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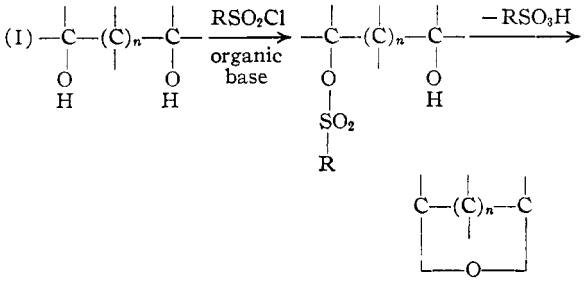
# Preparation and Reactions of Sulfonic Esters. V. Synthesis of Cyclic Tertiary Amines

BY D. D. REYNOLDS AND W. O. KENYON

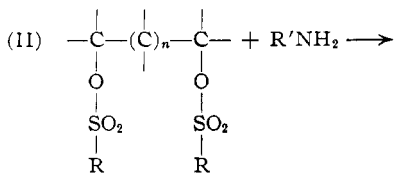
## Introduction

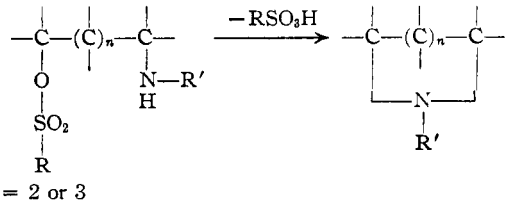
Recent studies in this Laboratory required a variety of tertiary amines. Cyclic tertiary amines of the N-substituted piperidine, morpholine and pyrrolidine types were not readily available. In studying the reactions of sulfonic esters, two methods were evolved for preparing such compounds. The first is partial amination of a glycol disulfonate, followed by cyclization, and the second is alkylation by an alkyl sulfonate of a cyclic secondary amine.

Cyclic ethers with five- and six-membered rings have been prepared[1] in good yields by the intramolecular reaction of a sulfonoxyl group with a properly located hydroxyl group as illustrated below.



Since alkyl sulfonates react with primary amines to yield the corresponding alkylated amine, cyclic amines should result by the intramolecular reaction of a sulfonoxyl group with the hydrogen of a properly situated amine group, as illustrated by Equation II.





$n$ = 2 or 3

Good yields of the desired amines are obtained under experimental conditions which allow the reaction to take place stepwise as shown.

Although alkyl sulfonates are known to be excellent alkylating agents for primary and secondary amines, no description of the alkylation of cyclic secondary amine which utilizes this fact has been found in the literature. The method offers a rapid and convenient preparation when the cyclic secondary amine involved is readily available. The preparation of N-methylpiperidine and N-methylmorpholine by treating methyl *p*-toluenesulfonate with piperidine and morpholine, respectively, illustrates this method.

## Experimental

A general procedure is given for the reaction of primary amines with glycol dibenzenesulfonates because of the similarity of the individual preparations. The specific amines prepared are listed in Table I.

TABLE I

CYCLIC TERTIARY AMINES PREPARED BY TREATING A PRIMARY AMINE WITH A GLYCOL DIBENZENESULFONATE

| Dibenzenesulfonate of | Primary amine | Product | B. p., °C. | Yield, % | Nitrogen, % Found | Nitrogen, % Calcd. |
|---|---|---|---|---|---|---|
| 1,5-Pentanediol | *n*-Butyl | N-Butylpiperidine | 175 | 50 | 9.6 | 9.9 |
| 1,5-Pentanediol | Cyclohexyl | N-Cyclohexylpiperidine | 234 | 81 | 8.4 | 8.4 |
| 1,5-Pentanediol | Aniline | N-Phenylpiperidine | 258 | 66 | 8.8 | 8.7 |
| 1,4-Butanediol | Aniline | N-Phenylpyrrolidine | 100 (6 mm.) | 75 | 9.8 | 9.5 |
| 1,4-Butanediol | Benzyl | N-Benzylpyrrolidine | 82 (5 mm.) | 62 | 8.9 | 8.7 |
| 2,5-Hexanediol | *n*-Butyl | N-Butyl-$\alpha,\alpha'$-dimethylpyrrolidine | 178 | 39 | 8.8 | 9.0 |
| 2,5-Hexanediol | Cyclohexyl | N-Cyclohexyl-$\alpha,\alpha'$-dimethylpyrrolidine | 233 | 27 | 7.8 | 7.7 |
| Diethylene glycol | *n*-Butyl | N-Butylmorpholine | 181 | 70 | 10.0 | 9.8 |
| Diethylene glycol | Benzyl | N-Benzylmorpholine | 79 (2 mm.) | 90 | 8.0 | 7.9 |

**Glycol dibenzenesulfonates** were prepared[2] by the reaction of two moles of benzenesulfonyl chloride with one mole of the appropriate glycol in pyridine at 0 to 10°.

**Amination and cyclization** resulted when 1.5 moles of primary amine was added dropwise during two hours to a refluxing solution of 0.5 mole of the glycol dibenzenesulfonate in 500 ml. of anhydrous dioxane. Sixty grams of sodium hydroxide (1.5 moles) in water was added and the volume of the reaction mixture reduced to one-half by distillation. The residue was cooled, stirred with ether, filtered and the filtrate distilled. Redistillation of the crude fraction obtained yielded the N-substituted cyclic amine. The methanesulfonyl, *p*-toluenesulfonyl, etc., esters of glycols may be employed similarly.

(1) D. D. Reynolds and W. O. Kenyon, THIS JOURNAL, **72**, 1593 (1950).

(2) R. S. Tipson, *J. Org. Chem.*, **9**, 235 (1944).

**Alkylation of cyclic secondary amines** was carried out (A) by addition of 0.5 mole of methyl *p*-toluenesulfonate dropwise to one mole of anhydrous morpholine. A vigorous reaction took place, after which distillation yielded 30 g. (60%) of N-methylmorpholine, b. p. 116–117°; (B) By replacing the morpholine by an equivalent amount of piperidine, 37 g. (74%) of N-methylpiperidine, b. p. 105–107°, was obtained.

## Summary

1. A new method has been developed for the preparation of cyclic tertiary amines which utilizes the reaction of a primary amine with a glycol disulfonate.

2. The following cyclic tertiary amines have been prepared to illustrate the applicability of this method: N-butylpiperidine, N-cyclohexylpiperidine, N-phenylpiperidine, N-phenylpyrrolidine, N-benzylpyrrolidine, N-butyl-$\alpha,\alpha'$-dimethylpyrrolidine, N-cyclohexyl-$\alpha,\alpha'$-dimethylpyrrolidine, N-butylmorpholine and N-benzylmorpholine.

3. Another method which may be used, and which is convenient when the secondary amine is readily available, utilizes the reaction of an alkyl sulfonate and a cyclic secondary amine. The preparation of N-methylmorpholine and N-methylpiperidine illustrates this method.

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[CONTRIBUTION NO. 70 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF TENNESSEE]

# Steric Hindrance in the Pfitzinger Reaction

BY GEORGE P. MUELLER AND ROBERT E. STOBAUGH

Although the condensation of isatin with ketones has been used frequently for the synthesis of quinoline derivatives, certain ketones do not enter into condensation. The failure to react is not easily explained in some instances, while in others steric inhibition is clearly present. For example, from a study of homologs of acetophenone, $C_6H_5CO(CH_2)_nCH_3$, Buu-Hoi and Cagniant[1] concluded that only such ketones in which $n$ was not greater than two would condense with isatin and that, *e. g.*, in *n*-caprophenone there was sufficient hindrance to prevent the reaction. It did not seem to us tenable that a single *n*-amyl substituent attached to the methylene carbon active in the condensation should provide steric hindrance in the ordinary sense. Therefore, *n*-caprophenone was prepared and found to condense with isatin under the usual conditions. Recently other examples have been reported[2] where similar objections seem to apply, for example, to the inability of 3-methyl-4-(isoamyloxy)-butyrophenone to condense as compared with 3-methyl-4-(isoamyloxy)-propiophenone which does form a cinchoninic acid.

Various examples can be mentioned of other failures where the ketones unquestionably offer sufficient hindrance to prevent the reaction. Several terpenones such as menthone, pulegone, camphor, tetrahydrocarvone, norcamphor and others of this group have been tried.[3] Also the di- and triketones dehydrocholic acid and dehydrodesoxycholic acid condensed with only one mole of isatin in each case.[4]

(1) Buu-Hoi and Cagniant, *Bull. soc. chim.*, 123 (1946).

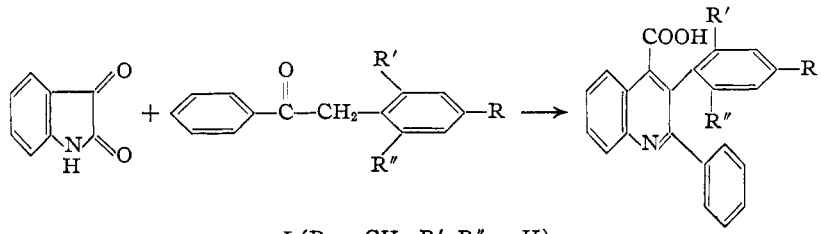
(2) de Clercq and Buu-Hoi, *Compt. rend.*, **227**, 1251 (1948).

(3) (a) Borsche and Rottsieper, *Ann.*, **377**, 70 (1910); (b) Buu-Hoi, *J. Chem. Soc.*, 795 (1946).

(4) Borsche, *Ber.*, **57**, 1373 (1924).

In a systematic approach Buu-Hoi[3b] had found that 2,4-dimethylacetophenone and 2,6-dimethyl-4-*t*-butylacetophenone both condense readily with isatin. However, where the active methylene group was more heavily substituted as in the corresponding benzyl aryl ketones the effects of increasing substitution in the benzoyl moiety became apparent in that 4-methyldesoxybenzoin gave 62% of the cinchoninic acid, 2,4-dimethyldesoxybenzoin a low yield and 2,4,6-trimethyldesoxybenzoin failed to react.

It was of interest to see what effect transposition of the methyl groups to the other ring of these ketones would have on their reactivity in the Pfitzinger condensation. The results show that I condensed to yield 37% of the cinchoninic acid, II yielded only 12% and III would not react at all. In fact besides the application at reflux of 33% aqueous alcoholic potassium hydroxide for forty-eight hours, which were the standard conditions used, this same reagent was tried for ninety-six hours and at 200° for twenty-four hours on isatin and 2′,4′,6′-trimethyldesoxybenzoin. Likewise sodium ethoxide in absolute alcohol and sodium amide in toluene were used for extended periods. In each case better than 90% of the original ketone was recovered.



I (R = $CH_3$, R′, R″ = H)
II (R, R′ = $CH_3$, R″ = H)
III (R, R′, R″ = $CH_3$)

These observations show the specific effect of an *o*-substituted aryl group attached to the active