TABLE I

CLEAVAGE OF KETONES, $R_1—CO—R_2$

R_1	R_2	R_1COOH	R_2COOH
		% by moles	
Phenyl	*o*-Tolyl	82	18
Phenyl	*m*-Tolyl	48	52
Phenyl	*p*-Tolyl	42	58
Phenyl	*p*-Biphenyl	49	51
o-Tolyl	*p*-Biphenyl	16	84
m-Tolyl	*p*-Biphenyl	48	52
p-Tolyl	*p*-Biphenyl	52	48
Phenyl	1-Phenanthryl[a]	96	4
Phenyl	2-Phenanthryl[a]	56	44
Phenyl	3-Phenanthryl[a]	55	45
Phenyl	9-Phenanthryl[a]	95	5

[a] For the preparation of these ketones see Bachmann, *ibid.*, **57**, 555 (1935).

TABLE II

RELATIVE TENACITIES OF GROUPS

p-Tolyl	1.38	2-Phenanthryl	0.79
m-Tolyl	1.08	*o*-Tolyl	.22
p-Biphenyl	1.04	9-Phenanthryl	.05
3-Phenanthryl	0.82	1-Phenanthryl	.04

It is apparent that not only the nature of the group but also the position of attachment to the ring are of importance; this is especially evident from a comparison of the tenacities of the four phenanthryl groups: the 1- and 9-phenanthryl groups are rapidly separated from the carbonyl group while the 2- and 3-phenanthryl groups are held more firmly. Similarly, the *o*-tolyl group is easily separated from the carbonyl while the *m*- and *p*-tolyl radicals are not.

Knowing the values of the tenacities of two groups R_1 and R_2 with respect to the phenyl group, one can calculate the manner in which the unsymmetrical ketone $R_1—CO—R_2$ will cleave. Thus, from the value 0.22 for *o*-tolyl and 1.04 for *p*-biphenyl the ratio of *o*-toluic acid to *p*-phenylbenzoic acid in the cleavage reaction should be 17 to 83%. In Table III a comparison is shown of the predicted and the actual results that have been observed in the three cases that have been investigated.

TABLE III

COMPARISON OF PREDICTED AND ACTUAL RESULTS

R_1	R_2	Predicted, % R_1COOH	Predicted, % R_2COOH	Found, % R_1COOH	Found, % R_2COOH
o-Tolyl	*p*-Biphenyl	17	83	16	84
m-Tolyl	*p*-Biphenyl	51	49	48	52
p-Tolyl	*p*-Biphenyl	57	43	52	48

It is seen that in these three instances the predicted results are of the same order as the experimental results. We are now engaged in determining the relative tenacities of a large number of groups and in testing the values in the manner indicated.

Summary

Eleven unsymmetrical aromatic ketones have been cleaved by potassium hydroxide and the proportions of the two acids in the mixture have been determined.

Values representing the relative tenacity with which the groups are held to the carbonyl group have been determined for eight radicals.

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[CONTRIBUTION FROM THE DEPARTMENT OF RESEARCH IN PURE CHEMISTRY, MELLON INSTITUTE OF INDUSTRIAL RESEARCH]

Cinchona Alkaloids in Pneumonia. II. Ketone Formation with Sodium Amide

BY ALICE G. RENFREW AND LEONARD H. CRETCHER

The preparation of α-aminopyridine from the action of sodium amide on pyridine is well known. In an attempt to prepare amino-cinchona alkaloids for use in chemotherapeutic investigations which have been under way in this Laboratory for some time, hydroquinine, quinine and cinchonine were treated with sodium amide. We were unable to isolate any amino-substituted alkaloid from the reaction mixture despite the patent claims of Chichibabin.[1] However, it was found that the alkaloid present in the reaction mixture had been transformed to the corresponding ketone in amounts equaling or exceeding the yield of ketone obtained in the usual method of oxidation by means of chromic acid.[2]

The conditions used in the present experiments were comparable with those employed by Chichibabin[3] for the amination of nicotine. Unchanged alkaloid was recovered, and varying amounts of ketone were formed—the latter involving a transformation of the secondary alcohol group of the

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(1) German Patent 374, 291; *C. A.* **18**, 2176 (1924).

(2) Rabe, *Ann.*, **364**, 330 (1909).

(3) Chichibabin and Kirssanov, *Ber.*, **57**, 1163 (1924).

alkaloid. Small amounts of ketone formed when metallic sodium was substituted for sodium amide.

Sodium Amide with Hydroquinine.—In a typical experiment an excess of sodium amide (8 g. or 0.2 mole) was added to a boiling solution of 15 g. of dry hydroquinine in 250 cc. of dry xylene. Heating with stirring was continued for twenty-four hours. In studying the reaction mixture, the xylene solution was decanted from a small amount of a dense sodium amide residue. It sometimes happened that on the addition of water to the cold mixture, a considerable amount of the original alkaloid separated and could be removed by filtration. The xylene solution was extracted with dilute hydrochloric acid and the solution of hydrochlorides, in turn, made alkaline for ether extraction of the alkaloid bases. Unchanged alkaloid crystallized during the evaporation of the ether solutions and a further recovery was effected by triturating the ether concentrates with benzene. The final very soluble residue was largely ketone, which was recrystallized from anhydrous ether; yield, 6 g. or 40%. If crystallization took place slowly, the ketone formed in large transparent plates. A much smaller yield of hydroquininone was obtained when a lower boiling solvent such as toluene was used. Alcoholic solutions of the ketone showed mutarotation. $[\alpha]_D$ +125.4° five minutes after solution; $c = 1.164$ g.; $l = 1$; $\alpha = +1.46°$. After fifteen hours $\alpha = +0.83$ and $[\alpha]_D$ +71.3° for the same solution. Rabe[4] has reported a similar mutarotation with a final value of $[\alpha]_D$ +73°.[5]

The identity of the ketone was further checked through the preparation of hydroquininone by the chromic acid oxidation of hydroquinine.[2] In melting point determinations the pure substances and their mixture melted at 98–99°.

Sodium Amide with Cinchonine.—Under the above conditions in the case of alkaloids with an unsaturated vinyl side-chain, less ketone was isolated. About 21% of cinchoninone was obtained from cinchonine. 9 g. of sodium amide was added to a boiling solution of 30 g. of cinchonine in 300 cc. of xylene. Heating and stirring were continued for twenty hours; 6.4 g. of cinchoninone was isolated; m. p. 125–127°. In absolute alcohol the following mutarotation was observed: $[\alpha]_D$ +3.3° ten minutes after solution; $c = 1.216$ g.; $l = 1$; $\alpha = +0.04°$. After twenty hours $[\alpha]_D$ +74.8°; $\alpha = +0.91°$. These constants agree with the values given by Rabe for cinchoninone.[2]

An orange-yellow gelatinous precipitate appeared when the xylene reaction mixture was cooled. Presumably this was a sodium salt, because in the presence of a little water the color disappeared and cinchonine was recovered.

Analysis of Sodium Amide.—The quality of the sodium amide was checked by the preparation of aminopyridine under the conditions described by Wibaut and Dingemanse.[6] Crystalline aminopyridine was obtained in a 50% yield, equaling the yield reported by Wibaut. Bergstrom and Fernelius[7] have noted the common impurities in commercial sodium amide. The material used in the present experiments gave a negative test with titanium sulfate when examined for the presence of peroxides. A quantitative estimate of oxidizing impurities was carried out according to the methods of Schrader.[8] Sodium amide was decomposed in ice water and the insoluble barium salts precipitated. The titration of the barium salt required 5 cc. of 0.1 N permanganate and the acidified filtrate required 36 cc. of 0.1 N permanganate for 1 g. of sodium amide—or 0.03 g. of oxygen as nitrates, peroxides, etc., per gram of sodium amide. The available oxygen is too small in amount to account for the ketone formation as a simple oxidation.

In a consideration of the observed dehydrogenation of the secondary alcohol group of hydroquinine and cinchonine, it seemed desirable to try the action of sodium under similar conditions; 20 g. of dry cinchonine in 300 cc. of dry xylene was refluxed for forty hours in the presence of 1.7 g. of metallic sodium; 0.8 g. of cinchoninone was isolated. This product showed mutarotation with a final dextro value of +70°. In the presence of 2 molecular equivalents of sodium per mole of cinchonine and a constant current of carbon dioxide-free air, a yield of 6–7% was obtained. A similar yield was obtained with 2 equivalents of sodium when a solution, previously boiled to expel air, was refluxed for twenty hours with the outlet tube protected from air by a mercury seal.

In order to determine the generality of the reaction, the action of sodium amide on methylisobutylcarbinol in xylene was tested. Most of the alcohol was recovered and no ketone was identified. In xylene solutions of benzhydrol treated with sodium amide, an intense purple color was observed, but no benzophenone was identified after brief or prolonged heating.

Summary

Some cinchona alkaloids were converted to ketones by the action of sodium amide and sodium. The reaction does not appear to be a general one.

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(4) Rabe, Huntenburg, Schultze and Volger, *Ber.*, **64**, 2498 (1931).

(5) Rabe's data have been incorrectly assigned to hydroquinicine in Abderhalden's "Handbuch der biologischen Arbeitsmethoden," Abt. I, Teil II, Heft 3, 1927, p. 358.

(6) Wibaut and Dingemanse, *Rec. trav. chim.*, **42**, 240 (1923).

(7) Bergstrom and Fernelius, *Chem. Rev.*, **12**, 43 (1933).

(8) H. Schrader, *Z. anorg. allgem. Chem.*, **108**, 44 (1919).