TABLE XIII.—RECOVERY OF VITAMINS A AND E USING PROPOSED PROCEDURE

Input		% Recovery	
Vitamin A Units	Vitamin E Units	Vitamin A	Vitamin E
50,000 (oil)	10 (oil, acetate)	99.1	101.9
25,000 (oil)	10 (oil, acetate)	100.3	104.0
50,000 (dry)	10 (dry, acetate)	98.0	102.8
25,000 (dry)	10 (dry, acetate)	95.7	99.4
50,000 (dry)	10 (succinate)	98.5	107.1
25,000 (dry)	10 (succinate)	96.5	102.9
5,000 (oil)	100 (oil, acetate)	100.1	101.8

tion which allows good recovery of both vitamins. The key change from previous procedures is the substitution of ascorbic acid for hydrochloric acid in acidifying the saponification mixture before extraction.

Hydrogenation is effective in removing the mutual interference of vitamins A and E upon each other.

These two new improvements have been combined with one previously described (using a single large volume of ether for extraction rather than several smaller ones) in a simplified procedure for the assay of these two vitamins in mixtures. The proposed assay is valid for a number of typical mixtures.

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Pinacol Rearrangement of Phenaglycodol I

Characterization of Products Produced

By HUBERT W. MURPHY

PHENAGLYCODOL[1] is one of a series of anticonvulsant ethylene glycols described by Mills, *et al.* (1), which has been evaluated in the clinic as an anticonvulsant and neurosedative agent by Gruber and Mosier (2). This compound is characterized by a somewhat persistent bitter taste. In the hope of obtaining a product with a sufficiently improved taste to permit the convenient administration of phenaglycodol in liquid preparations, several attempts were made to prepare derivatives of this glycol.

All attempts to esterify one or both of the hydroxyl groups with acid anhydrides or acid chlorides were fruitless, even when special methods developed for tertiary hydroxyl groups were carried out. Likewise, all efforts at transesterification with a number of commonly used catalysts and attempted etherifications were unsuccessful. It was observed that a characteristic odor developed in those instances in which acidic conditions were maintained during attempted esterification. Moreover, it was difficult to recover the unreacted phenaglycodol in crystalline form from these experiments. The possibility of a pinacol rearrangement was considered, and a typical odoriferous reaction mixture was treated with 2,4-dinitrophenylhydrazine reagent. The presence of a ketone was revealed by the separation of an orange, crystalline 2,4-dinitrophenylhydrazone.

Further experimentation furnished a substantially quantitative method of converting phenaglycodol into a ketone by refluxing the glycol with 10% sulfuric acid. The ketonic liquid obtained was immediately subjected to careful fractionation at reduced pressure. The main component was 2-methyl-2-(*p*-chloro-

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[1] Marketed as Ultran by Eli Lilly and Co.

phenyl)-3-butanone (*B*, Fig. 1). In addition, very small amounts of 2-(*p*-chlorophenyl)-3-methylbutadiene-1,3 and *p*-chlorophenyl *tert*-butyl ketone were present. Any delay in fractionation allows the substituted butadiene to polymerize readily (probably catalyzed by peroxides) by a 1:4 addition to form an amorphous insoluble polymer.

A literature search produced no reference to *p*-chlorophenyl *tert*-butyl ketone. It was, therefore, necessary to synthesize this compound for comparison with the conjugated ketone detected in the reaction mixture. The first attempted synthesis of this ketone was from chlorobenzene and trimethyl-acetyl chloride *via* a Friedel-Crafts reaction. A ketone was separated by careful fractionation of the reaction product, but infrared absorption studies indicated that it was not a conjugated ketone. An alternate synthesis from *p*-chloroacetophenone and methyl iodide furnished the desired ketone.

Investigators have established rules for predicting the "migration aptitude" and percentage migration which can be expected for symmetrical pinacols (3), but no satisfactory rules have been formulated to predict the extent of migration of the groups of an unsymmetrical pinacol (4). Collins, in a recent review, states: "Every unsymmetrically substituted glycol can rearrange in two conceivable ways, depending upon which of the two hydroxyl groups is lost during reaction." (See Fig. 1.)

To confirm that 2-methyl-2-(*p*-chlorophenyl)-3-butanone was formed in almost quantitative yield and that it had not resulted from rearrangement during fractionation, a typical reaction mixture was subjected to a selective oxidation process for methyl ketones (5). A substantially quantitative yield of a mixture of *p*-chlorophenyl-dimethylacetic acid along with a small amount of *p*-chlorobenzoic acid was obtained. The mother liquor and washings from the oxidation process were worked up, and a small amount of nonoxidized ketone was isolated as the crystalline 2,4-dinitrophenylhydrazone. The powder X-ray diffraction pattern of this crystalline hydrazone was identical with that of the hydrazone prepared from the fractionated 2-methyl-2-(*p*-chlorophenyl)-3-butanone. The possibility that *p*-chlorophenyl *tert*-butyl ketone might form a 2,4-dinitrophenylhydrazone with difficulty or not at all was considered, but studies with the synthetic ketone prepared for comparison revealed that it formed the 2,4-dinitrophenylhydrazone even more readily than the unconjugated isomer.

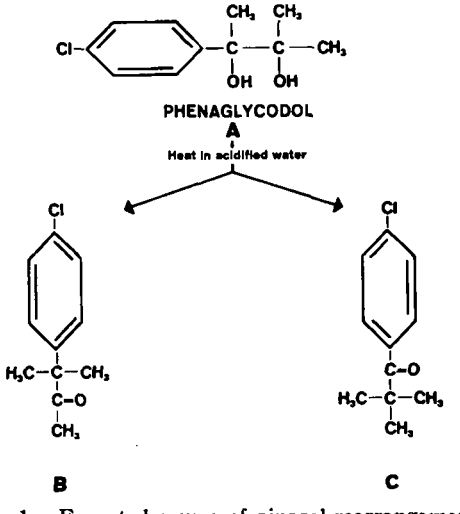

Fig. 1.—Expected course of pinacol rearrangement.

PHARMACOLOGICAL STUDIES

2-Methyl-2-(*p*-chlorophenyl)-3-butanone which had been purified by fractionation was studied in mice for neurosedative activity and in rats for anticonvulsant activity. Quite unexpectedly, this ketone displayed one-third to one-half the pharmacological activity of phenaglycodol. The acute toxicity (LD_{50} 1650 ± 50 mg. per Kg.) by mouth in white mice was about one-half that of phenaglycodol. Since *p*-chlorophenyl-dimethylacetic acid is a possible metabolite of phenaglycodol, the toxicities of the sodium salt by mouth and after intravenous injection in white mice were determined.

EXPERIMENTAL[2]

2-Methyl-2-(p-chlorophenyl)-3-butanone (B, Fig. 1).—One-hundred grams of commercial phenaglycodol was added to a solution of 20 ml. of concentrated sulfuric acid in 180 ml. of water in a round-bottomed flask. This mixture was refluxed gently with constant stirring for 16 hours. The heavier molten glycol separated to the bottom of the flask at first, but as rearrangement progressed the lighter ketonic layer rose to the surface.

The acidic mixture was cooled, transferred to a 500-ml. separator and the lower aqueous phase separated and discarded. The yellow, oily liquid was washed six times with about 80 ml. of 10% sodium chloride solution, then dried with 20 Gm. of anhydrous sodium sulfate. The dried product was filtered into a still pot which was attached to a spinning band reflux column. The column had a calculated efficiency of 28 theoretical plates. The liquid was fractionated at 3 mm. Hg and its composition was as indicated in Table I.

The fraction boiling at 105° was 2-methyl-2-(*p*-chlorophenyl)-3-butanone displaying characteristic infrared absorption bands at 5.83 μ for the unconjugated ketone, at 9.09 μ and 9.82 μ, characteristic of *p*-chlorophenyl, and at 11.96 μ, characteristic of *p*-substituted phenyl. Nuclear magnetic resonance studies supported the assigned structure.

Anal.—Calcd. for $C_{11}H_{13}ClO$: C, 67.17; H, 6.66; Cl, 18.03. Found: C, 67.18; H, 6.50; Cl, 17.62.

[2] All boiling points and melting points reported have not been corrected.

TABLE I.—COMPOSITION OF REACTION MIXTURE FROM PHENAGLYCODOL REARRANGEMENT

Reflux Ratio	B.p., °C.	Volume, ml.	$n_D^{25°}$	$d_4^{24°}$	
9:1	80–82	0.62	...	...	
5:1	82–84	2.56	1.5564	...	
7:1	84–87	0.67	...	...	
7:1	87–90	0.33	...	...	
8:1	90–94	0.77	...	...	
8:1	94–98	0.67	...	...	
8:1	98–102	0.67	...	...	
8:1	102–105	0.67	...	...	
2:1	105	75.8	1.5250	1.0964	
5:1	106–140	1.3	...	...	
Residue	...	...	...	...	6.3 Gm.

2,4-Dinitrophenylhydrazone (6) recrystallized from isopropanol, m.p. 199°.

2-(p-Chlorophenyl)-3-methylbutadiene-1,3.—The fraction boiling at 82–84° (Table I) consisted principally of a butadiene with displayed infrared absorption peaks at 6.25, 6.68, 9.09, 9.82, 11.03, and 11.96 μ. The 9.09 and 9.82-μ bands are characteristic of *p*-chlorophenyl; the 11.96-μ band is characteristic of the *p*-substituted-phenyl group. The absorption at 11.03 μ is characteristic of a terminal methylene group. There was also present in this fraction small amounts each of an unconjugated ketone which displayed carbonyl absorption at 5.83 μ and a conjugated ketone which displayed absorption at 5.92 μ, respectively. The butadiene structure of the principal component was confirmed by nuclear magnetic resonance studies.

Upon standing at room temperature, this fraction became very viscous; most of it became insoluble in acetone and in methanol. An insoluble, amorphous solid was obtained by repeated washing with boiling methanol. The infrared absorption of this solid indicated a complete loss of all terminal methylene absorption, but the absorption band at 6.68 μ and the two bands for *p*-chlorophenyl and that for *p*-substituted phenyl were still present, although all absorption peaks were shifted to slightly longer wavelengths.

Anal.—Calcd. for $(C_{11}H_{11}Cl)_n$: C, 73.95; H, 6.21; Cl, 19.85. Found: C, 74.07; H, 6.24; Cl, 19.56.

Trimethyl-acetyl Chloride.—Meyer (7) has reported that this chloride was easily made by using thionyl chloride, but he gave no details. A 33.4-ml. quantity of thionyl chloride (0.47 mole, 56 Gm.) was placed in a round-bottomed flask provided with a magnetic stirrer and a water cooled reflux condenser. This was heated on a water bath at 65° while being stirred, and trimethyl-acetic acid, 40.85 Gm. (0.4 mole), was added in small portions through the condenser during the course of 1 hour. The fumes from the condenser were collected in a water trap. When all the acid had been added, the reaction mixture was refluxed for 0.5 hour. The reaction mixture was then distilled from a glycerin bath and 25 ml. of a fraction boiling at 102–105° at 757 mm. Hg was collected [Butlerov (8) 105–106° at 760 mm.]. Some unconverted acid, 8 ml., was collected 62–64° at 5 mm. Hg.

Attempted Synthesis of p-Chlorophenyl tert-Butyl Ketone by Friedel-Crafts Reaction.—This reaction was carried out by a slight modification of the procedure described by Schweitzer (9, 10) for bromobenzene and acetyl chloride. The reaction product from chlorobenzene and pivalyl chloride was fractionated on a spinning band column and a ketonic fraction boiling at 109° at 2 mm. Hg was isolated; $n_D^{25°} = 1.5250$. Infrared absorption studies revealed absorption bands at 5.83 μ (unconjugated ketone), the *p*-chlorophenyl bands at 9.09 μ and 9.82 μ, and the *p*-substituted phenyl band at 11.96 μ. However, the phenyl absorption bands were of much lower intensity with respect to the carbonyl absorption band than they were in the spectrum of 2-methyl-2-(*p*-chlorophenyl)-3-butanone. There were other spectral differences which left little doubt that this ketone was different from the one isolated from the rearrangement of phenaglycodol. Nuclear magnetic resonance studies confirmed this difference, but the structure of the synthesized ketone was not established. A 2,4-dinitrophenylhydrazone of this ketone was not obtained by the usual method of preparation.

TABLE II.—COMPOSITION OF REACTION MIXTURE FROM METHYLATION OF *p*-CHLOROACETOPHENONE

Reflux Ratio	B.p., °C.	Volume, ml.	$n_D^{25°}$	$d_4^{24°}$
5:1	85–88	0.33	...	...
3:1	88–90	11.86	1.5497	1.1787
5:1	90–94	2.0	...	...
5:1	94–98	2.0	...	...
7:1	98–100	2.7	...	...
3:1	100–102	21.9	1.5288	1.1196

No conjugated ketone was detected by infrared absorption studies in any of the fractions separated from the reaction mixture or in the considerable amount of high boiling residual liquid which remained in the still pot.

p-Chlorophenyl tert-Butyl Ketone (C, Fig. 1).—This ketone was prepared by exhaustive methylation of *p*-chloroacetophenone by a modification of the method of Haller and Bauer (11). One-hundred-fifty milliliters of benzene, which had been dried over sodium, was placed in a round-bottomed three-necked flask provided with a water bath, a magnetic stirrer, a reflux condenser, and a dropping funnel. Sodium amide (35.2 Gm., 0.9 mole) was added to the dry benzene and mixed well. A mixture of 45.5 Gm. (0.295 mole) of *p*-chloroacetophenone and 149.5 Gm. (1.05 moles) of methyl iodide was added slowly from the dropping funnel. The rate of addition was adjusted so that the reaction never became violent. After all of the *p*-chloroacetophenone and methyl iodide had been added, the reaction mixture was gently refluxed with constant stirring for 3

hours. The reaction mixture was allowed to stand at room temperature for 12 hours, then 50 ml. of distilled water was added slowly and carefully from the dropping funnel to decompose any excess of sodium amide. The reaction mixture was transferred to a separator, 100 ml. of distilled water was added, and the benzene phase was extracted. The aqueous layer was separated and discarded. Extraction with 150 ml. of distilled water was repeated five times; then the benzene phase was separated and dried with 20 Gm. of anhydrous sodium sulfate. The sodium sulfate was removed by filtration, and the filtrate was fractionated in a spinning band column at 4 mm. Hg. The composition was as indicated in Table II.

The fraction collected at 88 to 90° was *p*-chloroacetophenone; the fraction boiling at 100 to 102° was a mixture containing about 45 mole per cent of the desired *p*-chlorophenyl *tert*-butyl ketone. The infrared absorption pattern displayed, in addition to the typical *p*-chlorophenyl bands at 9.09 and 9.82 μ and *p*-substituted phenyl band at 11.96 μ, the conjugated carbonyl absorption at 5.92 μ. Nuclear magnetic resonance studies of this fraction indicated that three species of ketones were present. A monomethylated ketone was present in about 7 mole per cent concentration, a dimethylated ketone (isopropyl) in about 48 mole per cent concentration, and the trimethylated ketone (*tert*-butyl ketone) in 45 mole per cent concentration. Since these ketones could not be separated by fractionation, a small amount was converted easily to a mixture of the 2,4-dinitrophenylhydrazones. These were separated into an isopropanol insoluble fraction with a melting point of 213° and a fraction that was recrystallized from isopropanol, m.p. 121°. Nuclear magnetic resonance studies revealed that the 2,4-dinitrophenylhydrazone melting at 121° was the dimethylated ketone (isopropyl), and the 2,4-dinitrophenylhydrazone melting at 213° was that of the trimethylated (*tert*-butyl) ketone.

Anal.—Calcd. for (2,4-dinitrophenylhydrazone of *p*-chlorophenyl isopropyl) $C_{16}H_{15}ClN_4O_4$: Cl, 9.77. Found: Cl, 9.86.

Anal.—Calcd. for (2,4-dinitrophenylhydrazone of *p*-chlorophenyl *tert*-butyl ketone) $C_{17}H_{17}ClN_4O_4$: Cl, 9.41. Found: Cl, 9.56.

p-Chlorophenyl-dimethylacetic Acid.—A mixture of 930 ml. of 3 *N* sodium hydroxide solution and 67 ml. of bromine was placed in a 2-L. three-necked, round-bottomed flask provided with a magnetic stirrer and a water bath. This mixture was stirred until homogeneous; 50 Gm. of the crude washed reaction mixture consisting primarily of 2-methyl-2-(*p*-chlorophenyl)-3-butanone was added all at once. The flask was heated to 68–70° while the contents were constantly stirred until bromine ceased to be liberated when a few drops of the reaction mixture was acidified with acetic acid. This required about 4 hours. Sulfur dioxide was then passed into the reaction mixture until no more bromine was liberated when a few drops of the reaction mixture was made strongly acidic with concentrated hydrochloric acid. The reaction mixture was filtered; the filtrate was made strongly acidic by the addition of 75 ml. of concentrated hydrochloric acid. The acidified liquid was stirred for 10 minutes, then stored overnight at 5°. The separated crystals were collected on a filter and washed with about 200 ml. of cold distilled water. The filtrate and washings were saved for the recovery of nonoxidized ketone. The washed crystals of precipitated acid were dried in a vacuum desiccator at 5 mm. Hg for 12 hours at 25°. Yield, 48 Gm. (Theory, 50.50 Gm.)

This product when examined by nuclear magnetic resonance proved to be a mixture of about 90% *p*-chlorophenyl-dimethylacetic acid and 10% *p*-chlorobenzoic acid. This benzoic acid was produced by oxidation of some unconverted phenaglycodol. Its formation from phenaglycodol was confirmed in a separate experiment.

Pure *p*-chlorophenyl-dimethylacetic acid was prepared by oxidizing a like amount of the fractionated 2-methyl-2-(*p*-chlorophenyl)-3-butanone by the same method. The yield of dried product was 50 Gm., m.p. 126°. The oxidation of the purified ketone proceeded at a much slower rate than that of the crude reaction mixture.

Anal.—Calcd. for $C_{10}H_{11}ClO_2$: C, 60.46; H, 5.58; Cl, 17.85. Found: C, 60.15; H, 5.62; Cl, 17.58.

Infrared and ultraviolet absorption spectra and a nuclear magnetic resonance study supported the assigned structure. The solubility in water at 26° was 2 mg. per ml. The pKa' in 66% dimethylformamide was 7.0, and the calculated molecular weight was 195 (theory 198.65). The acute toxicities for the sodium salt determined in fasted white mice after 7 days' observation were: LD_{50} by mouth, 1052 ± 129 mg. per Kg.; LD_{50} intravenous, 553.9 ± 67.6 mg. per Kg.

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