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-α,α'-dimethylpyrrolidine, N-cyclohexyl-α,α'-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.

ROCHESTER 4, NEW YORK RECEIVED JULY 16, 1949

[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).

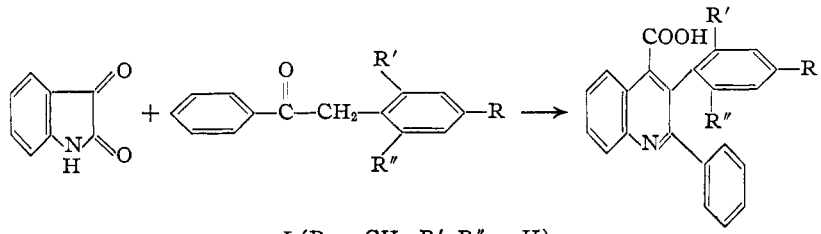
(2) de Clercq and Buu-Hoi, *Compt. rend.*, **227**, 1251 (1948).

(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

methylene carbon. Likewise, considered together with Buu-Hoi's experience in the desoxybenzoin series they lead to the conclusion that a simple aryl group on either the carbonyl or methylene carbon will make the ketone subject to steric inhibition by a bulky substituent attached at the other reactive carbon atom. However, it would appear that complete hindrance of a non-ω-substituted acetophenone is not readily obtained.

Experimental

2-Phenyl-3-*n*-butylcinchoninic Acid.—In a 200-ml., round-bottomed flask were placed 17.6 g. (0.10 mole) of *n*-caprophenone,[5] 14.7 g. (0.10 mole) of isatin, 45.7 g. (0.29 mole) of 33% potassium hydroxide and 90 ml. of alcohol. After refluxing forty-eight hours, the alcohol was distilled, and the residue diluted with water and extracted with two 15-ml. portions of ether to remove 2.1 g. of unreacted ketone. Acidification of the aqueous layer with 10% acetic acid precipitated 13.7 g. of the crude cinchoninic acid which was decolorized in glacial acetic acid and crystallized therefrom three times to give 4.5 g. (30%) of 2-phenyl-3-*n*-butylcinchoninic acid, m. p. 237–238° (dec.). *Anal.* Calcd. for $C_{20}H_{19}NO_2$: C, 78.66; H, 6.27; N, 4.59; neut. equiv., 305. Found: C, 78.42; H, 6.37; N, 4.62; neut. equiv., 304. Following a similar procedure, the mixture was heated for twenty-four hours, but no cinchoninic acid was obtained. Increasing the time of reflux to seventy-two hours did not increase the yield; however, none of the original ketone was recovered in the latter experiment.

2-Phenyl-3-*n*-butylquinoline Methiodide.—The above cinchoninic acid, 0.3 g., was dissolved in 3 ml. of 10% sodium hydroxide and the sodium salt which crystallized overnight collected, washed with 1 ml. of water and dried at 100° for an hour. An intimate mixture of this with soda lime was pyrolyzed for twenty minutes at 280–300° (oil-bath) in a Hickman still at 1 mm. The yellow oil collected was treated in absolute ether with 1 ml. of methyl iodide, warmed, and the fine, yellow needles collected after a day. The product was recrystallized three times from absolute alcohol diluted with absolute ether; m. p. 204° (dec.).

Anal. Calcd. for $C_{20}H_{22}IN$: C, 59.56; H, 5.50; N, 3.47. Found: C, 59.66; H, 5.57; N, 3.72.

2-Phenyl-3-*p*-tolylcinchonic Acid.—4′-Methyldesoxybenzoin was prepared after the method of Strassmann[6] where the benzene solution containing *p*-tolylacetyl chloride, from 20 g. (0.2 mole) of the acid and 13.6 g. (0.1 mole) of phosphorus trichloride, was treated with 30.7 g. (0.23 mole) of anhydrous aluminum chloride, warmed for one hour and worked up as usual to yield 20.0 g. (73%) of the distilled ketone, b. p. 148–150° (3 mm.); m. p. of product from alcohol, 94–95°. This ketone, 6.3 g. (0.03 mole) and 5.2 g. (0.035 mole) of isatin were treated with 16.8 g. (0.10 mole) of 33% potassium hydroxide and 30 ml. of alcohol in the manner described for forty-eight hours. Unreacted ketone was recovered, 4.8 g., and 2.5 g. of crude precipitated acid was collected, decolorized in alkali, reprecipitated and recrystallized three times from glacial acetic acid. The final yield was 1.2 g. (37%); m. p. 271–272° (dec.). Similar experience with twenty-four and seventy-two hour reaction times was had here as above.

Anal. Calcd. for $C_{23}H_{17}NO_2$: C, 81.39; H, 5.05; N, 4.13; neut. equiv., 339. Found: C, 81.18; H, 5.45; N, 4.09; neut. equiv., 338.

2-Phenyl-3-*p*-tolylquinoline Picrate.—Decarboxylation of the acid itself was accomplished at 320–340° (1 mm.) as before and the viscous, yellow quinoline dissolved in alcohol and treated with alcoholic picric acid. The purified picrate melted at 208–209°.

Anal. Calcd. for $C_{28}H_{20}N_4O_7$: C, 64.12; H, 3.84; N, 10.68. Found: C, 63.82; H, 3.79; N, 10.77.

2-Phenyl-3-(2,4-dimethylphenyl)-cinchoninic Acid.—2′,4′-Dimethyldesoxybenzoin was synthesized by a method not previously reported for this ketone. 2,4-Dimethylphenylacetonitrile,[7] 13.1 g. (0.09 mole) in 80 ml. of dry ether was added during thirty minutes to the Grignard reagent prepared from 18.8 g. (0.12 mole) of bromobenzene in 40 ml. of dry ether. The resulting mixture was poured with vigorous stirring into 1 kg. of crushed ice and 40 g. of concentrated sulfuric acid. The separated ether layer was suitably washed and concentrated, yielding a brown oil which solidified on standing. This was recrystallized twice from alcohol giving 4.8 g. (25%) of 2′,4′-dimethyldesoxybenzoin, m. p. 106–107°.[7]

This ketone, 6.7 g. (0.03 mole) and 5.2 g. (0.035 mole) of isatin were treated with 16.8 g. (0.10 mole) of 33% potassium hydroxide and 30 ml. of alcohol as above. The unreacted ketone, 3.1 g., this time precipitated when the water was added. Acidification of the filtrate precipitated 1.5 g. of the crude cinchoninic acid which after the usual purification weighed 0.7 g. (12%); white needles, m. p. 282–283° (dec.).

Anal. Calcd. for $C_{24}H_{19}NO_2$: C, 81.56; H, 5.42; N, 3.96; neut. equiv., 353. Found: C, 80.65, 80.44; H, 5.49, 5.26; N, 3.95; neut. equiv., 352.

2-Phenyl-3-(2,4-dimethylphenyl)-quinoline Picrate.—The cinchoninic acid was heated in the still for five minutes at 320–340°; then vacuum was applied and the quinoline collected. The picrate was crystallized three times from alcohol; m. p. 203–204°.

Anal. Calcd. for $C_{29}H_{23}N_4O_7$: C, 64.68; H, 4.12; N, 10.41. Found: C, 64.37; H, 3.89; N, 10.34.

Summary

4′-Methyl-, 2′,4′-dimethyl- and 2′,4′,6′-trimethyldesoxybenzoin have been tried with isatin in the Pfitzinger reaction and only the latter found completely resistant to condensation. The decreasing yield of condensed products with increasing *ortho* substitution indicates steric hindrance of the reactive methylene group. *n*-Caprophenone, previously reported inactive, has been found to condense. The corresponding cinchoninic acids and some quinoline derivatives have been characterized.

KNOXVILLE, TENNESSEE RECEIVED SEPTEMBER 16, 1949

(5) Tiffeneau and Levy, *Compt. rend.*, **183**, 969 (1926).

(6) Strassmann, *Ber.*, **22**, 1229 (1889).

(7) Harispe, *Ann. chim.*, **6**, 247 (1936).