dicated contamination by at least 1.5% of 5,6,7,8-tetrahydro-2-naphthol.

Physical constants found for the two tetrahydronaphthols were: 1,2,3,4-tetrahydro-2-naphthol, b. p. 120.5–121.5° (5.0 mm.), m. p. 22.9°, $n^{25}D$ 1.5630 ± 0.0002; 5,6,-7,8-tetrahydro-2-naphthol; b. p. 128–129° (10.0 mm.), m. p. 60–61° (34–35°), $n^{25}D$ 1.5674 ± 0.0005. Melting point determination afforded the best criterion of purity since refractive index differences were small and diazonium color reactions detected only phenolic impurities. Pure 1,2,3,4-tetrahydro-2-naphthol is a colorless, hygroscopic, very viscous liquid with a fluorescent cast and shows little tendency to become colored on standing.

Labile Form of 5,6,7,8-Tetrahydro-2-naphthol.—Crystalline material was separated from a commercial sample[13] of tetrahydro-2-naphthol by filtration and recrystallized from petroleum ether to give platy crystals, m. p. 34–35°.

Anal. Calcd. for $C_{10}H_{18}O$: C, 81.06; H, 8.17. Found: C, 80.58; H, 7.72.

The tetrahydronaphthol indicated by analysis was identified as 5,6,7,8-tetrahydro-2-naphthol by preparing the *p*-nitrobenzoate derivative; m. p. and m. m. p. 113–114°, from acetic acid or ethanol. 5,6,7,8-Tetrahydro-2-naphthol usually crystallized as needles, m. p. 60–61°, but on recrystallization from petroleum ether selective seeding enables isolation of either the stable needle form, m. p. 60–61°, or the labile plate form, m. p. 34–35°. No mention of the labile form was found in the literature.

Autoxidation of 1,2,3,4-Tetrahydro-2-naphthol.—Enhanced repellency times were found for samples of pure 1,2,3,4-tetrahydro-2-naphthol which had been exposed to air.[14] The ready autoxidizability of tetralin[15] and the substituted tetralin structure of 1,2,3,4-tetrahydro-2-naphthol suggested autoxidation as cause of increased repellent times. Negligible oxidation occurs, as judged by peroxide tests and refractive index changes, on passage of oxygen through pure 1,2,3,4-tetrahydro-2-naphthol in Pyrex vessels even at 70° in the presence or absence of strong artificial light irradiation. Samples of 1,2,3,4-tetrahydro-2-naphthol in quartz flasks in a shaking, volumetric hydrogenation apparatus absorbed oxygen at the rate of approximately 0.4 cc. per hr. per g. at 65° on exposure to ultraviolet light irradiation. Rates of absorption were dependent on intensity of ultraviolet irradiation and decreased gradually after absorption of about 0.1 molar equivalent. The yellow-colored product had increased refractive index and contained hydroperoxide groups, as indicated by iodimetric titration, to the extent of about 15% of oxygen absorbed. No definite oxidation product could be isolated by direct crystallization, either before or after treatment with dilute alkali, nor any derivatives obtained on treatment with carbonyl reagents.

Summary

Hydrogenation of 2-naphthol over copper-chromite catalyst yields at least 77% of pure 1,2,-3,4-tetrahydro-2-naphthol, 7–8% of 5,6,7,8-tetrahydro-2-naphthol and about 13% of slightly impure 1,2,3,4-tetrahydro-2-naphthol from which more pure material may be isolated. Simple separation of the mixture was accomplished by conversion of the phenol constituent to its non-volatile sodium salt and distillation of the alcoholic constituent from the mixture.

A new labile crystalline form of 5,6,7,8-tetrahydro-2-naphthol and the melting point of *dl*-1,2,3,4-tetrahydro-2-naphthol are reported. Autoxidation of 1,2,3,4-tetrahydro-2-naphthol occurs in the presence of oxygen and ultraviolet light.

CAMBRIDGE 38, MASS.

RECEIVED JULY 15, 1948

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[13] Material was prepared on order by a commercial hydrogenation company with a catalyst purported to be similar to copper chromite. The hydrogenated material supplied contained at least 62% 5,6,7,8-tetrahydro-2-naphthol. Considerable crystalline material had separated in shipment during the cold winter months.

[14] Private communication from M. Pijoan.

[15] Hock and Süsemihl, *Ber.*, **66**, 61 (1933).

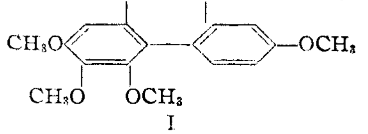
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF ROCHESTER]

The Cyclization of β-2-(3-Bromo-4,5,6,4'-tetramethoxybiphenyl)-propionic Acid[1]

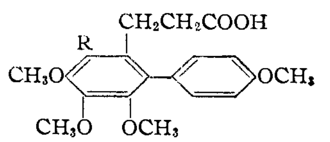
BY H. T. HUANG, D. S. TARBELL AND H. R. V. ARNSTEIN

A recent paper[2] reported experiments on a projected synthesis of compound I, which is a probable structure for an important degradation product of colchicine, N-acetylcolchinol methyl ether.[3] The synthesis of the latter is highly desirable in order to establish the position of the acetamino group and to confirm the structure of ring B in colchicine.

The proposed synthesis involved cyclization of the bromo acid III to the ketone IV, followed by debromination and conversion of the carbonyl group of IV to an acetamino group. In the previous work[2] the bromo acid III had been synthesized, and it had been found that it could be cyclized, although in poor yield, to a bromo ketone.



I



II, R = H
III, R = Br

A further study of the cyclization of III, which is now reported, has shown the cyclization to be accompanied by halogen migration, with the formation of a five-membered ring instead of a seven-membered one. The final product of the

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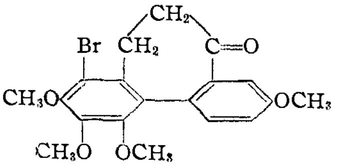
[1] Aided by a grant from the National Institute of Health.

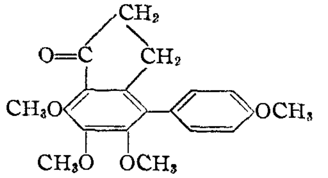
[2] Frank, Fanta and Tarbell, THIS JOURNAL, **70**, 2314 (1948).

[3] *Cf.* Cohen, Cook and Roe, *J. Chem. Soc.*, 194 (1940), and later papers; also Tarbell, Frank and Fanta, THIS JOURNAL, **68**, 502 (1946).

synthesis is therefore an isomer of I, as shown in the subsequent discussion.



IV



V

Cyclization of the acid chloride of III gave a bromo ketone of the composition corresponding to IV; the oxime was formed and reduced catalytically to the corresponding amine, the bromine being removed at the same time. It was hoped that the acetyl derivative obtained from the amine would represent the *dl* form of N-acetylcolchinol methyl ether. The synthetic product melted lower than the optically active compound derived from colchicine[4]; this might be compatible with the relationship of the *dl* modification of a compound to the active form. The ultraviolet absorption curves for the synthetic and natural products, however, were distinctly different, as shown in Fig. 1.

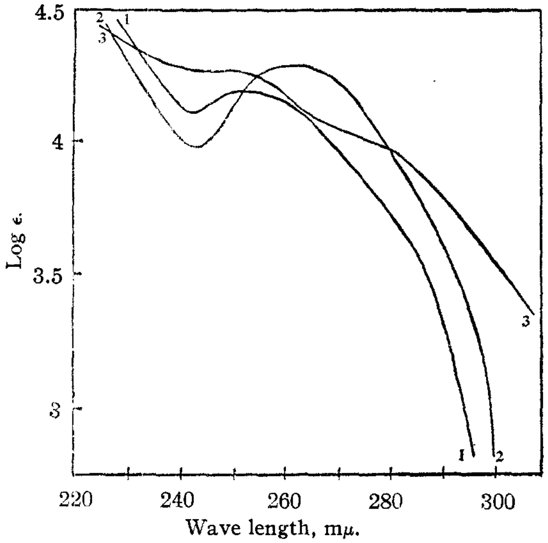
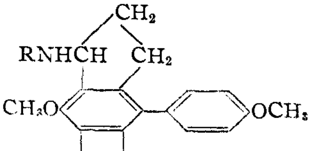
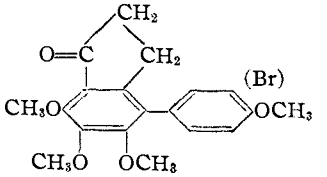


Fig. 1.—Molar extinction curves in methanol: (1) 1-acetamino-4-(4-methoxyphenyl)-5,6,7-trimethoxyhydrindane (VII); (2) natural N-acetylcolchinol methyl ether; (3) 4-(4-methoxy-3-bromophenyl)-5,6,7-trimethoxyhydrindone.

The synthetic product was shown to have structure VII, and not I, by the following reactions. The unbrominated acid II was cyclized to the previously reported[2] ketone V, which was converted by the sequence mentioned above to the corresponding amine VI. The acetyl derivative VII from this amine was found to be identical with the acetylated amine obtained as above from cyclization of the bromo acid III.

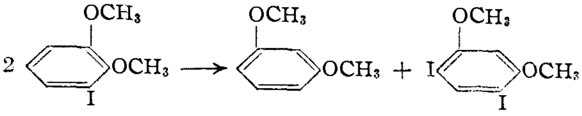


VI, R = H
VII, R = CH_3CO



VIII

Cyclization of III must have been preceded by a migration of the bromine atom, so that the bromo ketone probably had the structure VIII instead of IV. Meerwein[5] has reported that 4-iodoresorcinol dimethyl ether undergoes the following reaction under mild conditions in the presence of a variety of acids, such as boron fluoride, aluminum chloride and sulfuric acid. The corresponding bromo compound gives the same reaction but more slowly. The same process probably takes place with III, causing a transfer of the bromine to the 3′-position, presumably, before cyclization occurs.



Some experiments were carried out on alternative methods of preparing β-(3,4,5-trimethoxyphenyl)-propionic acid, in addition to the one used before.[2] Diethyl 3,4,5-trimethoxybenzoylmalonate was prepared, but reduction with Raney nickel at low temperature and pressure, followed by acid hydrolysis, did not yield the desired propionic acid.

Experimental[6]

3,4,5-Trimethoxybenzaldehyde.[7]—On a Glas-col heating mantle is placed a 500-cc. three-neck flask (ground-glass joints), fitted with a Hershberg stirrer sealed with

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[4] Windaus, *Sitzber. Heidelberg, Akad. Wiss., math. naturw. Klasse*, **16** abh. (1919).

[5] Meerwein, Hofmann and Schill, *J. prakt. Chem.*, **154**, 266 (1940).

[6] Analyses by the Microtech. Laboratories and Mrs. G. Sauvage; all melting points are uncorrected.

[7] The preparation of this starting material by the Rosenmund reduction of trimethoxybenzoyl chloride (*cf.* Spath, *Monatsh.*, **40**, 141 (1919); Slotta and Heller, *Ber.*, **63**, 3029 (1930); Mauthner, *J. prakt. Chem.*, **129**, 283 (1931); Nierenstein, *ibid.*, **132**, 200 (1932)), is erratic, and may give almost none of the desired product, unless all variables are carefully controlled.

rubber tubing, a reflux condenser, and a gas inlet tube with a sintered glass disc (10 mm. diameter, medium mesh), extending as low and centrally as possible without touching the stirrer. 3,4,5-Trimethoxybenzoyl chloride[8] (65 g., 0.27 mole), 230 cc. of xylene (dried by distillation over sodium), 20 g. of palladium–barium sulfate catalyst[9] and 1 cc. of stock poison[10] are introduced into the flask. The top of the condenser is connected by glass tubing to an inverted funnel dipping (about 5 mm. below the surface) into 50 cc. of water in a 500-cc. beaker. Approximately 2*N* alkali solution is run into the beaker at a convenient rate to follow the evolution of the hydrogen chloride during the reaction. Commercial electrolytic hydrogen, dried over concentrated sulfuric acid, is passed into the solution at such a speed that one bubble in about eight seconds emerges from the inverted funnel.

When the air in the apparatus has been replaced by hydrogen, heating is commenced and continued to keep the contents of the flask gently refluxing, and the stirring is started. After about three hours, 95% of the theoretical amount of hydrogen chloride is evolved and the rate of evolution then begins to slow down very considerably. The reaction is stopped.

On cooling, the contents of the flask are decanted and filtered free from solid material. The filtrate is mechanically shaken with a saturated solution containing 390 g. of sodium bisulfite for half an hour. The resulting thick paste of the bisulfite compound of the aldehyde is filtered by suction through a hard filter paper first wet with xylene. The crystalline bisulfite compound is washed well with ether and dissolved in water. When the aqueous solution is filtered free from solid material, 6 *N* sodium hydroxide solution is added and the pure aldehyde is precipitated almost immediately. This is filtered, washed well with cold water and dried *in vacuo;* it melts at 74–75°. An additional 1–2 g. of aldehyde is obtained from decomposing the aqueous portion of the filtrate from the bisulfite compound mixture. The total yield is 33–36 g. (60–64%). This procedure has been used repeatedly on larger amounts by Mr. R. G. Nelb of this Laboratory with comparable yields.

β-2-(4,5,6,4′-Tetramethoxy)-biphenylpropionic Acid (II).—The following procedure is an improvement over the one previously used.[2] A mixture of 4.2 g. of methyl β-(2-iodo-3,4,5-trimethoxyphenyl)-propionate,[2] 20 g. of *p*-iodoanisole and 10 g. of copper bronze in a large test-tube was immersed in a metal-bath held at 250–260° and stirred vigorously with a glass rod. After ten minutes, the mass became extremely viscous and the stirring was continued at regular intervals for a further thirty-five minutes. The reaction mixture on cooling soon set to a solid, and was removed with the glass rod. The material was then finely ground in a mortar together with 5 g. of activated charcoal; this mixture was continuously extracted in a Soxhlet with 200 cc. of acetone for four hours. The extracts were evaporated in a current of air, taken up in 125 cc. of methanol and saponified by refluxing with 8 cc. of 10% sodium hydroxide and 12 cc. of water. The saponification was complete after four hours; the mixture was evaporated once more to dryness, and the residue was warmed with 100 cc. of water. On cooling, 4,4′-dimethoxybiphenyl and unchanged *p*-iodoanisole were filtered off and the filtrate cautiously acidified. The oily acids were taken up in benzene and the required acid crystallized out in fine needles. Ten such runs yielded 19.4 g. of product, m. p. 100–103° (49% yield). A more intensive search in the mother liquor revealed the presence of a small amount of 2,2′,3,3′,-4,4′-hexamethoxy-6,6′-di-(β-carboxyethyl)-biphenyl,[2] m. p. 190–192°, after recrystallization from benzene.

4-(4-Methoxy-3-bromophenyl)-5,6,7-trimethoxyhydrindone-1 (VIII) from Cyclization of β-2-(3-Bromo-4,5-6,4′-tetramethoxybiphenyl)-propionic Acid (III).—The following procedure represents the best one developed in about ten small-scale experiments. A mixture of 5 g. of the acid, 8 cc. of thionyl chloride and 10 cc. of dry benzene was refluxed gently on the steam-bath for one hour. The volatile material was then removed by cautious evaporation under reduced pressure, and the process repeated twice, each time after dissolving the residue in 10 cc. of dry benzene. Finally the system was exposed to high vacuum (hyvac pump) for fifteen minutes to remove the last traces of volatile matter. To the residual viscous oil was added quickly a cooled solution of 1.6 g. of anhydrous aluminum chloride in 40 cc. of nitrobenzene (redistilled) and the greenish-yellow solution warmed on the steam-bath for fifteen minutes, during which time the color deepened to a brownish-green. The solution was stirred with dilute hydrochloric acid (0.8 *N*, 40 cc.) and the mixture distilled in steam. When all the nitrobenzene had been removed, the residue was cooled and extracted with ether. The ether extract was then washed twice with 25 cc. of 2.5 *N* sodium hydroxide solution, and dried over calcium sulfate. A considerable amount of oily gum separated from the sodium hydroxide washings, which was found to contain a ketonic and phenolic component.

The dried ether solution was evaporated and the solid which remained behind was recrystallized (charcoal treatment) from methanol, giving 1.285 g. of tiny glistening prisms, m. p. 134–136° with previous softening. Methylation of the alkaline washings with dimethyl sulfate was ineffective. The mixture was acidified and extracted with ether, the ether solution dried overnight with calcium sulfate, and subsequently treated with excess ethereal diazomethane. When a test portion had ceased to give a positive ferric chloride color (after ten hours), the solution was evaporated in a stream of air. From the residues, a further 350 mg. of ketone melting at 134–136° was obtained by repeated crystallizations from methanol. The total yield of the bromo ketone was thus 1.635 g., corresponding to 34%.

The combined product was recrystallized from ethanol (charcoal) to raise the m. p. to 140–141° (1.4475 g.) and used as such for further reactions. Four further recrystallizations provided the analytical sample, m. p. 145–146°.

Anal. Calcd. for $C_{19}H_{19}O_6Br$: C, 56.03; H, 4.70; Br, 19.62. Found: C, 55.84; H, 4.82; Br, 19.50.

The Oxime.—The bromo ketone (200 mg.), 48 mg. of hydroxylamine hydrochloride, and 120 mg. of sodium acetate dihydrate were dissolved in 2.5 cc. of water and 5 cc. of ethanol. The solution was refluxed gently for fifteen minutes, when crystals of the oxime began to separate. The mixture was kept warm for about two hours, cooled, and the oxime collected. Recrystallization from methanol gave 200 mg. of rectangular plates, m. p. 190–198°. The analytical sample was obtained after four further recrystallizations, m. p. 202–205°.

Anal. Calcd. for $C_{19}H_{20}O_5NBr$: C, 54.01; H, 4.77; Br, 18.91. Found: C, 54.28; H, 4.92; Br, 18.84.

1-Amino-4-(4-methoxyphenyl)-5,6,7-trimethoxyhydrindone (VI).—The above oxime (284 mg.), dissolved in 50 cc. of 95% ethanol previously saturated with ammonia at 0° and containing 0.3 cc. of 2.5 *N* aqueous sodium hydroxide, was hydrogenated over Raney nickel (1 g.) at room temperature and pressure. The rate of hydrogen uptake fell off sharply after three and a half hours, when the uptake corresponded to 3 moles. The solution was filtered free from catalyst, the catalyst washed well with ethanol and the filtrate evaporated to dryness in a current of air. The residue was suspended in 15 cc. of 5% aqueous sodium hydroxide and extracted thoroughly with ether. A test portion of the aqueous fraction on acidification with nitric acid showed voluminous precipitation of silver bromide when treated with aqueous silver nitrate. The ether extracts were dried overnight over calcium sulfate and evaporated. Attempts to crystallize the residual gum with ether and petroleum ether (b. p. 40–50°) were unsuccessful. It was then redissolved in a convenient volume of dry ether and the solution saturated with dry hydrogen chloride. Almost immediately a white powdery precipitate began to appear. This was collected (172 mg.) and recrystallized

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(8) Prepared from 3,4,5-trimethoxybenzoic acid and phosphorus pentachloride, and distilled twice at 1 mm. pressure.

(9) Prepared according to Mozingo, "Organic Syntheses," Vol. 26, p. 77.

(10) Nierenstein, *J. prakt. Chem.*, **132**, 200 (1931).

twice from dilute hydrochloric acid, to give clusters of fine soft fibrous needles, melting sharply at 225–226° with slight previous sintering. Analysis showed conclusively that the hydrochloride is derived from a halogen-free amine.

Anal. Calcd. for $C_{19}H_{23}O_4N{\cdot}HCl$: C, 62.36; H, 6.33; N, 3.86; Cl, 9.69. Found: C, 62.17; H, 6.65; N, 3.98; Cl, 9.90.

The picrate recrystallized from ethanol in light yellow silky needles, m. p. 172–173°.

Anal. Calcd. for $C_{25}H_{26}O_{11}N_4$: N, 10.03. Found: N, 9.96.

N-Acetyl Derivative (VII).—To a solution of the above hydrochloride (95 mg.) in 4 cc. of dry pyridine, 5 drops of acetyl chloride was added cautiously with continuous swirling of the flask. The mixture was warmed gently until most of the precipitated pyridine hydrochloride had dissolved. After standing at room temperature for ten hours, it was evaporated in a stream of air, and the gummy residue, when rubbed with water, crystallized giving 74 mg. of the acetyl derivative, m. p. 178–179°, raised to 179.5° after two recrystallizations from aqueous methanol.

Anal. Calcd. for $C_{21}H_{25}O_5N$: C, 67.89; H, 6.78; N, 3.77. Found: C, 67.86; H, 6.83; N, 3.82.

The ultraviolet absorption spectrum was quite different from that of N-acetylcolchinol methyl ether, as shown in Fig. 1.

4-(4-Methoxyphenyl)-5,6,7-trimethoxyhydrindone-1 (V) by Cyclization of II.—β-2-(4,5,6,4′-Tetramethoxy)-biphenylpropionic acid (II, 1.10 g.) was cyclized by essentially the procedure described above, to yield 650 mg. (62%) of the crude ketone V, m. p. 85°; recrystallization from methanol gave glistening needles of m. p. 89°, which is the reported value.[2]

The *oxime* was obtained in 81% yield, melting at 215°; the reported value[2] is 217°.

1-Amino-4-(4-methoxyphenyl)-5,6,7-trimethoxyhydrindone (VI).—Reduction of the above oxime with hydrogen and Raney nickel by the procedure used on the bromo ketone oxime, gave 80% of the expected amine. There was no depression on mixed melting point of the hydrochlorides, picrates and acetyl derivatives of the amine derived from the oximes of the bromo ketone VIII and the bromine-free ketone V.

Diethyl 3,4,5-Trimethoxybenzoylmalonate.—3,4,5-Trimethoxybenzoyl chloride (12 g.) was added slowly to a well-stirred suspension of the sodio derivative of diethyl malonate in benzene (*ca.* 100 cc.), prepared by treating powdered sodium (2.3 g.) in benzene with diethyl malonate (16 g.). After stirring overnight, dilute hydrochloric acid was added, the benzene layer separated, and washed with aqueous sodium bicarbonate and water. The dried solution was evaporated under reduced pressure, giving a crystalline residue (16 g., 87%), m. p. 87°. After crystallization from ethanol–water the pure product had the m. p. 89–90°.

Anal. Calcd. for $C_{17}H_{22}O_8$: C, 57.62; H, 6.26. Found: C, 57.43; H, 5.77.

Reduction of this product with hydrogen and Raney nickel at low temperature and pressure, followed by hydrolysis with 10% sulfuric acid, did not yield β-(3,4,5-trimethoxyphenyl)-propionic acid. Instead, some 3,4,5-trimethoxybenzoic acid was obtained, and a neutral compound, of uncertain structure, which was insoluble in ether, and which melted, after several recrystallizations from benzene, at 201–202°.

Anal. Found: C, 66.6; H, 6.7.

Summary

β-2-(3-Bromo-4,5,6,4′-tetramethoxybiphenyl)-propionic acid is cyclized under Friedel–Crafts conditions to a hydrindone derivative, the bromine migrating during the reaction. The structure is proved by conversion to 1-acetamino-4-(4-methoxyphenyl)-5,6,7-trimethoxyhydrindone, which is an isomer of N-acetylcolchinol methyl ether, and which is also obtained from the ketone prepared by cyclization of β-2-(4,5,6,4′-tetramethoxybiphenyl)-propionic acid.

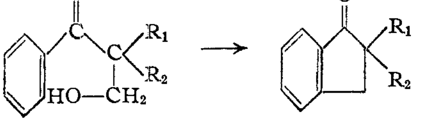
Rochester, N. Y. Received July 19, 1948

[Contribution from the Noyes Chemical Laboratory, University of Illinois]

2-Alkyl-1-indanones

By J. H. Burckhalter[1] and Reynold C. Fuson

The discovery that β-hydroxy-α-methylpropiophenone (Ia), when treated with sulfuric acid, underwent ring closure to yield 2-methyl-1-indanone (IIa)[2] suggested that this type of reaction might afford a superior method of preparation of compounds of this general class.



I II

	R_1	R_2
a	H	CH_3
b	H	C_2H_5
c	H	C_3H_7
d	CH_3	CH_3

The procedure has now been extended to ring closures of β-hydroxy-α-ethylpropiophenone (Ib) and β-hydroxy-α-propylpropiophenone (Ic), and although β-hydroxy-α,α-dimethylpropiophenone (Id) was reconverted by both sulfuric and phosphoric acids to isobutyrophenone, it was conveniently cyclized by phosphorus pentoxide to the desired 2,2-dimethyl-1-indanone (IId).

Despite success in obtaining from β-hydroxy ketones the four indanones whose synthesis has so far been attempted, the low yields in both steps render the method impractical. In a search for a more practical synthetic approach, the possibility of utilizing β-amino ketones instead of the isosteric β-hydroxy ketones was considered. Indeed β-dimethylaminopropiophenone (IIIa) has been made available by means of the Mannich reaction, and its hydrochloride has been degraded by steam distillation to acrylophenone (IVa) and dimethylamine hydrochloride.[3] The fact that acrylophenone can be so readily obtained from a Mannich base suggested the possibility of an extension of the method to the preparation of α-alkylacrylo-

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[1] Present address: Department of Pharmaceutical Chemistry, School of Pharmacy, University of Kansas, Lawrence, Kansas.

[2] Fuson, Ross and McKeever, This Journal, **60**, 2935 (1938).

[3] Mannich and Heilner, *Ber.*, **55**, 356 (1922).