solution was distilled to dryness, finally under vacuum. Aqueous sodium carbonate and a large amount of water were added, and the suspension was steam distilled at 70 mm. to remove steam-volatile material. The mixture was cooled and left to stand for some time, and the solid product filtered, washed with water, and dried. The weight of crude ester was 11.61 g. (85.1%). A 12-hr. reflux period also gave 85%. The material was recrystallized from acetone-water 6 times and formed a white powder of m.p. 139–141°.

*Anal.* Calcd. for $C_{22}H_{25}NO_5$: C, 68.94; H, 6.53. Found: C, 68.77; H, 6.60.

DL-*beta*-(*5-Acenaphthenyl*)*alanine hydrochloride.* A solution of 2.77 g. of the ester in 25 ml. of ethanol was mixed with 20 ml. of concentrated hydrochloric acid and the solution refluxed 15 hr. It was then cooled and diluted with 8 volumes of water and left several hours. A white substance and some tar separated and these were removed by filtration. The filtrates were now boiled to a small volume and cooled to yield a crystalline deposit weighing 1.23 g. The filtrates from this, on further concentration, gave an additional 0.23 g. The total of 1.46 g. represents a 73% yield of hydrochloride. The amino acid hydrochloride was recrystallized by adding an excess of petroleum ether to the solution in a minimum of hot ethanol, and cooling. The first and last portions to crystallize were removed and the center fraction crystallized again. After 5 recrystallizations, a white powder was obtained.

*Anal.* Calcd. for $C_{15}H_{16}NO_2Cl$ (monohydrochloride): C, 64.86; H, 5.77. Found: C, 64.45; H, 5.80.

The hydrochloride and the free amino acid were difficult to purify. The best sample of hydrochloride, on heating, sintered above 190° with beginning discoloration, and melted indefinitely at 220–232° to a brownish-orange melt.

DL-*beta*-(*5-Acenaphthenyl*)*alanine.* The amino acid was best prepared from its hydrochloride by vacuum concentration of its ammoniacal solution. This operation was accompanied by much foaming and had to be done slowly. If concentrated at atmospheric pressure, considerable darkening occurred, while the product obtained by acidifying alkaline solutions with acetic acid was also usually dark and formed slowly in poor yield. If the ammoniacal solution was decolorized by Norit, only small amounts of the latter could be employed due to the ready adsorption of the amino acid on the charcoal. The free amino acid separated as a crystalline powder when the ammonia solution was distilled at 60 mm. to a small volume. This recrystallization was repeated 3 times and the white product dried 4 days in vacuum.

*Anal.* Calcd. for $C_{15}H_{15}NO_2$: C, 74.69; H, 6.22. Found: C, 74.25; H, 6.38.

The acenaphthenyl alanine is very sparingly soluble in water, even when hot. With ninhydrin in dilute acetic acid, on heating, a purple color was formed. The amino acid darkened (brown) at 218–220° and melted at 228–231° forming a dark brown melt.

*N*-(*benzenesulfonyl*)-DL-*beta*-(*5-acenaphthenyl*)*alanine.* A solution of 300 mg. of the amino acid hydrochloride in 20 ml. of 1*N* KOH was acylated by stirring at room temperature with benzenesulfonyl chloride and ether, for 3 hr. More KOH was added, and the alkaline solution separated and acidified with hydrochloric acid to yield a partly resinous precipitate of the acid. The acid was collected, washed with water, and dried. The yield was 300 mg. or 72.8%. The product was purified by concentration of its ether solution to a small volume and seeding with scratching. It was recrystallized 3 times and dried in vacuum, m.p. 203–205°.

*Anal.* Calcd. for $C_{21}H_{19}NSO_4$: C, 66.14; H, 4.99. Found: C, 66.10; H, 5.02.

BERKELEY, CALIF.

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[CONTRIBUTION FROM THE LABORATORY OF CHEMISTRY OF NATURAL PRODUCTS, NATIONAL HEART INSTITUTE, NATIONAL INSTITUTES OF HEALTH, U. S. PUBLIC HEALTH SERVICE, DEPARTMENT OF HEALTH, EDUCATION AND WELFARE]

# Piperidine-Catalyzed Condensation of 1,3-Dicarbonyl Compounds with Ethyl β-Ketoglutarate

GORDON N. WALKER

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Acetylacetone, benzoylacetone, and the hydroxymethylene derivatives of phenylacetone, cyclopentanone, cyclohexanone, and cycloheptanone have been condensed with ethyl β-ketoglutarate in the presence of piperidine to give, after hydrolysis, substituted 2-hydroxyisophthalic acids, III a, b, c, d, e, and f, respectively. With the exception of IIc, a new compound, these products are the same as those obtained in the corresponding reactions carried out earlier using sodium ethoxide as the basic agent. Spectroscopic, degradative, and other data confirming the structures of the products are presented. Generally speaking, α-hydroxymethyleneketones are found to react selectively with one mole of ethylene glycol in the presence of benzenesulfonic acid, giving acetal-ketones IV.

The discovery was made by Prelog and his colleagues[1,2] in 1947, that 2,6-dicarbalkoxyphenols-(II) may be prepared directly by condensation of a variety of 1,3-dicarbonyl compounds with ethyl β-ketoglutarate in the presence of sodium ethoxide. This reaction and related condensation of 1,4-dicarbonyl compounds[3,4] with ethyl β-ketoglutarate appeared to be worthy of further study, in view of the fact that unexpected products are sometimes encountered,[4] and in the hope that the reaction might possibly be extended to condensation of dicarbonyl compounds with ethyl ketipate, EtOOC-$CH_2$-CO-CO-$CH_2$COOEt, with consequent formation of tropolones. While the latter idea has not

(1) V. Prelog, O. Metzler, and O. Jeger, *Helv. Chim. Acta*, **30**, 675 (1947).

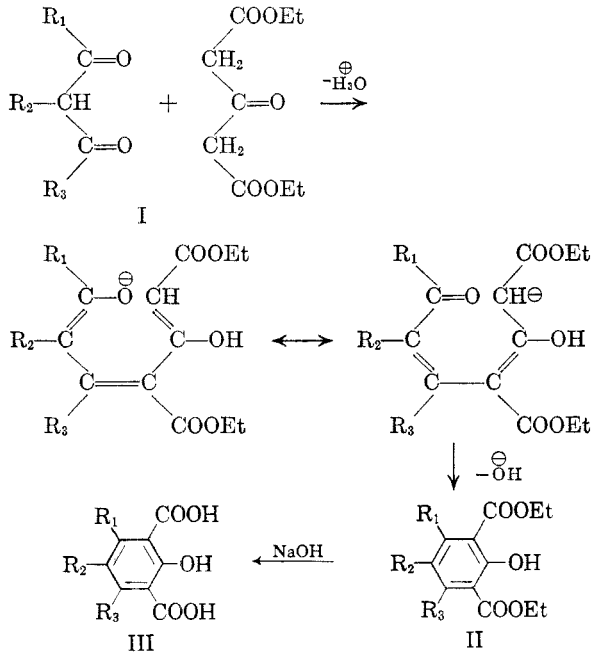
(2) V. Prelog, L. Ruzicka, and O. Metzler, *Helv. Chim. Acta*, **30**, 1883 (1947).

(3) J. Thiele and J. Schneider, *Ann.*, **369**, 287 (1909).

(4) D. S. Tarbell and B. Wargotz, *J. Am. Chem. Soc.*, **76**, 5761 (1954).

been realized, some interesting results have been seen in examining the known reactions.

In seeking new ways to carry out condensation of 1,3-dicarbonyl compounds with substances having reactive methylene groups, it was found that anhydrous piperidine may be substituted for sodium ethoxide in reaction of 1,3-dicarbonyl compounds with ethyl β-ketoglutarate. It was necessary to use about one equivalent of piperidine to promote the condensation, and to perform the reaction in boiling methanol. In this particular reaction, there is no evidence yet to show whether the process takes place all at once or involves two aldol-dehydration steps, the first intermolecular and the second a cyclization; however the latter eventuality seems more probable, in which case the initial aldol condensation probably governs the entire process. Various tautomeric and resonant-anion pictures of presumed intermediates can be drawn, and the two most likely to be involved are shown here.[5]



I

III II

a: $R_1 = R_3 = CH_3$; $R_2 = H$
b: $R_1$ = phenyl; $R_2 = H$; $R_3 = CH_3$
c: $R_1 = CH_3$; $R_2$ = phenyl; $R_3 = H$
d: $R_1R_2 = -(CH_2)_3-$; $R_3 = H$
e: $R_1R_2 = -(CH_2)_4-$; $R_3 = H$
f: $R_1R_2 = -(CH_2)_5$; $R_3 = H$

Employing piperidine in boiling methanol, acetylacetone, benzoylacetone, and the formyl (hydroxymethylene) derivatives of phenylacetone, cyclopentanone, cyclohexanone, and cycloheptanone were condensed with ethyl β-ketoglutarate. Fortunately for the purpose of isolation of the products (II) these hydroxy-esters proved to be nearly insoluble in 2% sodium hydroxide solution (cryptophenolic), as anticipated, and thus it was possible to remove unchanged starting material and acidic cleavage products by extraction with dilute sodium hydroxide. Fairly pure "neutral" products were obtained in this way. Only two diesters (IIb and IIf) were obtained in crystalline form, and ester IIb alone among those studied was appreciably soluble in 2% sodium hydroxide. The phenolic esters gave purple or deep red color tests with ferric chloride. They were hydrolyzed readily with 5% sodium hydroxide solution, and crystalline 2,6-dicarboxyphenols III were obtained. Data for these products, compared with their characteristics as reported previously[1,2] are given in Table I. The acids gave, as expected, indigo-like color tests with ferric chloride. Correct analytical figures (carbon, hydrogen, and neutral equivalent) were found in each case. The phenolic groups in the acids, as in their corresponding diesters, were masked, as is evident from the fact that normal end points (phenolphthalein indicator) were reached in titration of the acids with dilute alkali when both carboxyl groups were neutralized; the phenolic group thus did not interfere significantly in determination of neutral equivalent. The infrared spectra of the phenolic acids (Nujol mull) uniformly showed bands representing bonded hydroxyl group (3.1–3.25 μ, weak or moderate), both normal and chelated carboxyl groups (two intense peaks, in the 5.8–5.9 and 6.0–6.1 μ regions, respectively), and the benzene nucleus (6.18–6.21 μ). In the ultraviolet spectra there was observed in some cases a shift in the relative intensity of minimum absorption with changing concentration, although the wave length of maximum absorption remained fairly well fixed and log $\epsilon_{max}$ did not deviate greatly from that required by Beer's Law. The phenomenon was especially evident with compounds IIId and IIIe. Other hydroxybenzoic acids have been observed to fluoresce in ultraviolet light. Solutions of the phenolic diacids in aqueous alcohol turned litmus paper red, indicating high acid strength as expected.

Further evidence for structure III of these acids was obtained in some cases by decarboxylation. All the compounds III effervesced strongly when melted. From fusions of IIIa, IIIc, IIIe (with palladium-charcoal added to bring about dehydrogenation as well), and IIIf there were isolated *sym-m*-xylenol, 3-methyl-4-phenylphenol, β-naphthol, and 7-hydroxybenzosuberene, respectively. The yields of these phenols were not high, and tars and other acidic materials, perhaps corresponding salicylic acids,[1,2,6] were formed as well. Best results in this thermal decarboxylation were experienced with the benzosuberan derivative IIIf.

Attempts to condense hydroxymethyleneaceto-

(5) The stepwise reaction shown should not be taken literally as a proposed mechanism, since it does not indicate the exact role played by piperidine in the condensation, other than as a proton acceptor. The actual mechanism probably involves piperidinium salts of the reactants or, as suggested by a referee, may depend upon initial formation of an amino alcohol from the 1,3-diketone and piperidine. Either process might require an equivalent or more of piperidine to be present.

(6) F. Tiemann and K. L. Reimer, *Ber.*, **10**, 1562 (1887).

TABLE I

PHYSICAL PROPERTIES OF SUBSTITUTED PHENOLS

| Compound | Yield,[a] % | M.P., °C. | Prelog Yield of Di-ester (M.P.) | Analysis | | | | | | Infrared $\lambda_{max}$ ($\mu$) (Nujol) | | | Ultraviolet Spectra (Ethanol) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Calcd. | | | Found | | | Normal COOR | Bonded COOR | Phenyl | $\lambda_{max}$ | Corresponding log $\epsilon$ |
| | | | | C | H | N.E. | C | H | N.E. | | | | | |
| IIa | 50 (A) | 40–42 | 92 (44°) | 63.14 | 6.81 | — | 62.5 | 6.78 | — | 5.82 | 6.05 | 6.20 | 216, 250, 314 | 4.44, 3.99, 3.76 |
| IIIa | 48 (B) | 218–220 | — (226°) | 57.14 | 4.80 | 105 | 57.39 | 4.89 | 101 | 5.94 | 6.09 | 6.20 | 218, 248, 316 | 4.43, 3.90, 3.68 |
| IIIb | 25 (AB) | 203–205 | 47 (205°) | 66.17 | 4.44 | 136 | 66.33 | 4.71 | 132 | 5.82 | 6.10 | 6.21 | 221, 266, 322 | 4.47, 4.10, 3.78 |
| IIIc | 25 (CD) | 256–258 | — (—) | 66.17 | 4.44 | 136 | 66.09 | 4.76 | 135 | 5.83 | 6.02 | 6.18 | 220, 232, 317 | 4.48, 4.39, 3.63 |
| IIId | 13 (BD) | 232–234 | 93 ? (—) | 59.46 | 4.54 | 111 | 59.38 | 4.71 | 109 | 5.92 | 6.03 | 6.20 | 216, 250, 327 | 4.53, 3.80, 3.75 |
| IIIe | 52 (B) | 222–224 | 83 (205°) | 61.01 | 5.12 | 118 | 61.01 | 5.29 | 119 | 5.82–5.85 | 6.02 | 6.20 | 214, 243, 320 | 4.51, 3.91, 3.69 |
| IIIf | 61 (E) | 57–58 | 61 (55°) | 66.65 | 7.24 | — | 66.38 | 7.29 | — | 5.80 | 6.00 | 6.19 | 212, 248, 317 | 4.28, 3.82, 3.56 |
| IIIf | 49 (B) | 214–216 | — (226°) | 62.39 | 5.64 | 125 | 62.61 | 5.69 | 120 | 5.82–5.86 | 6.02–6.05 | 6.20 | 212, 245, 315 | 4.51, 3.95, 3.70 |

[a] Solvents used for recrystallization are indicated in this column. A = cyclohexane; B = ethylacetate; C = benzene; D = methanol; E = ether.

phenone and 2-hydroxymethylene-1-tetralones with ethyl $\beta$-ketoglutarate in the presence of piperidine did not give appreciable amounts of isophthalates, but rather led in part to decomposition of the compounds to the parent ketones. The reaction, unlike the sodium ethoxide-catalyzed process,[1] does not appear to be applicable to formyl derivatives of phenyl ketones, although the more stable diketones (benzoylacetone) undergo condensation to some extent. Formylphenylacetone (Ic) also appeared to be degraded to some extent during condensation, as evidenced by the low yield of IIIc. In the cyclic compounds, the six- and seven-membered ring formylketones (e) and (f) gave much better results than did the five-membered ring compound (d). Decomposition of the unstable formylcyclopentanone during condensation, as well as less favorable steric factors may account for the low yield in this case.

Mention should be made here of some of the properties of hydroxymethylene ketones which were observed during the course of this work. Their infrared spectra all showed intense double peaks in the region 6.0–6.4 $\mu$, while carbonyl and hydroxyl bands were weak or absent. This fact is in accord with the modern point of view regarding such compounds, *i.e.* that virtually complete chelation, and perhaps also resonance stabilization of the pseudo-six-membered ring thus produced. does away with both normal carbonyl and hydroxyl stretching:



When one mole of each hydroxymethyleneketone was treated in turn with one mole of ethylene glycol in the presence of a trace of benzenesulfonic acid in refluxing benzene, more or less selective acetal formation at the formyl group took place and led to dioxolane-ketones, IV:




Ic, $R_1$ = phenyl; $R_2$ = H
I, $R_1$ = H; $R_2$ = phenyl
Id
Ie
If

IVa, $R_1$ = phenyl; $R_2$ = $CH_3$
b, $R_1$ = H; $R_2$ = phenyl
c, $R_1R_2$ = $(CH_2)_3$
d, $R_1R_2$ = $(CH_2)_4$
e, $R_1R_2$ = $(CH_2)_5$

These products were neutral and did not give ferric chloride tests. The infrared spectra of the derivatives (see Table II) showed in each case a return of the intense absorption band characteristic of the ketone from which the hydroxymethylene compound had originally been prepared, and disappearance of the spectral features associated with the hydroxymethylene derivatives. 2,4-Dinitrophenylhydrazones were prepared from the dioxo-

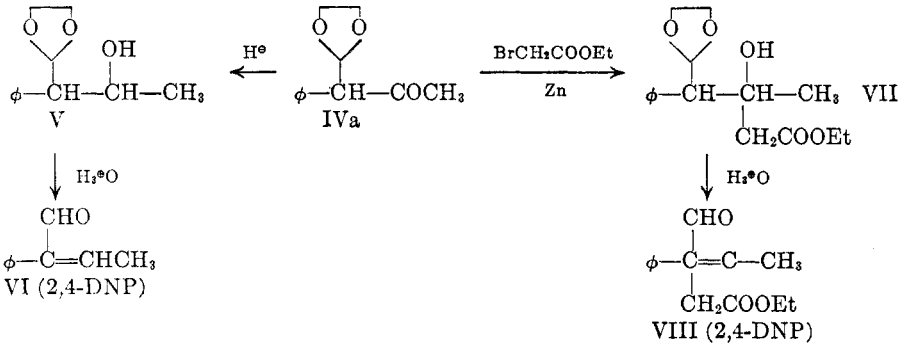
TABLE II

PROPERTIES OF DIOXOLANE-KETONES

| Parent Ketone | | | | | | 2,4-Dinitrophenylhydrazones | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Analysis | | | |
| | | | | | | | Calcd. | | Found | |
| Name | Infrared $\lambda_{max}$ ($\mu$) (chf.) | Compound | Yield, % | B.P., °C. (Mm.) | Infrared $\lambda_{max}$ ($\mu$) (Chf.) | M.P., °C. | C | H | C | H |
| Phenylacetone | 5.85 | IVa | 50 | 125–139 (0.8) | 5.84 | 151–153 | 55.96 | 4.70 | 56.11 | 4.42 |
| Acetophenone | 5.95 | IVb | 63 | 144–148 (2.8) | 5.94 | 174–176 | 54.84 | 4.33 | 55.05 | 4.46 |
| Cyclopentanone | 5.75 | IVc | 10 | 90–107 (1.0) | 5.75 | — | — | — | — | — |
| Cyclohexanone | 5.80 | IVd | 36 | 133–147 (3–4) | 5.80 | 186–188 | 51.42 | 5.18 | 51.53 | 5.07 |
| Cycloheptanone | 5.93 | IVe | 60 | 99–103 (0.85) | 5.90 | 120–142 | 52.74 | 5.53 | 53.00 | 5.63 |

lane derivatives without appreciable hydrolysis of the dioxolane ring in all cases but IVc, and these dinitrophenylhydrazones gave acceptable analytical results. The derivative of IVe did not melt sharply, indicating that IVe contained an impurity, probably the ketal-aldehyde. Compound IVc did not react satisfactorily with 2,4-dinitrophenylhydrazine, possibly because of its relative instability in the presence of acids. Thus, with certain exceptions, hydroxymethyleneketones react selectively (at the hydroxymethylene group) with ethylene glycol, as was found earlier in studying a more complex compound of this type.[7]

As further evidence for the structure of Ic, and consequently also of IIIc, some additional results may be described. Compound IVa gave a positive iodoform test, indicating the presence of the methyl ketone group; on the other hand IVa did not react appreciably with alkali alone of the same strength as used in the iodoform reaction. Reduction of IVa with either sodium borohydride or lithium aluminum hydride gave hydroxyacetal V, which with 2,4-dinitrophenylhydrazine reagent gave a single, pure 2,4-dinitrophenylhydrazone corresponding in analytical figures to that derivative of unsaturated aldehyde VI. Compound IVa also underwent smooth Reformatsky reaction with ethyl bromoacetate giving, after decomposition of the metal complex with dilute acetic acid, the hydroxy acetal ester VII, as indicated by the infrared spectrum of the product. Like V, this hydroxy compound with 2,4-dinitrophenylhydrazine reagent gave the 2,4-dinitrophenylhydrazone of the corresponding unsaturated aldehyde-ester, VIII. The ease with which both V and VII undergo simultaneous dehydration and acetal-hydrolysis in the presence of dilute sulfuric acid and 2,4-dinitrophenylhydrazine is good evidence for the structures shown.




It is interesting to note that attempts to dehydrate and hydrolyze V and VII in dilute acid without added 2,4-dinitrophenylhydrazine gave very poor results, owing to decomposition, and thus compounds such as VI and VIII can be obtained in good yield only in the form of derivatives by this route.

## EXPERIMENTAL[8]

*α-Hydroxymethyleneketones.* Formylation of ketones mentioned in the discussion was carried out in each case by adding a solution of the ketone (0.40 mole) and ethyl formate (1.00 mole) in dry ether (500 ml.) to a suspension of freshly prepared, dry sodium methoxide (0.4–0.5 mole) in 500 ml. of dry ether. With phenylacetone the reaction was vigorous, and it was advisable to cool the mixture in an ice bath during the addition. The mixture was swirled for several hours and was allowed to stand at room temperature overnight, except in the case of phenylacetone when the reaction was complete after 0.5 hr. The suspension was treated with 500 ml. of cold water, and the resulting aqueous solution was washed with ether. The product was isolated by acidification with hydrochloric acid and extraction with ether. The ether solution was washed with water, dried over magnesium sulfate, and the ether was evaporated. The products were stored in closed containers at 0°. Yields of crude, oily formylketones from phenylacetone, acetophenone, cyclopentanone, cyclohexanone, and cycloheptanone were 85, 98, 66, 86, and 76 percent, respectively.

(7) G. N. Walker, *J. Am. Chem. Soc.*, 75, 3393 (1953).

(8) Melting points are corrected.

*Acetal-ketones* (IV). In each case a mixture of 0.20 mole of hydroxymethylene ketone, 0.20 mole of ethylene glycol, 0.15 g. of benzenesulfonic acid, and 160 ml. of benzene was refluxed under a constant water separator for 3 hr. A dark heavy layer which was present at first gradually disappeared, and a dark brown solution was obtained. The cooled solution was diluted with ether and was washed with 4 portions of 5% sodium hydroxide solution and 3 portions of water. The solvents were removed from the dried (magnesium sulfate) solutions by evaporation, and the residue was distilled *in vacuo*. Boiling points, yields, and infrared data of the products are given in Table II. The materials were colorless oils, some of which (notably IVa and IVd) turned dark gradually upon standing at room temperature; it was advisable to store the materials in closed containers at 0°.

*2,4-Dinitrophenylhydrazones* were prepared from the acetal-ketones by treatment with 5% alcoholic 2,4-dinitrophenylhydrazine solution containing some excess 50% sulfuric acid. These derivatives were recrystallized from ethanol or ethanol–ethyl acetate, and their properties are recorded in Table II.

*General procedure in condensation of dicarbonyl compounds with ethyl β-ketoglutarate.* A solution of 0.050 mole of 1,3-dicarbonyl compound and 0.051 mole of ethyl β-ketoglutarate in 25 ml. of reagent methanol was warmed to 50° and 5–6 ml. of piperidine was added. The solution became red or orange and heat was evolved. The solution was boiled on a steam cone for 40 min., allowing about two-thirds of the methanol to escape. The residual material was cooled, diluted with 100 ml. of water, and acidified with hydrochloric acid. The oily material was extracted with ether, and the ether solution was washed successively with one portion of water, four portions of 2% sodium hydroxide solution, and three portions of water. The ether solution was dried (magnesium sulfate) and the ether was evaporated. The crude products were oils ranging in color from light yellow to red. They gave in each case a purple color test with ferric chloride solution.

Compound IIa crystallized on standing; in this case additional product was obtained by acidification of the alkaline wash solutions, bringing the total yield to 50%.

Acidification of the alkaline wash solutions after isolation of IIb resulted in 45% recovery of benzoylacetone. The yield of product in this case reported in Table I is based upon benzoylacetone consumed in the condensation.

Compound IIf crystallized gradually after standing at room temperature for several weeks.

*2-Hydroxyisophthalic acids.* The crude hydroxy-esters obtained as described in the preceding experiment were refluxed in turn with 12 parts (by weight) of 5% sodium hydroxide solution for 2 hr. The cooled solution in each case was washed with several portions of ether and was acidified with hydrochloric acid. After the mixture had been kept at ice temperature overnight, the product was collected, washed with 2 small portions of cold water, and air-dried. The crude acids, yields of which are recorded in Table I, melted 5–15° lower than corresponding pure samples. They were purified by recrystallization from the respective solvents indicated in Table I. Moderately concentrated solutions of the pure acids in dilute alcohol turned litmus paper red. The acids all gave very intense bluish purple colors with ferric chloride solution, and effervesced strongly when melted.

*Decarboxylation of 2-hydroxyisophthalic acids.* Pure, dry samples (2–4 g.) of the acids III were placed in loosely-stoppered 50-ml. flasks, and the flasks were placed in a wax bath preheated to 230°. The samples were allowed to remain in the bath for 0.5 hr., during which time the temperature of the bath was raised gradually to 260°. Evolution of carbon dioxide was pronounced at first, and appeared to be complete after about 15 min. In the case of compound IIIe, 0.5 g. of 10% palladium-charcoal was added to the melt after 10 min. In each case, the cooled material was boiled with 30 ml. of methanol and the solution was filtered free of insoluble, tarry material (and catalyst, in the IIIe case). The methanol was evaporated, and the clarified, crude product was treated as described below.

Fractional crystallization of the crude products from IIIa and IIIe (aqueous methanol), after reprecipitation from washed alkaline solutions or short-path microdistillation, gave small amounts of *3,5-dimethylphenol*, m.p. 62–64°, and *β-naphthol*, m.p. 121–123°, respectively. These did not depress the melting point of respective authentic compounds, and the infrared spectrum of each was identical with that of the respective authentic compound.

*3-Methyl-4-phenylphenol.* Short-path distillation of the crude product from IIIc gave 20% of viscous, pale yellow oil, b.p. 130–140° (1.0 mm.). This phenol did not crystallize, and analysis indicated that it was somewhat contaminated with hydroxyacids. The infrared spectrum (chf.) had moderately intense bands at 2.78, 5.99, and 6.23 μ. The ultraviolet spectrum (ethanol) had $\lambda_{max}$ 250 and 315 mμ (log ε 4.03 and 2.70, respectively). Bromination in acetic acid and titration of excess bromine as iodine showed consumption of 1.70 moles of bromine per mole of phenol, after 0.5 hr., and 1.85 moles of bromine in 2.5 hr. The *dibromo* derivative was prepared by bromination in chloroform and was recrystallized from hexane; colorless crystals, m.p. 65–66°. The infrared spectrum (chf.) had a peak at 2.87 μ.

*Anal.* Calcd. for $C_{13}H_{10}OBr_2$: C, 45.65; H, 2.95; Br, 46.73. Found: C, 45.82; H, 3.2; Br, 46.67.

*7-Hydroxybenzosuberene.* Short-path distillation of the product from IIIf afforded 60% of an oil, b.p. 111–118° (0.7 mm.) which crystallized readily. Recrystallization from cyclohexane gave colorless crystals, m.p. 69–70° (reported[2,9] m.p. 72°). The infrared spectrum (chf.) had sharp peaks at 2.78 and 6.22 μ. The ultraviolet spectrum (ethanol) had $\lambda_{max}$ 220, 227, 280 and 285 mμ (log ε 3.82, 3.81, 3.32, and 3.28, respectively).

*Anal.* Calcd. for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.22; H, 8.60.

This phenol absorbed 2.06 moles of bromine in acetic acid solution, but the dibromo derivative was not crystalline.

*Compounds V and VI.* Reactions of IVa with sodium borohydride in methanol and with lithium aluminum hydride in dry ether were carried out by the usual procedures. The product in each case was a fragrant, pale yellow oil. The infrared spectra of the two products were identical, having a moderately strong band at 2.82–2.84 μ, an intense band around 8.85 μ (ether), and no carbonyl peak. *The 2,4-dinitrophenylhydrazone* of VI was prepared from both samples by the customary procedure, and was recrystallized from ethanol–ethyl acetate; orange crystals, m.p. 179–181°. The infrared spectrum of this derivative (chf.) had sharp peaks at 3.01 and 6.15 μ.

*Anal.* Calcd. for $C_{16}H_{14}O_4N_4$: C, 58.89; H, 4.32. Found: C, 58.99; H, 4.50.

Attempts to prepare VI itself by hydrolysis of V in warm, dilute acids resulted in formation of brown, viscous gum from which crystalline materials or derivatives could not be obtained.

*Compounds VII and VIII.* A Reformatsky reaction was carried out in the usual way with 10.7 g. of IVa, 13.5 g. of ethyl bromoacetate, and 15 g. of HCl-activated, dry 30-mesh zinc, in 200 ml. of dry benzene. When the vigorous initial action was complete, the mixture was refluxed and stirred vigorously for an hour. The cooled suspension was diluted with ether and was treated with 10% acetic acid. The organic solution was washed with successive portions of water, 5% sodium hydroxide solution (3 portions), and water, and was dried over magnesium sulfate. Evaporation of the solvents gave crude compound VII as a red oil. The infrared spectrum (chf.) had bands at 2.90 and 5.82 μ (hydroxyl and ester groups, respectively), and also showed

(9) R. H. Burnell and W. I. Taylor, *J. Chem. Soc.*, 3486 (1954).

the same intense ether band in the 8.5–8.9 $\mu$ region as was evident in the spectrum of V and the starting material. The *2,4-dinitrophenylhydrazone of* VIII was prepared from VII by the customary procedure, and was recrystallized from ethanol; yellow-orange crystals, m.p. 178–180°. The infrared spectrum of this derivative (chf.) had sharp peaks at 3.01, 5.75, and 6.16 $\mu$.

*Anal.* Calcd. for $C_{20}H_{20}O_6N_4$: C, 58.25; H, 4.89. Found: C, 58.09; H, 4.76.

As with V, attempts to hydrolyze VII in warm, dilute acids resulted in formation of dark gum, and partial recovery of the starting material. Alkaline hydrolysis of VII gave a polymeric substance.

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BETHESDA 14, MD.

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

# p-Cyclopentylacetophenone and Its Derivatives

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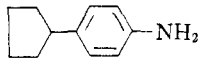
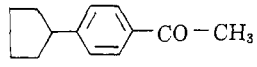
The preparation of cyclopentylbenzene, and of *p*-cyclopentylacetophenone obtained therefrom, has been investigated, and the use of the latter ketone as an intermediate for the synthesis of various aromatic and heterocyclic cyclopentyl compounds, especially *p*-cyclopentylaniline, is described. In the course of this work, a large number of derivatives of *p*-cyclohexylaniline have been prepared for evaluation of their tuberculostatic activity.

As part of a general investigation on the relationship between tuberculostatic properties and chemical structure,[1] several derivatives of *p*-cyclopentylaniline were required for comparison of their activity with that of similar derivatives of *p*-cyclohexylaniline. The most promising method for preparing *p*-cyclopentylaniline (I) free from position isomers seemed to be *via* Beckmann rearrangement of the oxime of *p*-cyclopentylacetophenone (II), a ketone which had already been briefly described[2] but which was now more thoroughly investigated. This in turn led us to examine the various procedures for the preparation of the main intermediate, *viz.* cyclopentylbenzene.



I



II

Since its discovery by Kursanoff,[3] cyclopentylbenzene has been synthesized by several methods: (1) by Friedel-Crafts reaction of chloro- or bromocyclopentane and benzene;[4] (2) by direct condensation of cyclopentanol with benzene in the presence of Lewis acids;[5] and (3) by addition of cyclopentene to benzene in the presence of aluminum chloride.[6] A reinvestigation of these various methods showed the condensation of cyclopentanol with benzene to be the most satisfactory, as regards both simplicity and yields; a study of the influence of the various factors of the reaction on the yield of cyclopentylbenzene showed the temperature to be the only important variable, and that the best yield was attained at a temperature of 50°. All the methods furnished from 10–20% of dicyclopentylbenzene (probably a mixture of the three position isomers).

Friedel-Crafts acetylation of cyclopentylbenzene furnished an excellent yield of *p*-cyclopentylacetophenone, giving a semicarbazone, m.p. 232°, at variance with von Braun and Kühn[7] who recorded a very poor yield for this ketone, and m.p. 212–215° for the semicarbazone. Table I lists some chalcones prepared by condensation of ketone II with various aromatic and heterocyclic aldehydes; oxidation of the same ketone with sodium hypobromite afforded *p*-cyclopentylbenzoic acid, identical with the acid which Kleene prepared by carbonation of cyclopentylphenylmagnesium bromide.[2] Beckmann rearrangement of *p*-cyclopentylacetophenone oxime to *p*-cyclopentylacetanilide was effected, in excellent yields, with phosphorus pentachloride in ether, and subsequent hydrolysis furnished *p*-cyclopentylaniline (I), a liquid amine which was characterized by several solid derivatives: 1-*p*-cyclopentylphenyl-2,5-dimethylpyrrole (III) (by condensation with acetonylacetone), 2-chloro-3-(*p*-cyclopentylanilino)-1,4-naphthoquinone (by condensation with 2,3-dichloro-1,4-naphthoquinone), 2,5-dichloro-3,6-bis(*p*-cyclopentyl-

(1) For tuberculostatic activity of thiocarbanilides, see N. P. Buu-Hoï and N. D. Xuong, *Compt. rend.*, **237**, 498 (1953); N. P. Buu-Hoï, N. D. Xuong, and N. H. Nam, *J. Chem. Soc.*, 1573 (1955); N. P. Buu-Hoï, N. D. Xuong, N. H. Nam, J. M. Gazave, J. Pillot, and L. Schembri, *Experientia*, **11**, 97 (1955); M. Welsch, N. P. Buu-Hoï, P. Danthinne, and N. D. Xuong, *Experientia*, **12**, 102 (1956); N. P. Buu-Hoï, N. D. Xuong, J. M. Gazave, J. Pillot, and G. Dufraisse, *Experientia*, **12**, 474 (1956).

(2) R. D. Kleene, *J. Am. Chem. Soc.*, **71**, 1893 (1949).

(3) N. Kursanoff, *Ann.*, **318**, 309 (1901).

(4) J. von Braun, *Ber.*, **60**, 1080 (1927).

(5) R. C. Huston and K. Goodemoot, *J. Am. Chem. Soc.*, **56**, 2432 (1934).

(6) P. Cagniant, A. Deluzarche, and G. Chatelus, *Compt. rend.*, **224**, 1064 (1947).

(7) J. von Braun and M. Kühn, *Ber.*, **60**, 2562 (1927).