sodium bicarbonate solution, and the extract then acidified and extracted continuously with ether. Distillation of the ethereal solution gave 1.6 g. (39%) of an oil, b.p. 140–145° (1.5 mm.); $\bar{\nu}_{max}$ 3500–2500 (carboxyl), 1710 cm.$^{-1}$ (carbonyl).

Anal. Calcd. for $C_8H_{12}O_3$: C, 61.5; H, 7.7. Found: C, 62.1; H, 8.0.

The oil was identified as X by its semicarbazone of m.p. 196°.[1]

Dehydrohalogenation of VII.—A solution of 6 g. of VII in 10 ml. of pyridine was refluxed for 10 hours. Benzene and, with cooling, hydrochloric acid were added and the benzene solution was washed with 10% hydrochloric acid and 10% sodium carbonate solution. Distillation of the benzene layer gave 1.1 g. (36%) of XI as an oil boiling at 109–112° (4 mm.); $\bar{\nu}_{max}$ 1070 (vinyl hydrogen), 1765 (γ-lactone carbonyl), 1668 (C=C stretching), 1621, 1430, 1337, 1303, 1231, 1178, 1100, 1077, 1057, 1000, 970, 937, 905, 885 cm.$^{-1}$.

Anal. Calcd. for $C_8H_{10}O_2$: C, 69.6; H, 7.3. Found: C, 69.2; H, 7.6.

The alkaline solution was acidified and extracted with benzene. Distillation yielded 0.7 g. (22%) of an oil, b.p. 117–118° (5 mm.), $\bar{\nu}_{max}$ 3500–2500 (carboxyl), 3040 (vinyl hydrogen), 1705 cm.$^{-1}$ (C=O). Analysis and infrared spectrum showed that VI had formed.

Anal. Calcd. for $C_8H_{12}O_2$: C, 68.6; H, 8.6. Found: C, 68.3; H, 8.2.

Reaction of VII with Ethyl Sodiomalonate.—To a solution of 2.5 g. of sodium metal in 50 ml. of absolute ethanol, 8.5 g. of diethyl malonate and then, dropwise during 7 hours at reflux, 13.3 g. of VII dissolved in 50 ml. of absolute ethanol was added. The heating was continued for 3 hours more, and the solution cooled, acidified, diluted with water and extracted with ether. The ethereal layer was distilled and gave 0.8 g. of an oil boiling at 110–115° (1.5 mm.), 2.5 g. of an oil XV, b.p. 150–160° (1 mm.), and 0.8 g. of an oil (XIV), b.p. 180–185° (1 mm.). The first fraction XIII showed the characteristic infrared peak at 1780 cm.$^{-1}$ (carbonyl of a γ-lactone).

Anal. Calcd. for $C_{10}H_{16}O_3$: C, 65.2; H, 8.7. Found: C, 65.1; H, 8.8.

The product XV absorbed at 1780 (γ-lactone) and 1730 cm.$^{-1}$ (ester carbonyl).

Anal. Calcd. for $C_{12}H_{18}O_4$: C, 63.7; H, 8.0. Found: C, 63.4; H, 8.3.

The oil XIV showed a peak of 1780 (γ-lactone) and 1730 cm.$^{-1}$ (ester carbonyl).

Anal. Calcd. for $C_{15}H_{22}O_6$: C, 60.4; H, 7.4. Found: C, 61.0; H, 7.7.

The product boils, on slow distillation, at 150–155° (0.8 mm.), to give a product identical with XV.

JERUSALEM, ISRAEL

[CONTRIBUTION FROM THE CHEMISTRY DIVISION OF OAK RIDGE NATIONAL LABORATORY]

Molecular Rearrangements. XVI. The Pinacol Rearrangement of the Diphenyl-*m*-tolylethylene Glycols[1]

BY CLAIR J. COLLINS AND NEWELL S. BOWMAN[2]

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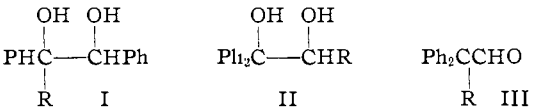
The rearrangements of *threo*- and *erythro*-1,2-diphenyl-1-*m*-tolylethylene glycol (I) and 1,1-diphenyl-2-*m*-tolylethylene glycol (II) in concentrated sulfuric acid at 0° have been examined. The yields of the two ketones (IV and V) produced have been determined by the isotope dilution method, and the fates of various carbon-14 labels of I and II have been established. From the foregoing data the contributions of several paths to the rearrangements of I and II were calculated, and it is shown from these that the *m*-tolyl/phenyl migration ratio in the rearrangement of the conjugate acid of diphenyl-*m*-tolylacetaldehyde is no less than 1. The present results support in every detail the mechanism previously[8-12] proposed for the rearrangements of triaryl glycols and triarylacetaldehydes.

Introduction

From 1930 to 1933, McKenzie and his coworkers,[3,5] Roger and McKay[4,7] and Koelsch[6] reported the identities of the products formed during the acid-catalyzed rearrangements of the tolyl-substituted glycols I (R = *o*, *m* or *p*-tolyl). In five recent papers[8-12] we have studied the rearrangements of the diphenyl *o*-tolyl[10] and of the diphenyl *p*-tolyl[9] compounds I, II and III (R = *o*-tolyl and *p*-tolyl) plus the analogous phenyl di-*p*-tolyl system.[11] Thus: (1) the effect of acid



catalyst upon the rearrangements has been elucidated[8,12]; (2) the relationship between the pinacol and the aldehyde–ketone rearrangements has been demonstrated[9] and (3) the question of the apparent reversal of migratory abilities of the groups involved during the aldehyde–ketone rearrangement[9-11] has been answered.

Of the compounds (I) studied by the earlier investigators,[3-7] we had previously neglected the rearrangement of 1,2-diphenyl-1-*m*-tolylethylene glycol[4,7] (I, R = *m*-tolyl). We therefore undertook the study of the rearrangements, in cold, concentrated sulfuric acid, of *threo*- and *erythro*-1,2-diphenyl-1-*m*-tolylethylene glycol (I) and of 1,1-diphenyl-2-*m*-tolylethylene glycol (II), since it appeared from our prior work[8-12] that we should be able to make certain predictions concerning the expected yields of the two ketones IV and V. Roger and McKay,[7] for example, state that in concentrated sulfuric acid at −2°, the "β-form" (*erythro*) of 1,2-diphenyl-1-*m*-tolylethylene glycol

(1) This paper is based upon work performed at Oak Ridge National Laboratory, which is operated for the Atomic Energy Commission by Union Carbide Corporation.

(2) Research Participant from the University of Tennessee, June–Sept., 1958.

(3) A. McKenzie, A. K. Mills and J. R. Myles, *Ber.*, **63**, 904 (1930).

(4) R. Roger and W. B. McKay, *J. Chem. Soc.*, 2229 (1931).

(5) A. McKenzie, R. Roger and W. B. McKay, *ibid.*, 2597 (1932).

(6) C. F. Koelsch, THIS JOURNAL, **54**, 2049 (1932).

(7) R. Roger and W. B. McKay, *J. Chem. Soc.*, 332 (1933).

(8) C. J. Collins, THIS JOURNAL, **77**, 5517 (1955).

(9) B. M. Benjamin and C. J. Collins, *ibid.*, **78**, 4329 (1956).

(10) V. F. Raaen and C. J. Collins, *ibid.*, **80**, 1409 (1958).

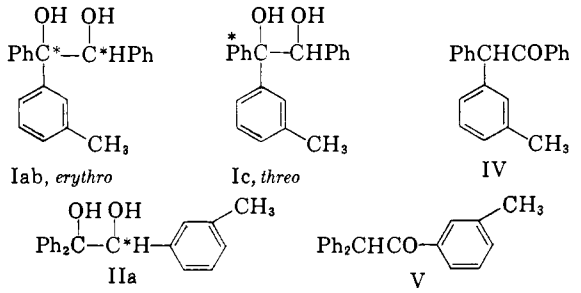
(11) L. W. Kendrick, B. M. Benjamin and C. J. Collins, *ibid.*, **80**, 4057 (1958).

(12) C. J. Collins, W. T. Rainey, W. B. Smith and I. A. Kaye, *ibid.*, **81**, 460 (1959).

(I) is converted to a mixture of the isomeric ketones IV and V, with benzhydryl *m*-tolyl ketone (V) "preponderating," whereas we would predict that both *threo*- and *erythro*-I should yield IV and V in the approximate ratio of 2:1.

Results

erythro-Iab (70.9% carbon-14 in C-1, 29.1% in C-2), *threo*-Ic and IIa, as well as the two ketones IV and V were prepared by standard methods (see



Experimental part). The radiochemical structures of Iab and Ic were proved by oxidative degradation of the glycols to phenyl *m*-tolyl ketone and benzoic acid followed by radioactivity assay of these fragments. Similarly the radiochemical structure of IIa was shown by oxidation to *m*-toluic-C^{14} acid and non-radioactive benzophenone. The yields of the ketones IV and V, upon rearrangement of *erythro*-Iab, *threo*-Ic and IIa in the presence of concentrated sulfuric acid at 0° were determined as before[9-12] by the isotope dilution method. The results of these yield determinations are given in Table I.

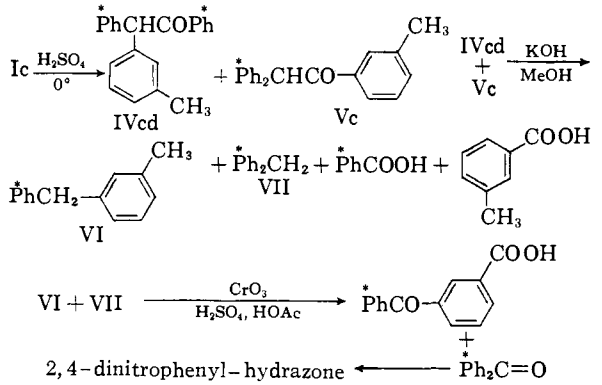
TABLE I

YIELDS OF KETONES IV AND V UPON REARRANGEMENT OF I OR II IN CONCENTRATED H_2SO_4 AT 0°

Reactant	Combined yields of IV and V, %	Yield of ketone,[a] % IV	V
erythro-Iab	94.9[b]	69.7	30.3
threo-Ic	97.0	70.9	29.1
IIa	99.5	63.2	36.8

[a] Adjusted to 100%. [b] In a gravimetric determination the yield was 94.6%.

The determination of the percentage carbon-14 scrambling exhibited by ketones IV and V after rearrangement of the appropriate glycol is illustrated for the rearrangement of *threo*-1,2-diphenyl-(*1-phenyl-C*^{14})-1-*m*-tolylethylene glycol (Ic)



Radioactivity assay of the *m*-benzoylbenzoic acid and benzophenone 2,4-dinitrophenylhydrazone so obtained provided a measure of the carbon-14 present in the *m*-methylbenzhydryl and benzhydryl groups, respectively, of IV and V. The results of such experiments performed on glycols Iab, Ic and IIa are given in Table II.

Given in Chart I are the reaction paths by which *erythro*-I and *threo*-I are presumed to rearrange in the presence of cold, concentrated sulfuric acid; *threo*-Ic is used as an example. In Chart II are the reaction paths for the rearrangement of glycol II. In Table III is given the contribution of each reaction path, calculated from the data of Tables I and

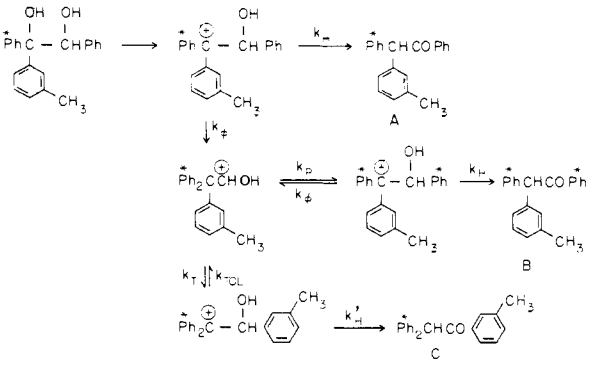


CHART I

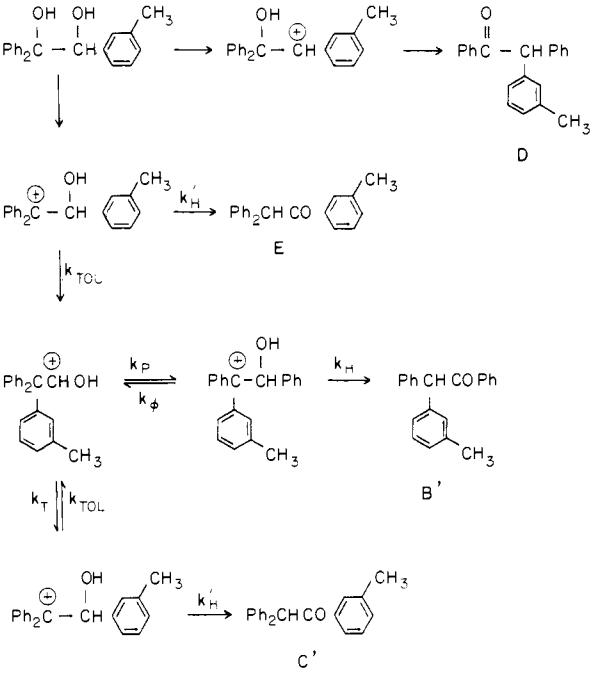


CHART II

II, and expressed as mole fraction (m_i) of product formed through each of the several paths. The calculations are given in the Experimental section. As has been our practice, these results are given to three places, even though the third figure is not always significant. This has been done to simplify the calculations. A more detailed discussion of error follows.

TABLE II

MOLAR RADIOACTIVITIES OF DEGRADATION PRODUCTS OF KETONES IV AND V OBTAINED BY THE ACTION OF CONCD. H_2SO_4 AT 0° UPON Iab, Ic AND IIa

Reactant[a]	*m*-Benzoylbenzoic acid from IV	Benzophenone from V
Iab[b]	0.709 ± 0.003	0.704 ± 0.002
Ic	.596 ± .003	1.000[d]
IIa[c]	.042 ± .000	0.012 ± 0.000

[a] Molar radioactivities of reactants taken as 1.000. [b] Iab contains 0.709 carbon-14 in tertiary carbon and 0.291 carbon-14 in the secondary carbon. [c] IIa upon oxidation degradation exhibited 0.009 carbon-14 in the tertiary carbon. [d] Single determination.

TABLE III

SUMMARY OF MOLE FRACTION (m_i) CALCULATIONS FROM THE DATA OF TABLES II AND III

Reactant	m_a	m_b	m_c	m_d	m_e	m'_b	m'_c
erythro or *threo*-I	0.135	0.568	0.297				
II				0.026	0.051	0.606	0.317

Discussion

The derivation and application of equation 1 to the rearrangement of triaryl glycols has been dis-

$$\frac{k_T}{k_P} = \frac{k_H}{k_{Ph}} \times \frac{k_{tol}}{k'_H} \times R \times \left[\frac{1 + (k'_H/k_{tol})}{1 + (k_H/k_{Ph})}\right] \quad (1)$$

cussed previously in detail,[9-11] and need not be repeated. The specific rate constants symbolized in the equations of Charts I and II are consistent with those employed in former studies[9-11] such that equation 1 ($R = m_c/m_b = m'_c/m'_b$) is directly applicable to the results of the present paper. Thus, from Table III, we now calculate

$$R = m_c/m_b = 0.52,\ k_H/k_{Ph} = 0.16 \text{ and } k_{tol}/k'_H = 18$$

By substitution of the foregoing quantities in equation 1, it can be calculated that $k_T/k_P = 1.35$, and that the *m*-tolyl/phenyl migration ratio ($2k_T/k_P$) is thus 2.7.

From Table I it can be seen that both *erythro*-I and *threo*-I are converted to the ketones IV and V in the ratio of about 2.4 to 1, with IV predominating. This observation is in agreement with what would be predicted on the basis of our former work[8-12] on the mechanism of similar rearrangements, but is contrary to the statement of Roger and McKay.[7]

From Table III the ratio (m_b/m_c) of ketone IV to ketone V, formed through the rearrangement of the conjugate acid of diphenyl-*m*-tolylacetaldehyde (Charts I and II) is 1.9. Thus, as often happens, that ketone IV formed through phenyl migration has been produced in greater quantity than the ketone V formed through migration of a group (in this case the *m*-tolyl) whose "migratory aptitude" is greater than phenyl. As we have now pointed out many times,[9-11] this apparently anomalous fact[13] is easily explainable on the basis of a dynamic equilibrium of intermediate ions (Charts I and II) and the data of Tables I–IV allow us to calculate that even though the ratio of ketone IV to ketone V produced is greater than one, the *m*-tolyl/phenyl migration ratio is about 2.7. An estimate of the reliability of our conclusion that the *m*-tolyl/phenyl migration ratio is, in the present instance, greater than one, can be made by assuming that (1) the yield determinations summarized in Table I are in error by 2 reaction per cent. in such a direction as to make k_T/k_P a minimum, and (2) the fraction of radioactivity remaining in the *m*-benzoylbenzoic acid obtained upon degradation of the products from rearrangement of Ic (Table II) is in error by 1.7% in such a direction as to make k_T/k_P a minimum. Even if we make these highly improbable and unlikely assumptions, the *m*-tolyl/phenyl migration ratio ($2k_T/k_P$) can be shown (see Experimental section) to be greater than unity.

It also should be noted that although *erythro*-I, and presumably also *threo*-I, undergo no secondary hydroxyl removal in cold, concentrated sulfuric acid, glycol II does exhibit a small fraction (m_d 0.026) of secondary hydroxyl loss. This observation is consistent with similar observations upon the rearrangement of 1,1-diphenyl-2-*p*-tolylethylene-2-C^{14} glycol.[9]

In summary, the rearrangements of *threo*- and *erythro*-1,2-diphenyl-1-*m*-tolylethylene glycol (I) and the isomeric 1,1-diphenyl-2-*m*-tolylethylene glycol (II) provide still more evidence in support of the mechanism originally proposed[8,9] to explain the peculiarities[13] of the rearrangements of triaryl glycols. There can thus remain very little doubt concerning the general validity of this mechanism.

Experimental

Preparation of Materials.—*erythro*-1,2-Diphenyl-1-*m*-tolylethylene glycol was prepared by the action of *m*-tolylmagnesium bromide upon benzoin, as described by Roger and McKay.[14] The carbon-14 labeled material (Iab) was obtained (m.p. 137–138°) by allowing labeled benzoin[15] to react with *m*-tolylmagnesium bromide. *threo*-1,2-Diphenyl-1-*m*-tolylethylene glycol (Ic, phenyl labeled), m.p. 123–124°, was prepared by the action of phenyl-C^{14}-magnesium bromide upon *m*-toluoylphenylcarbinol, as described by McKenzie and Kelman.[16] *m*-Methylbenzhydryl phenyl ketone (IV), m.p. 87–88°, was obtained through the rearrangement of *erythro*-I, as described[14] by Roger and McKay.

Benzhydryl *m*-Tolyl Ketone (V).—The Grignard reagent prepared from 34.4 g. of *m*-bromotoluene and 5.0 g. of magnesium turnings was converted with 18.5 g. of $CdCl_2$ to di-*m*-tolylcadmium. Following the procedure described by Bonner and Collins,[17] 21.0 g. of diphenylacetyl chloride was added to the mixture to yield 17 g. of crude product, m.p. 93–95°. After one crystallization from 95% ethanol, and Norit treatment, the m.p. became 99–100°. In the preparation of carbonyl-labeled V, diphenylacetyl-1-C^{14} chloride[17] was employed.

1,1-Diphenyl-2-*m*-tolylethylene-2-C^{14} Glycol (IIa).—Following the procedure of Biltz,[18] 7.7 g. of benzhydryl *m*-tolyl ketone-C^{14} (Va) was dissolved in 31 cc. of glacial acetic acid, and to the solution was added 8.2 cc. of concentrated HNO_3. The mixture was heated for 40 minutes under gentle reflux, then poured onto ice. The resulting mixture was extracted with chloroform, the chloroform layer was washed with saturated bicarbonate, water, then taken to dryness and desiccated overnight. The oil which resulted was not characterized, but was treated directly with $LiAlH_4$ in ether solution. The resulting mixture was worked up after hydrolysis with water and hydrochloric acid. Upon concentration of the ether extract from 95% ethanol after treatment

(13) For a discussion of this fact and of "migratory aptitudes" see G. W. Wheland, "Advanced Organic Chemistry," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1949, p. 494–495; and C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p. 479.

(14) R. Roger and W. B. McKay, *J. Chem. Soc.*, 2234 (1931).

(15) V. F. Raaen and C. J. Collins, THIS JOURNAL, **80**, 1413 (1958).

(16) A. McKenzie and A. L. Kelman, *J. Chem. Soc.*, 412–418 (1934).

(17) W. A. Bonner and C. J. Collins, THIS JOURNAL, **75**, 5376 (1953).

(18) H. Biltz, *Ber.*, **32**, 650 (1899).

TABLE IV

SUMMARY OF RADIOACTIVITY DETERMINATIONS FOR *erythro*-Iab, AND ITS DEGRADATION AND REARRANGEMENT PRODUCTS

	Radioactivity assay, mc./mole of degradation fragment				
	Benzoic acid	Benzaldehyde	Phenyl *m*-tolyl ketone	Benzophenone	*m*-Benzoylbenzoic acid
erythro-Iab[a]	2.582 ± 0.003	2.556 ± 0.008	6.255 ± 0.006		
IVab[b]					6.336 ± 0.030
Vab[b]				6.291 ± 0.002	

[a] Radioactivity assay, 8.933 ± 0.053 mc./mole. [b] Mixture of ketones IVab and Vab obtained upon rearrangement of *erythro*-Iab in cold, concentrated H_2SO_4.

TABLE V

SUMMARY OF RADIOACTIVITY DETERMINATIONS FOR *threo*-Ic AND ITS DEGRADATION AND REARRANGEMENT PRODUCTS

	Radioactivity assay, mc./mole of degradation fragment		
	m-Benzoylbenzoic acid	Phenyl *m*-tolyl ketone	Benzophenone
threo-Ic[a]		6.218 ± 0.026	
IVcd[b]	3.709 ± 0.022		
Vc[b]			6.226[c]

[a] Radioactivity assay, 6.237 ± 0.014 mc./mole. The benzoic-C^{14} acid prepared from labeled bromobenzene-C^{14} used as a precursor for *threo*-Ic was 6.214 ± 0.036 mc./mole. [b] Mixture of ketones IVcd and Vc obtained upon rearrangement of *threo*-Ic in cold, concentrated H_2SO_4. [c] Single determination.

TABLE VI

SUMMARY OF RADIOACTIVITY DETERMINATIONS FOR IIa AND ITS DEGRADATION AND REARRANGEMENT PRODUCTS

	Radioactivity assay, mc./mole of degradation fragment		
	m-Toluic acid	Benzophenone	*m*-Benzoylbenzoic acid
IIa[a,b]	8.526 ± 0.041	0.080 ± 0.0003	.....
IVab			0.359 ± 0.006
Va		0.106 ± 0.0007	

[a] Radioactivity assay, 8.540 ± 0.036 mc./mole. [b] The diphenylacetic-1-C^{14} acid used as a synthetic precursor was 8.640 ± 0.016 mc./mole.

extracted with chloroform. The chloroform layer was washed with aqueous sodium hydroxide and concentrated; the aqueous extracts were then acidified, extracted with chloroform and concentrated. The benzophenone fraction was converted to 344 mg. (95%) of 2,4-dinitrophenylhydrazone, and crystallized four times from chloroform–ethanol to yield 194 mg. of product, whose m.p. was 240–241°. The *m*-toluic acid fraction was crystallized once from water, then sublimed at 60–80° at 1 mm. pressure. The middle fraction only (m.p. 112°) was used for radioactivity assay.

Rearrangements Catalyzed by H_2SO_4 at 0°C.—In a typical experiment 1.01 g. of the appropriate glycol was placed in a 125-cc. glass-stoppered erlenmeyer flask and chilled in an ice-bath. To it was added 26 cc. of C.P. concentrated sulfuric acid (B and A, 99.5–96.5%, sp. gr., 1.84). The mixture, while still surrounded by the ice-bath, was stirred vigorously by means of a strong magnetic-bar and motor. If the stirring was not vigorous enough, the glycol sometimes "balled up" and could not then be induced to dissolve. As soon as solution was complete—usually in less than 10 minutes—the mixture was poured over ice, the flask wall was washed with water and chloroform, and the washings also were poured over the ice. The mixture now was extracted repeatedly with chloroform, the chloroform layer was washed with aqueous sodium bicarbonate, then water, and concentrated to dryness. The weight of the resulting mixture of ketones IV and V represented 95–100% of the theoretical yield.

Determination of Carbon-14 Rearrangement in Ketones Produced from *erythro*-Iab, *threo*-Ic and IIa.—The mixture of ketones IV and V, produced as described in the foregoing

TABLE VII[a]

SUMMARY OF YIELD DETERMINATION EXPERIMENTS

	Reactant		Aliquot, %		Wt. of added ketone, g.		Mc./mole of reisolated ketone	
Identity	Wt., g.	mc./mole	IV	V	IV	V	IV	V
erythro-Iab	6.588	8.933 ± 0.05	47.34	52.66	2.940	3.019	3.652 ± 0.000	2.219 ± 0.000
threo-IC	0.5137	6.225 ± .027	50.00	50.00	0.97982	1.01518	0.9013 ± .0003	0.3917 ± .001
IIa	0.52401	8.540 ± .036	50.00	50.00	1.01450	1.01140	1.1358 ± .0075	0.7025 ± .0019

[a] The yields, calculated from these data, are given in Table I.

of the warm solution with Norit, there was obtained 6.9 g. of tan crystals whose m.p. was 138°. The material was dissolved in 95% of hot ethanol, passed through a bed of Norit, and allowed to crystallize. The yield was 5.92 g. (70% of theory) of 1,1-diphenyl-2-*m*-tolylethylene-1-C^{14} glycol, white crystals, whose m.p. was 138°.

Anal. Calcd. for $C_{21}H_{20}O_2$: C, 82.85; H, 6.63. Found: C, 83.13, 83.13; H, 6.66, 6.75.

Radiochemical Structure Proofs.—The radiochemical structures of *erythro*-Iab, *threo*-Ic and IIa were proved by oxidation of samples of each glycol with CrO_3 in acetic acid to phenyl *m*-tolyl ketone or to benzophenone, followed by radioactivity assay of these fragments as the 2,4-dinitrophenylhydrazones. During the oxidation of *erythro*-Iab a smaller quantity of CrO_3 was employed, with the result that benzaldehyde was isolated in addition to benzoic acid. During the oxidation of IIa, *m*-toluic acid was isolated. All of these fragments were assayed for radioactivity, and the results are given in Tables IV, V and VI, together with the results of other pertinent assays.

Following is a typical procedure for oxidation of the glycols, IIa being used as an example: glycol IIa (305 mg.) was dissolved in 5 cc. of acetic acid, and to it was added 300 mg. of CrO_3 dissolved in 2 cc. of water and 3 cc. of acetic acid. The mixture was allowed to stand at room temperature for 15 minutes, then for 30 minutes was placed on a steam-bath; the mixture was then poured into water and

section (900–950 mg. from 1.01 g. of glycol), was boiled gently with 40 cc. of 20% potassium hydroxide in methanol for 21 hours. The major portion of methanol was removed by distillation, and the remaining mixture was poured into water and repeatedly extracted with chloroform. The washed, dried chloroform extract was concentrated to dryness, and to the mixture of diphenylmethane and phenyl-*m*-tolylmethane so obtained there was added 32 cc. of acetic acid, 3.2 g. of CrO_3, 32 cc. of water and 4.2 cc. of concentrated H_2SO_4. The mixture was boiled under reflux with stirring for 45 minutes, then poured into water. After repeated extraction with chloroform, the chloroform solution was extracted with aqueous sodium hydroxide solution, then taken to dryness. The benzophenone obtained was converted to 344 mg. of 2,4-dinitrophenylhydrazone. After 4 crystallizations from dioxane or chloroform–ethanol there was obtained 90 mg. of pure product, m.p. 240–241°. The foregoing aqueous alkali washings were acidified, cooled and filtered, yielding 276 mg. of *m*-benzoylbenzoic acid, m.p. 163°. The acid was sublimed at 1 mm. pressure, the temperature being raised slowly to 160°. The receiver was cleaned from time to time after the melting point of the sublimate was taken. When the melting point reached 165° a very small fraction (about 20 mg.) was sublimed for radioactivity assay. The results of the appropriate assays are given in Tables IV, V and VI.

Determinations of Yields of Ketones IV and V Upon Rearrangement of *erythro*-Iab, *threo*-Ic and IIa.—After the

glycol had been subjected to sulfuric acid at 0°, then worked up as described in a foregoing section, the product was dissolved in ethanol, and diluted to 100 cc. in a volumetric flask. Exactly 50.0 cc. of the solution was added to a weighed portion of non-radioactive *m*-methylbenzhydryl phenyl ketone (IV), and 50.0 cc. was added to a weighed portion of benzhydryl *m*-tolyl ketone (V). Each mixture was then homogenized, and by successive alternate crystallizations from 95% ethanol and hexane, the ketones were reisolated and assayed for radioactivity. In certain of the experiments "hold-back carrier"[19] was added and the samples were repurified and reassayed. All pertinent data relative to these yield determinations are given in Table VII.

Calculations of m_i of Table III.—From Table I, the average yields of IV and V, respectively, from *threo*-I and *erythro*-I are 70.3 and 29.7%. Thus: $m_a + m_b = 0.703$; $m_c = 0.297$. From Chart I and Table II

$$m_a + \frac{m_b}{2} = 0.596 \times 0.703$$

Thus $m_a = 0.135$; $m_b = 0.568$; and $m_c = 0.297$

$$\frac{k_{Ph}}{k_H} = \frac{m_b + m_c}{m_a} = 6.4 \text{ and } \frac{m_c}{m_b} = 0.523$$

From Table I, the yields of IV and V, respectively, from IIa are 63.2% and 36.8%. Thus

$$m_d + m'_b = 0.632;\ m_e + m'_e = 0.368$$

From Table II

$$m_d = 0.632 \times 0.042 - 0.026$$
$$m'_b = 0.632 - 0.026 = 0.606$$
$$m'_e = 0.606 \times \frac{m_c}{m_b} = 0.317$$

and $m_e = 0.051$; $\frac{k_{tol}}{k'_H} = 18$; and $\frac{2k_T}{k_P}$ (from equation 1) = 2.7

Estimate of Error in Calculation of $2k_T/k_P$.—Assuming all pertinent factors are in error by 0.02 such that $2k_T/k_P$ is a minimum

$$m_e + m'_e = 0.388;\ m_d + m'_b = 0.612$$
$$m_a + m_b = 0.723;\ m_c = 0.277$$

and the value (0.596 ± 0.003) for fraction of radioactivity in *m*-benzoylbenzoic acid from rearrangement of Ic (Table II) becomes 0.586, thus

$m_a = 0.121$; $m_b = 0.602$; $m_c = 0.277$; $m'_e = 0.270$; $m'_b = 0.586$

$m_c = 0.118$; and $m_d = 0.026$. Thus:

$\frac{k_H}{k_{Ph}} = 0.14$; $\frac{k_{tol}}{k'_H} = 8.25$; $\frac{m_c}{m_b} = 0.46$; and

$\frac{2k_T}{k_P}$ (from equation 1) $\cong 1.05$

(19) See E. J. Dewitt, C. T. Lester and G. A. Ropp, THIS JOURNAL, **78**, 2101 (1956), for a good discussion of the use of "hold back carrier."

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[CONTRIBUTION FROM THE RESEARCH DIVISION, CUTTER LABORATORIES]

Hypotensors. 2-Ammonioalkyl 3-Ammonioalkanoate Salts[1]

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A series of 2-ammonioalkyl 3-ammonioalkanoate salts has been prepared in which the quaternary ammonium groups have been derived from lower aliphatic amines and heterocycles such as pyrrolidine, piperidine, morpholine and pyridine. Data on these and their intermediate compounds are reported and the methods of synthesis are discussed. A number of these diammonio esters exhibited marked hypotensive activity *via* ganglionic blockade.

Introduction

The use of hexamethylenebis-(trimethylammonium chloride) (hexamethonium chloride) in the treatment of hypertension has led to the synthesis of many related structures. Some of these, such as 1,1′-pentamethylenebis-(1-methylpyrrolidinium hydrogen tartrate) (pentolinium tartrate), have been more potent but have had similar side effects. Prominent among these is intestinal stasis due to parasympathetic blockade.

A more limited use of hexamethonium chloride has been for the lowering of blood pressure during surgical operations in order to reduce hemorrhage. Here its long action has been disadvantageous and shorter acting hypotensors such as *d*-1,3-dibenzyldecahydro-2-oxo-imidazo[*c*]thieno[1,2-*a*]thiolium *d*-camphorsulfonate (trimethaphen camphorsulfonate) have been more useful.

This paper reports the preparation of members of the $R_1R_2R_3\overset{+}{N}CH_2CH_2COOCH_2CH_2\overset{+}{N}R_4R_5R_6 \cdot 2X^-$ series and derivatives in which certain of the CH_2 groups have alkyl substituents. These compounds, which are listed in Tables I and II, may be considered to be derived from the hexamethonium series by replacing two adjacent methylene groups by an ester linkage.

Discussion

Five routes (excluding anion exchange methods used to prepare the salts of Table II) were followed in these syntheses (see formular).

Route 1.—Fusco, *et al.*,[3] used this synthesis to prepare the first member of our ester series, 2-trimethylammonioethyl 3-trimethylammoniopropionate diiodide, I-1 (Table I, compound 1), but did not report any testing of its hypotensive activity. In repeating this work, we have found that the second step of the series may give ditertiary aminoester which is contaminated with unreacted halogen ester in cases where the boiling points do not differ greatly, *e.g.*, compound V-1 by method B of Table V (method V-B). If desired, this can be purified through the dihydrochloride salt.

Route 2.—This procedure, the second step of which appears as method I-B, has been used to prepare compounds I-1, I-2 and I-57 and this last one, 2-pyridinioethyl 3-pyridiniopropionate di-

(1) In agreement with the proposals of H. J. Barber and K. Gaimster, *Chemistry & Industry*, 670 (1952); J. F. Bunnett, *et al.*, THIS JOURNAL, **75**, 642 (1953); A. M. Patterson, *Chem. Eng. News*, **32**, 90 (1954), and A. P. Gray, *et al.*, THIS JOURNAL, **77**, 3534 (1955), we wish to use the term "ammonio" as the prefix form of "ammonium."

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(3) R. Fusco, G. Palazzo, S. Chiavarelli and D. Bovet, *Gazz. chim. ital.*, **79**, 836 (1949).