yield formaldehyde from C-21 and formic acid from C-20. The formaldehyde was precipitated as formadone and the formic acid was oxidized with mercuric oxide to carbon dioxide. The carbon dioxide was trapped in carbonate-free sodium hydroxide and subsequently precipitated as barium carbonate. No significant counts could be detected in the formadone which indicated that less than 50 counts/min./mM could have been present. On the other hand, 7.77×10^3 counts/min./mM were found in the barium carbonate.

The distribution of radioactivity in carbons 20 and 21 in 3α,17α,21-trihydroxypregnan-20-one-C^{14} agrees with that obtained in cortisol-C^{14} by calf adrenal perfusion.[3] On the basis of the scheme postulated by Woodward and Bloch[4] we would expect ten radioactive carbons to be incorporated into the first 21 carbons of cholesterol from acetate-1-C^{14}. If one assumes that corticosteroids are biosynthesized from acetate-1-C^{14} through cholesterol then the arrangement of all carbons of C^{14} atoms in corticosteroids would be expected to be the same as that found in the first 21 carbons of cholesterol. The present findings support the view that the carboxyl and the methyl carbons of acetate are incorporated into carbon 20 and 21, respectively, of a corticosteroid. The distribution of methyl and carboxyl carbons in the corticoid side chain is identical to that of carbons 20 and 21 of cholesterol.

EXPERIMENTAL

The specific activities were determined by the method of Karnovsky *et al.*[6] using a Robinson proportional counter.

Isolation and purification of C^{14}-labeled 3α,17α,21-trihydroxypregnan-20-one. Following the administration of 2 mc. of 1-C^{14}-acetate to a female patient[2] the urine was collected for 5 days.[5] The urine was hydrolyzed with β-glucuronidase and extracted with ethyl acetate. The ketonic fraction, prepared by a modified Girard separation,[7] was chromatographed on a silica gel column. The crystalline material eluted with benzene-ethyl acetate (3:1) was rechromatographed in the same system. Repeated recrystallization from acetone and finally ethanol gave crystals melting at 197–204° with a constant specific activity.

Specific activity determination of carbons 20 and 21. Chromatographically pure unlabeled 17α,21-dihydroxy-4-pregnene-3,20-dione (211 mg.) was added as carrier to the C^{14}-labeled 3α,17α,21-trihydroxypregnan-20-one (32.6 mg.) described in the section above. The specific activity of the mixture was 80.5×10^3 counts/min./mM. A 103 mg. portion of the mixture was dissolved in 15 ml. of methanol and stirred overnight at room temperature with 500 mg. of sodium borohydride. Water was added and following acidification with hydrochloric acid the mixture was extracted with ethyl acetate. The extract was washed with water, a saturated solution of sodium bicarbonate, water, dried over sodium sulfate, and taken to dryness *in vacuo.* The residue (108 mg.) was dissolved in 25 ml. of carbon dioxide–free ethanol, 36 ml. of a stock periodate solution were added and the solution was left for 135 min. at room temperature in the dark. The stock periodate solution was prepared by dissolving 1 g. of sodium metaperiodate in 70 ml. of water, adjusting the *p*H to 4 with $2N$ sulfuric acid, and making up the volume to 100 ml. The reaction mixture was distilled *in vacuo* to dryness and the distillate was collected in two flasks cooled with a dry ice–acetone mixture. The contents of both flasks were combined (80 ml.).

Oxidation of formic acid to carbon dioxide. A portion of the distillate (55 ml.) was flushed for 5 min. with oxygen to expel carbon dioxide; 2 g. of red mercuric oxide were added, the oxygen stream continued, and the mixture boiled for 30 min. The evolving gases were collected through a reflux condenser into two traps containing carbon dioxide-free sodium hydroxide. The collected carbon dioxide was precipitated as barium carbonate[8] and counted.

Precipitation of formadone. To a portion (25 ml.) of the distillate obtained following periodic oxidation, 1 ml. of glacial acetic acid was added and the solution was buffered with 300 mg. of sodium acetate. The formaldehyde was precipitated with dimedone[9] and the crystals collected, m.p. 193–194°. The formadone was recrystallized from methanol to a constant specific activity.

For the specific activity determinations blank experiments were carried out and the appropriate corrections were introduced.

Acknowledgment. We are indebted to Dr. M. L. Karnovsky of Harvard Medical School for his valuable suggestions and permission to use his counting equipment.

WORCESTER FOUNDATION FOR EXPERIMENTAL BIOLOGY,
SHREWSBURY, MASS.

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[6] M. L. Karnovsky, J. M. Foster, L. I. Gidez, D. D. Hagerman, C. B. Robinson, A. K. Solomon, and C. A. Villee, *Anal. Chem.*, **27**, 852 (1955).

[7] J. J. Schneider, *J. Biol. Chem.*, **194**, 338 (1952); **183**, 365 (1950).

[8] M. Calvin, C. Heidelberger, J. C. Reid, B. M. Tolbert, and P. E. Yankwich, *Isotopic Carbon*, John Wiley & Sons Inc., N. Y., 1949, p. 84.

[9] E. Müller, editor, *Methoden der Organischen Chemie, Georg Thieme Verlag, Stuttgart, 1953,* Vol. 2, 456.

Electrical Effect of the Triphenylmethyl Group on an Aromatic Ring

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The rates of the reactions of *meta-* and *para-*tritylbenzoic[1] acids with diphenyldiazomethane and those of *meta-* and *para-*tritylphenoxides with ethyl iodide have been obtained. These were treated in the usual manner to obtain the values of Hammett's "Substituent Constant[2] (σ)" for the triphenylmethyl group.

The *meta-* and *para-*tritylbenzoic acids were obtained by the oxidation of the corresponding tolyl compounds.[3]

*Para-*tritylphenol was prepared by the tritylation of phenol. *Meta-*tritylphenol was synthesized

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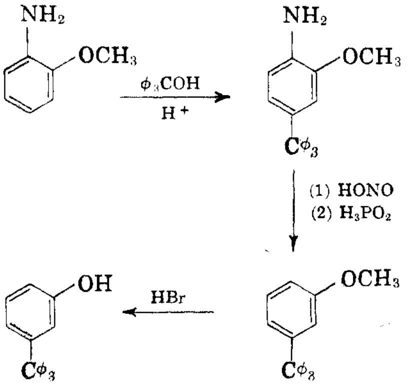
[1] "Trityl" has been used as a trivial name for the triphenylmethyl group.

[2] L. P. Hammett, *Physical Organic Chemistry*, McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p. 184.

[3] R. A. Benkeser and R. B. Gosnell, *J. Am. Chem. Soc.*, **78**, 4914 (1956).

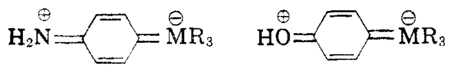
rather indirectly by the tritylation of *o*-anisidine, followed by deamination to give *m*-tritylanisole. The ether was then cleaved with hydrobromic acid to give the desired phenol.



The rates of the reaction of the benzoic acids with diphenyldiazomethane were followed spectrophotometrically,[4] while those of the phenoxides with ethyl iodide were determined titrimetrically.[5]

Assuming no resonance effects the almost identical values for σ_m and σ_p clearly indicate that the electrical effect of the triphenylmethyl group on an aromatic ring is small.

Earlier work from this laboratory[5] demonstrated that silicon and germanium atoms are capable of valence shell expansion when conjugated with strong electron-supplying groups like amines or phenols.



M = Si or Ge

This was indicated by the distinctly positive value of the expression[6] $\sigma^* - \sigma_p$ for the R_3Si- and R_3Ge- groups.

It is well known that carbon cannot expand its valence shell. This is nicely corroborated by the $\sigma^* - \sigma_p$ expression for the trityl group which in this instance is somewhat negative.

Sufficient data are not available to justify comment concerning the negative sigma values obtained in the *meta*- and *para*-phenoxide reactions. Additional cases must be studied to determine whether the slight electron supplying ability which these values indicate is real.

One can conclude, however, that both the triphenylsilyl and triphenylgermanyl groups are electron attracting in contrast to the trityl group which is essentially neutral. Apparently the electrical influence of the three phenyl groups is more pronounced when attached to silicon and germanium than to carbon.

TABLE I

RATE CONSTANTS FOR REACTION OF BENZOIC ACIDS WITH DIPHENYLDIAZOMETHANE IN ETHANOL AT 30°

Substituent	k_2(l./Mole Sec.) × 10^{-2}
m-CH_3	1.54
None	1.83
m-ϕ_3C	1.85
p-ϕ_3C	2.01
p-Cl	3.12
p-Br	3.21
p-NO_2	8.80

TABLE II

RATE CONSTANTS FOR REACTION OF SODIUM PHENOXIDES WITH ETHYL IODIDE IN ETHANOL AT 35°

Substituent	k_1(Sec.$^{-1}$) × 10^{-5}
m-CH_3	77.0
m-ϕ_3C	76.5
p-ϕ_3C	74.3
None	64.8
p-Br	36.3
m-Cl	29.0
p-NO_2	5.08

TABLE III

CONSTANTS FOR THE TRIPHENYLMETHYL GROUP

Reaction	ρ	log k_o[a]	r[b]	σ_p	σ_m
Sodium phenoxides with ethyl iodide	0.877	−3.194	0.02	−0.07	−0.09
Benzoic acids with diphenyldiazomethane	0.867	−1.717	0.02	0.02	−0.01

[a] The unit of time for all rate constants is seconds. [b] Median deviation of the sigma value.

It was hoped that these values for sigma might be useful in establishing the operation of a "bulk effect".[7] However since the electrical effect is so small, no interpretation can be made.

EXPERIMENTAL

p-Tritylphenol. This material was prepared as described by McKenzie and Chuchani.[8]

Tritylation of o-anisidine. The following materials were refluxed for 4 hr.: 7 g. (0.057 mole) of *o*-anisidine, 13 g. (0.050 mole) of triphenylcarbinol, 60 ml. of glacial acetic acid, and 5 ml. of concentrated hydrochloric acid. At the end of this time the solution was poured into water. The resulting solid was separated and dissolved in boiling pyridine. This solution was poured into water and the solid was recrystallized from 95% ethanol. Finally, sublimation gave *o*-methoxy-*p*-tritylaniline with a melting point of 185°–186°. The yield was 44%.

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(4) J. D. Roberts, E. A. McElhill, and R. Armstrong, *J. Am. Chem. Soc.*, **71**, 2923 (1949).

(5) R. A. Benkeser, C. E. DeBoer, R. E. Robinson, and D. M. Sauve, *J. Am. Chem. Soc.*, **78**, 682 (1956).

(6) σ^* represents the σ_p value when the group in question is situated *para* to an amine or phenol. See H. H. Jaffe [*Chem. Revs.*, **53**, 225 (1953)] where this designation was introduced. The sigma constant of a group substituted in a para position to an electron withdrawing group, *e.g.* carboxyl, is designated simply as σ_p.

(7) C. C. Price and D. C. Lincoln, *J. Am. Chem. Soc.*, **73**, 5836 (1951).

(8) C. A. McKenzie and G. Chuchani, *J. Org. Chem.*, **20**, 342 (1955).

Anal. Calcd. for $C_{26}H_{23}NO$: C, 85.44; H, 6.35; N, 3.83. Found: C, 85.59; H, 6.46; N, 3.95.

m-Tritylanisole. The product from the tritylation of *o*-anisidine was deaminated by dissolving 4 g. of this material in 150 ml. of acetic acid and adding 120 ml. of 50% hypophosphorous acid. This clear solution was cooled to 0° and 4 g. of sodium nitrite was added. The mixture was allowed to stand for 2–3 hr. and thus reach room temperature. A solid precipitated which was removed by filtration and recrystallized from a mixture of toluene and petroleum ether. Sublimation gave *m*-tritylanisole with a melting point of 169°–170°. The yield was *ca.* 60%.

Anal. Calcd. for $C_{26}H_{22}O$: C, 89.10; H, 6.33. Found: C, 89.45; H, 6.60.

m-Tritylphenol. The ether prepared above was cleaved with hydrobromic acid in a conventional manner to yield *m*-tritylphenol with a melting point of 278°–280°. The infrared spectrum of this material had a fairly strong absorption peak at 12.8 μ, characteristic of a meta disubstituted benzene. The yield was ca. 60%.

Anal. Calcd. for $C_{25}H_{20}O$: C, 89.24; H, 5.95. Found: C, 89.11; H, 6.21.

Structure proof for m-tritylanisole. Aniline was tritylated in the usual way with *m*-methoxyphenyldiphenylcarbinol (from *m*-bromoanisole and benzophenone, *via* the Grignard reagent). The resulting *m*-methoxyphenyl-*p*-aminophenyldiphenylmethane was deaminated in the same manner described for *o*-methoxy-*p*-tritylaniline to give *m*-tritylanisole. The latter gave no depression in a mixed melting point with material obtained from the tritylation product of *o*-anisidine. The infrared spectra of the two materials were identical. Both could be cleaved to yield *m*-tritylphenol.

Tritylphenetoles. The tritylphenetoles were isolated from their respective reaction mixtures obtained from the rate studies. The *para*-ethyl ether melted at 189°–190°.

Anal. Calcd. for $C_{27}H_{24}O$: C, 88.97; H, 6.64. Found: C, 89.21; H, 6.76.

The *meta* ethyl ether melted at 139°–140°.

Anal. Calcd. for $C_{27}H_{24}O$: C, 88.97; H, 6.64. Found: C, 88.84; H, 6.60.

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Reaction of Hydroxylamine with Ethyl α-(2,2,2-Trichloroethylidene)acetoacetate

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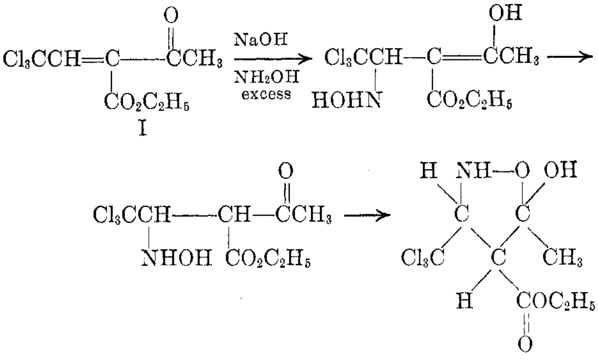
The preparation of ethyl α-(2,2,2-trichloroethylidene)acetoacetate (I) by the reaction of chloral with ethyl acetoacetate in the presence of acetic anhydride, was reported by Claisen and Matthews.[2]

$$Cl_3CCHO + H_2C(CO_2C_2H_5)COCH_3 \xrightarrow{Ac_2O} Cl_3CCH{=}C(CO_2C_2H_5)COCH_3 + H_2O$$

We have found that the use of basic catalysts, to effect the condensation, results in considerably lower yields. In an effort to prepare an oxime of this substance, we obtained a crystalline derivative which exhibited the analysis required for an addition rather than a condensation reaction product. An infrared study of the hydroxylamine addition product showed no apparent carbon to carbon or carbon to nitrogen double bonds while the ethyl α-(2,2,2-trichloroethylidene)acetoacetate (I) did show a band (6.1 μ) for the carbon to carbon double bond. It was therefore concluded that no oxime was present in the reaction product but that a probable 1,4-addition of hydroxylamine to ethyl α-(2,2,2-trichloroethylidene)acetoacetate had occurred to form a single racemate of ethyl α-(2,2,2-trichloro-1-hydroxaminoethyl)acetoacetate. To our knowledge, such an exclusive addition of hydroxylamine to an α,β-unsaturated ketone is unique. The probable reactions occurring are shown below.



II

Ethyl α-(2,2,2-trichloroethylidene)acetoacetate (I) showed a rather broad and complex carbonyl band at 5.8 μ whereas its addition product with hydroxylamine exhibited a simple and very sharp carbonyl band at 5.7 μ. In the absence of predictable[3] evidence for both ester and ketonic (possibly enolized) bands in the final product, a cyclic structure (II) is suggested tentatively for it.

By arrangement with the Chemical-Biological Coordination Center, 2101 Constitution Ave., Washington 25, D. C., the trichloroketo ester and the hydroxamino ester, herein described, were tested for various types of biological activity, but no significant results were obtained.

EXPERIMENTAL

Ethyl α-(2,2,2-trichloroethylidene)acetoacetate (I). The method briefly described by Claisen and Matthews[2] was employed. A solution of 200 ml. (301 g. or 2 moles) of chloral, 254 ml. (260 g. or 2 moles) of ethyl acetoacetate and 190 ml. (204 g. or 2 moles) of acetic anhydride was refluxed for 18 hr. The ethyl α-(2,2,2-trichloroethylidene)acetoacetate distilled at 99–100° at 1 mm. on a 10-inch Widmer column; yield 203 g. (39% based on ethyl acetoacetate),

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(1) Bristol Laboratories Research Associate (R. M. H.) and Research Fellow (J. R.) of The Ohio State University Research Foundation (Project 224).

(2) L. Claisen and F. E. Matthews, *Ann.*, **218**, 175 (1883).

(3) L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," Methuen Co., Ltd., London, 1954, p. 157.