TABLE I

PYRAZINIUM SALTS

Salt of pyrazine with	Reaction time[a]	Yield, %	Recrystallized from	Color	M. p., °C.[b]	Formula	Analyses, % Calcd.	Found
Methyl iodide[4]	6 d.	38	Abs. EtOH	Bright yellow	136	$C_5H_7IN_2$	C, 27.06 H, 3.16	27.17 3.38
Ethyl iodide	122 d.	92[c]	Abs. EtOH	Bright yellow	162	$C_6H_9IN_2$	C, 30.53 H, 3.82	30.50 3.88
β-Cyclohexylethyl bromide	79 d.	23	Abs. EtOH + isoprop. eth.	Tan	176	$C_{12}H_{19}BrN_2$	N, 10.29	10.29
β-Phenylethyl iodide	75 d.	16[c] 34	Abs. EtOH + isoprop. eth.	Bright yellow	182	$C_{12}H_{13}IN_2$	C, 46.18 H, 4.17	46.37 4.42
Styrene bromohydrin	71 d.	6	Abs. EtOH	White	206	$C_{12}H_{13}BrN_2O$	C, 51.26 H, 4.63 N, 9.97	51.36 4.71 9.51
Phenacyl bromide	5 d.	62[c] 53	Abs. EtOH	White[d] yellow	193–194	$C_{12}H_{11}BrN_2O$	C, 51.63 H, 3.97 N, 10.04	51.57 4.22 9.87
p-*t*-Butylphenacyl bromide	5 min.	72[c]	Abs. EtOH + isoprop. eth.	Bright yellow	200	$C_{16}H_{19}BrN_2O$	C, 57.32 H, 5.71 N, 8.35	57.24 5.68 7.45
p-Fluorophenacyl bromide	10 d.	15	Abs. EtOH	Light brown	185	$C_{12}H_{10}BrFN_2O$	N, 9.32	9.30
p-Chlorophenacyl bromide	18 hr.	77[c] 56	Abs. MeOH + isoprop. eth.	Light tan	234	$C_{12}H_{10}BrClN_2O$	N, 8.93	8.73
p-Bromophenacyl bromide	18 hr.	69[c]	Washed with $CHCl_3$	Light brown	254[e]	$C_{12}H_{10}Br_2N_2O$	N, 7.82	7.75
p-Iodophenacyl bromide	7 d.	20	Washed with $CHCl_3$	White	249	$C_{12}H_{10}BrIN_2O$	C, 35.56 H, 2.47	35.39 2.68
m-Nitrophenacyl bromide	4 d.[f]	58	Washed with $CHCl_3$	White	205–208	$C_{12}H_{10}BrN_3O_3$	C, 44.46 H, 3.11	44.59 3.28
p-Methoxyphenacyl bromide	41 d.[f]	83	MeOH and isoprop. eth.	Tan	217	$C_{13}H_{13}BrN_2O_2$	N, 9.06	8.91
p-Phenylphenacyl bromide	30 d.	43	Abs. EtOH + isoprop. eth.	Orange	186	$C_{18}H_{15}BrN_2O$	N, 7.89	7.92
α-Bromopropiophenone	13 d.	22	Abs. EtOH	Grayish brown	186–187	$C_{13}H_{13}BrN_2O$	N, 9.78	9.70
α-Naphthacyl bromide	3 d.	67[c] 30	Abs. EtOH + isoprop. eth.	Light brown	193	$C_{16}H_{13}BrN_2O\cdot H_2O$	N, 8.07	7.98
β-Naphthacyl bromide	40 d. (3 d.	68[c] 49)	Abs. EtOH	Light brown	210	$C_{12}H_{11}BrN_2O\cdot{}^1/_2H_2O$	N, 8.29	8.07
5,6,7,8-Tetrahydro-β-naphthacyl bromide	2 d.	78[c] 59	Abs. MeOH + isoprop. eth.	Pale yellow	218	$C_{16}H_{17}BrN_2O$	N, 8.41	8.26
1-Bromoethyl-β-naphthyl ketone	39 d.	19	Abs. EtOH + isoprop. eth.	Tan	205	$C_{17}H_{15}BrN_2O$	N, 8.16	8.37

[a] At 35–40°. [b] Determined by rapid heating. Decomposition accompanied melting in nearly all cases. [c] Crude yields. All other yields refer to purified material. [d] White when first obtained from chloroform. Yellow on recrystallization. [e] Darkens at 235°. [f] Reaction much more rapid than time suggests.

Summary

A series of quaternary salts of pyrazine have been prepared for screening as oncolytic agents. The salts formed readily from pyrazine, and the appropriate organic halide, but only one of the two nitrogen atoms of the pyrazine was ever found to have reacted.

JEFFERSON CITY, TENN. RECEIVED JANUARY 11, 1950

[CONTRIBUTION FROM THE WM. H. CHANDLER CHEMISTRY LABORATORY, LEHIGH UNIVERSITY]

Acyl Aldehydes. The Synthesis of Para-Acetylbenzaldehyde

BY W. K. DETWEILER[1] AND E. D. AMSTUTZ

This work was undertaken to determine the applicability of certain useful aldehyde and ketone synthetic methods for the preparation of acetylbenzaldehydes, specifically *p*-acetylbenzaldehyde. This particular isomer was chosen since it was believed to represent the maximum reactivity possible with those substituent groups and yet one likely to yield polymolecular products on self-condensation.[2] Thus the *o*-isomer would be expected to cyclize monomolecularly while in the *m*-isomer the groups are not mutually activating. Furthermore, in *p*-acetylbenzaldehyde itself, there are present no basic substituents (—OH or —OCH_3, for example) which may diminish the reactivity of either or both carbonyl groups.[2b,3] The process by which the two groups interact is of the aldol type and takes place under the influence of both acids and bases and at high temperatures. This seemed to limit the choice of methods immediately if the monomeric keto-aldehyde were to be the main product.

The only method tried which led to a pure product in reasonable yield was the Rosenmund reduction of *p*-acetylbenzoyl chloride. The pres-

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(1) Taken from the M.S. thesis of W. K. Detweiler, February, 1949.

(2) (a) Hass and Bender, THIS JOURNAL, **71**, 1767 (1949), obtained the polychalcone instead of acetylbenzaldehyde by reaction of *p*-acetylbenzyl bromide with sodium 2-propane-nitronate. (b) See also Russell, *ibid.*, **70**, 2864 (1948).

(3) Gray and Bonner, *ibid.*, **70**, 1249 (1948).

ence of the *p*-acetyl group apparently hinders the reduction for, in the presence of the usual sulfurized-quinoline poison, the reduction was extremely sluggish. In its absence, however, the reduction was completed in about the normal time. *p*-Acetylbenzaldehyde, obtained in this research, appeared as colorless crystals melting at 32.9 to 34.0°. The compound gave an immediate violet color with Schiff reagent, a sodium bisulfite addition product, a positive test for methyl ketones with both sodium nitroprusside and *o*-nitrobenzaldehyde,[4] iodoform and terephthalic acid on treatment with hypoiodite and the derivatives listed in Table I. A comparison of the physical properties of the ketoaldehyde and several reported derivatives appears in Table I.

TABLE I

Compound	Reported by Meyer and Bernhauer[5]	This work
p-Acetylbenzaldehyde	Sweet-smelling oil b. p. 135–138° under diminished pressure	Colorless, sweet-smelling crystals m. p. 32.9–34.0°
phenylhydrazone	Colorless needles m. p. 121°	Yellow needles m. p. 189.6–190.8°
oxime	Colorless leaves m. p. 177°	Colorless needles m. p. 180.6–181.2°

It is conceivable that the discrepancies in the melting points of the derivatives are due to differences in geometric form but it also appears that the ketoaldehyde prepared by Meyer and Bernhauer was not pure.

When sulfurized-quinoline was used in the Rosenmund reduction a reaction period of twelve hours was required for the evolution of 80% of the calculated quantity of hydrogen chloride. The main product obtained (m. p. 210–220° in closed capillary, preheated bath) was a high-melting solid which appears to be made up mainly of dimer (acetylformylchalcone). On further heating this material lost water and afforded a substance which, by analysis, appears to be mainly the trimer.

The Stephen reduction of *p*-acetylbenzonitrile appeared to proceed normally in that a complex salt precipitated out after passage of dry hydrogen chloride for several hours. The complex salt was extremely resistant to hydrolysis however and invariably afforded a small amount of impure starting material along with heavy oils and tars from which no pure substance could be isolated.

An investigation was also made of the hydrolysis of *p*-α,α-dibromoethylbenzal bromide with water alone and with dilute alkalies or a slurry of lime. In every experiment approximately three moles of hydrogen bromide were produced for each mole of tetrabromide. The products were, for the most part, dark rubbery semi-solids which contained halogen and were insoluble in ether but soluble in warm sodium bisulfite solution. It would appear therefore that the intermediate product was a *p*-α-bromovinylbenzaldehyde.

Experimental

p-Cyanoacetophenone was prepared in 47% yield by means of the Sandmeyer reaction from *p*-aminoacetophenone. The white crystalline product boiled at 117° at 4 mm. and melted at 57.0–58.6°.[6] Hydrolysis of the nitrile with an aqueous solution of acetic and sulfuric acids afforded pure white *p*-acetylbenzoic acid, m. p. 208.6–209.4°[7] in 83% yield. There was also obtained a small quantity of yellow condensation product which sublimed at 325°.

***p*-Acetylbenzoyl Chloride.**—To a suspension of 3.15 g. (0.0192 mole) of *p*-acetylbenzoic acid in 13 ml. of dry chloroform contained in a 50-ml. Claisen flask was added 12.9 g. (0.108 mole) of thionyl chloride. After 3.5 hours heating at 70° about 7 ml. of chloroform was distilled off and heating continued for a further period of about five hours. Removal of the chloroform and excess thionyl chloride left a straw-colored solid which was recrystallized several times from petroleum ether. The total yield of material, most of which melted at 67.4–68.0°, was 2.48 g. (71%).

Anal. Calcd. for $C_9H_7O_2Cl$: Cl, 19.42. Found: Cl, 19.82.

By the action of excess thionyl chloride (16.4 g., 0.14 mole) on *p*-acetylbenzoic acid (5 g., 0.0304 mole) in the presence of a drop of pyridine there was obtained as the main product (59%) a slightly tan colored solid, b. p. 121–124° at 10 mm., which, after crystallization from petroleum ether, melted at 81.4–82.4° and appeared to be the *p*-α-**chlorovinylbenzoyl chloride.**

Anal. Calcd. for $C_9H_6OCl_2$: Cl, 35.27. Found: Cl, 34.94, 34.68.

By boiling the above vinyl chloride with water for forty minutes there was obtained a white solid, soluble in dilute sodium hydroxide and pyridine, insoluble in ether, benzene, chloroform and nitrobenzene. It did not melt at 360°.

***p*-Acetylbenzaldehyde.**—The Rosenmund reduction was performed in the usual manner using 2.29 g. (0.0125 mole) of *p*-acetylbenzoyl chloride, 0.26 g. of 5% Pd-$BaSO_4$ and 21 ml. of absolute xylene. During about four hours at reflux 82% of the theoretical amount of hydrogen chloride was evolved. After removal of the barium sulfate the aldehyde was taken up in saturated sodium bisulfite solution, transferred first to ether and then to petroleum ether, evaporation of which afforded 0.8 g. (43%) of colorless crystals melting at 30–31.5°. By extraction and evaporation with petroleum ether this melting point can be raised to 32.9–34.0°.

Anal. Calcd. for $C_9H_8O_2$: C, 72.96; H, 5.44. Found: C, 72.96; H, 5.66.

The bis-phenylhydrazone, yellow needles from alcohol, melting at 189.6–190.8°, was prepared by standard procedures.[8]

Anal. Calcd. for $C_{21}H_{20}N_4$: C, 76.80; H, 6.14. Found: C, 77.01; H, 6.16.

The bis-oxime, colorless needles, melted at 180.6–181.2°.

Anal. Calcd. for $C_9H_{10}O_2N_2$: C, 60.66; H, 5.66. Found: C, 60.75; H, 5.85.

The Rosenmund reaction was also run using 1.27 g. (0.0695 mole) of *p*-acetylbenzoyl chloride 0.14 g. Pd-$BaSO_4$, 0.0014 g. of sulfurized quinoline and 10 ml. of xylene. After twelve hours 77% of the calculated amount of hydrogen chloride had been evolved. After removal of the

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(4) Feigl, "Quantitative Analysis by Spot Tests," Elsevier Pub. Co., New York, N. Y., 1946.

(5) Meyer and Bernhauer, *Monatsh.*, **53** and **54**, 721–752 (1929), obtained the material in small yield as a by-product in the oxidation of *p*-cymene.

(6) Ahrens, *Ber.*, **20**, 2956 (1887), reported m. p. 58–59°.

(7) Rupe and Steinbach, *ibid.*, **43**, 3466 (1910), reported a m. p. of 205°.

(8) Shriner and Fuson, "Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1940.

catalyst the xylene was stepwise evaporated giving two fractions (both gave negative Schiff tests) of small quantity which melted at 153.2–159° and 175–180° (partially). Complete evaporation afforded a pleasant-smelling mobile yellow oil which solidified under low pressure of nitrogen over phosphorus pentoxide and gave a strong aldehyde test with Schiff reagent. Extraction with hot dry ether removed a small amount of material responsible for the aldehyde test and left a residue (0.35 g.) which did not melt up to 360° but when placed in a sealed capillary in a previously heated bath melted at 210–220°. The material was insoluble in hot and cold, concentrated and dilute aqueous solutions of sodium bisulfite.

Anal. Calcd. for $C_{18}H_{14}O_3$: C, 77.68; H, 5.07. Found: C, 76.39, 76.39; H, 5.00, 4.86.

When 0.0704 g. of the above dimer was heated for five minutes at 285° the loss in weight amounted to 0.0031 g. or 4.4%.

Anal. Calcd. for $C_{27}H_{20}O_4$: C, 79.39; H, 4.94. Found: C, 79.12; H, 4.91.

Attempted Reduction of *p*-Cyanoacetophenone.—To a solution of 3.1 g. (0.016 mole) of anhydrous stannous chloride in 35 ml. of anhydrous ether saturated with dry hydrogen chloride was added over a five-minute period a solution of 1.6 g. (0.011 mole) of *p*-cyanoacetophenone in 20 ml. of dry chloroform. The resulting light yellow solution was stirred and treated with hydrogen chloride for four hours at which time a light yellow colored solid had formed. This was removed, washed with ether and then added to 15 ml. of warm water. The dark brown oil which formed contained much inorganic salt and gave a negative Schiff test. It was therefore subjected to a series of hydrolyses and extractions with various solvents. In this way were obtained two solid fractions. One, which melted at 51.2–58.0° appeared to be impure nitrile and the other (also in small amount) melted mainly at 59–72° and may have been partially hydrolyzed nitrile. Most of the product persisted as an oil which did not give the strong immediate Schiff test characteristic of the aldehyde. It was therefore discarded.

***p*-α,α-Dibromoethylbenzal Bromide.**—*p*-α-Bromoethyltoluene was prepared from methyl *p*-tolylcarbinol in 70% yield by the action of phosphorus tribromide and pyridine in benzene solution (b. p. 101.6–103° at 12 mm.). To a solution of 25 g. (0.126 mole) *p*-α-bromoethyltoluene in 25 ml. of carbon tetrachloride (at 60°) was added, over a period of three hours, a solution of 60.5 g. (0.378 mole) of bromine in 185 ml. of dry carbon tetrachloride. Two 300-watt bulbs provided the radiation. Upon removal of the solvent there was obtained 51.9 g. (97%) of heavy brown oil, $n^{25}\text{D}$ 1.6496, d^{25} 2.1254.

Anal. Calcd. for $C_9H_8Br_4$: Br, 73.35. Found: Br, 73.11.

On standing for several months in the refrigerator the oil solidified and, after recrystallization from ether and then ether–petroleum ether mixture, melted at 133.2–134.3°.

Anal. Calcd. for $C_9H_8Br_4$: C, 24.80; H, 1.85. Found: C, 24.98; H, 2.43.

Attempted Hydrolysis of *p*-Ethyltoluene Tetrabromide.—The following is typical of the runs made. A mixture of 20.1269 g. (0.0461 mole) of tetrabromide, 100 ml. of water and 1 g. of hydroquinone was refluxed for ten hours during which time the mixture frequently was brought to the brom thymol blue end-point by titration with standard base. At the end of the reaction period, when base consumption had practically ceased, a total of 81.4 ml. of 1.7079 *N* sodium hydroxide had been consumed. This is equivalent to 0.1390 mole of hydrogen bromide as compared to the theoretical value of 0.1385 mole (on the basis of 3 moles of hydrogen bromide per mole of original tetrabromide). The product was a dark-brown polymeric substance which was only slightly soluble in saturated sodium bisulfite solution. It was not investigated further.

Summary

Of the methods tried the only practical synthesis of *p*-acetylbenzaldehyde is by means of the Rosenmund reduction of *p*-acetylbenzoyl chloride.

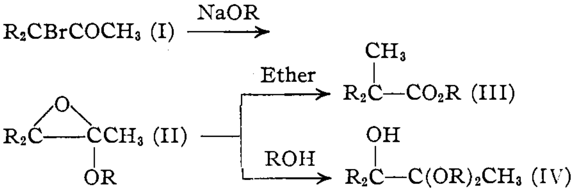
Bethlehem, Pa. Received November 7, 1949

[Contribution from the Whitmore Laboratories of the School of Chemistry and Physics, The Pennsylvania State College]

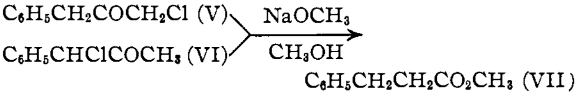
The Reaction of the Isomeric α-Bromomethyl Cyclohexyl Ketones with Sodium Methoxide

By R. B. Wagner and James A. Moore[1]

The conversion of an α-bromo-α-alkyl ketone (I) to a trisubstituted acetic ester (III) or a hydroxyl ketal (IV) has been recognized by Aston and Green[2] to be a general reaction, which was considered to proceed *via* an intermediate oxide (II), the latter precursor giving rise to the ester (III) when ether was employed as the medium, and to a hydroxyketal (IV) if alcohol was present, *viz.*



However, the postulation of an ethylene oxide intermediate appears inadequate to explain the formation of the same ester by rearrangement of isomeric chloroketones. This was shown to occur by McPhee and Klingsberg[3] who treated the isomeric α-chlorophenylacetones (V and VI) with sodium methoxide in methanol and obtained methyl hydrocinnamate (VII) in each case, *viz.*



$$\left.\begin{array}{l}C_6H_5CH_2COCH_2Cl\ (V)\\ C_6H_5CHClCOCH_3\ (VI)\end{array}\right\rangle \xrightarrow[CH_3OH]{NaOCH_3} C_6H_5CH_2CH_2CO_2CH_3\ (VII)$$

Recently, another example of this phenomenon was observed in the steroidal series, in which both the 17-bromo and 21-bromopregnenolones (VIII and IX) were transformed with potassium meth-

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[1] Research Department, Parke, Davis and Company, Detroit 32, Michigan.

[2] Aston and Green, This Journal, **62**, 2590 (1940).

[3] McPhee and Klingsberg, *ibid.*, **66**, 1132 (1944).