levels employed. Samples II and III showed the presence of both FSH and ICSH, concurrently with luteinizing, antagonistic and thyrotropic activity. Sample II was also tested for adrenotropic activity and it was found that this factor was present. The gonadotropic activity of 40% alcohol extracts of samples II and III is of the same order as that of similar preparations obtained from sheep and pig pituitary. The absence or presence of the multiple properties of the LH (ICSH) factor agrees with our assumption that they are due to one principle only.

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Alkyl Nitrites V.
The Pharmacology of the High Molecular Weight Alkyl Nitrites.*

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In previous studies[1] the pharmacology of a series of new brominated and non-brominated alkyl nitrites of relatively high molecular weight was described. The properties and action of 2-ethyl-n-hexyl-1-nitrite[2] prompted a more complete investigation of this compound, which resulted in its use as a therapeutic agent in angiospastic disease. Cash and Dunstan[3] many years ago studied the activity of the primary and secondary alkyl nitrites from methyl to amyl. In general, they found that the higher nitrites, butyl and amyl, gave a greater fall in blood pressure than those of lower molecular weight. On the other hand, they found a greater duration of response when the lower molecular weight esters were administered. These investigators expressed the view that the magnitude of the fall in blood pressure was a function of the instability of the higher members and not of their molecular weight. The greater duration of the response of the lower members was attributed to their greater degree of stability. It oc-

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1 Krantz, J. C., Jr., Carr, C. J., and Forman, S. E., *J. Pharmacol. and Exp. Therap.*, 1938, **64**, 298.

2 Krantz, J. C., Jr., Carr, C. J., and Forman, S. E., *J. Pharmacol. and Exp. Therap.*, 1938, **64**, 302.

3 Cash, J. Th., and Dunstan, W. R., *Phil. Trans. Roy. Soc.*, 1893, **184** B, 505.

curred to the authors to extend this investigation further to include the nitrites of the higher molecular weight alcohols.

Compounds Studied and Methods. The method of synthesis and many of the constants of these compounds will be reported in a suitable journal. In the main, the compounds were odoriferous liquids with odors resembling the alcohols from which they were prepared. The assays were conducted by the nitrometer method set forth in the tenth revision of the United States Pharmacopoeia.

The vapor pressures were measured at 28°C in a Van Slyke apparatus.

Under nembutal anesthesia in the dog, the drugs were administered in 0.3 cc doses per animal. The ester was placed in a small aspirating bottle and was drawn into the trachea after volatilization. Table I shows the effect of this series of drugs on blood pressure.

Fig. 1 shows the relationship between the number of carbon atoms in the molecule of the alkyl nitrite, its vapor pressure and depressor response.

The graph shows that the depressor activity of the alkyl nitrites of high molecular weight is a function of their vapor pressures when administered by inhalation. The minimal effective vapor pressure of 0.5 mm is exhibited by n-decyl nitrite. Higher molecular weight compounds with equal vapor pressures are devoid of pharmacologic response when administered by inhalation. However, when these substances are dissolved in a hydroalcoholic solvent and injected intravenously they elicit full depressor responses. Branched chain compounds appear to be more active than those of the same molecular weight with straight chains. The former compounds exhibit a higher vapor pressure.

TABLE I.
Summary of the Effect of Alkyl Nitrites, 0.3 cc, on the Blood Pressure of the Dog.

Compound	No. of C atoms in molecule	Purity, %	No. of exper.	Original bl. p., mm Hg	Max. fall bl. p. %
n-hexyl nitrite	6	94	6	133	58
n-heptyl "	7	93	7	126	47
n-octyl "	8	99	3	151	30
2-et-n-hexyl-1 nitrite	8	92	5	130	46
n-nonyl nitrite	9	89	14	135	21
n-decyl "	10	93	4	123	16
5-et-n-nonyl-2-nitrite	11	85	5	129	4
n-duodecyl nitrite	12	93	4	125	0
7-et-2-me-undecyl-1-nitrite	14	78	3	132	5
n-tetradecyl nitrite	14	85	4	136	0
n-hexadecyl "	16	88	3	120	0
n-octadecyl "	18	99	4	130	0

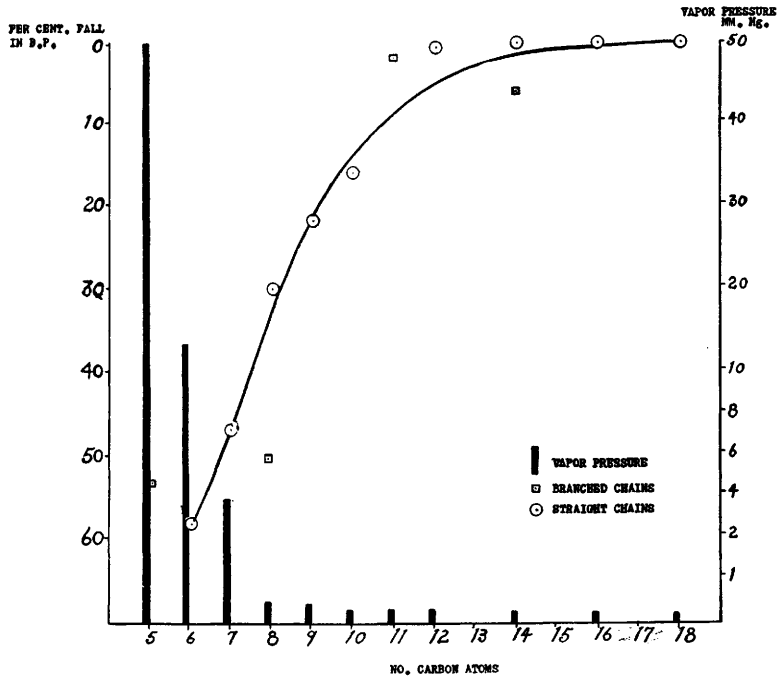

FIG. 1.
Blood Pressure, Vapor Pressure and Molecular Weight of Alkyl Nitrites.

These present studies do not agree entirely with the findings of Cash and Dunstan. First,[1] we have shown previously that ethyl nitrite gives as great a fall in blood pressure as does amyl nitrite. Second,[2] it was further established by studies on the speed of hydrolysis of amyl nitrite and 2-ethyl-n-hexyl-l-nitrite, that although their hydrolytic rates were practically identical, the higher molecular compound produced a depressor response lasting seven times as long as that elicited by the amyl ester. The authors attribute this to the lesser degree of water solubility of the 2-ethyl-n-hexyl-l-nitrite and its corresponding greater degree of oil solubility.

The vapor pressure of the compounds of this series reaches an optimum between 3 and 4 mm; higher vapor pressures give rise to compounds which produce an unnecessary plethora of methemoglobin in the animal's blood and, owing to a low oil solubility, exert a response which is ephemeral.

Conclusions. 1. The pharmacology of the higher alkyl nitrites has been investigated. 2. The relationship between molecular weight, vapor pressure and depressor response is demonstrated. 3. Certain theoretical considerations of the desiderata in physical properties necessary for depressor response are discussed.