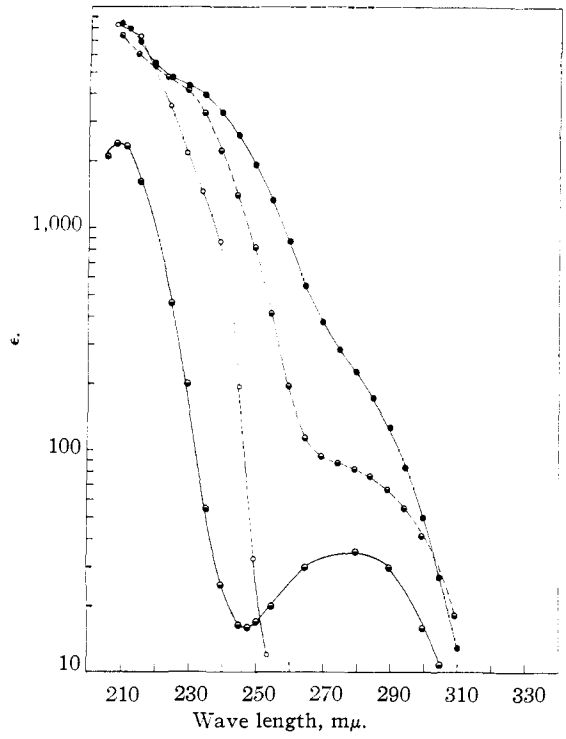

Fig. 2.—Ultraviolet absorption spectra of: 1-acetyl-2,2-dimethyl-3-(2-methyl-1-propenyl)-cyclopropane (III): ●–●, in 95% ethanol; ◒--◒, in isoöctane; 1-(α-hydroxyethyl)-2,2-dimethyl-3-(2-methyl-1-propenyl)-cyclopropane in 95% ethanol: ○–○; β-dihydroumbellulone (V) in 95% ethanol: ◒–◒.

support the essential features of the hypothesis that the unsaturation electrons of the cyclopropane ring lack the property of π-electrons in general of functioning centrally in a chain of conjugation.

Experimental

1-Acetyl-2,2-dimethyl-3-(2-methyl-1-propenyl)-cyclopropane.—Following the procedure of Cason, Sumrell and Mitchell[12] the cadmium Grignard reagent was prepared using 33.5 g. of magnesium, 200 g. of methyl iodide and 200 g. of anhydrous cadmium chloride, with 400 ml. of dry benzene to displace by distillation the 1 liter of ether used in preparation of the methyl Grignard. To the cadmium Grignard reagent thus prepared was added during one hour, while maintaining a reaction temperature of 40–50°, 130 g. of *dl-trans*-chrysanthemumic acid chloride[13] (b.p. 98.3° at 15 mm. in a 14 TP helices-packed column, n^{25}D 1.4830) in 170 ml. of benzene. When the addition was complete the reaction mixture was brought to the boiling point (70°) and held there for an additional hour. The reaction mixture was decomposed first with 400 ml. of water, then by the addition of 68.5 ml. of concentrated hydrochloric acid in 100 ml. of water, and the product was steam distilled along with the solvent. The steam distillate was freed of solvent in a 13 TP glass-helices packed column and the product fractionated. After a small fore-run there was obtained 60 ml. of pale-yellow oil, b.p. 90–91° at 15 mm., $n^{20.5}$D 1.4661–1.4670 first to last cut. A center cut of 35 ml. was refractionated in the same column giving, after a small fore-run, 30 ml. of colorless oil, n^{23}D 1.4666, b.p. 90.8–91.2° at 15 mm.

Anal.[14] Calcd. for $C_{11}H_{18}O$: C, 79.46; H, 10.92. Found: C, 79.39, 79.49; H, 10.93, 10.89.

The semicarbazone was prepared from 3.0 g. of ketone using semicarbazide acetate in ethanol, and the crude material (3.9 g. m.p. 157–60°) was crystallized four times from ethanol to yield 2.0 g. of white crystalline solid, m.p. 162–163.5° (cor.).

Anal. Calcd. for $C_{12}H_{21}ON_3$: C, 64.54; H, 9.36; N, 18.82. Found: C, 64.52; H, 9.36; N, 18.64.

In view of the possible influence of impurities on the spectrum of such a weakly absorbing substance particular care was taken to obtain the purest sample of the ketone III possible. The ultraviolet and infrared spectra[15] (C=O, 5.91 μ) were invariant on samples purified by: (a) chromatography on alumina, (b) regeneration from the semicarbazone by oxalic acid hydrolysis, and (c) passage through a 12 ft. by 10 mm. liquid–vapor partition column of the type described by James and Martin.[16] In particular the liquid–vapor partitionogram provided no evidence for the existence of a mixture of *cis* and *trans* isomers. It is not known with which isomer we were dealing.

The carbinol, 1-(α-hydroxyethyl)-2,2-dimethyl-3-(2-methyl-1-propenyl) cyclopropane, corresponding to the ketone was prepared from 0.8 g. of the ketone by reduction with 1 g. of sodium borohydride in 25 ml. of 50% methanol at 50° for 1 hr. The product was separated by dilution and ether extraction. Sublimation at 30 mm. and 100° gave 0.50 g. of colorless, viscous oil which showed no absorption in the region 5.0–5.6 μ, showing that reduction was complete. The ultraviolet absorption of this material is reported in Fig. 2.

Anal. Calcd. for $C_{11}H_{22}O$: C, 78.51; H, 11.98. Found: C, 78.52, 78.63; H, 11.94, 12.19.

Spectra.—Ultraviolet absorption spectra were obtained with a Beckman model DU instrument, using the photomultiplier attachment below 230 mμ; and infrared determinations were made with a Perkin–Elmer model 21 recording spectrophotometer.

(12) T. Cason, G. Sumrell and R. S. Mitchell, *J. Org. Chem.*, **15**, 850 (1950).

(13) We wish to thank Benzol Products, Inc., for a generous gift of the acid chloride used in this work.

(14) Analyses by Microchemical Specialties, Berkeley, Calif.

(15) The small bathochromic shift in the C=O frequency from 5.88 μ shown by methyl cyclopropyl ketone is attributed to the effect of the *gem*-dimethyl substitution, not to coupling through the cyclopropane ring since it has been shown [E. R. Blout, M. Fields and R. Karplus, THIS JOURNAL, **70**, 194 (1948)] that a γ,δ-double bond produces an inappreciable shift in the C=O frequency of an α,β-unsaturated aldehyde.

(16) A. T. James and A. J. P. Martin, *Analyst*, **77**, 915 (1952). The column used contained G. E. Silicone Oil SF-96 on graded 545 Celite and gave substantial resolution of terpene ketones boiling within 3° near 200°.

DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING
STANFORD UNIVERSITY
STANFORD, CALIF., AND
BENZOL PRODUCTS, INC.
NEWARK 5, N. J.

Some Substituted α-(Aryloxy)-isobutyric Acids and Amides[1]

BY HENRY GILMAN AND GENE R. WILDER

RECEIVED JULY 5, 1955

During the course of investigation of the formative activity of various plant hormones, it was found desirable to include in this work a series of α-disubstituted aryloxyacetic acids.[2]

It has been reported[3] that some compounds of this type have recently been studied as plant hormones, but no chemical details have yet been provided.

The compounds were prepared by treating a phenol with acetone, chloroform and sodium hydroxide, using acetone as the solvent.[4]

(1) This work was supported by a contract with the Chemical Corps, Camp Detrick, Maryland.

(2) The results of the biological tests will be reported elsewhere.

(3) D. J. Osborne and R. L. Wain, *Science*, **114**, 92 (1951).

(4) (a) P. Galimberti and A. Defranceshi, *Gazz. chim. ital.*, **77**, 431 (1947) [*C. A.*, **42**, 3362 (1948)]; (b) G. Link, German Patent 80,986 [*Chem. Zentr.*, **66**, [II] 90 (1895)].

TABLE I

SOME α-(ARYLOXY)-ISOBUTYRIC ACIDS AND DERIVATIVES

Phenol	Product	Yield, %	M.p.,[a] °C.	Analyses Calcd. Neut. equiv.	Calcd. Hal.	Calcd. N	Found Neut. equiv.	Found Hal.	Found N
4-Fluoro	α-(4-Fluorophenoxy)-isobutyric acid	32.3[b,c]	83	198.2	...	...	199.5	...	..
	Amide	34.0[b]	85	...	...	7.10	...	...	7.20
4-Chloro	α-(4-Chlorophenoxy)-isobutyric acid	37.2[d]	117	215.0	...	...	217.5	...	..
	Amide	60.5[e]	121	...	16.59	6.56	...	16.76	6.29
	4-Chlorophenyl orthoformate	16.5[f]	106	...	26.89	...	...	26.81	..
2-Chloro	α-(2-Chlorophenoxy)-isobutyric acid	62.0[b,g]	72	215.0	16.52	...	216.4	16.56	..
	Amide	36.0[b,h]	92	...	16.59	6.56	...	16.61	6.65
2,4-Dichloro	α-(2,4-Dichlorophenoxy)-isobutyramide	26.0[e,h]	110	...	28.60	5.64	...	28.38	5.46
4-Bromo	α-(4-Bromophenoxy)-isobutyric acid	39.6[b]	135	259.1	30.82	...	258.8	30.97	..
	Amide	48.2[b]	128	...	30.97	5.43	...	31.06	5.65
2-Bromo	α-(2-Bromophenoxy)-isobutyric acid	84.0[b,g]	76	259.1	30.82	...	257.0	30.98	..
	Amide	23.9[b,h]	76	...	30.97	5.43	...	30.99	5.28
4-Iodo	α-(4-Iodophenoxy)-isobutyric acid	37.8[e]	135	306.1	41.46	...	307.7	41.33	..
	Amide	71.6[e]	124	...	41.59	4.59	...	41.54	4.65
4-Cyano	α-(4-Cyanophenoxy)-isobutyramide	4.0[i,k]	185	...	...	13.72	...	...	14.0

[a] All melting points are uncorrected. [b] Compound recrystallized from petroleum ether (b.p. 60–70°). [c] *Anal.* Calcd. for $C_{10}H_{11}FO_3$: C, 60.60; H, 5.595. Found: C, 61.34, 61.45; H, 6.185, 5.951. [d] Compound recrystallized from water. [e] Compound recrystallized from petroleum ether (b.p. 77–115°). [f] By-product from 4-chlorophenol run. [g] Yield based on hydrolysis of amide. [h] Amide prepared without isolation of pure acid. [i] *Anal.* Calcd. for $C_{11}H_{12}N_2O_2$: C, 64.72; H, 5.929. Found: C, 64.31; H, 6.077. [k] Compound prepared from α-(4-bromophenoxy)-isobutyramide and cuprous cyanide.

An equation for the main reaction is

$$ArOH + (CH_3)_2CO + CHCl_3 + 4NaOH \longrightarrow ArOC(CH_3)_2CO_2Na + 3NaCl + 3H_2O$$

The corresponding amides were prepared in the customary manner by treating the acid with an excess of thionyl chloride and subsequent reaction with concentrated ammonium hydroxide.

Physical constants and analytical data are given in Table I.

A compound not previously reported from the reaction of 4-chlorophenol, acetone, chloroform and sodium hydroxide was 4-chlorophenyl orthoformate

$$3(4\text{-}ClC_6H_4OH) + CHCl_3 + 3NaOH \longrightarrow (4\text{-}ClC_6H_4O)_3CH + 3NaCl + 3H_2O$$

Experimental

Preparation of α-(4-Bromophenoxy)-isobutyric Acid.—A mixture of 27 g. (0.156 mole) of 4-bromophenol, 150 g. (2.58 moles) of practical grade acetone, 16.8 g. (0.212 mole) of chloroform and 30 g. (0.75 mole) of sodium hydroxide was allowed to reflux for four hours with stirring; the excess acetone was then distilled off, and the remaining viscous, material was diluted with 100 ml. of water, stirred until homogeneous, allowed to cool in an ice-bath filtered and acidified with 6 *N* hydrochloric acid to congo red. An oil which solidified separated and was collected by filtration, and was dried and recrystallized twice from petroleum ether (b.p. 60–70°), using Norit-A each time. The pure product melted at 135°. The yield was 16.0 g. (39.6%).

Preparation of α-(4-Bromophenoxy)-isobutyramide.—To 5 g. (0.0193 mole) of α-(4-bromophenoxy)-isobutyric acid was added 30 ml. of thionyl chloride and the mixture was refluxed until the evolution of gas had ceased. The excess thionyl chloride was removed, the mixture allowed to cool and then decanted slowly into 300 ml. of cold, concentrated ammonium hydroxide with stirring. The crude amide was collected by filtration, dried and recrystallized from petroleum ether (b.p. 60–70°) using Norit-A to give 2.4 g. (48.2%) of the pure amide, m.p. 127–128°.[5]

Preparation of α-(2-Chlorophenoxy)-isobutyric Acid.—Sixty ml. of an alcoholic solution containing 6 g. (0.107 mole) of potassium hydroxide, 20 ml. of water and 4 g. (0.018 mole) of α-(2-chlorophenoxy)-isobutyramide was allowed to reflux for four hours, diluted with 100 ml. of water allowed to cool, and then acidified with 6 *N* hydrochloric acid and placed in an ice-bath. The resulting precipitate was collected, dried and recrystallized from petroleum ether (b.p. 60–70°). The pure product melted at 72°. The yield was 2.5 g. (62.0%).

Identification of 4-Chlorophenyl Orthoformate.—In the synthesis of α-(4-chlorophenoxy)-isobutyric acid 4.0 g. of base-insoluble needles was obtained prior to the acidification of the aqueous solution. Recrystallization from petroleum ether (b.p. 60–70°) afforded 3.4 g. of needles, m.p. 106°, the analysis of which showed 26.81% of chlorine. The compound did not give a ferric chloride test nor an alcoholic silver nitrate test, indicating the absence of a phenol or moderately reactive halogen. Upon treatment with dry hydrogen chloride in ether, subsequent removal of the ether and treatment with ferric chloride, there was obtained a blue to violet coloration indicative of a phenol. A solution of 0.082 g. of the compound in 10 ml. of ether was treated with dry hydrogen chloride for 0.5 hour, and concentrated. The residue was treated with 6 ml. of 10% sodium hydroxide and 0.5 ml. of benzoyl chloride, shaken for 20 minutes and extracted with ether. The residue remaining after the removal of the ether was recrystallized from ethanol–water to yield 0.067 g. of plates which melted at 87° and gave no melting point depression with an authentic specimen of 4-chlorophenyl benzoate.

Preparation of 4-Chlorophenyl Orthoformate.—Five grams (0.039 mole) of 4-chlorophenol, 2.2 g. (0.039 mole) of potassium hydroxide, 1.5 g. (0.013 mole) of chloroform and 20 ml. of dioxane was allowed to reflux for 4 hours, at the end of which the contents were decanted into 100 ml. of water and cooled in an ice-bath. The crystals obtained by filtration were recrystallized from petroleum ether (b.p. 60–70°) to give 1.1 g. (21.6%) of needles melting at 106°. The infrared spectrum of this substance was identical with that of the compound obtained as a by-product from the α-(4-chlorophenoxy)-isobutyric acid run and gave no depression in melting point with this compound.

Preparation of α-(4-Cyanophenoxy)-isobutyramide.—To 10 g. (0.028 mole) of α-(4-bromophenoxy)-isobutyramide, 10 g. (0.056 mole) of cuprous cyanide and 0.05 g. of copper sulfate was added 100 ml. of freshly distilled quinoline and the mixture was heated for 24 hours at a temperature just below that at which the mixture became homogeneous. The solution was then allowed to cool somewhat and decanted into 500 ml. of 6 *N* hydrochloric acid which resulted in the formation of a precipitate. This was collected by filtration and the filtrate was extracted with several portions of ether. The ethereal solution was dried over sodium sulfate, filtered and concentrated to leave a residue which was combined with the precipitate obtained from the acidified

(5) The acids and amides described in Table I were prepared essentially as described for the acid and amide from 4-bromophenol.

solution. The combined residues were recrystallized from benzene, using Norit-A to give 0.32 g. (4.0%) of the amide melting at 185–186°.

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DEPARTMENT OF CHEMISTRY
IOWA STATE COLLEGE
AMES, IOWA

Derivatives of ζ-Truxinic Acid

BY MARTIN G. ETTLINGER

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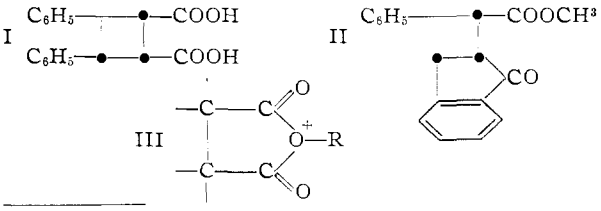
ζ-Truxinic acid (I by the Linstead convention), the resolvable *cis*-truxinic acid,[1] contains two non-equivalent carboxyl groups. Six positionally isomeric pairs of unsymmetrical derivatives of the acid functions have been characterized and the attachments of the substituents to the carboxyl groups, arbitrarily designated a and b, correlated throughout the series.[2] From the observation[2] that ζ-truxinic a-chloride b-methyl ester, but not its isomer, gave methyl ζ-truxinonate (II), in small yield,[3] on treatment with aluminum chloride, the a-carboxyl group was inferred to be the one *cis* to the adjacent phenyl group. The formulation of the keto ester as the hydrindone II rather than the possible tetralone rests on analogy to the facile cyclizations of truxillic acids and on pyrolysis of the truxinonic acid to cinnamic acid,[4] and seems probable but not proved. Further, serious difficulty with the argument arises from the recent demonstration by Cason and Smith[5] that Friedel–Crafts reactions of ester halides of 1,2-dicarboxylic acids may proceed through the symmetrical cation III. In ester chlorides of cyclobutane *trans*-diacids, formation of an intermediate such as III and consequent migration of an alkoxyl group are sterically prevented, and the structural assignments of unsymmetrical derivatives of *neo*-truxinic[4] and *epi*-truxillic[6] acids from Friedel–Crafts cyclizations agree with considerations of steric hindrance and inversion. However, substituents may easily shift between the carboxyl groups of ζ-truxinic acid: for example, the a-anilic acid with methanolic hydrogen chloride gave the ester of the b-anilic acid, presumably by way of the anil.[2] The two ζ-truxinic ester chlorides should give identical products on attempted cyclization, and the isolation of II from only one appears fortuitous.



(1) R. Stoermer and F. Scholtz, *Ber.*, **54**, 85 (1921).

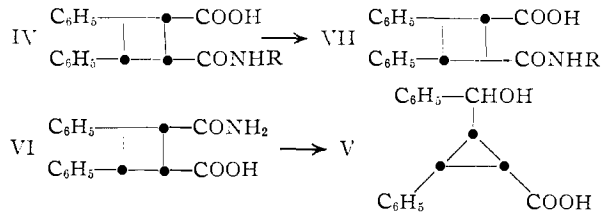
(2) R. Stoermer and P. Klockmann, *ibid.*, **58**, 1164 (1925).

(3) The product from 2 g. of ester chloride was insufficient for complete purification.

(4) R. Stoermer and E. Asbrand, *Ber.*, **64**, 2796 (1931).

(5) J. Cason and R. D. Smith, *J. Org. Chem.*, **18**, 1201 (1953); *cf.* B. H. Chase and D. H. Hey, *J. Chem. Soc.*, 553 (1952).

(6) R. Stoermer and F. Moeller, *Ber.*, **68**, 2124 (1935).



When ζ-a-truxinamic acid, previously formulated as IV (R = H), was subjected to the Hofmann reaction and the resultant amino acid nitrosated,[7,8] the product was the lactone of an all *cis*-substituted[7,9] cyclopropane V. Since the phenyl and carboxyl groups that are *cis* in V would be *trans* in IV, such a ring contraction would imply configurational inversion of the migrating group, in contradiction to established knowledge of carbonium ion rearrangements, including similar degradations of other truxinic and truxillic acids. However, as previous authors[7,8] noted, V would be the expected product from the ζ-amido acid VI. The proper deduction is that ζ-a-truxinamic acid is VI and the old allocation of structures must be reversed.

The conclusion that the a-carboxyl group of I is *trans* to the adjacent phenyl group is confirmed by independent evidence. The a-position is the less hindered[10]; in particular, the anhydride, imide and anil undergo cleavage of the heterocyclic rings by addition exclusively[11] to the a-carbonyl group. Furthermore, the ζ-b-amido and anilic acids are isomerized by base, under conditions that do not affect the a-compounds, to the half amides (VII, R = H or C_6H_5) of δ-truxinic acid.[2] The configuration of δ-truxinic acid is established by its formation from all other truxinic acids on fusion

(7) F. Schenck, *J. prakt. Chem.*, [2] **134**, 215 (1932). The deamination was cited from Rasenack (Dissertation, Rostock, 1928).

(8) I. S. Goldstein and H. I. Bernstein, THIS JOURNAL, **66**, 760 (1944).

(9) The complete stereochemistry of the deamination product (Schenck's[7] lactone Ia, obtained also from γ-truxillic acid) can be plausibly defined by the postulate that the phenyl group on the lactone ring is *cis* to the hydrogen atoms at the ring junctions. The deamination product is formed in acid from both epimeric alcohols V and apparently is more stable than the epimeric lactone of V, in which the phenyl groups may be in contact. Furthermore, the directly correlated configurations of the carboxyl epimers of V (Schenck's series III, of which IIIa is obtained from α-truxillic and δ-truxinic acids) would agree with the course of Meerwein–Ponndorf reduction of 1-benzoyl-2-*cis*-phenylcyclopropane-3-*trans*-carboxylic ester according to Cram's rule of asymmetric induction (D. J. Cram and F. A. Abd Elhafez, *ibid.*, **74**, 5828 (1952)). Application of the Cram–Abd Elhafez rule to the reduction of 1-benzoyl-2-*trans*-phenylcyclopropane-3-*cis*-carboxylic ester indicates that the lactonized product (Schenck's IIb, obtained from β-truxinic and ε-truxillic acids) has the same configuration about the lactone ring as that assumed for Schenck's Ia. The stereochemical result at the newly exocyclic carbon atom of the cited, principal ring contractions would be retention of configuration for truxillic and inversion for truxinic acids, formally as if the oxygen atom approached from the direction of the carboxyl group. Lactonization, if possible, and ring contraction may be simultaneous, but the attachment of the oxygen atom to the benzyl group need not be concerted with the rearrangement, notably in deaminations with nitrosyl bromide, where bromo acids may intervene, and may proceed simply to give the more stable product.

(10) Partial esterification gave the a-ester, and the a-amido acid was more rapidly hydrolyzed by acid than its isomer.[2] Esterification of the b-amido acid was anomalously difficult, presumably because of interaction of carboxyl and amide groups.

(11) The *cis*-phenyl group must retard attack from the opposite side at the adjacent b-position, which would drive the carbonyl oxygen atom toward the phenyl group.