Ester werden durch Umkristallisieren aus *n*-Butanol, die flüssigen Ester durch fraktionierte Destillation gereinigt (Tabelle 1).

Analyse. Die von Huggins und Lapides [1] beschriebene Methode wurde für die Bestimmung der Ester bis zur *n*-Valeriansäure verwendet, bei Estern höherer Säuren musste jedoch die Methode abgeändert werden. 0,33 Millimol des Esters werden in 100 ml 0,1 N methylalkoholischer Natronlauge gelöst und 6 Stunden unter Rückfluss gekocht. Von dem Hydrolysat werden 1 ml auf 100 ml mit wässriger 0,1 N Natronlauge verdünnt. An dieser Lösung werden die kolorimetrischen Bestimmungen ausgeführt. Als Standardlösungen werden Lösungen von *p*-Nitrophenol verwendet, welche 100 bis 700 Mikromol per Liter enthalten. Die Messungen wurden bei einer Wellenlänge von 400 mμ durchgeführt. Zur Verwendung gelangte ein Beckmann B Spektrophotometer.

Herrn Laborator Dr. Gunnar Jungner danke ich für die Förderung dieser Arbeit.

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New Synthesis of 3-Hydroxy-2-piperidone

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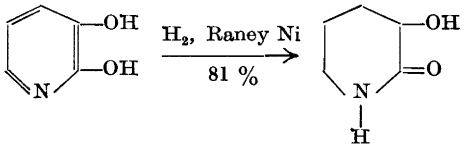
Catalytic hydrogenation of 2,3-pyridinediol has been shown to give the expected 3-hydroxy-2-piperidone *cf.* [1, 2]. This compound has previously been obtained by cyclization of *α*-hydroxy-*δ*-amino-*n*-valeric acid, but no detailed directions were reported [3].



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Experimental. 2,3-Pyridinediol [4-6] (0.56 g) and anhydrous methanol (40 ml) were shaken (6 h) with Raney nickel (0.2 g) under hydrogen (140 atm) at 160—180°. The Raney nickel was removed by filtration and the filtrate evaporated in a vacuum. The crystalline residue was crystallized from methanol-ether. The yield was 0.47 g (81 %) of 3-hydroxy-2-piperidone [white crystals, m. p. 133—135° (Hershberg apparatus, corr.), previously found [3] 134.3°]. (Found: C 52.3; H 7.8; N 12.2. Calc. for $C_5H_9NO_2$ (115.1): C 52.2; H 7.9; N 12.2).

Sublimation (100—110°/0.05 mm) also gave white crystals, m. p. 133—135°.

In a first experiment carried out at 95—100° under 110 atmospheres of hydrogen for one hour only starting material was isolated.

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On the Mechanism of Alkylation of β-Keto Esters

I. Methylation of β-Hydroxycoumarilic Acid Ethyl Ester

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The mechanism of the alkylation of metallic derivatives of tautomeric substances has been the subject of many investigations and theories [1]. As late as 1953 Brändström [2,3] published a new theory and in 1955 Kornblum *et al.* [4] proposed a theory seen from a different aspect.

In an attempt to elucidate the mechanism we have begun to study the alkylation of *β*-keto esters. The methylation of *β*-hydroxycoumarilic acid ethyl ester was

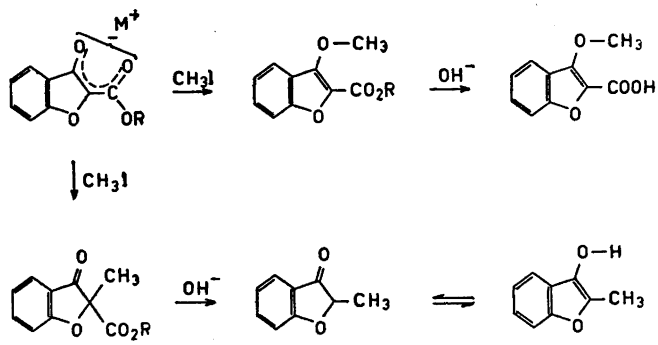

Fig. 1.

selected for study. The reaction has earlier been the subject of a somewhat superficial investigation [5,6] and is well suited to the present purpose as it gives both the C- and O-alkyl product. In order to find out the extent to which the free anion and the metal chelate give C- and O-alkylation, the rate and order of the different reactions must be studied under conditions which lead to different degrees of dissociation.

The β-hydroxycoumarilic acid ethyl ester was prepared in a pure enol-form by an improved method according to Friedländer [7]. Through IR-spectra we have shown that it changes only very slowly into the keto-form at 0°C.

A method to determine the proportion of C- and O-alkyl product formed in alkylation has been worked out. The alkylation reaction is stopped by adding acid; the mixture is diluted with water and the ester extracted with carbon tetrachloride. The residue is titrated with NaOH to determine the velocity of the total reaction. From the carbon tetrachloride solution the unalkylated ester is extracted with 1 N KOH and the residue saponificated, decarboxylated, acidified and extracted with ether.

The acid from the O-alkyl product, which does not decarboxylate, is titrated to pH 6.5—7.0. At that pH the enol-form of 2-methyl coumarone does not interfere. The difference between the rate of the total reaction and that of the O-alkylation is taken as the rate of C-alkylation.

Table 1. Methylation in CH_3OH.

Metal	k_{C+O}	k_C	k_O	C/O
Li	1.20	1.03	0.17	6.0
Na	2.96	2.26	0.70	3.2
K	3.45	2.78	0.67	4.2

Table 2. Methylation with Li.

Solution	k_{C+O}	k_C	k_O	C/O
CH_3OH	1.20	1.03	0.17	6.0
C_2H_5OH	0.89	0.76	0.13	5.7
n-C_3H_7OH	0.54	0.44	0.10	4.5
n-C_4H_9OH	0.36	0.27	—0.09	—3

k_{C+O}, k_C and k_O are, respectively, the velocity constants for the total, C- and O-alkylation. They are given in units of $10^{-2} \cdot$ l/mole $\cdot$ min. C/O is the quotient of the rates of the C- and O-alkylation.

Hitherto the methylation reaction has been studied at 50°C with methyl iodide in methanol solution using Li, Na and K as catalysts, and in ethanol, *n*-propanol and *n*-butanol with Li as catalyst. The concentration of alkali was 0.1 M; the ester was used in 5 % and the methyl iodide in 100 % excess. Both the C- and O-alkylation reactions are of the second order. The preliminary results are shown in Tables 1 and 2.

It has been found that the rate of the C-alkylation decreases more rapidly than that of the O-alkylation through the solvent series $CH_3OH > C_2H_5OH > n\text{-}C_3H_7OH > n\text{-}C_4H_9OH$. Thus the yield of C-alkyl product falls in the same series. In methanol the rate of C-alkylation increases through the series Li<Na<K and the O-alkylation through the series Li < Na ~ K. Thus the ratio C/O decreases in the series Li > K > Na.

This suggests that the mechanism is rather complicated and depends on more factors than the dissociation degree.

In order to find out the extent to which the results depend on the occurence of the alkali salts as ions or a chelate in the reaction medium, the degree of dissociation must be known. We have begun to determine this quantity, by a method due to Brändström [8], from electrical conductance measurements. The complete elucidation of the mechanism requires that other aspects of the reaction should be investigated. Further studies along these lines are in progress at this institute.

Experimental: Salicyl-O-acetic acid [O-(carboxymethoxy)-benzoic acid] was prepared from salicylic acid and chloroacetic acid [9]. Unchanged salicylic acid was separated from the product by continued extraction with benzene.

Salicyl-O-acetic acid diethyl ester was prepared by esterification in the usual way with benzene as water-removing agent [10]. Yield 84 %; m. p. 43.0—44.5°C (not earlier published).

β-Hydroxycoumarilic acid ethyl ester was prepared according to Friedländer [7] with the following modification: After condensation and acidification with 50 % H_2SO_4 at 0°C the product was dried in air at room temperature for a few hours, and than in a desiccator over night. Yield 93 %; m. p. 70.5—71.5°C. The ester contained a little Na_2SO_4 and after recrystallization from dry ether it was obtained as white needles with the same m. p. The low m. p. (65°) earlier reported is probably due to the change of ester into its keto-form during recrystallization from water-alcohol mixture (The velocity of tautomerisation increases with the temperature and polarity of the solvent [11]). It is important that the ester after acidification be kept at as low a temperature as possible.

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