NEW GUAIACOL DERIVATIVES.*[1]

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The experimental results here recorded constitute a part of a study of new remedies and their literature conducted during two academic years since 1919. The work accomplished during the academic year 1919–20 was done under a grant by the Newport Chemical Works of Milwaukee. The work of the academic years 1920 to 1922 was interrupted by sickness that caused a break in the work of a twelve month. This part of the work was supported by a grant from the Research Committee of the American Pharmaceutical Association. The crystalline guaiacol used in the syntheses recorded below was kindly supplied by the Newport Chemical Company. The library investigations on new remedy book literature will be reported separately.

GUAIACYL PHENYL URETHANE.

The preparation of guaiacyl urethane was carried out in four experiments under slightly different conditions with the following results.

In the first experiment 3 grams of liquid guaiacol and 3 grams phenylisocyanate were heated with 30 mils of petroleum, b. p. 179°, for 40 minutes in an acetylization flask over a free flame. While heating, the mixture congealed to a white crystalline mass. After cooling the crystals were collected on a suction filter, washed with petroleum, dried, and then recrystallized first from petroleum and later from alcohol.

Yield = 73%.

M. p. after recrystallization from P. E. = 208–220° C.

M. p. after recrystallization from alcohol = 228° C.

Nitrogen as determined by the Kjeldahl method on the alcohol purified portion = 14.14%.

The above experiment was repeated using the same quantities of reagents but heating only 30 minutes and then allowing the mixture to stand over night. Crystallization took place very slowly, but by concentration in the cold a total yield of 75% was obtained. The product on recrystallization from alcohol showed a wide variation in melting point, *viz.*, from 143° to 226° C. No nitrogen determination was made on this product.

In the third experiment 10 grams of crystalline guaiacol and 9.7 grams of phenylisocyanate were heated with 50 mils of petroleum, b. p. 179° C., for $3^1/_2$ hours. The crystalline product which formed upon cooling was removed and the heating of the mother liquor was continued for 2 hours longer during 4 intervals. After each interval the crystalline product was removed and the melting point taken of each portion which was found to be uniform.

M. p. of crude product = 146° C.

Yield = 81.3%.

The combined portions were recrystallized from alcohol and the melting point was found to be 148° C.

The original mother liquor was then concentrated by distillation and by

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evaporation. A very small quantity of white crystals was obtained which melted at 235° C.

A nitrogen determination was made by the Kjeldahl method on the portion of the product melting at 148° C. with the following results:

Sample No. 1, N = 5.91%.
Sample No. 2, N = 6.60%.

In the fourth experiment the same quantities of reagent were used as in Experiment III. The mixture was heated for 1 hour and then allowed to stand for a period of 10 days. The crystals obtained were collected and purified from alcohol.

Yield = 95.0%.
M. p. of crude product = 146° C.
M. p. after recrystallization = 148° C.

Nitrogen determinations made by the Kjeldahl method showed the following results:

Sample No. 1, N = 5.98%.
Sample No. 2, N = 5.83%.

Three nitrogen determinations were made with the combustion method with the following results:

Sample No. 1, N = 8.69%.
Sample No. 2, N = 6.60%.
Sample No. 3, N = 6.97%.

Guaiacyl phenyl urethane contains 5.76 % nitrogen.

α-NAPTHYL GUAIACYL URETHANE.

The preparation of the α-naphthyl urethane of guaiacol was carried out several times by using equimolecular proportions of the reagents under varying conditions. It will be noticed from the following results that, in the experiments where only a small quantity was prepared, the product obtained consisted of a mixture of substances as will be seen from the variations in melting point as well as in solubility, while in the experiment where a larger quantity was prepared a uniform product was obtained.

In the first experiment 3 grams of crystalline guaiacol and 4.08 grams of α-naphthyl isocyanate were mixed with petroleum ether, b. p. 80–90°, shaken and allowed to stand for several days. The crystalline product obtained was removed by filtration and found to melt at about 270° C. with decomposition.

In attempting to purify the product difficulty was encountered in finding a suitable solvent. Such solvents as ethyl alcohol (95%), ether, chloroform, benzene, xylene, acetone, amyl alcohol, ethyl acetate, heptane and glacial acetic acid were used with relatively slight effects on the substance in question. Absolute alcohol was then used with more favorable results. The substance was boiled in this solvent and a portion removed which melted at 117–118° C. The insoluble portion was then heated in acetone and the product removed therefrom upon crystallization was found to melt at 259° C. The acetone and alcohol-insoluble portions were then dissolved in glacial acetic acid. This product melted at 269° C.

In the second experiment the same quantities of reagents were used but petroleum, b. p., 179–200°, was used for the solvent. The mixture was heated 1 hour. The crystalline product obtained was treated as in the first experiment with identical results.

In the third experiment 10 grams of α-naphthyl isocyanate and 7.3 grams of guaiacol were heated a few minutes in heptane. A uniform product with a melting point of 117° C. and which was completely soluble in 95% ethyl alcohol was obtained.

M. p. after recrystallization = 116–117° C.

A nitrogen determination made by the Kjeldahl method produced the following results:

Sample No. 1, N = 4.76%.
Sample No. 2, N = 4.98%.

GUAIACYL ACETOPHENONE.

The preparation of guaiacyl acetophenone was carried out in four experiments under slightly different conditions which, however, produced similar results. In all cases equimolecular proportions or nearly so of bromacetophenone and potassium guaiacolate were used in heptane as a reaction medium.

In the first experiment 3 grams potassium guaiacolate and 3.9 grams bromacetophenone were mixed with heptane and allowed to stand at room temperature for 3 days. The mixture was then heated to boiling, filtered and allowed to crystallize. The crystals obtained were separated and recrystallized from alcohol.

M. p. of crude product = 101.5° C.
M. p. after recrystallization = 104° C.

In the second experiment 4.1 grams of potassium guaiacolate and 5.0 grams of bromacetophenone were heated in heptane for 40 minutes on a water-bath. The resulting crystals were filtered and recrystallized from alcohol.

M. p. of crude product = 101.5° C.
M. p. after recrystallization = 104° C.
Yield = 57.4%.

In the third experiment 10 grams of bromacetophenone and 8.2 grams potassium guaiacolate in heptane were heated for $^1/_2$ hour on a water-bath. The reaction mixture was allowed to stand over night, then heated another $^1/_2$ hour. The resulting crystals were removed and recrystallized from alcohol.

M. p. of crude product = 102–103° C.
M. p. of recrystallized product 104° C.
Yield = 47.9%.

In the fourth experiment 13.3 grams of bromacetophenone and 11.0 grams of potassium guaiacolate (theoretical amount, 10.84 grams) were allowed to stand for 24 hours in heptane after which the reaction mixture was heated 1 hour, filtered, and the product recrystallized from alcohol.

M. p. of crude product = 92–98° C.
M. p. of recrystallized product = 104° C.
Yield = 54.3%.

In all experiments there was a reddish brown, somewhat oily liquid with a very pungent odor left after the heptane had been recovered by distillation. In the fourth experiment this residue was weighed and found to be approximately 5 grams. This oily liquid and the pungent odor were also very noticeable in the alcoholic mother liquid of the recrystallized product. In the fourth experiment about

1.5 grams of crystals were obtained from this oily residue and dried between filter papers. The melting point of this product lay between 78 to 97° C.

The products of the four experiments were combined, recrystallized from alcohol and found to melt at 104° C. No change in melting point being observed, this product was regarded as pure.

GUAIACYL ACETOPHENONE PHENYL HYDRAZIDE.

One gram of guaiacyl acetophenone and 0.50 gram of phenyl hydrazine were mixed with 25 cc. of alcohol and the mixture warmed on a water-bath. A fluffy yellow crystalline product was obtained which melted from 108–111° C. Upon recrystallization from hot alcohol the melting point dropped to 106–108° C.

GUAIACYL ACETOPHENONE SEMICARBAZONE.

0.8 Gm. of sodium acetate and 0.5 Gm. of semicarbazide hydrochloride were dissolved in the smallest possible quantity of warm water. To this solution 1 gram of guaiacyl acetophenone and sufficient alcohol were added to produce a clear solution when hot. The heating was continued a few minutes longer. The solution was then filtered and the resulting crystals obtained were removed in fractions. There was a great range in the melting point in the same fraction as well as variation in the different fractions. The first fraction showed a range of from 103 to 130° C., while the second fraction melted from 130 to 163°+ C. Each portion was first washed with water and then with ether with the following results:

M. p. of water-insoluble portion = 115–145° C.
M. p. of ether-soluble portion = 103–104° C.
M. p. of ether-insoluble portion = 134–145° C.

It will be noted that the water removed the portion with the melting point of 163°+ which was undoubtedly undecomposed semicarbazide hydrochloride, while the ether removed the portion having the low melting point 103–104° which is the melting point of guaiacyl acetophenone.

A second semicarbizone reaction was carried out using 5 grams of guaiacyl acetophenone with an equimolecular amount of semicarbazide hydrochloride and $1^1/_2$ times as much sodium acetate as semicarbizide under the same conditions as before except that the heating was continued for 4 hours. The resulting crystals were removed in fractions with the following results:

M. p. of 1st crop of crystals = 103–145° C.
M. p. of 2nd crop of crystals = 116–165° C.

The second crop of crystals turned a deep yellow color while the first crop remained white.

Each fraction was washed successively with water and then with ether with the following results:

M. p. of water-insoluble portion, 1st fraction = 134–145° C.
M. p. of water-insoluble portion, 2nd fraction = 103–146° C.
M. p. of ether-insoluble portion, 1st fraction = 148–152° C.
M. p. of ether-insoluble portion, 2nd fraction = 130–158° C.

The products of the semicarbizone reactions were then mixed and recrystallized from alcohol and collected in fractions.

M. p. of 1st fraction = 142–147° C.