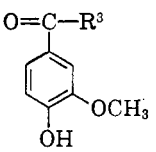
that these compounds show physiological activity, notably as analeptics,[5,6] prompted us to investigate other amides of this acid.

Kratzl and Kvasnicka[2a] noted that an additional carboxyl group on the aromatic ring of several analeptics increased their activity. It occurred to us that an extra carboxylic function in an alkyl side chain might have the same effect. To test this assumption, we prepared the series of vanillamides which are listed in Table I.

We have listed in Table II several vanillamides which were prepared but which do not belong in the above series.

TABLE II

SIMPLE VANILLAMIDES



R^3	M.P.	Nitrogen, % Calcd.	Nitrogen, % Found	Yield, %
	86–87	6.76	6.99	25
$-N(CH_2CH{=}CH_2)_2$	63–64	5.66	5.75	64
	128–129	6.33	6.28	40
$-N(CH_2)_2N(C_2H_5)_2$	115–116	10.52	10.43	45
$-N(CH_2)_3N(CH_3)_2$	139–140	11.10	11.08	40

These compounds were prepared by a simple two step procedure which is similar to that used by previous workers.[2,4] Acetylvanilloyl chloride was treated with the appropriate amine and the resulting acetylvanillamide, which usually was not isolated, was then saponified with aqueous potassium carbonate.

When compared with metrazole, the compounds reported here did not show significant analeptic activity. For example, at dose of 10 mg./kg. in dogs, they did not show effects on respiration or blood pressure while metrazole at dose of 1 mg./kg. gave an increase in both heart rate and respiratory volume.

EXPERIMENTAL

The preparation of *N,N*-diallyl-2-(*N'*-vanilloyl-*N'*-ethylamido)acetamide will illustrate the method that was used to prepare these vanillamides.

N,N-Diallyl-2-(N'-vanilloyl-N'-ethylamido)acetamide. To a cooled solution of 30 g. (0.13 mole) of acetylvanilloyl chloride in 100 ml. of dry benzene was added a solution of 22.4 g. (0.13 mole) of *N,N*-diallyl-2-ethylaminoacetamide and 9 g. of triethylamine in 50 ml. of dry benzene. The reaction mixture was allowed to stand at room temperature for 1 hr. The triethylamine hydrochloride which had formed was then removed by filtration and the filtrate was concentrated to dryness. The residue was heated on a steam bath for 2 hr. with 12 g. of potassium carbonate in 100 ml. of water.[7] The solution was made strongly basic by the addition of aqueous potassium hydroxide (10%) and, after unchanged starting material had been removed by extraction with chloroform, the aqueous phase was acidified with concentrated hydrochloric acid. The acidified solution was extracted with chloroform and the chloroform extract was dried and concentrated to dryness. The residue was crystallized from methanol-ether to give 24 g. of *N,N*-diallyl-2-(*N'*-vanilloyl-*N'*-ethylamido)acetamide, m.p. 112–113°.

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(7) In a number of cases it was necessary to add ethanol in order to increase the solubility of the reactants in this solution.

Methylation of the Salts of *N,N'*-Dinitroso-*p*-phenylenedihydroxylamine

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The dimethyl ether of *N,N'*-dinitroso-*p*-phenylenedihydroxylamine has been reported in a previous paper.[1] The dimethyl ether as reported was prepared via the disilver salt in diethyl ether as the solvent. The methylation with a large excess of methyl iodide took nine days, giving less than 10% yield.

This study was undertaken in order to find an improved method of preparing the ethers of *N,N'*-dinitroso-*p*-phenylenedihydroxylamine. It has been found that when the disodium *N,N'*-dinitroso-*p*-phenylenedihydroxylamine is treated with methyl iodide in dry dimethylformamide with a catalyst, a high yield of the dimethyl ether of *N,N'*-dinitroso-*p*-phenylenedihydroxylamine is obtained. The catalyst employed is a quaternary ammonium salt which is soluble in dimethylformamide.

The use of quaternary ammonium salts in the

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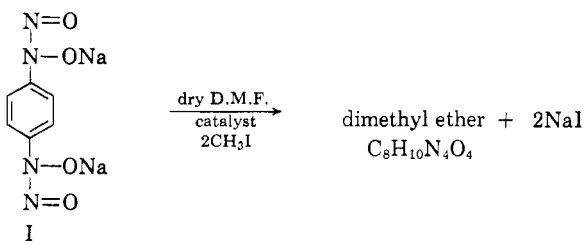
alkylation of phenols has been reported.[2] It has been shown that if the quaternary ammonium salt is insoluble, little effect is noted; whereas, when a soluble quaternary ammonium salt is used, a marked increase in rate is observed. Because of the extremely low solubility of the disodium *N,N'*-dinitroso - *p* - phenylenedihydroxylamine, alkylation with methyl iodide is insignificant after three days at room temperature. In the presence of the soluble quaternary salt, however, the alkylation proceeds and the yield of product is improved. It is believed that an equilibrium is established between disodium *N,N'*-dinitroso-*p*-phenylenedihydroxylamine and the quaternary ammonium salt to establish a soluble intermediate which is then methylated.

To establish the possible identity of the intermediate involved, dipiperidine-*N,N'*-dinitroso-*p*-phenylenedihydroxylamine was methylated with and without the catalyst under identical conditions. With the increased soubility of the dipiperidine salt over the disodium salt, the reaction in dry dimethylformamide proceeds. However, if the soluble quaternary ammonium salt is introduced in the above reaction, the methylation takes place much more rapidly and a higher yield of product is obtained.

Because of reasons previously described,[1] the exact structure of the diether is unknown.



I

EXPERIMENTAL

Dimethyl ether of I. Three grams of the disodium *p*-phenylene-*N,N'*-dinitrosodihydroxylamine (I), 3 g. of methyl iodide, and 6 g. of dry triethylallylammonium bromide were introduced into 30 ml. of dry dimethylformamide.

The reaction mixture was let stand at room temperature for 24 hr. under desiccant and stirring. The reaction mixture was diluted with water and extracted with chloroform. The chloroform was removed and a small amount of ether added to facilitate crystallization of the crude product. The product was filtered and washed with cold ether and cold acetone. The product was recrystallized from ethanol. Yield: 1.3 g. (68%); m.p., 205–207° uncorrected.

Dimethyl ethers from the dipiperidine salt. The procedure was the same as above except that the reaction was carried out in the absence of the quaternary ammonium salt catalyst. Yield: 0.44 g. (24.1%); m.p., 205–207° uncorrected.

Dimethyl ether of the dipiperidine salt. The reaction was carried out with the quaternary ammonium salt catalyst and a 3-hr. reaction time. Yield: 1.0 g. (53.6%); m.p., 204–206° uncorrected.

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The *gem*-Dimethyl Effect in Thiacyclodecanes

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We would like to report the synthesis of two new cyclic sulfides, thiacyclodecane and 6,6-dimethylthiacyclodecane. While thiacyclooctane and thiacyclononane have been prepared in yields of 34% and 6.6%, respectively,[1] the next higher cyclic sulfide to have been prepared was thiacyclotridecane,[2] the hiatus between the nine- and thirteen-membered rings emphasizing the difficulties usually experienced in the synthesis of medium ring compounds.

To determine if the "*gem*-dimethyl effect"[3] would counteract the usual "medium-ring effects"[4] in a ring closure proceeding by a nucleophilic displacement by sulfide ion on a saturated carbon atom, parallel syntheses of the sulfides reported above were carried out.

In view of the comparatively large yield of the substituted compound we conclude that the *gem*-dimethyl effect is operative in this reaction. The preparation of the medium ring homologs of 6,6-dimethylthiacyclodecane is now in progress and the results should further test the above conclusion.

EXPERIMENTAL

5,5-Dimethyl-1,9-nonanediol. A solution of 9.0 g. (0.033 mole) of diethyl-δ_1,δ-dimethyl azealate[5] in 10 ml. of anhydrous ether was added dropwise to a well stirred mixture of 1.9 g. (0.05 mole) of lithium aluminum hydride and 100 ml. of anhydrous ether. The mixture was stirred for 90 min. after the addition was complete, and 10 ml. of water was cautiously added. After 20 min. stirring the ether solution was filtered from the white precipitate which was then triturated with an additional 50 ml. of ether. The combined ether solutions, after drying yielded 5.4 g. (87.2%) of the diol, b.p. 118–119° (1 mm.), $n^{21.5}D$ 1.4625.

Anal. Calcd. for $C_{11}H_{24}O_2$: C, 70.16; H, 12.84. Found: C, 70.16; H, 12.92.

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