at atmospheric pressure until absorption was complete (24 hours). The acid absorbed 0.0042 ± 0.0002 mole of hydrogen to give a quantitative yield of stearic acid (1.13 g.; m.p. 68–69°).

trans-2-Octadecenoic acid (1.128 g., 0.004 mole) (I), m.p. 58.2–58.5°, was hydrogenated similarly and 0.0038 ± 0.0002 mole of hydrogen was absorbed to give a quantitative yield of stearic acid (1.13 g., m.p. 68–69°).

Isomerization of *cis*-2-Octadecenoic Acid to the *trans* Form.—Attempts to effect this isomerization with warm aqueous nitrous acid (conditions suitable for conversion of oleic to elaidic acid) were unsuccessful. Although VIII is relatively stable in 10% alcoholic potassium hydroxide solution, it can be converted to I with more concentrated alkaline solutions.

cis-2-Octadecenoic acid (0.3 g.) and 1 g. of potassium hydroxide in 4 cc. of alcohol were refluxed for three hours and then acidified and extracted with ether. The ether extract was concentrated and the residue (0.319 g., m.p. 47–52°) was purified by chromatographing from a 4:1 silicic acid:Celite column to give 0.114 g. (38% yield) of *trans*-2-octadecenoic acid, m.p. 57–58°. No unchanged VIII was recovered.

When I was treated similarly, only 41% was recovered unchanged and no *cis*-2-octadecenoic acid was found.

Preparation of the Isomeric 2,3-Dibromostearic Acids.—The high-melting dibromide was prepared by a modification of the procedure used by Ponzio.[3] *trans*-2-Octadecenoic acid (16.92 g., 0.06 mole) was added to a cold solution of 14.4 g. (0.09 mole) of bromine in 45 cc. of dry, alcohol-free chloroform. The solution so obtained was allowed to stand at room temperature for several hours, and then warmed to 50° for 12 hours. The reaction mixture was dissolved in ether and the excess bromine was destroyed with aqueous sodium sulfite. Evaporation of the ether gave 26.5 g. of crude 2,3-dibromostearic acid, m.p. 68–69°. Two crystallizations from petroleum ether raised the m.p. to 71–72° (78% yield).

cis-2-Octadecenoic acid (0.1 g., 0.000355 mole) was treated with 0.3 g. (0.0019 mole) of bromine in 2 cc. of alcohol-free chloroform. After standing for three days, the reaction mixture was processed to give 0.156 g. of crude low-melting 2,3-dibromostearic acid isomer; m.p. 52–54°. This was recrystallized several times from petroleum ether to give 0.095 g. (61% yield) of 2,3-dibromostearic acid (IX), m.p. 57–57.2°.

Anal. Calcd. for $C_{18}H_{34}O_2Br_2$: C, 48.9; H, 7.76; Br, 36.15. Found: C, 49.4; H, 8.13; Br, 35.9.

Ultraviolet Spectra.—Hexane was used as the solvent for each acid. It was purified by agitating four times with fuming sulfuric acid and was finally washed with water, dried over sodium sulfate and distilled.

Acknowledgments.—The author is indebted to the late Professor R. G. Sinclair for his interest and encouragement in this work. This study was made possible through a Grant-in-aid for Research to the Department of Biochemistry, Queen's University, by the Ontario Cancer Research Foundation. The author wishes to thank Dr. G. Papineau-Couture and Dr. R. N. Jones for supplying the infrared data and Dr. G. Papineau-Couture for the determination of the ultraviolet absorption curves.

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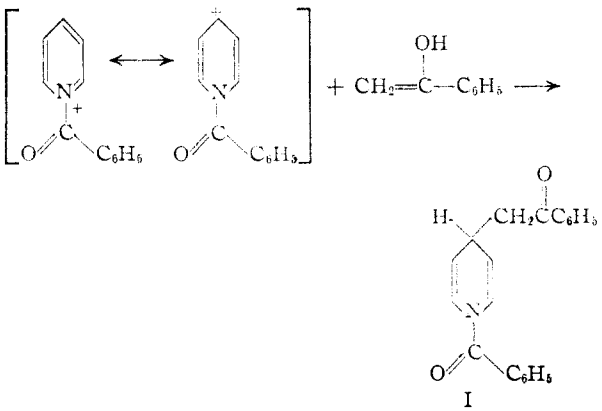
[CONTRIBUTION FROM THE CHANDLER LABORATORY, COLUMBIA UNIVERSITY]

Condensation of Ketones with Acylpyridinium Salts[1]

BY W. VON E. DOERING AND WILLIAM EDWIN MCEWEN[2]

Claisen's product, $C_{20}H_{17}NO_2$, of the reaction of pyridine, benzoyl chloride and acetophenone has been shown to be 1-benzoyl-4-phenacyl-1,4-dihydropyridine. The product from pyridine, acetic anhydride and acenaphthenone does not have the structure assigned to it by E. Ghigi but rather is 1-acetoxy-2-(1′-acetyl-1′,4′-dihydro-4′-pyridyl)-acenaphthylene. These interesting reactions of acylpyridinium salts at the γ-position of pyridine have been extended to the condensation with propiophenone and cyclohexanone, where the same type of product is produced.

Claisen and Haase[3] have reported the formation of a yellow, crystalline compound (I), $C_{20}H_{17}NO_2$, from the reaction of acetophenone, benzoyl chloride and pyridine for six weeks. For this uninvestigated molecule we have hypothesized the structure I on the mechanistic grounds that an intermediate acylpyridinium salt,[4] electron deficient in the α and γ positions, react with the electron-donating, enolic tautomer of acetophenone.[5] Hydrolysis of I with dilute sulfuric acid, effected by Claisen and Haase,[3] reformed the starting fragments, acetophenone, pyridine and benzoic acid, but did not permit a structural assignment.



I

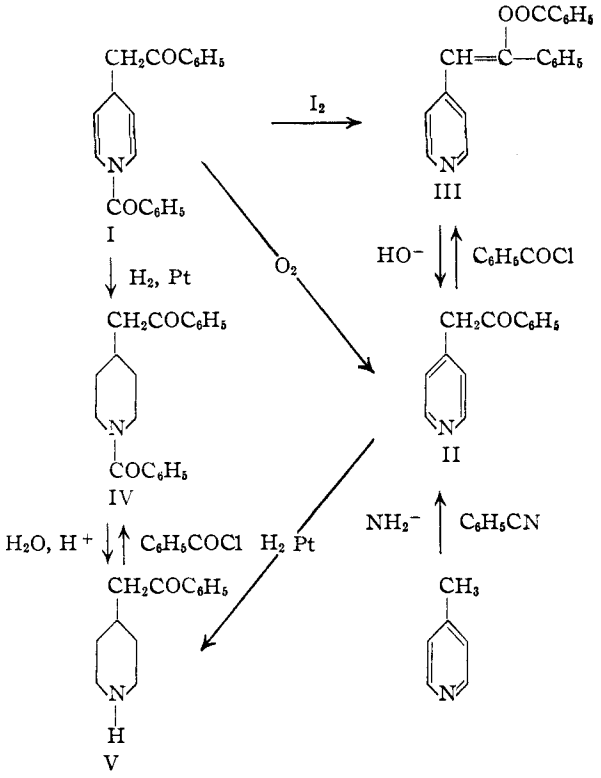
(1) Taken from a dissertation submitted May 23, 1947, in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Faculty of Pure Science of Columbia University.

(2) E. I. du Pont Fellow, 1946-1947.

(3) L. Claisen and E. Haase, *Ber.*, **36**, 3674 (1903).

(4) Although V. Prey, *ibid.*, **75**, 537 (1942), has failed to isolate benzoylpyridinium chloride, the existence of this compound in equilibrium is very likely in view of Prey's successful isolation of acetylpyridinium chloride and *p*-nitrobenzoylpyridinium chloride. This latter salt has also been isolated by B. M. Bogoslovskii, *J. Gen. Chem. (U. S. S. R.)*, **7**, 255 (1937); *C. A.*, **31**, 4319 (1937).

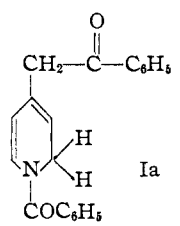
(5) The few reactions in the literature support the contention that acylpyridinium salts are substituted at the γ-position in contrast to alkylpyridinium salts which react generally at the α-position: E. Koenigs and E. Ruppelt, *Ann.*, **509**, 142 (1934), obtained 4-(*p*-dimethylaminophenyl)-pyridine and benzaldehyde from dimethylaniline, benzoyl chloride and pyridine; O. Dimroth and R. Heene, *Ber.*, **54**, 2934 (1921), reduced pyridine and acetic anhydride with zinc dust to 1,1′-diacetyltetrahydro-4,4′-dipyridyl, a reaction in which 4-ethylpyridine was also produced [M. Dohru and H. Horsters, German Patent 390,333; *Frdl.*, **14**, 517 (1926)], by way of 1,4-diacetyl-1,4-dihydropyridine as intermediate [I. P. Wibaut and J. F. Arens, *Rec. trav. chim.*, **60**, 119 (1941)].



Oxidation of I with oxygen[6,7] produced the known 4-phenacylpyridine (II)[8] whereas oxidation with iodine in benzene[6] gave a small amount of II, mainly O-benzoyl-4-phenacylpyridine (III), and some benzoyl iodide characterized as benzanilide. The structure of III was confirmed by hydrolysis to II and benzoic acid and by synthesis from II and benzoyl chloride.

Catalytic hydrogenation of I produced 1-benzoyl-4-phenacylpiperidine (IV), the structure of which is proved by hydrolysis to 4-phenacylpiperidine (V) and benzoic acid and by synthesis from II by way of V.

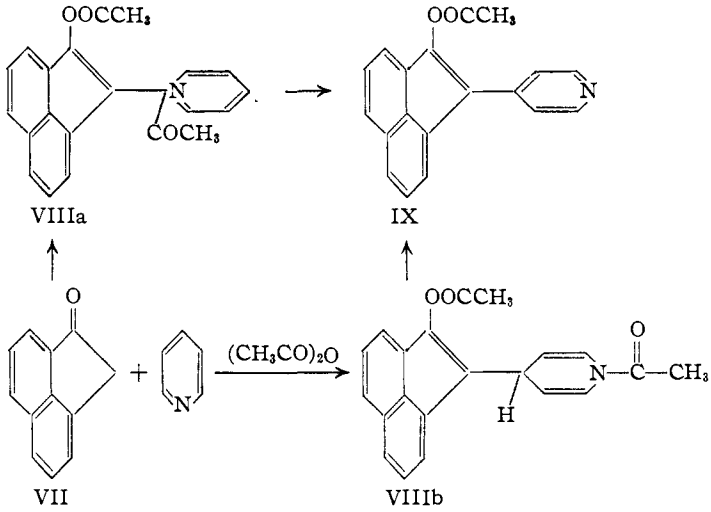
These reactions leave no doubt that the product of Claisen and Haase has the structure I or a tautomer thereof. Specifically no evidence exists to place the hydrogen at the γ-position rather than at the α-position (Ia).



Ia

More detailed examination of the condensation showed that attempted acceleration of the reaction by heat produced tars and that better yields were obtained by lengthening the time of reaction. After one, two, three and four months time, I was produced in 8.2, 19.0, 27.6 and 33.1% of the theoretical yield, respectively. As by-products, O-benzoyl-4-phenacylpyridine (III) was isolated in 0.18 and 0.47% of the theoretical yield after three and four months, respectively, and O-benzoylacetophenone (VI) was obtained from the four-month reaction (3.4%). From an experiment in which I, benzoyl chloride and pyridine produced III in 5% of the theoretical amount after three months standing, but no VI, it may be concluded that I is an intermediate in the formation of III but not VI. The fact that VI does not react to form I in the presence of pyridine, pyridine hydrochloride or pyridine and benzoyl chloride makes it highly improbable that VI be an intermediate in the formation of I.

The related reaction of acenaphthenone (VII), acetic anhydride and pyridine has been found by Ghigi[9] to give a compound, $C_{21}H_{17}NO_3$ (VIII), for which the untenable structure VIIIa containing pentavalent nitrogen was proposed. On heating VIII rearranges to acetaldehyde and IX, the structure of which is well substantiated by ultimate degradation to isonicotinic acid.[9] That VIII is more properly represented by VIIIb by analogy with Claisen's product (I) is substantiated by oxidation with iodine to IX. Hydrolysis of VIII with sodium



carbonate gives not only 1-hydroxy-2-acetylacenaphthalene (X), reported as the only product by Ghigi, but acenaphthenone VII (77%) as well.

The production of VII may be formulated simply as a base-catalyzed reversal of the condensation proceeding, by way of illustration, through the intermediate XI, whereas the formation of X may hypothetically be accommodated by assuming an initial Claisen-type rearrangement of VIII to XII followed by hydrolysis to X.

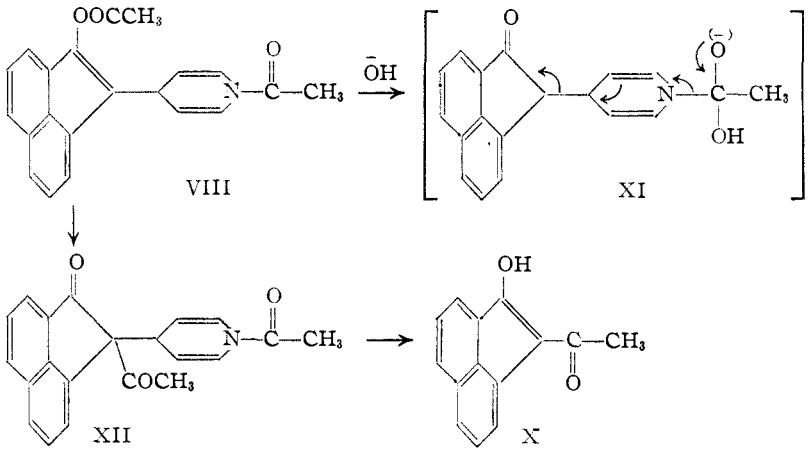
The condensation has been extended to propiophenone and cyclohexanone. From the reaction of the former ketone with benzoyl chloride and pyri-

(6) O. Dimroth and R. Heene, *Ber.*, **54**, 2934 (1921) and O. Dimroth and F. Frister, *ibid.*, **55**, 1223 (1922) oxidized 1,1'-diacetyltetrahydro-4,4'-dipyridyl either with oxygen or iodine to 4,4'-dipyridyl.

(7) E. Weitz, A. Roth and A. Nelken, *Ann.*, **425**, 161 (1921) had similarly oxidized 1,1'-dibenzoyltetrahydro-4,4'-dipyridyl with oxygen or bromine.

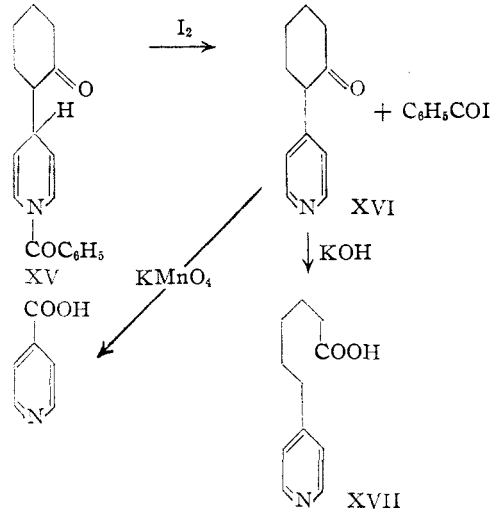
(8) A. E. Chichibabin, *Rec. trav. chim.*, **57**, 582 (1938) synthesized II from γ-picoline and benzonitrile using sodamide as catalyst.

(9) E. Ghigi, *Ber.*, **73**, 677 (1940); **75**, 764 (1942); *Gazz. chim. ital.*, **76**, 352 (1946).



dine for three months the expected α-(1-benzoyl-1,4-dihydro-4-pyridyl)-propiophenone could not be isolated but iodine oxidation of the crude reaction product afforded 4.7% of O-benzoyl-α-(4-pyridyl)-propiophenone (XIII). Hydrolysis of XIII gave benzoic acid and α-(4-pyridyl)-propiophenone (XIV), the independent synthesis of which was accomplished by methylating 4-phenacylpyridine with methyl iodide in the presence of sodium ethoxide.

Cyclohexanone, pyridine and benzoyl chloride reacted in a month to give 40% of the theoretical yield of α-(1-benzoyl-1,4-dihydro-4-pyridyl)-cyclohexanone (XV) and a trace (0.2%) of α-(pyridyl)-cyclohexanone (XVI).

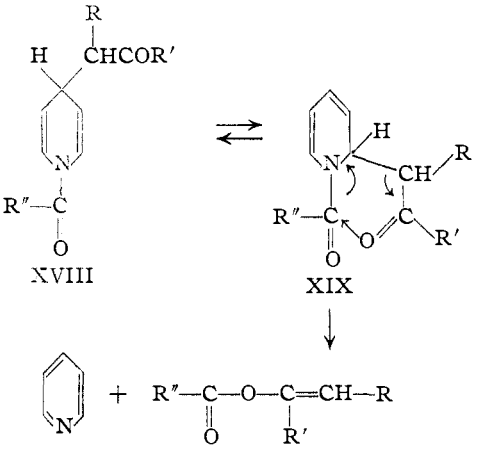


Oxidation of XVI with potassium permanganate produced isonicotinic acid in good yield, whereas fusion with potassium hydroxide produced an acid considered to be ε-(4-pyridyl)-caproic acid (XVII).

In contrast to simple ketones, ethyl benzoylacetate reacts exclusively by O-acylation when treated with benzoyl chloride and pyridine. This fact has been observed by McElvain and Kundiger,[10] confirmed here and extended by showing that the product, ethyl β-benzoxycinnamate, does not react with pyridine and benzoyl chloride either.

There are a few other examples where β-keto-esters react with acid chlorides and anhydrides under various conditions to give C-alkylation but react in the presence of pyridine to give O-acylation and this unaccompanied by any apparent reaction with pyridine.[11]

These phenomena can be accommodated speculatively by the following hypotheses. With the simple ketones reported here it has been shown that a reaction occurs with the acylpyridinium salt at the γ-position which is not sensibly reversed under the conditions of the experiment. Presumably some reaction occurs at the α-position and, to account for the consistent failure to isolate the corresponding product, it is proposed that the α-substituted product may rearrange in a relatively rapid reaction to the enol ester by a mechanism involving the pseudo six-membered transition indicated by XIX.



With β-ketoesters it is proposed that the initial reaction still involves carbon–carbon bond formation at the α-and γ-positions of the acyl pyridinium salt,[12] and that the enhanced acidity of the β-keto esters makes the interconversion of XVIII and XIX relatively rapid. The product is, therefore, the O-acyl derivative of the β-keto ester, derived exclusively from XIX.

Experimental[13]

Reaction of Acetophenone, Pyridine and Benzoyl Chloride.—Effected according to Claisen and Haase[3] but for periods of one, two, three and four months, the reaction is reported in detail for the four months period, the results of the other reaction times being enclosed in parentheses.

As 264.0 g. (3.34 moles) of pyridine, dried over anhydrous barium oxide, was distilled into a mixture of 200.0 g. (1.67 moles) of acetophenone and 216.0 g. (1.54 moles) of benzoyl chloride, a colorless precipitate appeared, heat was evolved and a red color developed. After four months in

(10) S. M. McElvain and D. Kundiger, THIS JOURNAL, **64**, 254 (1942).

(11) *Cf.* L. Claisen, *Ann.*, **291**, 25 (1896); L. Claisen and E. Haase, *Ber.*, **33**, 1242 (1900); W. Dieckmann and R. Stein, *ibid.*, **37**, 3370 (1904).

(12) The isolation of the sodio derivative of tetraethyl 1,3,5-heptatriene-1,1,4,4-tetracarboxylate from the reaction of γ-pyridylpyridinium chloride and sodiomalonic ester (Doering, unpublished work) supports in some measure this postulated initial reaction.

(13) Melting points are corrected; boiling points uncorrected. Analyses are by Miss Lois May.

the dark, the brown, half-solid mass was triturated with 250 cc. of ether, filtered, washed with 1 l. of ether in 5 portions (the united ether solution and washings are called A) and stirred into 500 cc. of water. The undissolved portion was filtered, washed with water and with ether and crystallized from 95% ethanol to give 124.0 g. (25%) of pale, yellow prisms of **1-benzoyl-4-phenacyl-1,4-dihydropyridine** (I), m.p. 108–110° (dec.) when the capillary tube was introduced at 100° and heated at 6° per min. Claisen and Haase[3] report m.p. 110°. I can be sublimed at 180° (0.5 mm.) (the three month reaction gave 67.0 g. (13.3%) of I).

Anal. Calcd. for $C_{20}H_{17}NO_2$: C, 79.18; H, 5.61; N, 4.62. Found: C, 78.77; H, 5.73; N, 4.67.

The ether solution A was concentrated first at atmospheric pressure, then at reduced pressure to remove pyridine. Small amounts of I which crystallized were filtered from the residue (B, 252.3 g.) and recrystallized from 95% ethanol: 38.3 g. (7.6%). (One month reaction: 41.4 g., 8.2%; two month: 96.0 g., 19.0%; three month: 56.0 g., 11.1%.)

When further volatile materials were removed from the oily filtrates (B) by steam distillation, traces of additional I crystallized from the involatile residue: 0.5% from the four month reaction, 3.2% from the three.

An ethereal solution of B (123.1 g.) from which the last traces of pyridine had been removed by distillation *in vacuo* was filtered from a small amount of tar and extracted with two 100-cc. portions of 3 *N* hydrochloric acid giving an ether solution (C) and an acid layer containing some insoluble material which was treated with sodium bicarbonate and extracted with three 75-cc. portions of ether. Dried over anhydrous magnesium sulfate, treated with Norit, and concentrated, the ether extract gave a sirup from which **O-benzoyl-4-phenacylpyridine** (III) crystallized. Recrystallization from 95% ethanol afforded 0.60 g. (0.24%), m.p. 121.0–121.5°, of needles showing no depression on admixture with authentic III.

Anal. Calcd. for $C_{20}H_{15}NO_2$: C, 79.71; H, 5.02; N, 4.65. Found: C, 79.37; H, 5.05; N, 4.92.

III is soluble in alcohol, acetone, ether, ethyl acetate and benzene, insoluble in water, and forms a hydrochloride which is insoluble in 3 *N* hydrochloric acid.

When the alcohol mother liquors were treated with a saturated, alcoholic solution of picric acid, **O-benzoyl-4-phenacylpyridine picrate**, precipitated. Upon recrystallization from absolute ethanol, 1.01 g. (0.23%) of yellow leaflets, m.p. 172.0–172.5° (dec.), was obtained.

Anal. Calcd. for $C_{26}H_{18}N_4O_9$: C, 58.87; H, 3.42; N, 10.56. Found: C, 58.60; H, 3.60; N, 10.88.

The ether solution C containing acidic and neutral material was extracted exhaustively with sodium bicarbonate, washed with water, dried with anhydrous magnesium sulfate and treated with Norit. Distillation at 20 mm. gave 24.1 g. (24.6%) of acetophenone and a waxy residue which was extracted continuously seven hours with petroleum ether. Distillation of this extract at 2 mm. gave 3.13 g. (3.2%) of additional acetophenone, b.p. 49–53°, 3.58 g. of material, b.p. 55–153° and 12.97 g. of a pale yellow oil, b.p. 155–163°. Redistillation of this latter fraction at 4 mm. gave 6.11 g. (3.4%) of **O-benzoylacetophenone** (VI), b.p. 174–178°, which solidified on cooling, m.p. 34–36°. It showed no depression on mixing with an authentic sample prepared according to Claisen and Haase[3] who report b.p. 190–200 (11 mm.) and m.p. 41°.

4-Phenacylpyridine (II).—A solution of 3.27 g. of O-benzoyl-4-phenacylpyridine (III) in 100 cc. of 95% ethanol was added to a solution of 8.0 g. of sodium carbonate in 100 cc. of water and refluxed for 30 minutes. The reaction mixture was concentrated by distilling 110 cc. of solvent, acidified with hydrochloric acid and extracted with three 30-cc. portions of ether. Evaporation of the ether extract gave material from which 1.13 g. (85%) of benzoic acid, m.p. 122°, was obtained by one crystallization from water.

Extraction of the neutralized, aqueous layer with three 50-cc. portions of ether afforded material, crystallization of which from acetone gave 1.73 g. (81%) of **4-phenacylpyridine** (II), m.p. 114.0–115.5°. Mixed with an authentic sample prepared by the method of Chichibabin[3] (who reports m.p. 100–105°) this sample showed no depression.

Anal. Calcd. for $C_{13}H_{11}NO$: C, 79.16; H, 5.62; N, 7.10. Found: C, 79.21; H, 5.84; N, 6.98.

II is insoluble in water and soluble in both 3 *N* hydrochloric acid and 10% sodium hydroxide solution. The **picrate of 4-phenacylpyridine** crystallizes from absolute alcohol as short, yellow needles, m.p. 170.0–170.5° (dec.).

Anal. Calcd. for $C_{19}H_{14}N_4O_8$: C, 53.52; H, 3.31; N, 13.14. Found: C, 53.55; H, 3.55; N, 12.92.

II was converted to **O-benzoyl-4-phenacylpyridine** (III) by refluxing 0.38 g. with 0.27 g. of benzoyl chloride in 25 cc. of benzene for ten hours. Extraction with 10 cc. of 3 *N* hydrochloric acid produced a precipitate which was filtered, triturated with 10 cc. of 10% sodium hydroxide solution, and extracted with ether. Recrystallization of the crude (0.23 g., 43%) material from 95% ethanol gave 0.12 g. (21%) of III, m.p. 121.0–121.5°. Unchanged II (0.12 g.) was recovered from the acidic extract.

Reactions of 1-Benzoyl-4-phenacyl-1,4-dihydropyridine (I). **A. Oxidation with Iodine.**—The reaction mixture obtained by dropping a solution of 6.80 g. of iodine in 300 cc. of dry benzene over a half-hour period into a boiling solution of 4.03 g. of I in 100 cc. of dry benzene was refluxed three hours, cooled and shaken with 2.0 g. of sodium sulfite in 50 cc. of water. The mixture, now containing a precipitate, was treated with 12 cc. of concentrated hydrochloric acid, shaken thoroughly, and filtered, the benzene and acidic aqueous layers of the filtrate being separated.

Trituration of the solid hydrochloride with 10% sodium hydroxide solution followed by fractional crystallization of the resulting material from 95% ethanol afforded 1.64 g. (41%) of **O-benzoyl-4-phenacylpyridine** (III), m.p. 121.0–121.5°, showing no depression of m.p. on admixture with an authentic sample.

The ether extract of the neutralized acid solution gave a small amount (0.09 g., 3.4%) of **4-phenacylpyridine** (II), m.p. 114.0–115.5°, on chilling and a like amount on being evaporated to dryness (total 7%).

After being extracted with three 15-cc. portions of 10% sodium hydroxide solution and being treated with 1 cc. of aniline, the benzene solution was concentrated to an oil which gave 0.26 g. (10%) of **benzanilide**, m.p. 160–161° upon recrystallization from 95% ethanol. No m.p. depression was shown when mixed with authentic benzanilide.

B. Autoxidation.—A suspension of 2.02 g. of I in 85 cc. of *t*-butyl alcohol was shaken with oxygen at 65° and 25 lb./sq. in. for two hours. Concentration of the reaction mixture by distillation left a residual oil that was dissolved in 50 cc. of ether and extracted with four 10-cc. portions of 3 *N* hydrochloric acid. The acidic extract was neutralized and extracted with five 10-cc. portions of ether. Concentration of the dried ether solution gave an oil which crystallized from acetone, yielding 0.24 g. (18%) of **4-phenacylpyridine** (II), m.p. 114.0–115.5° (no m.p. depression with an authentic sample). A second crop weighed 0.10 g. (8%).

C. Catalytic Reduction.—Hydrogenation[14] of 1.69 g. of I in 100 cc. of 95% ethanol was complete in one hour in a Parr apparatus using 0.05 g. of platinum oxide and hydrogen at 38 lb./sq. in. The solution was filtered from platinum, concentrated *in vacuo* to 7 cc., diluted with 50 cc. of ether, washed first with two 10-cc. portions of 3 *M* hydrochloric acid and then with two 10-cc. portions of 10% sodium hydroxide solution, dried with magnesium sulfate and concentrated to 5 cc. Upon cooling a first crop (0.85 g.) crystallized and a second crop (0.25 g.) was obtained by concentrating and dissolving the residue in a minimum quantity of boiling ethanol. Recrystallization from 95% ethanol afforded colorless prisms of **1-benzoyl-4-phenacylpiperidine** (IV), 0.76 g. (44%), m.p. 119.0–119.2°, which did not depress the m.p. of authentic IV.

Anal. Calcd. for $C_{20}H_{21}NO_2$: C, 78.14; H, 6.89; N, 4.56. Found: C, 78.17; H, 6.95; N, 4.74.

Hydrolysis of 1-Benzoyl-4-phenacylpiperidine (IV).—A suspension of 1.00 g. of IV in 50 cc. of 20% sulfuric acid was refluxed for four hours, extracted with two 60-cc. portions of ether (A), made basic with 10% sodium hydroxide solution and extracted with three 60-cc. portions of ether (B). Concentration of B afforded 0.27 g. of a yellow oil (positive test with 2,4-dinitrophenylhydrazine) which reacted with saturated ethanolic picric acid to give 0.51 g. (34%) of **4-phenacylpiperidine** (V) **picrate** (yellow needles), m.p. 183.0–183.5° (dec.) after several crystallizations from absolute ethanol. This material failed to depress the m.p. of an authentic sample (*vide infra*).

(14) B. Emmert and A. Wolpert, *Ber.*, **74**, 1015 (1941), catalytically reduced 1,1'-diacetyltetrahydro-4,4'-dipyridyl.

Anal. Calcd. for $C_{19}H_{20}N_4O_8$: C, 52.78; H, 4.64; N, 12.96. Found: C, 52.88; H, 4.70; N, 13.09.

Ether extract A was extracted with two 15-cc. portions of 10% sodium hydroxide to give 0.18 g. (45%) of benzoic acid, m.p. 121–122° alone and when mixed with an authentic sample. From the ether solution 0.49 g. (49%) of unchanged starting material was recovered.

Authentic 4-Phenacylpiperidine (V).—By a procedure similar to that of Hamilton and Adams[15] for the reduction of pyridine, 4-phenacylpyridine hydrochloride, prepared by passing dry hydrogen chloride into an absolute ethereal solution of 0.43 g. of 4-phenacylpyridine and decanting the supernatant liquid, was hydrogenated in 125 cc. of absolute ethanol in a Parr apparatus with 0.05 g. of platinum oxide and hydrogen at 43 lb./sq. in. in 30 minutes. The filtered solution was concentrated *in vacuo* to an oil which was triturated with 10% sodium hydroxide solution and extracted with ether. The oil remaining after evaporation of the ether was converted to the picrate salt which was fractionally crystallized to give 4-phenacylpyridine picrate as the less soluble component and **4-phenacylpiperidinium picrate**, m.p. 183.0–183.5°, as the more soluble.

4-Phenacylpiperidinium picrate (0.06 g.) suspended in ether was decomposed with dilute aqueous lithium hydroxide. The ether extract was washed with additional lithium hydroxide until colorless and evaporated to give 0.02 g. of yellow oil, which was boiled for 15 minutes with 0.03 cc. of benzoyl chloride in 5 cc. of benzene. The benzene solution was washed with 0.5 cc. of 3 *N* hydrochloric acid, with 1 cc. of 10% sodium hydroxide solution and with two 0.5-cc. portions of water and evaporated to dryness. The residue crystallized from 80% ethanol to give 0.01 g. of **1-benzoyl-4-phenacylpiperidine (IV)**, m.p. 119.0–119.2°.

1-Acetoxy-2-(1′-acetyl-1′,4′-dihydro-4′-pyridyl)-acenaphthylene (VIII). (a) Reaction with Sodium Carbonate.—VIII was prepared by the method of Ghigi[9] and crystallized from alcohol as orange-yellow needles, m.p. 140–145° (dec.) when introduced at 105° and heated at 10° per minute (Ghigi reported m.p. 145–147°).

Anal. Calcd. for $C_{21}H_{17}NO_3$: N, 4.22. Found: N, 4.02.

The mixture of a solution of 1.00 g. of VIII in 30 cc. of hot 95% alcohol and a solution of 1.00 g. of sodium carbonate in 30 cc. of 50% alcohol was heated for five minutes on the steam-bath. Concentrated to 20 cc. *in vacuo*, the reaction mixture was extracted with 200 cc. of ether. Two extracts of this ether layer with 30-cc. portions of 10% aqueous sodium hydroxide were added to the aqueous layer and acidified with 12 *M* hydrochloric acid.

The yellow precipitate (0.14 g., 22%) was recrystallized from 50% alcohol to give **1-hydroxy-2-acetylacenaphthylene (X)**, m. p. 116–117°. Admixture with authentic material[9] gave no depression.

The ether extract was washed with 3 *M* hydrochloric acid, dried with anhydrous magnesium sulfate, and evaporated to give 0.39 g. (77%) of acenaphthenone (VII), m.p. 119–121° after treatment with Norit and crystallization from 95% ethanol. Mixed with authentic material prepared according to Fieser and Cason,[16] the material melted without depression.

(b) **Oxidation with Iodine.**—A dry benzene (200 cc.) solution of 3.06 g. of iodine was added dropwise to a refluxing solution of 2.00 g. of VIII in 100 cc. of dry benzene over a period of one-half hour. After being refluxed two hours, the benzene solution was shaken with 350 cc. of saturated sodium sulfite solution. The separated sulfite layer was mixed with 100 cc. of 12 *M* hydrochloric acid and then used in four portions to extract the benzene layer. The acid layer which contained an orange suspension was treated with excess sodium carbonate precipitating a dark, red solid. Recrystallized from toluene, this material afforded 0.24 g. (13.9%) of brick-red **1-acetoxy-2-(4-pyridyl)-acenaphthylene (IX)**, m.p. 240–245° (dec.). Admixture with material of the same m.p. prepared according to Ghigi[9] who reported m.p. 245–247° produced no lowering of the m.p.

Reaction of Propiophenone, Benzoyl Chloride and Pyridine.—Dry pyridine (208 g., 2.64 moles) was distilled from fresh anhydrous barium oxide into a mixture of 186 g. (1.38 moles) of propiophenone and 186 g. (1.32 moles) of benzoyl chloride. After three months in a dark, cool place, the tightly stoppered reaction mixture was a semi-solid, dark brown mass. The mixture was triturated with 500 cc. of ether and filtered to remove a tarry residue which was washed with 250 cc. of ether. Distillation of the ether solution, ultimately at reduced pressure, left 350 g. of a dark, brown oil which failed to crystallize.

Extraction of 72.7 g. of this oil in 50 cc. of benzene with three 50-cc. portions of 3 *M* hydrochloric acid gave only 0.60 g. of basic material, non-crystalline itself and giving rise to an ill-defined picrate.

Another portion (70.0 g.) of the crude product was refluxed for three hours in 300 cc. of benzene with 26.0 g. of iodine. The mixture was shaken thoroughly with 150 cc. of saturated sodium sulfite solution. The aqueous extract was treated with 37 cc. of 12 *M* hydrochloric acid and then used in three portions to extract the benzene solution again. The acid extract was treated with excess sodium bicarbonate and extracted with one 150-cc. and one 50-cc. portion of ether. Drying and concentrating gave an oil (*ca.* 7 cc.) which could be induced to crystallize. Fractional crystallization from ethyl acetate afforded 4.08 g. (4.75%) of **O-benzoyl-α-(4-pyridyl)-propiophenone (XIII)** as colorless needles, m.p. 117.4–117.6°.

Anal. Calcd. for $C_{21}H_{17}NO_2$: C, 79.98; H, 5.43; N, 4.44. Found: C, 80.10; H, 5.66; N, 4.74.

XIII is easily soluble in alcohol, ether, acetone, benzene and ethyl acetate and is insoluble in pentane and water.

α-(4-Pyridyl)-propiophenone (XIV). (a) By Hydrolysis of O-Benzoyl-α-(4-pyridyl)-propiophenone (XIII).—A mixture of 0.54 g. of XIII, 2.0 g. of sodium carbonate, 25 cc. of water and 25 cc. of alcohol was refluxed for half an hour, concentrated to 20 cc. by distillation, diluted with 25 cc. of water and extracted with three 30-cc. portions of ether. Removal of the ether left 0.34 g. of uncrystallizable, yellow oil which was treated with a saturated alcoholic solution of picric acid to give 0.58 g. (77%) of the **picrate of α-(4-pyridyl)-propiophenone (XIV)**, m.p. 152–152.5° after several recrystallizations from absolute alcohol.

Anal. Calcd. for $C_{20}H_{16}N_4O_8$: C, 54.55; H, 3.66; N, 12.72. Found: C, 54.71; H, 3.77; N, 13.50.

The carbonate solution above was acidified and extracted with ether to give 0.19 g. (90%) of benzoic acid, m.p. 121.5–122° after crystallization from water.

(c) By Synthesis from 4-Phenacylpyridine (II).—To a refluxing solution of sodium ethoxide (from 0.13 g. of sodium) and 1.11 g. of 4-phenacylpyridine in 10 cc. of absolute ethanol contained in a 100-cc. flask fitted with a reflux condenser and dropping funnel and protected by calcium chloride tubes, there was added dropwise over a period of one hour a solution of 0.5 cc. of methyl iodide in 5 cc. of absolute ethanol. After refluxing an additional 90 minutes, the alcohol was removed by a stream of dry air to give a crude product which was dissolved in 100 cc. of ether and extracted with two 25-cc. portions of 3 *M* hydrochloric acid. The acid solution was treated with excess sodium bicarbonate and extracted with three 30-cc. portions of ether. Evaporation of the dried ether solution gave 0.70 g. of orange oil, a portion of which was converted to the **picrate**, m.p. 152–152.5° (dec.) after several crystallizations from absolute alcohol. A mixture of this material with that from the previous experiment melted undepressed.

Reaction of Cyclohexanone, Benzoyl Chloride and Pyridine.—A mixture of 132.0 g. (1.67 moles) of dry pyridine, freshly distilled from barium oxide, 81.8 g. (0.835 moles) of cyclohexanone and 117.0 g. (0.835 moles) of benzoyl chloride was kept in a tightly stoppered flask for one month. The reaction mixture was then diluted with 100 cc. of ether and filtered from a solid which was washed with three 100-cc. portions of ether. The combined ether solutions were concentrated ultimately *in vacuo*, leaving a viscous, brown oil. Crystalline seed was obtained by dissolving a portion of this oil in the minimum quantity of absolute alcohol and keeping at 4° for several days. When the main portion was then dissolved in half its volume of 95% alcohol and seeded, 129.0 g. of yellow crystals was obtained. Recrystallization afforded 80.0 g. (34%) of **α-(1-benzoyl-1,4-dihydro-4-pyridyl)-cyclohexanone (XV)**, m.p. 81–83°. A second crop amounted to 13.9 g. (6%).

Anal. Calcd. for $C_{18}H_{19}NO_2$: C, 76.8; H, 6.8; N, 5.0. Found: C, 76.2; H, 7.0; N, 5.5.

(15) T. S. Hamilton and R. Adams, THIS JOURNAL, **50**, 2260 (1928); G. Scheuing and L. Winterhalder, *Ann.*, **473**, 126 (1929), found that α-phenacylpyridine was reduced by platinum oxide in glacial acetic acid to phenyl-2-pipecolylcarbinol.

(16) L. F. Fieser and J. Cason, THIS JOURNAL, **62**, 432 (1940).

Although XV is unstable at room temperature, it can be kept in the refrigerator for several weeks. XV is very soluble in acetone, soluble in alcohol, ethyl acetate and benzene, poorly soluble in ether and insoluble in water and pentane.

The alcohol mother liquor from the crystallization was concentrated, dissolved in ether and extracted with four 30-cc. portions of 3 *M* hydrochloric acid. Ether extraction of the neutralized solution gave 0.51 g. of tan crystals. Crystallization from ethyl acetate afforded 0.45 g. (0.19%) of **α-(4-pyridyl)-cyclohexanone (XVI)**, m.p. 107.0–108.5°.

Anal. Calcd. for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.23; H, 7.53; N, 8.24.

Soluble in the common organic solvents and insoluble in water and pentane, XVI dissolves in 3 *M* hydrochloric acid and 10% aqueous sodium hydroxide.

Oxidation of α-(1-Benzoyl-1,4-dihydro-4-pyridyl)-cyclohexanone (XV) with Iodine.—The reaction mixture obtained by refluxing 46.5 g. (0.165 mole) of XV and 84.0 g. (0.33 mole) of iodine in 600 cc. of benzene for three hours was shaken with 500 cc. of saturated sodium sulfite solution. The sulfite solution was acidified with 125 cc. of 12 *M* hydrochloric acid and used in five portions to extract the benzene solution, following which two more extractions with 75 cc. each of 9 *M* hydrochloric acid were carried out.

A tarry material, filtered from the benzene solution, was triturated with 10% sodium hydroxide solution which was filtered and used to neutralize the combined acid extracts. The ether extracts (five 200-cc. portions) of the neutralized solution were washed with water, dried, treated with Norit and concentrated by distillation ultimately *in vacuo*. The residual oil (15.6 g.) solidified and was fractionally crystallized from 95% alcohol to give 9.8 g. (33.9%) of colorless prisms of **α-(4-pyridyl)-cyclohexanone (XVI)**, m.p. 107.0–108.5°, showing no depression of m.p. in admixture with XVI obtained above.

Extraction of the benzene solution above with 5% aqueous sodium bicarbonate gave 6.21 g. (30.8%) of benzoic acid. The benzene solution was then mixed with 10 cc. of aniline and evaporated to dryness to give 12.25 g. (37.7%) of benzanilide, m.p. 160–161°.

Reactions of α-(4-Pyridyl)-cyclohexanone (XVI). (a) **Oxidation with Potassium Permanganate.**—A mixture of 6.1 g. of potassium permanganate, 1.00 g. of XVI and 50 cc. of water was refluxed 90 minutes. Decolorized by sodium bisulfite, the reaction mixture was filtered, acidified with concentrated hydrochloric acid to *p*H 6, and concentrated to 40 cc. The addition of aqueous copper acetate produced an immediate precipitate which was washed with hot water, suspended in 50 cc. of water and decomposed with hydrogen sulfide. Filtration of the copper sulfide and evaporation to dryness afforded 0.43 g. (63%) of **isonicotinic acid**, m.p. 314–315°, showing no depression on admixture with authentic isonicotinic acid.

(b) **Fusion with Potassium Hydroxide.**—One gram of XVI was added to a molten mixture of 5 drops of water and 10.0 g. of potassium hydroxide in a nickel crucible and fused at 250° for ten minutes. The cooled mixture was dissolved in 100 cc. of water, partially neutralized with concentrated hydrochloric acid and then made acidic with acetic acid. To the hot solution, 300 cc. of saturated copper acetate was added followed by sodium bicarbonate in small portions until a green precipitate appeared. The filtered and washed copper salt was suspended in water and decomposed with hydrogen sulfide. The filtrate remaining after removal of the copper sulfide was evaporated to dryness leaving 0.41 g. (31.4%) of **ε-(4-pyridyl)-caproic acid dihydrate (XVII)**, m.p. 197.8–198.8° after several crystallizations from absolute ethanol.

Anal. Calcd. for $C_{11}H_{15}N_2 \cdot 2H_2O$: C, 57.62; H, 8.35; N, 6.11. Found: C, 57.81; H, 7.93; N, 6.23.

XVII is very soluble in and crystallizable from cold water, is moderately soluble in hot, absolute ethanol and insoluble in ether. The ultraviolet absorption spectrum of XVII in water showed a maximum at 252 mμ (log ε 3.55) as compared with 256 mμ (log ε 3.5) for pyridine hydrochloride in water.[17]

(17) Landolt-Börnstein, "Physikalisch-chemische Tabellen," 5th ed., 3rd suppl., part 2, J. Springer, Berlin, p. 1416.

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Alkyl Phenyl-(2-pyridyl)-methyl Sulfones. Sulfonium Salts as Alkylating Agents

BY T. R. LEWIS AND S. ARCHER

A series of alkyl phenyl-(2-pyridyl)-methyl sulfones were prepared by condensing alkyl benzyl sulfones with 2-bromopyridine and its homologs in the presence of sodium amide. The yields ranged from poor to moderate, due mainly to the failure of the condensation to proceed to completion. Complicating side-reactions, such as the formation of stilbenes from the unalkylated benzyl sulfones, were noticed. Methylation of benzyl mercaptan with methyl iodide furnished the expected product and a small amount of dibenzyl sulfide. An explanation of the formation of the symmetrical sulfide is offered which requires the intermediate formation of benzyldimethylsulfonium iodide. That a sulfonium salt may act as an alkylating agent was demonstrated by the behavior of trimethylsulfonium mesitoate on gentle heating. The ester, methyl mesitoate, was isolated from the reaction.

A few years ago we prepared a series of alkyl dialkylaminoalkylbenzohydryl sulfones for pharmacological testing.[1] In view of the interesting properties shown by this group of compounds, we thought it desirable to extend our work in the sulfone field to cover a series of alkyl phenyl-(2-pyridyl)-methyl sulfones.

The compounds were prepared according to the general equations

$$\underset{\text{I}}{C_6H_5CH_2SH} \longrightarrow \underset{}{C_6H_5CH_2SR} \longrightarrow \underset{\text{II}}{C_6H_5CH_2SO_2R} \xrightarrow[NaNH_2]{\text{2-Bromopyridine}} \underset{\text{III}}{C_6H_5(2\text{-}C_5H_4N)CHSO_2R}$$

(1) M. M. Klenk, C. M. Suter and S. Archer, THIS JOURNAL, **70**, 3846 (1944).

Originally, we planned to prepare a number of sulfones, III, in which the alkyl group (R) was varied considerably. Consequently the sulfides (I) were prepared from the benzyl mercaptans and the alkyl halides rather than by the reverse procedure. The substituted benzyl mercaptans were obtained in good yield by means of the thiourea synthesis.[2] They were not obtained analytically pure but were suitable for further work. Alkylation of the sodium salts was accomplished by warming in alcohol solution with the requisite alkyl halide. The crude sulfides were oxidized to the nicely crystalline, readily purified sulfones, II, with the aid of 30% hydrogen peroxide.[3] The properties of the alkyl benzyl sul-

(2) G. G. Urquhart, J. W. Gates, Jr., and R. Connor, *Org. Syn.*, **21**, 36 (1941).

(3) Superoxol (Merck and Co., Inc.) was used throughout this work.