yield. Thus, when cholestan-3β-ol and 7,22-ergostadien-3β-ol were refluxed in xylene in the presence of three times their weight of copper chromium oxide, cholestan-3-one and 7,22-ergostadien-3-one were isolated in a 60–65% yield. This is believed to be the lowest temperature (139°) at which a copper chromium oxide catalyst has been found effective for the dehydrogenation of alcohols. This reaction is usually carried out in the vapor phase[2] above 300°, although liquid phase[3–5] oxidation of alcohols has been reported in the temperature range of 200-300°.

EXPERIMENTAL[6]

Hydrogenation experiments. The hydrogenations under high pressure were carried out in a stainless steel pressure vessel. Heating was accomplished with a jacket which allowed the rate of temperature increase to be the same in all cases. It was approximately 1°/min. Temperature and pressure changes were continuously recorded on automatic devices. The product of the various hydrogenations of acetone was identified as 2-propanol by its boiling point (80.5–81.8°) and index of refraction (n_D^{20} 1.3779). The used catalyst was always considerably more black in color than the catalyst which, in agreement with Adkins, *et al.*,[1] was a brownish black. The results of the hydrogenation experiments are summarized in Fig. 1.

Activation of copper chromium oxide. A mixture of 150 ml. of cyclohexanol and 6 g. of unactivated copper chromium oxide was refluxed with stirring under a stream of nitrogen for 4 hr. The jet-black catalyst was filtered off. From 10.0 g. of the filtrate was obtained 1.67 g. of cyclohexanone semicarbazone, m.p. 166–168°. The melting point was undepressed on admixture with an authentic sample. The recovered catalyst was washed with acetone and then used for the reduction of 20 ml. of acetone under 210 atm. pressure of hydrogen (Fig. 1, Curve B).

Oxidation of cholestan-3β-ol. A mixture of 2.0 g. of cholestan-3β-ol, 150 ml. of xylene, and 6.0 g. of unactivated copper chromium oxide was refluxed with stirring for 4 hr. The catalyst was filtered off and extracted with 200 ml. of hot ethanol. The combined filtrates were evaporated to dryness under reduced pressure. Chromatography of the residue on alumina and elution with ether afforded 1.34 g. (67%) of cholestan-3-one (λ_{max} 5.82 μ) which from methanol formed colorless microcrystals, m.p. 128–129°, $[\alpha]_D$ 42°. Lit.[7] m.p. 129–130°, $[\alpha]_D$ 40°.

Oxidation of 7,22-ergostadien-3β-ol. A mixture of 2.0 g. of 7,22-ergostadien-3β-ol, 150 ml. of xylene, and 6.0 g. of unactivated copper chromium oxide was refluxed with stirring under a stream of nitrogen for 2 hr. The catalyst was filtered off and extracted with 300 ml. of boiling ethanol The combined filtrates were evaporated to dryness under reduced pressure and the residue (1.7 g.) was chromatographed on alumina. The material which was eluted with ether was crystallized from ether-methanol and afforded 0.8 g. of 7,22-ergostadien-3-one as colorless flakes, λ_{max} 5.82 μ, m.p. 183–185°, $[\alpha]_D$ ±0°, Lit.[8] m.p. 182–183°, $[\alpha]_D$ 2°. Concentration of the mother liquor gave an additional 0.1 g. of the ketone (combined yield: 60% based on unrecovered starting material). Elution of the alumina with chloroform-ethanol and crystallization of the resulting steroid from ethyl acetate-methanol-water yielded 0.5 g. of starting material as colorless flakes, m.p. 182–183°, which readily formed a digitonide and possessed an infrared spectrum identical with authentic 7,22-ergostadien-3β-ol. The spectrum was quite different from that of samples (melting variously up to 203°) of the digitonin non-precipitable hydroxy compound (λ_{max} 2.76 μ) obtainable by allowing 7,22-ergostadien-3β-ol to react at 150° in the presence of copper chromium oxide under pressure of hydrogen.[9]

When 7,22-ergostadien-3β-ol was refluxed in xylene as described above with one particular batch of copper chromium oxide, instead of the ketone an "intermediate" was obtained by chromatography (alumina; elution with petroleum ether) which possessed neither hydroxyl nor carbonyl bands in the infrared, but which did possess a strong band at 9.03 μ. It was usually obtained in *ca.* 35% yield. It melted at 110–111° (from ether-methanol) and was converted to 7,22-ergostadien-3-one (m.p. 178–179°, λ_{max} 5.82 μ) simply by recrystallizing it from aqueous acetic acid. This compound was obtained on several occasions, but only with the one sample of catalyst. Other catalyst preparations gave the ketone directly. The structure of this material has not been elucidated.

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(2) See, for instance, R. E. Dunbar and M. R. Arnold, *J. Org. Chem.*, **10**, 501 (1945) and the references cited therein. This process has also been the subject of a number of patents, *e.g.*, T. Kritchevsky, U. S. Patent **2,462,107**, Feb. 22, 1949; *Chem. Abstr.*, **43**, 3841 (1949).

(3) L. P. Kyrides, W. Groves, and F. B. Zienty, U. S. Patent, **2,382,071**, Aug. 14, 1945; *Chem. Abstr.*, **40**, 90 (1946).

(4) O. J. Weinkauff, U. S. Patent **2,455,631**, Dec. 7, 1948; *Chem. Abstr.*, **43**, 1797 (1949).

(5) J. G. M. Bremner and D. G. Jones, British Patent **583,344**, Dec. 16, 1946; *Chem. Abstr.*, **41**, 2746 (1947).

(6) The infrared spectra were determined on a Perkin-Elmer double beam spectrophotometer by Mr. H. K. Miller and Mrs. Phyllis Smeltzer in CS_2. The melting points were determined on a Kofler block and are recorded as read. The rotations were determined at 20° in chloroform in 1–2% concentrations. The copper chromium oxide was prepared exactly according to the directions of Adkins, *et al.*[1]

(7) A. E. Lippman, E. W. Foltz, and C. Djerassi, *J. Am. Chem. Soc.*, **77**, 4364 (1955).

(8) A. Windaus and E. Auhagen, *Ann.*, **472**, 185 (1929).

(9) W. R. Nes and E. Mosettig, *J. Org. Chem.*, **18**, 276 (1953).

Oxidation of 3-Methylisoquinoline

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In connection with studies to be reported elsewhere we had the occasion to repeat the synthesis of 3-aminoisoquinoline from 3-methylisoquinoline (I)

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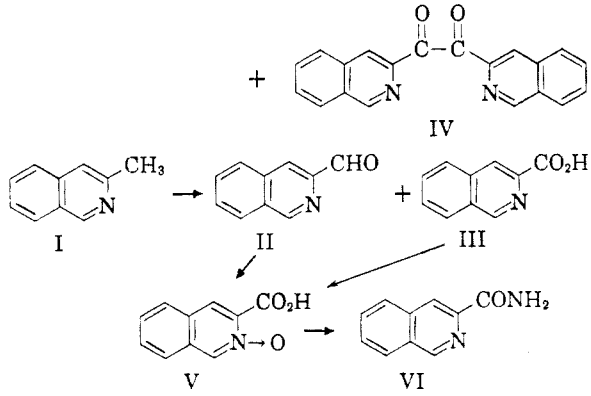
as described by Teague and Roe.[2] Because of two deviations from their experimental procedure we observed the formation of products not described by them. The first deviation consisted of carrying out the selenium dioxide oxidation of I to 3-isoquinolinecarboxaldehyde (II) under reflux rather than in an open vessel from which the water formed in the reaction (as well as some of the reactant and product) might escape. Under our conditions the temperature of the oxidation was 40–50° below that of Teague and Roe. Three substances were isolated from the reaction mixture. The first, II, was obtained in 25–37% yield (based on I consumed), which is about 10–20% lower than the yield reported by Teague and Roe. The second product was 3-isoquinolinecarboxylic acid (III), isolated only in trace amounts. The third product was di(3-isoquinolinyl)glyoxal (IV), which was obtained in about 3% yield. When the reaction was carried out under the conditions of Teague and Roe, the results were substantially as reported by them and none of the diketone (IV) was obtained.



The second deviation consisted of an attempt to eliminate the fractional distillation of the two solids, I and II. The crude mixed substances were oxidized with hydrogen peroxide in acetone solution, the amount of oxidant being based on an assumed yield equivalent to that of Teague and Roe. When the acetone-insoluble oxidation product was boiled with water, only a trace of the expected acid (III) was obtained. The principal product was 3-isoquinolinecarboxylic acid-2-oxide (V), obtained in 14% yield (based on I). The identity of this material was confirmed by comparison with a sample prepared by the oxidation of authentic III with hydrogen peroxide in acetic acid solution. Oxidation of purified II with hydrogen peroxide in acetone solution gave after treatment with boiling water only III and none of the N-oxide (V).

Ochiai[3] has shown that 4-nitropyridine-1-oxide may be converted to 4-nitropyridine by treatment with phosphorus trichloride. When V was treated with phosphorus trichloride, the N-oxide function was reduced and the carboxylic acid function converted to the acid chloride, for addition of the crude product to ammonium hydroxide gave 3-isoquinolinecarboxamide (VI) in 38% yield. The latter was identical with VI prepared by the procedure of Teague and Roe and could be converted to 3-aminoisoquinoline as described by them.

The infrared spectrum of IV in Nujol has fairly strong bands at 1694, 1674, 1642, 1617 and 1584 cm.$^{-1}$ Buehler and Edwards[4] have reported that 6,6′-dimethylquinaldil has bands at 1697, 1682, and 1651 cm.$^{-1}$ (medium unspecified), which may be regarded as partial support for the structural assignment made here. The origin of the several bands is obscure. Although benzil[5] has only a single ν(C=O) band at 1681 cm.$^{-1}$ (in chloroform), the proximity of the ring nitrogens to the carbonyl oxygens in IV may make certain conformations of the molecule more or less favorable, giving rise to rotational isomers. The skew structure assigned to compounds like IV[4,6] adds to the complexity of the system. Finally, the spectrum of IV has strong bands at 951, 758, 723, and 697 cm.$^{-1}$ The calculated combination tones derived from these fall at at 1709 (758 + 951), 1674 (723 + 951), 1648 (697 + 951), and 1581 (723 + 758) cm.$^{-1}$ Although the observed bands are of greater intensity than is usually associated with combination tones, Fermi resonance between a fundamental in the carbonyl region and one of the combination tones could result in the intensification of the latter.

In the infrared spectrum in Nujol of V the ν(O—H) band is broad and partially buried under the Nujol ν(C—H) bands near 2900 cm.$^{-1}$ The ν(C=O) band is quite broad (roughly 100 cm.$^{-1}$), centered at about 1675 cm.$^{-1}$ and has a spike at 1627 cm.$^{-1}$ Hydrogen bonding between the hydrogen atom of the carboxyl group and the oxygen atom of the *N*-oxide function is probably responsible for the broadening and shifting toward lower frequencies of these bands.

EXPERIMENTAL[7]

Oxidation of 3-methylisoquinoline. In a 500-ml., 3-necked round-bottomed flask fitted with a heating mantle, mechanical stirrer, thermometer, and water-cooled powder funnel 64.5 g. (0.45 mole) of 3-methylisoquinoline was heated with stirring to 180°. To the hot liquid 50 g. of selenium dioxide (freshly prepared and purified by sublimation) was added in 5-g. portions as rapidly as the reaction would allow. The temperature rose to 210°, refluxing began, and the temperature fell to 170° (increasing the heat input did not increase the temperature). About 15 min. was required for the addition. After an additional 15 min. of heating, the reaction mixture was cooled, then extracted with three 100-ml. portions of ether (with heating under reflux) giving extract A.

(2) C. E. Teague, Jr., and A. Roe, *J. Am. Chem. Soc.*, **73**, 688 (1951).

(3) E. Ochiai, *J. Org. Chem.*, **18**, 534 (1953).

(4) C. A. Buehler and S. P. Edwards, *J. Am. Chem. Soc.*, **74**, 977 (1952).

(5) R. A. Rasmussen, D. D. Tunnicliff, and R. R. Brattain, *J. Am. Chem. Soc.*, **71**, 1068 (1949).

(6) N. J. Leonard, R. T. Rapala, H. L. Herzog, and E. R. Blout, *J. Am. Chem. Soc.*, **71**, 2997 (1949).

(7) Melting points are corrected. Analyses are by Micro-Tech Laboratories, Skokie, Ill.

The oily residue was covered with water and the mixture was neutralized by addition of solid sodium carbonate and filtered, giving aqueous extract B. The residue (C) was a mixture of black metallic selenium and a yellow solid.

The ether extract A was dried over magnesium sulfate, filtered, and evaporated.[8] On the assumption that the yield of Teague and Roe[2] was realized in the oxidation step (*i.e.*, 30 g. of 3-isoquinolinecarboxaldehyde) the crude mixture of 3-isoquinolinecarboxaldehyde and 3-methylisoquinoline was dissolved in 300 ml. of acetone and 30 ml. of 30% hydrogen peroxide was added to the solution. The temperature rose to 45° and remained there for several hours. An additional 40 ml. of 30% hydrogen peroxide was added and the mixture was allowed to stand overnight. The fluffy white precipitate was collected by filtration, air-dried, and suspended in 350 ml. of water. The suspension was boiled for one hour, but the solids did not dissolve.[9] The mixture was filtered. Evaporation of the filtrate gave 0.3 g. of 3-isoquinolinecarboxylic acid, m.p. 164–166° (lit.[10] m.p. 167–168°). The solid was dissolved in dilute sodium hydroxide solution; the solution was treated with charcoal, filtered, acidified with acetic acid, and the resultant mixture was filtered. The pale cream colored solid remaining after air drying (14 g., m.p. 210–211°) was recrystallized from acetone, giving 12 g. of 3-isoquinolinecarboxylic acid-2-oxide, m.p. 211–211.5° dec.

Anal. Calcd. for $C_{10}H_7NO_3$: C, 63.49; H, 3.73; N, 7.40. Found: 63.97; H, 3.98; N, 7.25.

Extract B was treated with charcoal, filtered, and acidified with acetic acid. The resultant solid was recrystallized from water, giving 0.6 g. of 3-isoquinolinecarboxylic acid, m.p. 166–167°.

Residue C was extracted in a Soxhlet apparatus with pyridine. On chilling the pyridine in ice and filtering 2.0 g. of bright yellow needles, m.p. 320–321° dec. was obtained. A small sample (sufficient to form a saturated solution) was recrystallized twice from 25 ml. of pyridine giving 0.08 g. of di(3-isoquinolinyl)glyoxal, m.p. 322–323° dec.

Anal. Calcd. for $C_{20}H_{12}N_2O_2$: C, 76.91; H, 3.87; N, 8.97. Found: C, 77.19; H, 3.33; N, 8.65.

3-Isoquinolinecarboxylic acid-2-oxide. To a solution of 1.0 g. of 3-isoquinolinecarboxylic acid in 20 ml. of glacial acetic acid, 10 ml. of 30% hydrogen peroxide was added and the solution was heated for 2 hr. on the steam bath. On cooling and diluting with water pale tan needles precipitated and were collected and recrystallized from acetone, giving 0.4 g. of 3-isoquinolinecarboxylic acid-2-oxide, m.p. 211–211.5° dec., mixed melting point with product described above the same.

3-Isoquinolinecarboxamide. To 17.5 g. (0.093 mole) of 3-isoquinolinecarboxylic acid-2-oxide suspended in 150 ml. of chloroform, 26 ml. (*ca.* 0.3 mole) of phosphorus trichloride was added, and the mixture was heated for one hour under reflux on the steam bath (protected from moisture). The solid did not appear to dissolve, but did change in appearance. The solid was filtered off and added quickly to 200 ml. of concentrated ammonium hydroxide containing some crushed ice. A vigorous reaction took place and a pale cream colored solid deposited, which was collected by filtration and recrystallized (without drying) from dilute methanol, giving 6.0 g. (38%) of 3-isoquinolinecarboxamide, melting point and mixed melting point with an authentic sample[2] 212–213° (lit.[2] m.p. 213°).

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(8) Fractional distillation of the residue under reduced pressure in other experiments gave 9–13 g. (25–37%, based on 3-methylisoquinoline consumed in the reaction) of 3-isoquinolinecarboxaldehyde, b.p. 140–160° (10 mm.), m.p. 48.5–50.5° (lit.[2] m.p. 47°).

(9) This quantity of hot water will dissolve at least 25 g. of 3-isoquinolinecarboxylic acid.

(10) F. H. Case, *J. Org. Chem.*, **17**, 1297 (1952).

Rates of Reaction of *m*- and *p*-Substituted-1,2-Epoxyethylbenzenes with Thiosulfate in Aqueous Ethanol

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The observation[1] that β-halogen and other electron-withdrawing groups increase the rates of reaction of 1,2-epoxyalkanes with thiosulfate is in marked contrast to the effect of β-halogen in displacement reactions on haloalkanes by thiosulfate[2] and thiophenolate,[3] although alkyl substituents decrease the rates of both epoxides and halides.

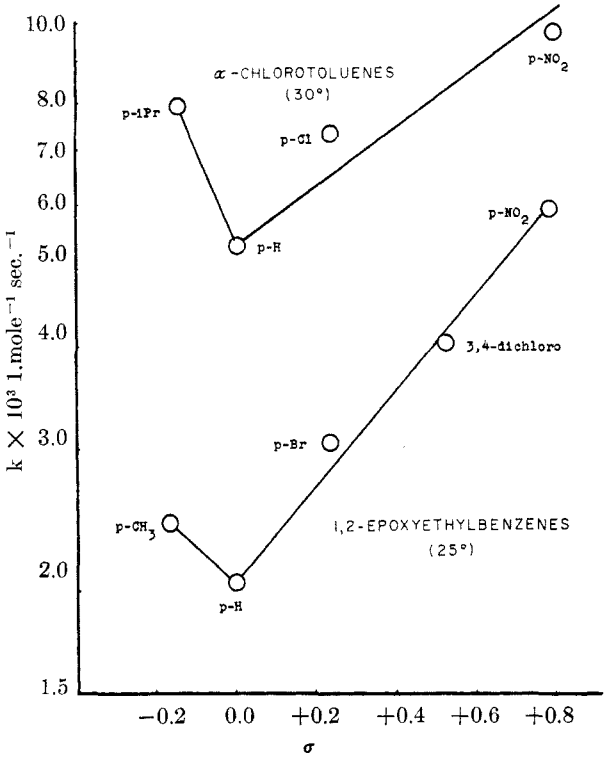

Fig. 1. Rates of reaction of 1,2-epoxyethylbenzenes and of α-chlorotoluenes with thiosulfate in 60% ethanol-40% water.

It was, therefore, of interest to compare the effect of substituents on rates of reaction of 1,2-epoxyethylbenzenes with that of *m*- and *p*-substituted-α-chlorotoluenes, in which substituents act predominently by electronic effects. It has been generally observed that both electron-withdrawing and electron-donating substituents increase the rate of reaction of α-chlorotoluenes with anions such iodide in

(1) W. C. J. Ross, *J. Chem. Soc.*, 2257 (1950).

(2) K. Akagi, S. Oae, and M. Murakami, *J. Am. Chem. Soc.*, **78**, 4034 (1956).

(3) J. Hine and W. H. Brader, *J. Am. Chem. Soc.*, **75**, 3964 (1953).