	47.8	50.5
Hydnocarpic acid	33.3	32.2	32.6	41.3	52.7
Total acids of <i>Hydnocarpus Wightiana</i> oil	31.5	30.2	30.5	37.8	59.2
Chaulmoogric acid	38.2	33.1	32.8	44.9	64.7

TABLE III
 ω-CYCLOHEXYL SUBSTITUTED FATTY ACIDS AND DI-(CYCLOHEXYLALKYL) ACETIC ACIDS

	Surface tension in dynes per cm. by tensiometer at 25°; 1:500										
$x =$	0	1	2	2	2	3	3	6	8	10	11
$y =$	2	2	2	3	4	3					
$C_8H_{11}(CH_2)_2COONa$	53.9						51.0	39.7	33.4	32.2	32.9
$C_8H_{11}(CH_2)_2CH(COONa)(CH_2)_2C_6H_{11}$	52.8	49.2	42.8	37.4	34.5	33.2					

TABLE IV
CYCLOHEXYL ALKYL ACETIC ACIDS, $C_6H_{11}CH(COONa)R$
Surface tension in dynes per cm.

R =	T^a	T^a	D^b	D^b
	25° 1:500	25° 1:1000	20° 1:1000	20° 1:1000 ^c
C_5H_{11}	52.1	53.0	55.3	41.5
C_6H_{13}	52.3	54.7	55.1	37.2
C_7H_{15}	37.2	43.2	42.0	35.6
C_8H_{17}	37.3	44.6	42.8	35.7
C_9H_{19}	33.5	38.5	39.0	37.8
$C_{10}H_{21}$	31.6	36.2	34.7	37.5
$C_{11}H_{23}$	31.7	33.5	33.1	39.6
$C_{12}H_{25}$	31.5	32.5	30.9	40.2

^a Tensiometer. ^b Drop weight method. ^c 5% Glycerol broth solution.

TABLE V
HEXADECANOIC ACIDS
Surface tension in dynes per cm. by tensiometer

	D^a		D^a		1:1000	1:10000	1:100000
	1:100	1:500	20° 1:500	20° 1:500 ^b			
$CH_3CH(COONa)C_{13}H_{27}$	33.4	28.3	28.2	22.9	24.6	28.6	41.3
$C_2H_5CH(COONa)C_{12}H_{25}$		30.3	29.3	24.9			
$C_3H_7CH(COONa)C_{11}H_{23}$		31.8	29.8	28.8			
$C_4H_9CH(COONa)C_{10}H_{21}$		31.7	30.8	30.2			
$C_5H_{11}CH(COONa)C_9H_{19}$		34.4	32.5	31.8			
$C_6H_{13}CH(COONa)C_8H_{17}$		33.8	31.9	30.7			
$C_7H_{15}CH(COONa)C_7H_{15}$	26.8	33.7	31.7	31.0	38.8	49.2	50.7
$CH_3CH(CH_3)CH_2CH(COONa)C_{10}H_{21}$	33.3	32.6	34.1	28.7	35.0	42.8	46.7
$CH_3CH(CH_3)CH(COONa)C_{10}H_{21}$		32.3	33.2	29.8			

^a Drop weight method. ^b 5% Glycerol broth solution.

TABLE VI
MISCELLANEOUS ACIDS
Surface tension in dynes per cm. by drop weight method at 20°

	1:500
Total acids of castor oil	36.6
Soluble reduced castor oil acids	59.1
Insoluble reduced castor oil acids	44.7
Dihydroxystearic acid	40.0
α -Bromopalmitic acid	30.6
Total acids of cod liver oil	30.6
$C_6H_{11}(CH_2)_2CH(COONa)CH(COONa)C_4H_9$	40.6
$C_6H_{11}CHOH(CH_2)_7COONa$	48.3 ^a

^a Tensiometer at 25°.

Summary

The surface tensions of aqueous and media solutions of the sodium salts of one hundred and twenty aliphatic acids, previously studied for bactericidal action to *Mycobacterium Leprae* have been determined. It

was shown that without exception all of the bactericidally effective aliphatic acids were marked surface tension depressants. Several general correlations between chemical structure and surface tension depressant action were revealed.

URBANA, ILLINOIS

[CONTRIBUTION NO. 74 FROM THE EXPERIMENTAL STATION OF E. I. DU PONT DE NEMOURS & COMPANY]

STUDIES OF POLYMERIZATION AND RING FORMATION. XI. THE USE OF MOLECULAR EVAPORATION AS A MEANS FOR PROPAGATING CHEMICAL REACTIONS

BY WALLACE H. CAROTHERS AND JULIAN W. HILL

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Reversible reactions involving the simultaneous formation of a volatile and a non-volatile product are often forced to completion by causing the volatile product to distil from the reaction mixture as fast as it is formed. The purpose of the present note is to call attention to the possibility of extending the application of this principle to instances in which the effective vapor pressure or escaping tendency of a volatile product or potential product is very small. In the molecular still¹ distillation or continuous evaporation can be effected even when the vapor pressure of the distilling substance is as low perhaps as 10^{-5} mm. The theory of the process has been discussed by Washburn,^{1b} and we need only to mention that successful operation requires a highly evacuated system comprising a condenser placed very close to the evaporating surface. The temperature of the condenser must be low enough to reduce the vapor pressure of the distillate to a negligible value. Under these conditions the mean free path of the molecules is less than the distance from the condenser to the evaporating surface; consequently most of the molecules that manage to escape from the evaporating surface are caught by the condenser with a negligible probability of return.

Mercury and apparently cane sugar can be evaporated in the molecular still at room temperature^{1b} and *n*-heptacontane can be distilled without decomposition.² The tendency to distil diminishes with increasing molecular weight, and it appears that, so far as practically useful rates are concerned, the upper limit of distillability for paraffin hydrocarbons may lie at as low a molecular weight as 1100 or 1200. For other types of organic compounds it will in general lie at still lower molecular weights.² Thus all substances of high molecular weight are practically completely

¹ Brönsted and Hevesy, *Phil. Mag.*, **43**, 31 (1922); (b) Washburn, *Bur. Standards J. Research*, **2**, 476 (1929); (c) Burch, *Proc. Roy. Soc. (London)*, **123**, 271 (1929); (d) Hickman, *Chem. Ind.*, **48**, 365 (1929).

² Carothers, Hill, Kirby and Jacobson, *THIS JOURNAL*, **52**, 5279 (1930).