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The Structure and Toxicity of DDT Insecticides

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1,1-Diphenyl-2,2-dimethylpropane has been synthesized by hydrogenolysis of 1,1-diphenyl-2,2-dimethylpropanol. Ring chlorination and bromination of the diphenyldimethylpropane gave potent contact insecticides. 1,1-Di-*p*-tolyl-2,2-dimethylpropane and 1,1-di-*p*-anisyl-2,2-dimethylpropane, prepared from the corresponding propanols, were also found to be insecticidal. The toxicants are isosteric with DDT and analogs. Structure–activity relationships have been explored by tests of many related, new compounds. Significant lack of activity was observed with 1,1-di-*p*-anisyl-3,3-dimethylbutane and *p,p'*-dichlorobenzhydryltrimethylammonium bromide. It is concluded that the basic structural requirement for insecticidal activity of the DDT type is a diphenylmethyl moiety substituted at the *p,p'*-positions by halogen, methoxy or methyl and joined at the central carbon atom to a relatively non-polar group of sufficient bulk to hinder rotation of the aryl rings. A flattened or "trihedralized" configuration of the diphenylmethyl moiety is thereby produced, similar to the steroids in shape and length. Molecular compounds with steroids are proposed as a mechanism for transport of DDT insecticides to fatty tissue. The toxicities of DDT-type compounds can be related to the possibility of combination with steroids.

DDT insecticides, in the usual meaning of the term, are 1,1,1-trichloro- (or tribromo)-2,2-diphenylethanes, substituted in the *p,p'*-positions by chlorine, bromine, fluorine, methyl or methoxyl. The best known, of course, is DDT (I) itself. Hypotheses concerning the relationship between the structure and the properties of these insecticides have been advanced by Läuger[1] and Martin.[2] Läuger ascribes the high contact activity of DDT to the presence in one molecule of the di-*p*-chlorophenylmethyl moiety, which is associated with stomach poison activity, and the lipoid-solubilizing trichloromethyl group. Martin, on the other hand, suggests that the toxicity is due to hydrogen chloride release from the central trichloroethinyl group, while the *p*-chlorophenyl groups promote lipoid solubility. The evidence for these hypotheses, which at present appears inconclusive, has been reviewed by Metcalf.[3]

Läuger and Martin base their conceptions of the structure–toxicity relationship upon specific chemical groups, so it would follow that the shape of the DDT molecule is of secondary importance. This conclusion is questioned in the present paper because a definite configuration can be suggested for the insecticide and the activities of both new and previously known DDT-type compounds can be correlated with the possibility of their existence in this configuration. Moreover this configuration appears to have biochemical significance.[4]

Shape of the DDT Molecule; Trihedralization.—What is the shape of the DDT molecule? On the basis of X-ray diffraction data,[4] Läuger[1b] states that the distance between the ring chlorine atoms is 11.0 Å. and that the phenyl–C–phenyl bond angle is 123°. Dipole moment measurements[5] indicate a normal Cl–C–Cl bond angle and afford the less exact value of 110–120° for the phenyl–C–phenyl angle. The shape of the molecule, within the limits of these dimensions, has not been considered. We have, therefore, sought enlightenment by examination of molecular models.

Models suggest that a novel steric effect is possible in diphenylmethanes which have a bulky substituent on the α-carbon atom. This effect is demonstrable when the α-substituent is a *t*-butyl group as in 1,1-diphenyl-2,2-dimethylpropane (II). In the model of this compound constructed with "atoms" from a Fisher–Hirschfelder set, it is found that the orientations of the phenyl groups are limited: free rotation of the aromatic rings about their bonds with the central carbon atom is extremely difficult due to the hindrance of the *t*-butyl group; free rotation of the *t*-butyl groups requires that the aromatic rings assume nearly coplanar positions. In that configuration of 1,1-diphenyl-2,2-dimethylpropane permitting greatest clearance for rotation of the *t*-butyl group, the phenyl groups lie, it appears, as if in the faces of a trihedral angle as indicated by Fig. 1.[6] The

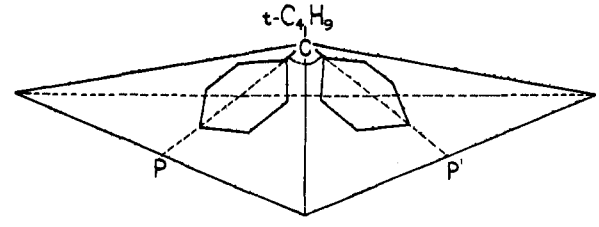


Fig. 1.—Configuration of 1,1-diphenyl-2,2-dimethylpropane.

steric situation may be generalized as follows: *In compounds having on one carbon atom two or three planar groups and a group sufficiently large to hinder the rotation of the planar groups, although capable of rotation itself, the planar groups will tend to positions of maximum clearance, that is to positions corresponding to the sides of a trihedral angle.* For purposes of discussion this steric effect will be called "trihedralization" and obvious variants of this term will also be employed. It will be assumed that the trihedralized configuration, the most salient feature of which is the nearly

(1) (a) P. Läuger, H. Martin and P. Müller, *Helv. Chim. Acta*, **27**, 892 (1944); Mylius and Koechlin, *ibid.*, **29**, 405 (1946). (b) P. Läuger R. Pulver, C. Montigel, R. Weismann and H. Wild, "Mechanism of Intoxication of DDT Insecticide in Insects and Warm-Blooded Animals," Lecture, Washington, D. C., July 31, 1945, Geigy Company Inc., New York, N. Y., 1946.

(2) H. Martin and R. Wain, *Nature*, **154**, 512 (1944).

(3) R. L. Metcalf, "The Mode of Action of Organic Insecticides," Chemical-Biological Coördination Center, National Research Council, Washington, 1948.

(4) H. Wild and E. Brandenberger, *Helv. Chim. Acta*, **28**, 1692 (1945); **29**, 1024 (1946); M. Schneider and I. Fankuchen, THIS JOURNAL, **68**, 2669 (1946).

(5) H. Wild, *Helv. Chim. Acta*, **29**, 487 (1946).

(6) It appears from models that diphenyldimethylpropanes, when substituted by like groups in the *o,o'*- or *m,m'*-positions should be separable into *one dl* and *two meso* forms. The group "overlap" distance, greater than 1 Å., is considerably in excess of the minimum "overlap" required for diphenyl resolutions [*cf.* W. M. Stanley and R. Adams, THIS JOURNAL, **52**, 1200 (1930)].

flat character of the diphenylmethyl moiety, approximates the actual shape of the 1,1-diphenyl-2,2-dimethylpropane molecule.

In 1,1-diphenyl-2,2-dimethylpropane the only rotation probable is that of the *t*-butyl group. The case of DDT is more complex. With a model of the insecticide molecule, it is possible to rotate one large group, either a *p*-chlorophenyl or a trichloromethyl group, about the central carbon atom. Since rotation of the latter group appears to involve less strain, it is assumed that DDT has a configuration similar to that suggested for 1,1-diphenyl-2,2-dimethylpropane. Wild[5] finds no evidence for hindered rotation in the dipole moments of *p,p'*-dialkoxy DDT analogs, but this result does not exclude the possibility that the trihedralized ring configuration is a major, although not exclusive, steric form.

The concept of trihedralization has implications outside of the DDT field. Of particular interest is the close connection between the trihedralized configuration and coplanarity, which seems pertinent to hexaarylethane dissociation. Considering Fig. 1, if the three upper faces of the tetrahedron shown are assumed equal, then enlargement of the carbon angle PCP' from 109.5° to 120° makes the phenyl groups coplanar without rotation of those groups about their bonds with the central carbon atom. In the case of hexaphenylethane, trihedralization of the triphenylmethyl moieties may be regarded as an intermediate stage between random orientation of the phenyl rings and the coplanarity of these rings in the free radicals.

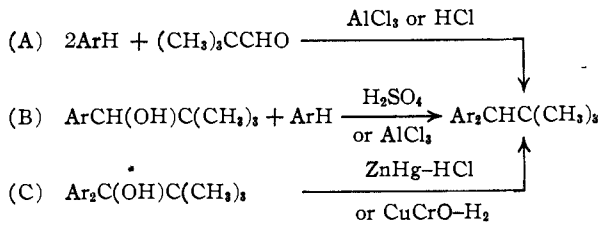
Insecticidal Activity of 1,1-Dianisyl-2,2-dimethylpropane.—If the trichloromethyl group of DDT has, as one of its functions, the trihedralization of the di-*p*-chlorophenylmethyl moiety, replacement of this group with other trihedralizing groups may give effective insecticides. Thus 1,1-di-*p*-chlorophenyl-2,2-dimethylpropane (III) should have activity of the same order as DDT provided the functions other than trihedralization which the trichloromethyl group may have are fulfilled by the *t*-butyl group. Certain characteristics of the *t*-butyl group make 1,1-diaryl-2,2-dimethylpropanes particularly suitable for a test comparison with DDT. Complications of interpretation are avoided because the group is physiologically inert and reasonably lipophilic. Also the *t*-butyl group is close in size to the trichloromethyl group, the van der Waals radii of the chlorine atom and methyl groups being 1.80 and 2.0 Å.,[7] respectively. Results secured with this group in diaryldimethylpropanes are, therefore, relevant to the isosteric trichloromethyl group of DDT insecticides.

These considerations led to the synthesis and entomological evaluation of 1,1-di-*p*-anisyl-2,2-dimethylpropane (1,1-dianisylneopentane) (IV), as described in a previous communication.[8] Choice of a *p*-anisyl rather than a *p*-chlorophenyl compound was dictated by the synthetic method employed. 1,1-Dianisyl-2,2-dimethylpropane was found to have insecticidal activity of the same order as the DDT analog "Methoxychlor" (1,1,1-trichloro-2,2-di-*p*-anisylethane) (V). The production of characteristic DDT tremors and the observation of decreased effectiveness against a strain of DDT-resistant flies left no doubt that the compound is a DDT-type insecticide. The activity of this product encouraged the study of related compounds as described in this paper.

Two earlier reports are concerned with replacement of the trichloromethyl group by groups of similar size. Erlenmeyer[9] synthesized di-*p*-chlorophenylacetic acid (VI) and 1,1-di-*p*-chlorophenylacetone (VII), both of which were found to be inactive. Skerrett, Stringer and Woodcock[10,11] have reported syntheses of three *p,p'*-disubstituted 1,1-diphenyl-2,2-dimethylpropanes (*p,p'*-dichloro, *p,p'*-dimethyl, *p*-chloro-*p'*-methyl) as well as the very interesting 1,1-di-*p*-chlorophenyl-2-methyl-2-chloropropane. The products were ineffective against *Calandra granaria* L. A similar negative result, the authors[11] add in a footnote, was obtained with 1,1-dianisyl-2,2-dimethylpropane. The synthetic method employed in preparing these compounds will be discussed below.

Synthesis of 1,1-Diaryl-2,2-dimethylpropanes.—The compounds synthesized for insecticide tests in connection with the present study are listed in Table I. For the most part the structures of these products are variants of the 1,1-dianisyl-2,2-dimethylpropane structure. The ring substituents have been altered in one set of compounds (II, III, VIII–XIII); in another (XVI-XXV), the central hydrocarbon group has been changed; in a third class (XXXI, XXXII), one anisyl group has been replaced. Compounds, XXVII, XXXIII and XXXIV are variants of 1,1-di-*p*-tolyl-2,2-dimethylpropane (VIII).

Of the compounds prepared only the 1,1-diaryl-2,2-dimethylpropanes presented a new synthetic problem. Possible routes to such structures are outlined below.



With the exception of the copper chromite hydrogenolysis method indicated under (C), the syntheses necessarily proceed through the mono- or diaryl neopentyl ions, $[ArCHC(CH_3)_3]^+$ or $[Ar_2CC(CH_3)_3]^+$. It is well known from Whitmore's work[12] that the unsubstituted neopentyl ion $[(CH_3)_3CCH_2]^+$ yields predominantly rearranged products and Marvel[13] has shown that 1,1-diphenyl-2,2-dimethylpropanol gives two isomeric chlorides.

(7) L. Pauling, "Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 1940, p. 189.

(8) H. D. Brown and E. F. Rogers, THIS JOURNAL, 72, 1864 (1950).

(9) H. Erlenmeyer, P. Bitterli and E. Sorkin, *Helv. Chim. Acta*, 31, 466 (1948).

(10) E. J. Skerrett, A. Stringer and D. Woodcock, *Nature*, 165, 853 (1950).

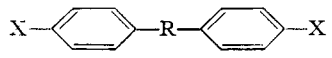
(11) E. J. Skerrett and D. Woodcock, *J. Chem. Soc.*, 2718 (1950).

(12) F. C. Whitmore, THIS JOURNAL, 54, 3274 (1932); F. C. Whitmore and H. S. Rothrock, *ibid.*, 54, 3431 (1932); F. C. Whitmore and G. H. Fleming, *J. Chem. Soc.*, 1269 (1934).

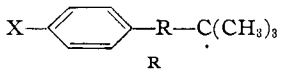
(13) D. E. Bateman and C. S. Marvel, THIS JOURNAL, 49, 2917 (1927).

TABLE I

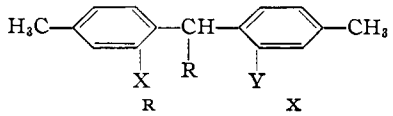
DDT-TYPE COMPOUNDS



	R	X
I	$CHCCl_3$	Cl
II	$CHC(CH_3)_3$	H
III	$CHC(CH_3)_3$	Cl
IV	$CHC(CH_3)_3$	OCH_3
V	$CHCCl_3$	OCH_3
VI	CHCOOH	Cl
VII	$CHCOCH_3$	Cl
VIII	$CHC(CH_3)_3$	CH_3
IX	$CHC(CH_3)_3$	OH
X	$CHC(CH_3)_3$	NO_2
XI	$CHC(CH_3)_3$	NH_2
XII	$CHC(CH_3)_3$	Br
XIII	$CHC(CH_3)_3$	F
XIV	$CHCCl_3$	F
XV	$CH\dot{N}(CH_3)_3]^+Br^-$	Cl
XVI	CH_2	OCH_3
XVII	$CHCH_3$	OCH_3
XVIII	$CHCH(CH_3)_2$	OCH_3
XIX	$C(CH_3)CH(CH_3)_2$	OCH_3
XX	$CHCH_2C(CH_3)_3$	OCH_3
XXI	$CHCH_2CH(CH_3)CH_2C(CH_3)_3$	OCH_3
XXII	$CHCOCH_3$	OCH_3
XXIII	$CHC(CH_3)(=NOH)$	OCH_3
XXIV	$-CH(CH_3)CH(CH_3)-$	OCH_3
XXV	$-CH(CH_3)C(CH_3)_2-$	OCH_3
XXVI	$-CH(CH_3)C(CH_3)_2-$	OH
XXVII	$CHCH(CH_3)_2$	CH_3
XXVIII	$C{=}CCl_2$	Cl
XXIX	$CHCF_3$	Cl
XXX	$CClCCl_3$	Cl



	R	X
XXXI	CH_2	OCH_3
XXXII	$CHCH_3$	OCH_3
XXXIII	$CH(C_6H_{10}CH_3\text{-}p)$	CH_3



	R	X	Y
XXXIV	$CH(CH_3)_2$	CH_3	H
XXXV	CCl_3	CH_3	CH_3
XXXVI	CCl_3	H	H

An added complication exists in reaction A. Danilov[14] has found that pivalaldehyde itself rearranges in acid media to methyl isopropyl ketone.

An aluminum chloride-catalyzed condensation of pivalaldehyde with anisole (scheme A) yielded no 1,1-dianisyl-2,2-dimethylpropane. A similar reaction of pinacolone with anisole was also unsuccessful. However, on condensation of pivalaldehyde with phenol in the presence of sulfuric acid, the expected dimethylpropane, 1,1-di-*p*-hydroxyphenyl-2,2-dimethylpropane (IX) was obtained. This result may be reconciled with Danilov's observation if one assumes that the rates of pivalaldehyde condensation and rearrangement are competitive.

Skerrett and Woodcock[11] failed to secure 1,1-di-*p*-chlorophenyl-2,2-dimethylpropane by reaction of 1-*p*-chlorophenyl-2,2-dimethylpropanol with chlorobenzene in sulfuric acid (scheme B). We have had no better results using aluminum chloride. An attempt to prepare 1-anisyl-1-chloro-2,2-dimethylpropane for use in such a reaction was likewise unsuccessful.

Both Skerrett and Woodcock and the present authors finally resorted to reduction of 1,1-diaryl-2,2-dimethylpropanols, using zinc amalgam–hydrogen chloride and hydrogen–copper chromite, respectively. 1,1-Di-*p*-tolyl-2,2-dimethylpropane is reported by both groups. While the boiling points and refractive indices of the preparations check reasonably well, it is felt that further comparison is necessary before these materials can be regarded as identical. In our hands zinc reduction of 1,1-dianisyl-2,2-dimethylpropanol failed to give the crystalline dianisyldimethylpropane obtained on hydrogenation.[15]

The copper chromite hydrogenolysis procedure has been used to prepare 1,1-diphenyl-2,2-dimethylpropane (II) and its *p,p'*-difluoro derivative (XIII), besides the dianisyl- and ditolyldimethylpropanes already mentioned. The method is unsuitable for synthesis of analogous chloro, bromo and nitro compounds (III, XII, X), which were made instead by halogenation and nitration of diphenyldimethylpropane. The *p,p'*-dihydroxy- and diaminodiphenyldimethylpropanes (IX, XI) were obtained from the methoxy and nitro compounds.

The hydrogenolysis route from alcohol to hydrocarbon was employed with several alcohols which are not of neopentyl type. 1,1-Di-*p*-anisyl-3,3-dimethylbutanol was reduced to the corresponding butane (XX) and a 2,3-dianisylbutanediol-2,3 was converted to *meso*-2,3-dianisylbutane (XXIV), a compound previously described by Sisido and Nozaki.[16] Barnes[17] has utilized a similar glycol hydrogenolysis in an interesting hexestrol synthesis.

1,1-Diphenyl-2,2-dimethylpropanol dehydrates with rearrangement to give 2-methyl-3,3-diphenylbutene-1.[13] To exclude the possibility that dehydration with rearrangement and subsequent hydrogenation, rather than hydrogenolysis, occurred on treatment of 1,1-dianisyl-2,2-dimethylpropanol (XXXVII) with hydrogen, the alcohol was submitted to these reactions. As indicated, in the accompanying chart, the dehydration–hydrogenation sequence (XXXVII → XXXVIII → XIX) gave a product differing in melting point from the hydrogenolysis reaction product (IV). The corresponding diphenols (IX, XXXIX) are also dissimilar. It follows that the hydrogenolysis reaction proceeded as expected and, therefore, that the structures of compounds IV and IX are repre-

(14) S. Danilov and E. Venus-Danilova, *Ber.*, **59**, 377 (1926).

(15) After submission of this manuscript for publication, papers by Skerrett and Woodcock (*J. Chem. Soc.*, 2804, 2806 (1952)) appeared which report preparation of compounds II, III, X and XI (Table I). Compound II was prepared by the method previously employed for synthesis of 1,1-di-*p*-anisyl-2,2-dimethylpropane.[8] Details of this method and a criticism of earlier methods[11] were communicated privately to the British authors.

(16) K. Sisido and H. Nozaki, THIS JOURNAL, **70**, 776, 778 (1948).

(17) R. A. Barnes, Abstracts of A. C. S. 117th Meeting, Phila., Pa. 76L (April 9-13, 1950).

TABLE II

INSECTICIDE TEST RESULTS

		Contact tests Mortality, %				Fabric protection tests			Larvicide tests	
			German cockroaches		Milkweed bugs		Fabric loss (mg.)			Mortality, %
	Compound	Dosage (mg./kg.)	M	F	mixed	Application, %	Clothes moth larvae	Carpet beetle larvae	Dosage (p.p.m.)	Mosquito larvae
II	1,1-Diphenyl-2,2-dimethylpropane	2000	0	0	0	2	34.4	11.0	10	10
III	1,1-Di-*p*-chlorophenyl-2,2-dimethylpropane									
	Fraction 24.6% chlorine	2000	70	20	50	0.25	3.7	0		
						0.10	56.8	0.5		
	Fraction 27.9% chlorine	2000	100	0	90	0.25	1.5	0.4		
		500	70	0		0.10	8.0	2.1		
	Fraction 32.3% chlorine	2000	100	60	100	0.25	1.6	0.3	10	100
		500	80	10	70	0.10	4.2	2.8	0.6	100
									0.16	40
IV	1,1-Dianisyl-2,2-dimethylpropane	2000	55	100	80	0.25	0.9	1.0	10	100
		1000	15	60	65	0.06	4.7	0.1	0.6	100
		500	10	15	80				0.16	40
V	Methoxychlor	2000	0	20	100	0.03	0.9	0	0.08	100
		400	0	0	100	0.015	1.5	12.3	0.04	16
VIII	1,1-Di-*p*-tolyl-2,2-dimethylpropane	2000	0	0	30	2.0	1.8	0.5	10	60
						0.5	0.7	9.0	5	0
XII	1,1-Di-*p*-bromophenyl-2,2-dimethylpropane									
	Fraction 32.5% bromine	2000	90	20	70	0.5	5.6	0		
	Fraction 40.8% bromine	2000	90	60	80	0.25	3.0	0		
XIII	1,1-Di-*p*-fluorophenyl-2,2-dimethylpropane	2000	0	0	10	1	77.5	26.1		
XV	*p,p'*-Dichlorobenzhydryltrimethylammonium bromide	2000	0	0	0	1	42.9	8.2	10	0
XVI	Dianisylmethane	1600	0	0	0	2	35.1	15.3	10	100
									5	40
									2.5	0
XVII	1,1-Dianisylethane	1600	0	0	0	2	24.9	16.1	10	90
									5	30
									2.5	0
XVIII	1,1-Dianisyl-2-methylpropane	2000	0	0	50	2	7.2	0.2	10	60
									5	40
									2.5	10
									1.3	10
XX	1,1-Dianisyl-3,3-dimethylbutane	2000	0	0	0	2	24.6	14.8	10	0

sented correctly. The infrared spectra of compound IV and the similarly prepared 1,1-di-*p*-tolyl-2,2-dimethylpropane (VIII) contain a weak band at 7.16 mμ which is identified with the *t*-butyl group.[18]

A troublesome complication arises in connection with the structures of the dianisyldimethylpropanol dehydration product and subsequent derivatives (XXXVIII, XIX, XXXIX) as Reid[19] has assigned the structure indicated for compound XXXIX to a higher-melting substance (XXVI) obtained by condensation of methyl isopropyl ketone with phenol. While Reid's formulation is orthodox it has not been confirmed. A possible alternate structure for this diphenol is 2,3-di-*p*-hydroxyphenyl-3-methylbutane. The structure of compound XXXVIII, the dianisyldimethylpropanol dehydration product, is based on the aforementioned study of 1,1-diphenyl-2,2-dimethylpropanol dehydration. An alternate, although improbable, cyclopropane structure (XL) was considered because this could be conceived as leading to 1,1-di-*p*-hydroxyphenyl-3-methylbutane (XLII) which was reported[20] to melt only slightly lower than compound XXXIX. However, on comparison, these phenols were found different; the melting point of XLII could not be raised and a marked depression in melting point was found on admixture with XXXIX. The structures of compounds XIX and XXXIX are supported by infrared evidence. Bands at 7.22 and 7.25 mμ, which are characteristic for the grouping $C(CH_3)CH(CH_3)_2$, are found in the spectrum of compound XIX but not in the dimethyl ether (XXV) derived from Reid's diphenol.

Entomological Tests; Correlation of Results.—The aryl and diaryl alkanes listed in Table I have been examined for insecticidal activity by contact tests on cockroaches and milkweed bugs, a mosquito larvicide test and fabric protection tests with

(18) We are obliged to Dr. N. R. Trenner and Mr. R. Walker for the infrared data. The identifications of bands were deduced from A.P.I. hydrocarbon spectra tables.

(19) E. E. Reid and F. Wilson, THIS JOURNAL, **66**, 967 (1944).

(20) A. Ivanov, *Chem. Zentr.*, **74**, 1, 705 (1918).

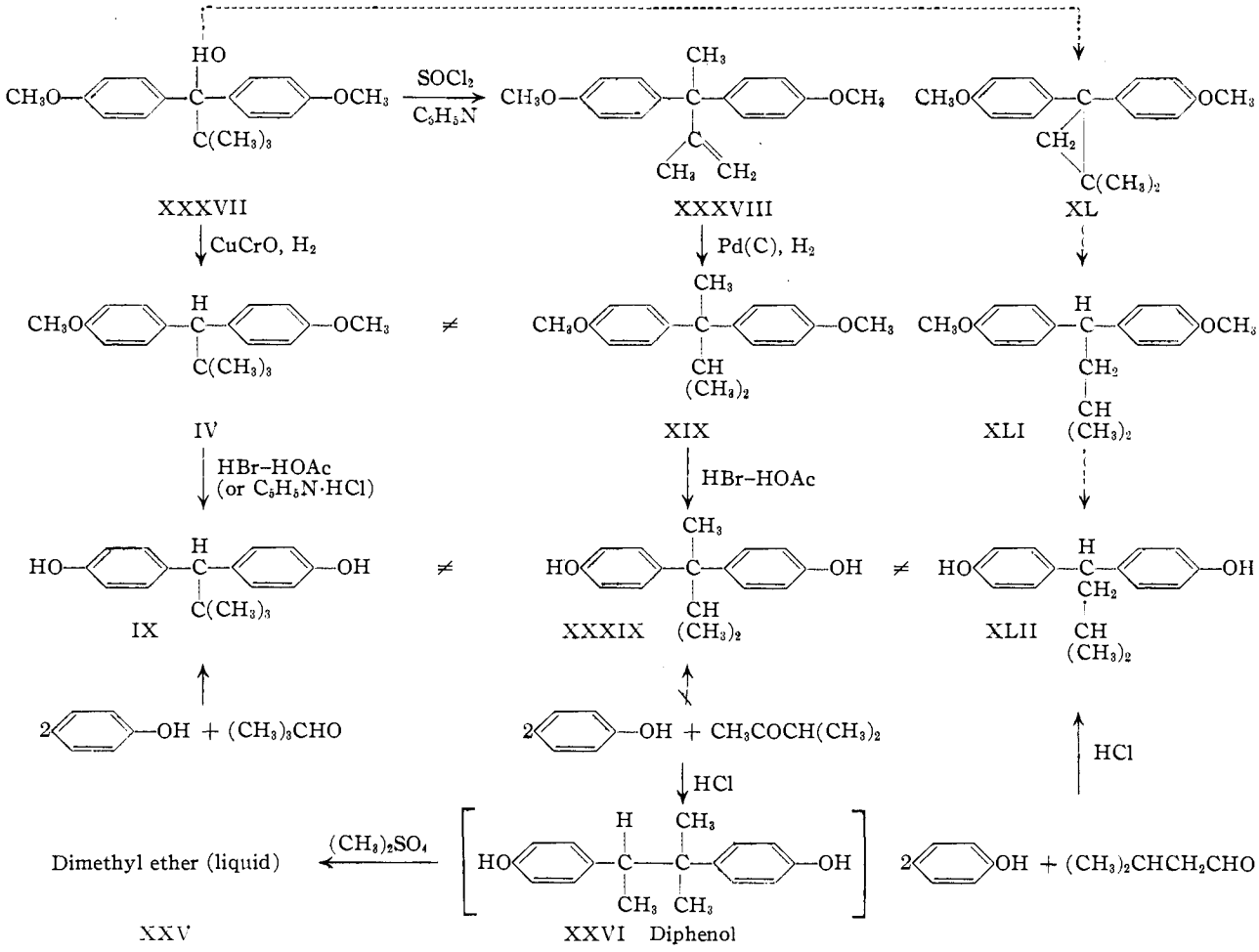
clothes moth and carpet beetle larvae. The techniques of these evaluation methods have been described by Nelson, Heal and others.[21]

Table II summarizes the entomological data on the more interesting materials. The results of the contact and larvicide tests are tabulated in per cent. kill at an application dosage which is expressed in mg./kg. or p.p.m. In the case of the fabric protection tests the results are expressed by the fabric weight loss resulting from feeding of larvae in treated wool patches. Good protection results in a low loss figure of 0–8 mg. Untreated wool, under the same conditions, suffers losses of about 50–70 mg. from clothes moth attack and 25-30 mg. from carpet beetle feeding.

The carbinol and olefin intermediates from the alkane syntheses, which are described in the experimental section, were also tested, but were found to have no significant activity.[22]

The results obtained are correlated below.

1,1-Diphenyl-2,2-dimethylpropane is non-insecticidal and substitutions in the 4,4′-positions with hydroxyl, amino, nitro and fluoro groups likewise give inactive compounds. The 4,4′-dimethyl compound, 1,1-di-*p*-tolyl-2,2-dimethylpropane (VIII) possesses definite although low activity. The dichloro- and dibromodiphenyldimethylpropanes (III, XII), like 1,1-dianisyl-2,2-dimethylpropane, are quite effective insecticides. As previously mentioned, it was necessary to prepare these derivatives by direct chlorination and bromination of the parent hydrocarbon. Oily distillation fractions were used in the entomological tests as the dichloro compound could not be crystallized and crystalline dibromodiphenyldimethylpropane was obtained only after completion of the biological work. It will be noted that those fractions analyzing high for two halogens appear somewhat more active. In view of the non-toxicity of 1,2,2,2-tetrachloro-1,1-di-*p*-chlorophenylethane (XXX) and the slight



A. Ring Substituents in 1,1-Diphenyl-2,2-dimethylpropane (Compounds II–IV, VIII–XIII).—

(21) F. C. Nelson, H. E. Buc, N. A. Sankowsky and M. Jernakoff, *Soap*, **10**, 85 (1934); R. E. Heal, *J. Econ. Entomol.*, **35**, 249 (1942); R. E. Heal, E. F. Rogers, R. T. Wallace and O. Starnes, *Lloydia*, **13**, (2) 89 (1950).

(22) The carbinols were not tested for miticidal activity although closely related compounds have been found highly effective. O. Grummitt, *Science*, **111**, 361 (1950); R. L. Metcalf, *J. Econ. Entomol.*, **41**, 875 (1948).

effectiveness of DDT derivatives containing additional ring halogen, the data may possibly be explained by competitive halogenation with formation of low activity by-products of these types.

The pattern of results on the ring-substituted diphenyldimethylpropanes is, with one exception, similar to that of DDT and its analogs.[3] 4,4′-Difluorodiphenyldimethylpropane (XIII) is inactive while 1,1,1-trichloro-2,2-di-*p*-fluorophenyl-

ethane (XIV) is reported to be highly toxic.[23] It is possible that the difluorodiphenyldimethylpropane falls short of a critical minimum length of molecule.

B. Substituents on Central Carbon of Dianisylmethane (Compounds IV, XV–XXIII).—Dianisylmethane (XVI) shows activity only against mosquito larvae. When the central carbon is substituted by a methyl group (XVII) the activity is about the same, but substitution of an isopropyl group (XVIII) broadens the spectrum and replacement with a *t*-butyl group (IV) gives a potent insecticide. The hindrance to free rotation caused by the *t*-butyl group is believed, as previously discussed, to produce the trihedralized and presumably toxic configuration of the dianisylmethyl moiety. The isopropyl group of compound XVIII may, because of limited hindrance of rotation, produce a greater proportion of the toxic configuration than exists in freely-rotating dianisylmethane (XVI) and 1,1-dianisylethane (XVII).

Comparison of compounds XVIII and XIX shows that replacement of the last hydrogen atom on the central carbon causes loss of insecticidal activity. This result recalls the inactivity of 1,2,2,2-tetrachloro-1,1-di-*p*-chlorophenylethane (XXX).

The inactivity of 1,1-dianisyl-3,3-dimethylbutane (XX) is especially interesting. In this compound the *t*-butyl group is separated from the dianisylmethyl moiety by a methylene group, thereby voiding the trihedralization effect. The contrasting results on this compound and 1,1-dianisyl-2,2-dimethylpropane (IV) illustrate the necessity for interaction between the *t*-butyl or trichloromethyl group and the diphenylmethyl moiety in DDT insecticides. The difference in activity of these two compounds is important in connection with Läuger's hypothesis which will be considered further in the next section.

One compound with a long branched chain, 1,1-dianisyl-3,5,5-trimethylhexane (XXI) was tested and found inactive. The necessity for lipoid-solubility in DDT insecticides is demonstrated by the inactivity of the completely polar 4,4′-dichlorobenzhydryltrimethylammonium bromide (XV). Since the ammonium radical of this compound is isosteric with DDT, no other explanation for the inactivity is apparent.

α,α-Dianisylacetone (XXII) is similar to Erlenmeyer's di-*p*-chlorophenylacetone,[9] the DDT "isostere" mentioned earlier, and like his compound is inactive. The ketone shows no tendency to form a hydrate as required for isosterism. Models indicate that while the acetyl group of α,α-dianisylacetone does not provide sufficient bulk to hinder rotation of the aromatic rings, restriction would be expected with the corresponding oxime. This product XXIII was found to have insecticidal activity, although of a very low order, perhaps because of its somewhat polar character.

C. Other Structures. (Compounds VIII, IX, XXIV, XXV, XXVII, XXXI–XXXVI).—In models of 1-*p*-tolyl-1-*m*-xylyl-2-methylpropane (XXXIV) and 1,1-di-*p*-tolyl-2,2-dimethylpropane (VIII), the same trihedralization of the aromatic rings is observed. The former compound, however, is an inferior insecticide, about equal to 1,1-di-*p*-tolyl-2-methylpropane (XXVII) in activity. The comparison of compounds XXXIV and VIII is not wholly satisfactory, since it has been shown that the *m*-xylyl analog of DDT (XXXV) is less active than the *p*-tolyl analog (XXXVI).[24]

Hydrogenation of one ring of 1,1-ditolyl-2,2-dimethylpropane or replacement of one anisyl group of dianisyldimethylpropane by either hydrogen or methyl results in complete loss of activity (XXXI, XXXII, XXXIII).

Meso-2,3-dianisylbutane (XXIV) and the methylated Reid phenol, which is believed to be 2,3-dianisyl-2-methylbutane (XXV), are non-insecticidal. The phenol corresponding to *meso*-2,3-dianisylbutane, which is called "butestrol," is highly estrogenic, approximately one-tenth as potent as hexestrol[25]; the Reid phenol also has estrogen activity.[20] On the other hand, the phenol IX derived from the insecticidal 1,1-dianisyl-2,2-dimethylpropane has been found to be non-estrogenic.[26] There is, therefore, judging by these three cases, no parallel between the estrogenic activity of a phenol and the insecticidal activity of the corresponding dimethyl ether. This point is considered because Läuger[1b] has drawn attention to the similar lengths of the stilbestrol and DDT molecules and also has mentioned that the stilbestrol analog, 2,3-bis-(*p*-chlorophenyl)-butene-2, is a contact insecticide.

The possibility of methyl–chlorine equivalence in other types of insecticides suggested comparison of 1,2,3,4,5,6-hexamethylcyclohexane[27] with γ-hexachlorocyclohexane. The hexamethyl compound, which is of unknown configuration, was inactive.

Discussion

The insecticide test results are consistent with the view that the prime function of the trichloromethyl or *t*-butyl group in DDT-type compounds is steric and this steric function is interpreted as production of a trihedralized configuration of the diphenylmethyl moiety. The data of previous workers also fit this concept. The inactivity of 1,1-di-*p*-chlorophenyl-2,2-dichloroethylene (XXVIII) and the low activity of 1,1-di-*p*-chlorophenyl-2,2,2-trifluoroethane (XXIX) are readily understood, since in these compounds the aryl groups can rotate freely, so that the trihedralized configuration is not formed. The potency of the promising nitro analogs of DDT synthesized by Hass and coworkers[28] is explained in part by the fact that the trichloromethyl group is replaced by 1-nitroalkyl groups of equal or greater bulk.

In the Läuger DDT hypothesis emphasis is placed

(23) R. L. Metcalf, *J. Econ. Entomol.*, **41**, 416 (1948). This author cites earlier references.

(24) R. L. Metcalf, *ibid.*, **41**, 875 (1948).

(25) E. Adler, H. v. Euler and G. Gie, *C. A.*, **39**, 3277 (1945).

(26) Dr. William Kleinberg, Princeton Laboratories, Inc., reports that this compound shows no estrogenic reaction at doses up to 1 mg. per rat.

(27) H. A. Smith and E. F. H. Pennekamp, THIS JOURNAL, **67**, 279 (1945).

(28) H. B. Hass, M. B. Neher and R. T. Blickenstaff, *Ind. Eng. Chem.*, **43**, 2875 (1951); T. A. Jacob, G. B. Bachman and H. B. Hass, *J. Org. Chem.*, **16**, 1572 (1951).

on the "lipoid-solubilizing" action of the trichloromethyl group. This action is supposedly demonstrated by the anesthetic properties of chloroform. Kirkwood and Phillips[29] have tested this idea. The potent insecticide 1,1-di-*p*-fluorophenyl-2,2,2-trichloroethane (XIV) and the feeble insecticide 1,1 - di - *p* - chlorophenyl - 2,2,2 - trifluoroethane (XXIX) were fed to rats. It was found that the former compound accumulated in the perirenal fat while the latter did not. As Henne[30] had previously shown that fluoroform, the hydride of the "lipoid-solubilizing group" in the latter compound, has no anesthetic properties, the results appear to fit Läuger's suggestion. A difficulty arises, however, when one considers the nitro analogs of DDT and the diaryldimethylpropanes. Hass has emphasized that the nitroalkanes have not been found to be anesthetic; the same is true for isobutane. Furthermore, the fact that 1,1-dianisyl-2,2-dimethylpropane (IV) is insecticidal while 1,1-dianisyl-3,3-dimethylbutane (XX) is not cannot be satisfactorily explained in terms of the *t*-butyl group alone. It would seem that the combination of the *p,p'*-dichlorodiphenyl moiety with the trichloromethyl, 1-nitroalkyl and *t*-butyl groups suffices to explain fat-deposition without consideration of anesthetic hydrides. Läuger has shown that DDT forms molecular compounds with cholesterol and desoxycholic acid, a fact which agrees very well with the notion of a trihedralized or near planar insecticide molecule. Such molecular compounds offer a mechanism for transport to fatty tissue. The failure of the non-insecticidal, oil-soluble DDT analog of Kirkwood and Phillips to accumulate in fat may be explained as a transport failure. As indicated earlier, this compound would not be expected to resemble DDT in shape, hence in ability to combine with steroids. The inactivity of 1,2,2,2-tetrachloro-1,1-di-*p*-chlorophenylethane may perhaps also be related to transport failure, if the "topside" chlorine prevents union with a steroid.

The analogy of DDT to steroids is attractive; possibly DDT is toxic because of some "anti-steroid" role in the nervous system. However the analogy may be pressed too far. As mentioned earlier, in the discussion of butestrol and similar compounds, no relation could be found between insecticide and estrogenic properties. Caution is further indicated by the failure of investigators to demonstrate that DDT is an enzyme inhibitor and by the interesting evidence that it may, in fact, function as an indifferent narcotic.[3,31]

In sum, it is the authors' opinion that the assignment of quasi-independent toxic and lipoid-solubilizing functions to parts of the DDT molecule is untenable. The toxicity of the insecticide is more satisfactorily explained in terms of a trihedralized *p,p'*-di-chlorophenylmethyl moiety. Since this configuration results from the mutual interaction of the trichloromethyl and dichlorophenylmethyl groups, one may say that DDT appears to owe its activity to the molecule as a whole.

(29) S. Kirkwood and P. H. Phillips, *J. Pharmacol. Exp. Ther.*, **87**, 375 (1946).

(30) A. L. Henne, THIS JOURNAL, **59**, 1200 (1937).

(31) P. Gauvaudan and H. Poussel, *Compt. rend.*, **224**, 683 (1947).

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Experimental

All melting points and boiling points are uncorrected.

The preparation of 1,1-di-p-anisyl-2,2-dimethylpropanol and 1,1-di-p-anisyl-2,2-dimethylpropane, which are described in detail below, serve as models of the many Grignard and hydrogenation reactions reported. Unless otherwise specified similar reaction conditions, catalysts, etc., were employed.

1,1-Di-*p*-anisyl-2,2-dimethylpropanol.—Ethyl pivalate (65 g., 0.5 mole), diluted with ether, was added to an ethereal solution of *p*-anisylmagnesium bromide (prepared from 200 g., 1.07 moles, of *p*-bromanisole), maintained at 0°. The reaction mixture was allowed to warm to room temperature, let stand 16 hours, refluxed for an additional 4 hours, then hydrolyzed by treatment with 200 ml. of 25% aqueous ammonium chloride. The ether layer, after drying over sodium sulfate, was evaporated to give 146 g. of a semi-solid, orange-colored material. Solution in boiling petroleum ether and slow cooling precipitated 3 g. of a product, m.p. 62–95°, which after three recrystallizations yielded pure dianisyl, m.p. 171–172°. Crude carbinol, 118 g. (78%), precipitated on chilling the filtrate. This melted at 66–76°. Several recrystallizations from petroleum ether, with rejection each time of the first 2–3 g. of precipitate, gave a colorless product, m.p. 81–83°.

Anal. Dianisyl. Calcd. for $C_{14}H_{14}O_2$: C, 78.44; H, 6.58. Found: C, 78.70; H, 6.68. Carbinol. Calcd. for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05. Found: C, 75.51; H, 7.84.

An attempt to prepare the carbinol by reaction of *t*-butylmagnesium chloride with *p,p'*-dimethoxybenzophenone was unsuccessful. Reaction of *t*-amylmagnesium chloride with the benzophenone also failed to give appreciable yields of the desired alcohol.

1,1-Di-*p*-anisyl-2,2-dimethylpropane (IV).—1,1-Di-*p*-anisyl-2,2-dimethylpropanol (30 g.), dissolved in 100 ml. of absolute alcohol, was hydrogenated at 6000 p.s.i. and 250° for 3 hours in the presence of 10 g. of barium stabilized copper chromite catalyst. One mole equivalent of hydrogen was absorbed. Filtration through Supercel and evaporation of the solvent *in vacuo* gave 26 g. of air-dried product, m.p. 51–57°. Two recrystallizations from petroleum ether raised the melting point to 58.5–60°. After drying this product over paraffin a melting point of 59–61° was observed.

Anal. Calcd. for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 80.47; H, 8.22.

1,1-Di-*p*-hydroxyphenyl-2,2-dimethylpropane (IX).—A mixture of 20 g. of pyridine hydrochloride and 8.5 g. of 1,1-di-*p*-methoxyphenyl-2,2-dimethylpropane was heated under reflux (bath temp. 220°) for 6 hours. On addition of water to the cooled mixture, the diphenol crystallized. Recrystallization from benzene gave 5.0 g. (66%) of product, m.p. 163–164°.

Anal. Calcd. for $C_{17}H_{20}O_2$: C, 79.65; H, 7.87. Found: C, 79.43; H, 8.16.

Condensation of Pivalaldehyde with Phenol.—Pivalaldehyde (3.5 g., 0.04 mole) was added to a chilled (0–5°) mixture of 50 ml. of concentrated sulfuric acid and 50 ml. of glacial acetic acid. A precipitate formed at once, presumably the aldehyde trimer. Phenol (7.5 g., 0.08 mole) was then introduced in small amounts over a 20-minute period. The solution, which became yellow during addition of the phenol, was kept at 0–5° for 2.5 hours, then poured onto crushed ice. The precipitated oil slowly crystallized to give 2.9 g. of product, m.p. 124–136°. Recrystallization from alcohol did not raise or sharpen the melting point. Purification was accomplished by extraction with 10% sodium hydroxide, precipitation with acid and several recrystallizations from benzene. The substance then melted at 158–160°.

Anal. Calcd. for $C_{17}H_{20}O_2$: C, 79.66; H, 7.87. Found: C, 78.03; H, 7.50.

The melting point of 2,2-di-*p*-hydroxyphenyl-3-methylbutane (XXXIX, m.p. 157–158°) was depressed by admixture with the phenol–pivalaldehyde condensation product, while that of 1,1-di-*p*-hydroxyphenyl-2,2-dimethylpropane (IX, m.p. 163–164°) was not.

2-Methyl-3,3-di-*p*-anisylbutene-1 (XXXVIII).—Thionyl chloride (16.5 g., 0.14 mole) was added dropwise to a well-stirred solution of 30 g. (0.1 mole) of 1,1-di-*p*-anisyl-2,2-dimethylpropanol in 50 ml. of toluene. During the addition the temperature was maintained at 0°, then was raised to 10° with stirring continued for 2 hours longer. After overnight standing at room temperature, removal of thionyl chloride and chilling caused precipitation of 1.2 g. of gray solid, m.p. 118–122°, possibly the rearranged chloride (*Anal.* Found: Cl, 10.34). Distillation of the filtrate gave 20 g. (71%) of product, b.p. 165–171° (1 mm.). When redistilled through a Todd column, a colorless viscous oil was obtained; b.p. 208–209° (9 mm.), d^{25}_4 1.075, $n^{25}D$ 1.5738. The material reacted instantly with permanganate and bromine. A sodium fusion test for chlorine was negative.

Anal. Calcd. for $C_{19}H_{22}O_2$: C, 80.81; H, 7.85. Found: C, 80.21; H, 7.75.

2,2-Di-*p*-anisyl-3-methylbutane (XIX).—The olefin XXXVIII was hydrogenated in alcohol solution at room temperature using palladium–charcoal catalyst. The butane, obtained in 64% yield, was recrystallized from alcohol, m.p. 100–102°.

Anal. Calcd. for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 80.43; H, 8.29.

2,2-Di-*p*-hydroxyphenyl-3-methylbutane (XXXIX).—2,2-Di-*p*-anisyl-3-methylbutane was demethylated in refluxing hydrobromic acid–acetic acid mixture. The product, crystallized from benzene, then alcohol, melted at 157–158°.

Anal. Calcd. for $C_{17}H_{20}O_2$: C, 79.65; H, 7.87. Found: C, 79.43; H, 7.79.

Methyl Isopropyl Ketone–Phenol Condensation Product, Dimethyl Ether (XXVI, XXV).—Hydrogen chloride-catalyzed condensation of phenol and methyl isopropyl ketone gave the product previously described by Reid,[19] m.p. 198–199°. The reaction proceeds very slowly; a yield of only 9% was obtained after one month at room temperature.

The diphenol was methylated with dimethyl sulfate and alkali. The Claisen-alkali washed product boiled at 200–210° (7 mm.), d^{25}_4 1.066, $n^{25}D$ 1.5670. The distilled material could not be crystallized on seeding with 2,2-di-*p*-anisyl-3-methylbutane (XIX).

Anal. Calcd. for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 80.49; H, 8.30.

1,1-Diphenyl-2,2-dimethylpropanol.—This alcohol was prepared in 53% yield by reaction of phenylmagnesium bromide with ethyl pivalate; b.p. 155–161° (1 mm.), $n^{25}D$ 1.5745, d^{25}_4 1.054.

1,1-Diphenyl-2,2-dimethylpropane (II).—Reduction of 1,1-diphenyl-2,2-dimethylpropanol gave a 56% yield of hydrocarbon, recrystallized from ethanol, m.p. 55–56°.

Anal. Calcd. for $C_{17}H_{20}$: C, 91.01; H, 8.99. Found: C, 91.27; H, 8.86.

Bromination of 1,1-Diphenyl-2,2-dimethylpropane (XII).—1,1-Diphenyl-2,2-dimethylpropane (11.2 g., 0.05 mole) was dissolved in 200 ml. of carbon tetrachloride and placed in a flask fitted with a stirrer and condenser. One gram of powdered iron was added and the mixture heated to 70°. Then 18 g. of bromine was introduced below the surface of the liquid over a 3.5-hour period, light being excluded. Hydrogen bromide evolution was continuous during this time. After addition of the bromine was completed the material was stirred and heated for an additional 2 hours at 70°. After standing overnight at room temperature the product was washed with 10% alkali, then dried over sodium sulfate. Evaporation of the solvent gave 17.2 g. of crude oil. A 16-g. portion of the oil was distilled to give the following fractions: (1) b.p. 150–164° (< 1 mm.) (0.8 g.); (2) b.p. 164–167° (< 1 mm.) (4 g.); (3) b.p. 183–187° (< 1 mm.) (5 g.). Fraction (3) crystallized on long standing. After several recrystallizations from petroleum ether a product melting at 84–86° was obtained. In later runs, in which the temperature during bromine addition (4 hours) and subsequent reaction (7 hours) was maintained at 55°, a 63% yield of a fraction boiling at 200–205° (1 mm.), $n^{25}D$ 1.6012, was secured and this afforded 24% of crystalline material, m.p. 83°.

Anal. Calcd. for $C_{17}H_{18}Br_2$: C, 53.43; H, 4.75; Br, 41.83. Found for (2): C, 62.78; H, 6.29; Br, 32.53. Found for (3): C, 55.45; H, 5.25; Br, 40.80. Found for product m.p. 84–86°: C, 53.91; H, 4.68; Br, 41.85.

Chlorination of 1,1-Diphenyl-2,2-dimethylpropane (III).—One gram of iron powder was added to a solution of 45 g. of 1,1-diphenyl-2,2-dimethylpropane in 150 ml. of carbon tetrachloride and the mixture was treated with chlorine at 0–5°, light being excluded. After three hours, when the increase in weight corresponded to disubstitution (15 g. of chlorine), chlorine treatment was stopped. The reaction flask was packed in ice and allowed to warm up slowly to room temperature overnight. The solution was then washed with dilute sulfuric acid and bicarbonate and dried over sodium sulfate. The solvent was removed *in vacuo* to give 61 g. of a light yellow-colored oil. Fifty-one grams of this crude oil was distilled at 1 mm. to give the following fractions: (1) b.p. 160–167° (16.2 g.); (2) b.p. 167–169° (20.2 g.); (3) b.p. 174–187° (8.6 g.).

Anal. Calcd. for $C_{17}H_{18}Cl_2$: C, 69.63; H, 6.19; Cl, 24.18. Found for (1): C, 68.40; H, 5.76; Cl, 24.58. Found for (2): C, 68.23; H, 5.96; Cl, 27.99. Found for (3): C, 63.82; H, 5.55; Cl, 32.28.

1,1-Di-*p*-nitrophenyl-2,2-dimethylpropane (X).—A mixture of 27 ml. of concentrated nitric acid (d. 1.42) and 30 ml. of concentrated sulfuric acid was added to 33.6 g. of 1,1-diphenyl-2,2-dimethylpropane at such a rate as to maintain the stirred slush at 40–50°. Then the reaction mixture was stirred and heated at 45–50° for 2 hours. When poured onto crushed ice an orange-colored tacky gum formed. This was triturated with 5% sodium bicarbonate and filtered. The insoluble sticky powder, when further milled with ether, gave 36 g. of almost white, crystalline product, m.p. 135–140°. Recrystallization from 300 ml. of alcohol raised the melting point to 145–147°. Ultraviolet and infrared absorption spectra indicate that the nitro groups are in the para position.

Anal. Calcd. for $C_{17}H_{18}N_2O_4$: C, 64.95; H, 5.77; N, 8.92. Found: C, 64.60; H, 6.93; N, 9.08.

1,1-Di-*p*-aminophenyl-2,2-dimethylpropane (XI).—Reduction of the dinitro compound X with platinum catalyst in alcohol at room temperature gave a nearly quantitative yield of diamine. After two recrystallizations from ether–petroleum ether this melted at 144°.

Anal. Calcd. for $C_{17}H_{22}N_2$: N, 11.02. Found: N, 11.06.

1,1-Di-*p*-fluorophenyl-2,2-dimethylpropanol.—This alcohol was prepared in 41% yield by reaction of *p*-fluorophenylmagnesium bromide with ethyl pivalate; m.p. 76–77° after recrystallization from petroleum ether.

Anal. Calcd. for $C_{17}H_{18}F_2O$: C, 73.89; H, 6.56. Found: C, 74.17; H, 6.39.

1,1-Di-*p*-fluorophenyl-2,2-dimethylpropane (XIII).—1,1-Di-*p*-fluorophenyl-2,2-dimethylpropanol was reduced over copper chromite. Removal of solvent alcohol left a viscous oil which slowly crystallized in the refrigerator; m.p. 40–50°, yield 87%. After distillation at 110–112° (< 1 mm.), the crystalline product recovered melted at 52–55°. It is highly soluble in all of the common organic solvents.

Anal. Calcd. for $C_{17}H_{18}F_2$: C, 78.43; H, 6.97. Found: C, 78.70; H, 6.93.

1,1-Di-*p*-tolyl-2,2-dimethylpropanol.—This alcohol was prepared in 53% yield by reaction of *p*-tolylmagnesium bromide with ethyl pivalate; b.p. 165–171° (1 mm.), $n^{25}D$ 1.5640, d^{25}_4 1.021. When redistilled in a small Todd column, a boiling point of 151–153° (0.5 mm.) was observed.

Anal. Calcd. for $C_{19}H_{24}O$: C, 85.04; H, 9.02. Found: C, 85.12; H, 9.02.

1,1-Di-*p*-tolyl-2,2-dimethylpropane (VIII).—Reduction of 1,1-di-*p*-tolyl-2,2-dimethylpropanol gave a 77% yield of distilled product; b.p. 128° (1 mm.), $n^{25}D$ 1.5528, d^{25}_4 0.959.

Anal. Calcd. for $C_{19}H_{24}$: C, 90.40; H, 9.59. Found: C, 90.60; H, 9.43.

1-*p*-Tolyl-1-(4-methylcyclohexyl)-2,2-dimethylpropane (XXXIII).—1,1-Di-*p*-tolyl-2,2-dimethylpropane (12 g.) was hydrogenated at 250° and 3500 p.s.i. in the presence of 2 g. of Raney nickel catalyst for 7 hours. Eight grams of distilled product was obtained; b.p. 122–124° (0.5 mm.), $n^{25}D$ 1.5090, d^{25}_4 0.915.

Anal. Calcd. for $C_{19}H_{30}$: C, 88.31; H, 11.70. Found: C, 88.41, 88.44; H, 12.00, 11.70.

1,1-Di-*p*-tolyl-2-methylpropene-1.—The crude carbinol obtained by reaction of *p*-tolylmagnesium bromide with ethyl isobutyrate was dehydrated by heating with iodine at 100° for 3 hours, giving a 60% over-all yield of olefin, b.p. 160° (8 mm.). The distillate crystallized and after recrystallization from methanol melted at 46–47°.

Anal. Calcd. for $C_{18}H_{20}$: C, 91 47; H, 8.53. Found: C, 91.61; H, 8.35.

1,1-Di-*p*-tolyl-2-methylpropane (XXVII).—Reduction of the above olefin gave an 80% yield of 1,1-di-*p*-tolyl-2-methylpropane, m.p. 48–49° after two recrystallizations from methanol.

Anal. Calcd. for $C_{18}H_{22}$: C, 90.70; H, 9.30. Found: C, 90.75; H, 9.36.

1-*p*-Tolyl-1-*m*-xylyl-2-methylpropene-1.—The crude carbinol obtained by reaction of *p*-tolylmagnesium bromide with 2,4-dimethylisobutyrophenone[32] was dehydrated by heating with iodine at 100° for 3 hours, giving a 45% overall yield of olefin; b.p. 167–168° (6 mm.), d^{25}_4 0.965, $n^{25}D$ 1.5717.

Anal. Calcd. for $C_{19}H_{22}$: C, 91.14; H, 8.86. Found: C, 90.86; H, 8.79.

1-*p*-Tolyl-1-*m*-xylylpropane (XXXIV).—The above olefin was quantitatively reduced to 1-*p*-tolyl-1-*m*-xylylpropane; b.p. 158° (5 mm.), d^{25}_4 0.960, $n^{25}D$ 1.5528.

Anal. Calcd. for $C_{19}H_{24}$: C, 90.40; H, 9.59. Found: C, 90.70; H, 9.49.

Meso-2,3-di-*p*-anisylbutane (XXIV).—2,3-Di-*p*-anisylbutanediol-2,3,[16] m.p. 192–193°, gave on reduction the *meso*-butane,[16,25] m.p. 138°. The yield was 40% after two recrystallizations from petroleum ether. The compound has a licorice odor.

Anal. Calcd. for $C_{18}H_{22}O_2$: C, 79.96; H, 8.24. Found: C, 80.08; H, 8.24.

1,1-Di-*p*-anisyl-2-methylpropane (XVIII).—Anisole (162 g., 1.5 moles) was treated with aluminum chloride (266 g., 2 moles) and the complex was then saturated with dry hydrogen chloride at 0°. Isobutyraldehyde (36 g., 0.5 mole) was added dropwise at 0° over 1 hour, then the solution was allowed to warm to room temperature overnight. The reaction mixture was poured onto crushed ice and the organic layer, after washing with bicarbonate, was steam-distilled to remove unchanged anisole (90 ml.). The residual oil gave on fractionation a 56% yield of product, b.p. 177–181° (1 mm.).

Anal. Calcd. for $C_{18}H_{22}O_2$: C, 79.97; H, 8.20. Found: C, 80.40; H, 8.67.

1,1-Dianisyl-3,5,5-trimethylhexane (XXI).—Aluminum chloride catalyzed condensation of anisole and 3,5,5-trimethylcaproaldehyde (nonylaldehyde (Rohm & Haas Company)) as above afforded a 30% yield of the hexane; b.p. 190–196° (1 mm.), $n^{25}D$ 1.5568, d^{25}_4 1.080.

Anal. Calcd. for $C_{23}H_{32}O_2$: C, 81.16; H, 9.48. Found: C, 81.62; H, 9.19.

1,1-Di-*p*-anisyl-3,3-dimethylbutanol.—Ethyl 2,2-dimethylbutyrate was required for the preparation of this compound. Diisobutylene was converted to 4,4-dimethylpentanone-2.[33] Hypobromite oxidation of the methyl ketone and esterification of the resulting *t*-butylacetic acid[34] gave the desired ester in good yield, b.p. 85–86° (105 mm.), $n^{25}D$ 1.4020.

This ester was treated with *p*-anisylmagnesium bromide to give 1,1-di-*p*-anisyl-3,3-dimethylbutanol, which melted at 78–79° after recrystallization from benzene–Skellysolve D.

Anal. Calcd. for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34. Found: C, 76.15; H, 8.16.

1,1-Di-*p*-anisyl-3,3-dimethylbutane (XX).—Reduction of the above alcohol yielded 75% of crystalline butane, m.p. 52–57°. Recrystallization from petroleum ether raised the melting point to 57–58°.

Anal. Calcd. for $C_{20}H_{26}O_2$: C, 80.50; H, 8.78. Found: C, 80.58; H, 8.94.

1-*p*-Anisyl-2,2-dimethylpropanol.—Reaction of *t*-butylmagnesium chloride with anisaldehyde gave a 77% yield of alcohol, b.p. 140° (12 mm.). The product crystallized on standing. After recrystallization from petroleum ether it melted at 41–42°.

Anal. Calcd. for $C_{12}H_{18}O_2$: C, 74.18; H, 9.34. Found: C, 74.35; H, 8.92.

1-*p*-Anisyl-2,2-dimethylpropane[35] (XXXI).—On reduction of the above alcohol, 77% of the propane was obtained. It boiled at 105–106° (10 mm.), $n^{25}D$ 1.4953.

Anal. Calcd. for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.89; H, 10.26.

2-*p*-Anisyl-3,3-dimethylbutanol-2.—This alcohol was prepared from *t*-butylmagnesium chloride and *p*-methoxyacetophenone in 60% yield. The distilled product, b.p. 140–146° (13 mm.), crystallized on standing and melted after recrystallization from acetone at 93–94°.

Anal. Calcd. for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.31; H, 8.70.

2-*p*-Anisyl-3,3-dimethylbutane (XXXII).—Reduction of the above alcohol gave 60% of 2-*p*-anisyl-3,3-dimethylbutane, b.p. 102–110° (8 mm.).

Anal. Calcd. for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 81.15; H, 10.29.

α,α-Di-*p*-anisylacetone, Oxime (XXII, XXIII).—*p*-Methoxymandelonitrile was coupled with anisole using boron trifluoride. The dianisylacetonitrile[36] (m.p. 154–155°) so obtained was then treated with excess methylmagnesium iodide. The neutral fraction from acid hydrolysis of the Grignard complex was distilled to give the desired ketone, b.p. 218–221° (3 mm.), in 48% yield. This compound solidified in the receiver. It was recrystallized from methanol and melted at 66–68°.

Anal. Calcd. for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.72; H, 6.55.

The oxime was made by a standard procedure. When recrystallized from methanol (or dilute ethanol) a mixture of isomers, m.p. 118–135°, was obtained. Crystallization from chloroform gave material melting sharply at 137–138°.

Anal. Calcd. for $C_{17}H_{19}NO_4$: C, 71.55; H, 6.70; N, 4.91. Found: C, 72.02; H, 6.60; N, 4.86.

***p,p'*-Dichlorobenzhydryltrimethylammonium Bromide (XV).**—*p,p'*-Dichlorobenzhydryl bromide[37] was treated with anhydrous trimethylamine in acetonitrile at −10°.[38] The crude quaternary salt was thoroughly dried in a vacuum desiccator and recrystallized from acetone–petroleum ether to a melting point of 185–187°. The product is very soluble in water. It lost 1.8% in weight when dried at 100° for analysis.

Anal. Calcd. for $C_{16}H_{18}NCl_2Br$: C, 51.23; H, 4.84; N, 3.74. Found: C, 51.49; H, 4.75; N, 3.68.

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(32) This ketone was prepared with isobutyric anhydride by the procedure of C. R. Noller and R. Adams, THIS JOURNAL, **46**, 1889 (1924), rather than by the original method of A. Claus, *J. prakt. Chem.*, **46**, 474 (1892).

(33) Procedure kindly furnished by Dr. J. D. Suramitis, Nutley, N. J.

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(35) E. Späth, *Monatsh.*, **34**, 2005 (1913), obtained this compound by coupling *t*-butylmagnesium chloride with *p*-methoxybenzyl bromide.

(36) A. Bistrzycki, J. Paulus and R. Pervin, *Ber.*, **44**, 2596 (1911).

(37) J. F. Norris and D. M. Tibbetts, THIS JOURNAL, **42**, 2091 (1920).

(38) E. D. Hughes and C. K. Ingold, *J. Chem. Soc.*, 69 (1933).