N-MENTHYL-SUBSTITUTED AMIDES

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Menthylurea has been shown to exert a marked narcotic action when injected intraperitoneally into white rats.¹ It acted rapidly and left no apparent after effects. Its rapid absorption action was somewhat unexpected since it is practically insoluble in water. The rather interesting physiological properties of menthylurea made it desirable to prepare and study other N-menthyl-substituted amides.

Read and Storey² prepared a series of N-menthyl-substituted amides for the purpose of correlating physical properties and structure in their series of papers "Researches in the Menthone Series." Physiological studies were not made.

The present series of amides consists of amides of monobasic acids. Structural variations were introduced by using normal and iso fatty acids, bromosubstituted acids, and aromatic acids. One additional compound (menthylidenehydantoin) was prepared. While it is not a simple substituted amide, the menthyl ring system is directly attached to one of the nitrogen atoms and in that sense is related to the other compounds prepared.

Seven of these compounds have been tested through the courtesy of the Merck Therapeutic Institute. Comparisons between the narcotic and toxic doses indicated that none of the compounds appear promising. The hydantoin has not yet been tested, but it appears that the mere attachment of the menthyl group to amide nitrogen is not sufficient in itself to enhance narcotic action.

EXPERIMENTAL

Preparation of the N-menthyl-substituted amides.—They were prepared by warming equivalent quantities of the free base and acyl chloride in dry benzene until no more hydrogen chloride was evolved. The benzene solution was washed with dilute sodium hydroxide solution, dilute hydrochloric acid, and finally with water. After drying over anhydrous sodium sulfate, the substituted amides were obtained by slow evaporation of the benzene solution. Compounds 1, 2, 3, 4, 6, 7, 9, 11, 12, 14, 15, and 16 were purified by recrystallization from aqueous alcohol. Compounds 8, 10 and 13 were recrystallized from ethylene glycol containing a little alcohol. The yields were good in all cases (80-90%) based on the menthylamine actually used. All of the compounds were obtained as colorless prisms or needles.

¹ BATEMAN AND DAY, J. Am. Chem. Soc., 57, 2496, 1935.

² READ AND STOREY, J. Chem. Soc., 1930, 2761.

Reduction of N-menthyl-p-nitrobenzamide.—Two grams of the nitro compound was dissolved in ethyl alcohol, and 4 cc. of concentrated hydrochloric acid was added. Three grams of iron powder was added in small portions with stirring, and the mixture was maintained at 15-20°. More hydrochloric acid was added as needed until a total of 10 cc. was used. When the solution became pale yellow, it was filtered, and the precipitate was extracted with hot alcohol. The amino compound was obtained from the alcohol extract by careful dilution with water.

Preparation of 5-(2-isopropyl-5-menthylpentamethylene)hydantoin.—This derivative was prepared by the method of Bucherer.³ One-tenth of a mole of *l*-menthone, 0.13

DERIVATIVE	M.P., [°] C. (CORR.)	a ²⁵ in 95% Alcohol	NITROGEN	
			Calc'd	Found
1. N-Menthylacetamide*	145°	-83.6	7.09	6.98
2. N-Menthylbromoacetamide*	106.5°	-57.2	5.07	5.09
3. N-Menthylpropionamide*	87.5°	-68.9	6.62	6.52
4. N-Menthyl- α -bromopropionamide	138.5°	-45.0	4.82	4.74
5. N-Menthyl-β-bromopropionamide	86°	-47.1	4.82	4.75
6. N-Menthyl-n-butyramide*	7 9°	-69.3	6.21	6.05
7. N-Menthylisobutyramide*	130.6°	-66.7	6.21	6.17
8. N-Menthyl- α -bromo-n-butyramide	150°	-52.9	4.60	4.41
9. N-Menthyl- α -bromoisobutyramide	94.5°	-49.9	4.60	4.45
10. N-Menthyl isovaleramide*	96°	-62.9	5.85	5.71
11. N-Menthyl- α -bromo- <i>n</i> -valeramide	166°	-47.3	4.40	4.55
12. N-Menthyl- α -bromoisovaleramide	184–184.5°	-41.03	4.40	4.38
13. N-Menthylphenylacetamide*	106°	-62.4	5.12	5.03
14. N-Menthyl-p-nitrobenzamide	172.5-173°	-67.5	4.60	4.40
15. N-Menthyl-p-aminobenzamide	190.5–191°	81.6	5.10	4.97
16. $5-(\alpha-\text{Isopropyl-5-methylpentamethyl-}$				
ene)hydantoin	223–5°	0.0	12.48	12.40

TABLE N-MENTHYL SUBSTITUTED DEBIVATIVES

* Previously prepared by Read and Storey.

mole of potassium cyanide, and 0.3 mole of ammonium carbonate in 50 per cent. alcohol solution were heated at 60° for 6-8 hours. The crude derivative was removed by filtration, washed thoroughly with water and recrystallized from alcohol. The resulting compound was optically inactive, racemization apparently having occurred during the reaction.

SUMMARY

1. Fifteen N-menthyl-substituted amides have been prepared, eight of which represent new compounds.

2. Seven of these compounds have been tested for narcotic action but appeared to be of little value as hypnotics.

3. 5-(2-Isopropyl-5-methylpentamethylene)hydantoin was prepared by the Bucherer method from laevo menthone.

³ BUCHERER, J. prakt. Chem., [2], 140, 291 (1934).