Anal. Calcd. for $C_{22}H_{23}N_5O_5$: C, 60.40; H, 5.30. Found: C, 60.53; H, 5.45.

Hydrogenation of I. (*a*) In neutral medium: A mixture of 500 mg. of I, 20 ml. of ethanol, and 50 mg. of the catalyst was hydrogenated at room temperature under one atmosphere of hydrogen. After one mole of hydrogen was absorbed the uptake stopped. The catalyst was removed by filtration and washed thoroughly with chloroform. The combined solution and washings were evaporated to dryness. The residue was taken up in 10 ml. of chloroform and the infrared spectrum taken. The isomer ratio was determined by comparing the length of the bands at 7.6, 7.7, and 9.1 microns with those of known mixtures.

(*b*) Acid or basic medium: A mixture of 500 mg. of I, 18 ml. of ethanol, 50 mg. of the catalyst, and 2 ml. of 3*N* hydrochloric acid or 10% aqueous sodium hydroxide was hydrogenated as above; the solution was filtered. The residue was washed with chloroform and the solution evaporated to a small volume. The residue was taken up in chloroform, washed with 3*N* hydrochloric acid, saturated sodium bicarbonate, and saturated sodium chloride, dried, and evaporated. The residue was taken up in chloroform at a volume of 1 ml. of chloroform to 50 mg. of the residue. The isomer ratio was determined as above.

(*c*) At three atmospheres: A mixture of 500 mg. of I, 20 ml. of ethanol, and 50 mg. of 10% palladium on charcoal was shaken on a Parr hydrogenation apparatus under 41 p.s.i. of hydrogen at room temperature for one hour and worked up as in (*a*). The infrared spectra showed no unsaturation nor hydroxyl peaks. The isomer ratio was determined as described above.

Lithium-liquid ammonia reduction of I. Four and one-half grams (0.015 mole) of I in 250 ml. of dioxane was added to 500 ml. of liquid ammonia. Seven tenths of a gram (0.1 mole) of lithium was added and the solution was stirred for 0.5 hr. The solution turned a dirty brown color. Another 0.7 g. of lithium was added and the solution turned blue. The

blue solution was stirred for 3 hr. and the reaction mixture decomposed by the addition of 50 g. of ammonium chloride. The ammonia was allowed to evaporate overnight. The residue was taken up in 500 ml. of water, the aqueous solution was made acidic with concentrated hydrochloric acid, saturated with sodium chloride, and extracted with chloroform. The chloroform solution was washed with saturated sodium bicarbonate and saturated sodium chloride solutions, dried, and evaporated giving one gram of a brown oil which smelled strongly of benzaldehyde.

The aqueous solution from the extraction was evaporated to a small volume. Five hundred milliliters of chloroform was added and enough sodium carbonate to neutralize the solution plus 10 g. excess was then added. This was followed by 10 g. of benzoyl chloride. The mixture was stirred and refluxed for 2 hr., 10 ml. of ethanol was added, and the solution refluxed an additional 0.5 hr. The mixture was cooled, water was added to dissolve the salts, and the chloroform was separated. The chloroform was washed with 10% sodium hydroxide solution, 3*N* hydrochloric acid, and saturated sodium chloride solution, dried, and evaporated, giving a dark brown oily residue. Treatment of the residue with carbon tetrachloride resulted in the precipitation of 200 mg. of water soluble crystals not identical with III. Since III is insoluble in carbon tetrachloride, none of this material was present. The nature of the crystals isolated was not determined.

# Reaction of Methyl Isopropenyl Ketone with Formaldehyde

CHARLES H. TIEMAN* AND MARVIN H. GOLD

Formaldehyde and methyl isopropenyl ketone in the presence of base were found to react with participation of the solvent methanol to give 3-methoxymethyl-2-butanone and 3-hydroxymethyl-3-methoxymethyl-2-butanone. When excess methyl isopropenyl ketone was used as solvent, a thermally unstable product, believed to be 1-hydroxy-4-methyl-4-penten-3-one, was obtained.

The aldol condensation of aldehydes with α,β-unsaturated ketones was recently investigated by Powell and Wasserman.[1] The products isolated included the olefins formed by dehydration of the intermediate β-ketols, but not the ketols themselves. Butyraldehyde and mesityl oxide, for example, were found to give 2-methyl-2,5-nonadien-4-one. In the present work the condensation of methyl isopropenyl ketone with formaldehyde was studied.

In methanol solution, methyl isopropenyl ketone

and paraformaldehyde with potassium carbonate as catalyst were found to produce 3-methoxymethyl-2-butanone (I) and 3-hydroxymethyl-3-methoxymethyl-2-butanone (II) in yields of about 20 and 50%, respectively.

I

II
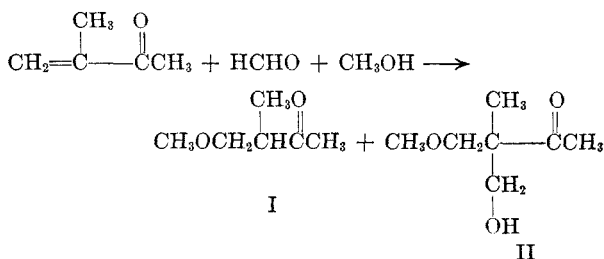
(1) S. G. Powell and W. L. Wasserman, *J. Am. Chem. Soc.*, **79**, 1934 (1957).

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Compound I was identified by elemental analysis and methoxyl number. Characterization of II was based on elemental analysis, methoxyl number, hydroxyl number, molecular refractivity, and heat of combustion. As would be predicted, II gives a positive iodoform reaction and is not dehydrated by heating in the presence of a trace of iodine.[2] An acetate and p-nitrobenzoate of II were prepared and show the predicted elemental analyses and molecular weight. A 1-naphthylurethane could be obtained with II only under strenuous conditions. Elemental analysis of the urethane indicated the reaction of two equivalents of 1-naphthyl isocyanate with one of II. This result could be rationalized by assuming a secondary reaction with the enol form of the carbonyl group. Attempts to establish this possibility by forcing reaction of 1-naphthyl isocyanate with I or the acetate of II were unsuccessful. The structure of the urethane therefore remains obscure.

The formation of I and II undoubtedly takes place by addition of the solvent alcohol to the double bond of methyl isopropenyl ketone to give I, followed by aldol condensation with formaldehyde to yield II. Condensation on the methinyl group instead of the methyl group has also been observed in the base-catalyzed condensation of aldehydes with methyl isopropyl ketone.[2]

In order to avoid solvent participation in the reaction, the use of excess methyl isopropenyl ketone as solvent was investigated. However, with anhydrous potassium carbonate and paraformaldehyde in methyl isopropenyl ketone no reaction was observed to occur. It was found necessary to use alcoholic base to produce a high enough base concentration to catalyze the condensation. With potassium hydroxide or benzyltrimethylammonium hydroxide concentrations of the order of 0.5 to 1 mole %, the condensation with paraformaldehyde proceeded smoothly to give a good yield of water-soluble, polymerizable product. Higher base concentrations in the range of 2 to 5% gave increasing amounts of water-insoluble materials. This sensitivity to catalyst concentration has been observed previously with simpler systems.[3] The crude condensation product was found to be thermally unstable and distillation by usual means under a high vacuum was accompanied by much decomposition with evolution of formaldehyde. Distillation in a falling-film still[4] was found to be satisfactory and the product was further purified by this procedure. The yield of once-distilled product, assuming it to be mostly 1-hydroxy-4-methyl-4-penten-3-one, was about 20% based on formaldehyde. Redistillation, again only possible on a falling-film still, gave ma-

terial found to contain about 90% of the calculated amount of hydroxyl function. Ethoxyl analysis indicated the presence of an impurity containing the ether function. This by-product undoubtedly arises from reaction with the alcohol used as solvent for the basic catalyst. Unsuccessful attempts were made to prepare solid derivatives of the β-ketol with p-nitrobenzoyl chloride and semicarbazide. An acetate was prepared, but it also was not distillable without decomposition.

The possibility of preparing a polymethylol derivative of methyl isopropenyl ketone by reaction of the ketone with an excess of formaldehyde was investigated. Paraformaldehyde was added along with alcoholic benzyltrimethylammonium hydroxide catalyst to a solution of methyl isopropenyl ketone in dioxan at 40° until the paraformaldehyde was no longer depolymerized. From the amount of paraformaldehyde recovered it was evident that only one mole of formaldehyde reacted per mole of ketone. The use of 37% aqueous formaldehyde with potassium carbonate catalyst was studied with and without tetrahydrofuran as solvent. Little or no reaction could be observed and in both cases only unreacted starting materials could be isolated.

EXPERIMENTAL[5]

Reaction of methyl isopropenyl ketone, paraformaldehyde, and methanol. A mixture of 4 l. of methanol, 300 g. (10 moles) of paraformaldehyde, 1680 g. (20 moles) of methyl isopropenyl ketone, and 40 g. of anhydrous potassium carbonate was stirred at room temperature for 7.25 hr. A total of 35 ml. of acetic acid was then added and the reaction mixture was stripped of methanol and excess methyl isopropenyl ketone. The 1931 g. of residue was washed with 2.5 l. of hexane in 4 portions to leave 1408 g. of product. Distillation under about 5 μ pressure gave the 3-methoxymethyl-2-butanone (I) as a forerun. This was fractionated twice to yield 250 g. of I, b.p. 48–49° (17 mm.), n_D^{25} 1.4070.[6]

Anal. Calcd. for $C_6H_{12}O_2$: C, 62.04; H, 10.42; OCH$_3$, 26.69. Found: C, 61.62; H, 10.12; OCH$_3$, 26.60.

After removal of I there was obtained 686 g. (47%) of 3-hydroxymethyl-3-methoxymethyl-2-butanone (II), b.p. 55–60° (ca. 0.3 mm.), n_D^{25} 1.4429.

Anal. Calcd. for $C_7H_{14}O_3$: C, 57.71; H, 9.65; OCH$_3$, 21.20. Found: C, 57.24; H, 9.40; OCH$_3$, 20.29.

Heat of combustion calcd.: 6638 cal./g. Found: 6700 cal./g.

Molecular refractivity calcd.: 37.71. Found: 37.75.

Hydroxyl number calcd.: 6.9 meq./g. Found: 6.0 meq./g.

A 14-g. sample of the alcohol was heated with a few crystals of iodine for 3 hr. at 120°. No water was evolved and 11 g. of the starting material was recovered by distillation. A p-nitrobenzoate was prepared, m.p. 85–85.5°.

Anal. Calcd. for $C_{14}H_{17}NO_5$: C, 56.94; H, 5.80; N, 4.74. Found: C, 56.84; H, 6.21; N, 5.07.

Molecular weight calcd.: 295. Found: 297.

A 1-naphthylurethane, m.p. 162–163° was prepared by

(2) A. T. Nielsen and E. B. W. Ovist, *J. Am. Chem. Soc.*, 76, 5165 (1954).

(3) G. Morgan, N. J. L. Megson, and K. W. Pepper, *Chem. & Ind. (London)*, 16, 885 (1938).

(4) M. H. Gold, *Anal. Chem.*, 21, 636 (1949).

warming the alcohol with excess 1-naphthyl isocyanate and a drop of pyridine.

Anal. Calcd. for $C_{28}H_{26}O_5N_2$: C, 71.47; H, 5.57; N, 5.96. Found: C, 71.61; H, 5.87; N, 6.09.

The acetate was prepared by warming with acetic anhydride and a small amount of zinc chloride. A 64% yield of 3-acetoxymethyl-3-methoxymethyl-2-butanone, b.p. 56–57° (0.5 mm.), n_D^{25} 1.4318, was obtained.

Anal. Calcd. for $C_9H_{16}O_4$: C, 57.42; H, 8.57; OCH₃, 16.49. Found: C, 57.66; H, 8.54; OCH₃, 15.82.

Molecular weight calcd.: 188. Found: 196.

Reaction of paraformaldehyde with methyl isopropenyl ketone. A mixture of 4299 g. (51 moles) of methyl isopropenyl ketone, 150 g. (5 moles) of paraformaldehyde, and 15 ml. of *N* alcoholic potassium hydroxide was stirred at room temperature for 22 hr. An additional 15 ml. of base was then added. The reaction was allowed to proceed for another 4 hr. until the solution was clear and gave a negative Tollens test. The base was neutralized with 3 ml. of acetic acid and the excess methyl isopropenyl ketone (3853 g.) was removed *in vacuo* to leave an almost colorless liquid residue of 327 g. This was washed 3 times with 200-ml. portions of *n*-hexane. The remaining 267 g. of crude product was dissolved in 500 ml. of water and extracted with 400 ml. of methylene chlo-

ride in 2 portions. Evaporation of the methylene chloride yielded 139 g. of product. This was distilled at 60 to 120° at 0.5 mm. on a falling-film still. The 126 g. of colorless product, n_D^{25} 1.4690, was water soluble. This preparation was carried out 6 times with similar results. The refractive index of various fractions from the distillation varied from 1.4600 to 1.4692. A sample redistilled on a falling-film still at 95–100° (0.5 mm.) (n_D^{25} 1.4652) give a hydroxyl number by the acetic anhydride pyridine method[7] of about 90% of the theoretical. This hydroxyl determination is of limited accuracy since the acetate formed is decomposed during titration for unreacted acetic acid. This leads to low values for the hydroxyl number.

Anal. Calcd. for $C_6H_{10}O_2$: C, 63.12; H, 8.83; OC₂H₅, 0.00. Found: C, 59.86; H, 8.61; OC₂H₅, 5.81.

The once-distilled product polymerized at 65° in the presence of methyl amyl ketone peroxide catalyst to give a stiff, colorless polymer, insoluble in acetone, dimethylformamide, and γ-butyrolactone.

AZUSA, CALIF.
AKRON, OHIO

(7) V. C. Mehlenbacher in *Organic Analysis*, Interscience, New York, N. Y., 1953, Vol. I, p. 26.

[CONTRIBUTION FROM THE RADIUM INSTITUTE OF THE UNIVERSITY OF PARIS]

Fluorinated Isatins and Some of Their Heterocyclic Derivatives

V. Q. YEN, N. P. BUU-HOÏ, AND N. D. XUONG

The Sandmeyer isatin synthesis has been applied with success to 4-fluoro-, 3,4-difluoro-, and 4-bromo-3-fluoroaniline, while 2-fluoro- and 2,4-difluoroaniline failed to give the corresponding isatins. The fluorinated isatins thus obtained were used for the synthesis of a large number of fluorine-containing quinolines, acridines, and indophenazines required for testing as potential carcinogens.

Nitrogen heterocyclic compounds containing fluorine have often shown interesting biological activity. Several fluorobenzacridines, for instance, are carcinogenic,[1] and it is known that fluorination enhances the tumor-producing effects of *N,N*-dimethylaminoazobenzene (butter yellow);[2] on the other hand, some 5-fluoropyrimidines have pronounced carcinostatic effects.[3] Thus, it was deemed of interest to investigate fluorinated quinolines, acridines, and other nitrogen heterocycles, few of which have so far been reported in the literature.

Obvious intermediates for the synthesis of such heterocycles were fluorinated isatins, which, unlike the chloro and bromo analogs, had hitherto scarcely been investigated. The Sandmeyer isatin synthesis[4] consisting of the condensation of primary arylamines with chloral and hydroxylamine to the corresponding isonitrosoacetanilides, and subsequent cyclization of the latter, was now ap-

plied with success to 4-fluoro-, 3,4-difluoro-, and 4-bromo-3-fluoroaniline, which gave, respectively, 5-fluoro- (I). 5,6-difluoro- (II), and 5-bromo-6-fluoroisatin (III). Although the Sandmeyer isatin synthesis with 3-substituted anilines generally leads to mixtures of 4- and 6-substituted isatins, a single compound was obtained in the cyclization of 3,4-difluoro- and 4-bromo-3-fluoroaniline, and the isatins formed were assigned the formulas II and III on grounds of their high melting points and the deactivating influence of the halogen atom on position 4. It is interesting to note that with 2-fluoro- and 2,4-difluoroaniline, the corresponding isonitrosoacetanilides were readily obtained, but failed to give the expected isatins on cyclization

I, R = H
II, R = F

III
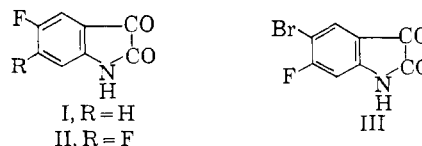
with sulfuric acid. Roe and Teague[5] mentioned the α-chloride of 5-fluoroisatin as an intermediate

(1) F. Zajdela and N. P. Buu-Hoï, *Acta Unio Intern. contra Cancrum*, 11, 736 (1955).

(2) *Cf.* H. W. Rumsfeld, W. L. Miller, and C. A. Baumann, *Cancer Research*, 11, 814 (1951).

(3) W. Bollag, *Schweiz. med. Wochschr.*, 87, 817 (1957); C. Heidelberger *et al.*, *Cancer Research*, 18, 305 (1958); *Nature*, 179, 663 (1957).

(4) T. Sandmeyer, *Helv. chim. Acta*, 2, 237 (1919).

(5) A. Roe and C. E. Teague, *J. Am. Chem. Soc.*, 71, 4019 (1949).