Synthesis of a Series of 5,6,7,8,10,10- Hexachloro-3a,4,4a,5,8,8a,9,9a-octahydro-α-(2-substituted)-1,3-dioxo-5,8-methanobenz(*f*)-isoindoline-2-acetic Acids

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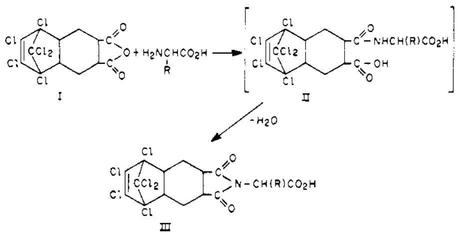
1,2,3,4,9,9 -Hexachloro- 1,4,4a,5,6,7,8,8a -octahydro- 1,4-methanonaphthalene-6,7-dicarboxylic anhydride, m.p. 278–280° C. reacts with the amino group in D,L-alanine, D,L-valine, D,L-leucine, L-isoleucine-D-allo-isoleucine, D,L-methionine, D,L-tyrosine, and D,L-phenylalanine at 140° to 155° C. in dimethylformamide to give the corresponding 5,6,7,8,10,10 -hexachloro-3a,4,4a,5,8,8a,9,9a-octahydro -α-(2-substituted) -1,3-dioxo -5,8-methanobenz(*f*) -isoindoline -2-acetic acids in 73, 78, 79, 92, 79, 88, and 88% yields, respectively.

THE synthesis of the isomeric anhydrides resulting from the Diels-Alder reaction of hexachlorocyclopentadiene and *cis*-4-cyclohexene-1,2-dicarboxylic anhydride, 1,2,3,4,9,9-hexachloro - 1,4,4a,5,6,7,8,8a - octahydro - 1,4 - methanonaphthalene - 6,7 - dicarboxylic anhydride has been described (*3*). The isolation of two isomeric anhydrides in pure form and the determination of the absolute configuration of each is the subject of a continuing investigation. While it may well be that the ring juncture between the bridged ring and the cyclohexane ring is endo (*4*) as described for other hexachlorocylopentadiene adducts, the authors are not able at this time to assign definitely such a configuration. The higher melting isomer, m.p. 278–280° C., is the predominant isomer isolated, and additional preparative work has been undertaken to investigate the reactivities of this compound in typical synthetic applications. This paper reports the synthesis of a series of *N*-substituted imides derived from the high melting anhydride and a series of D,L-amino acids.

The reaction scheme for the chemistry of this report follows. The anhydride, I, reacts with the amino moiety of the amino acid to form a transient intermediate, the amic acid, II, which in turn loses a molecule of water under the conditions of the reaction to produce the *N*-substituted imide, III.



The compounds prepared (Table I) were isolated in good yields from relatively short reaction times using dimethylformamide as reaction solvent. Other reaction media—i.e., benzene, toluene, etc.—were not as satisfactory as that described here. Attempted reaction of the anhydride with L-cystine gave no isolable product. Reaction of the anhydride with L-glutamic acid gave a poor, 40%, yield of an impure product. The compounds successfully prepared were characterized in the usual fashion including elemental analysis, infrared spectra, and NMR spectra. Neutral equivalents were determined on each of the products and gave satisfactory figures in light of the calculated values.

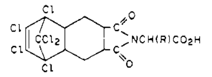
As noted above, these compounds were prepared to determine the extent to which the anhydride would react normally with the amino moiety. In addition, there are numerous examples of *N*-substituted imides which possess biological activity, and it was hoped that the salt forming and solubilizing carboxyl group would lead to an interesting series of biologically active derivatives. Imides and particularly several of the *N*-substituted imides are known to possess useful activity as agricultural chemicals (*1, 2*); the compounds described in Table I possess some herbicidal and fungicidal activity.

EXPERIMENTAL

All melting points are capillary and corrected. A typical set of preparative details are given; the other compounds listed in Table I were prepared in a similar fashion.

Preparation of 5,6,7,8,10,10-Hexachloro-3a,4,4a,5,8,8a,9,9a-octahydro-a-sec-butyl, 1,3-dioxo-5-8-methanobenz(*f*)-isoindoline-2-acetic Acid. In a 250-ml. single-necked, round-bottomed flask equipped with a thermometer and reflux condenser was placed 10.60 grams (0.025 mole) of 1,2,3,4,9,9-hexachloro - 1,4,4a,5,6,7,8,8a - octahydro - 1,4-methanonaphtha-

Table I. 5,6,7,8,10,10-Hexachloro-3a,4,4a,5,8,8a,9,9a-octahydro-α-(2-substituted)-1,3-dioxo-5,8-methanobenz(*f*)-isoindoline-2-acetic Acids

			Percentage Composition									
	Yield,[a] %	M.P., °C.	Carbon		Hydrogen		Chlorine		Nitrogen		Neutral Equivalent	
Substituent, *R*			Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
CH_3—	73	235–236.5	38.74	38.67	2.64	2.73	42.89	42.54	2.82	3.01	496.0	490.0
iso-C_3H_7—	78	264–248	41.25	41.45	3.37	3.31	40.59	40.22	2.67	2.15	524.1	523.5
iso-C_4H_9—	79	284–285	42.41	42.44	3.56	3.57	39.54	39.35	2.60	2.66	534.1	533.0
sec-C_4H_9—	92	260–261	42.41	42.35	3.56	3.51	39.54	39.24	2.60	2.42	534.1	533.0
$CH_3SCH_2CH_2$—	79	239–241	38.87	39.15	3.08	3.18	38.26	37.73	2.53	2.39[b]	556.4	557.0
$C_6H_5CH_2$—	88	278–279.5	46.18	45.90	2.99	2.86	37.19	36.80	2.45	2.29	572.1	571.0
p-$HOC_6H_4CH_2$—	88	258–260	44.93	44.40	2.92	2.93	36.17	36.10	2.38	2.26	588.1	586.1

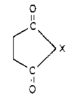
[a] Yields based upon final recrystallized product. [b] Calculated for sulfur, 5.76%; found, 5.79%.

lene-6,7-dicarboxylic anhydride (m.p. 278° C.), 3.28 grams (0.025 mole) of a mixture of L-isoleucine and D-allo-isoleucine, and 50 ml. of dimethylformamide. The slurry was heated with a Glas-Col mantle to reflux, 151–152° C., and was then a clear solution. The reaction mixture was maintained at this temperature for 2 hours, cooled to room temperature, and slowly added with stirring to 500 ml. of an ice water mixture. A white precipitate formed; the mixture was let stand for 12 hours, and was then filtered by suction, and washed with 50 ml. of cold water.

The crude product was dried in a vacuum oven for 16 hours at 100° C. to give 12.9 grams (96%) of material, m.p. 258–260° C. The recrystallization of the crude product from 60 ml. of methyl alcohol gave 12.5 grams (92%) of pure compound, m.p. 260–261° C.

Spectra. Infrared spectra were recorded using a Beckman IR-9 spectrometer in the 400 to 3800 cm.$^{-1}$ region. Solid state spectra were recorded using the mull technique, and the mulling agents used were Nujol (400 to 1333 cm.$^{-1}$) and Fluorolube (1333 to 3800 cm.$^{-1}$). The infrared spectra obtained showed the absence of the original reactants, and these spectra support the structures of the synthesized products. Several bands in the infrared spectrum of each product are useful in characterizing this type of compound, and these characteristic bands are given in Table II.

The two characteristic C=O stretching vibrations in the imide group occur in the 1770 to 1780 and 1700 to 1712 cm.$^{-1}$ regions. The higher frequency band is weak, while the lower frequency band is strong, which is characteristic of the system:

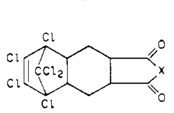


where X is oxygen or nitrogen.

The carbonyl stretching vibration of the carboxylic acid group is not always resolved from the lower frequency imide C=O stretching vibration, but in this case the COOH group can still be verified by the presence of a broad band with subsidiary maxima in the region 2400 to 3400 cm.$^{-1}$, which is characteristic of the the OH stretching vibrations of intermolecularly hydrogen bonded carboxylic acids.

All these compounds show a medium band in the region 1599 to 1607 cm.$^{-1}$, which results primarily from C=C stretching. $\nu_{C=C}$ occurs in a lower frequency region, and the band is relatively more intense than it is for cyclohexene, where $\nu_{C=C}$ occurs at ~1650 cm.$^{-1}$, and the band is relatively weak.

Several bands consistently occur in the 675 to 875 cm.$^{-1}$ region for compounds which contain the



group X = oxygen or nitrogen

and it is expected that vibrations characteristic of carbon-chlorine stretching would occur in this region. Table II lists these characteristic bands, which probably result principally from carbon chlorine stretching vibrations.

Proton NMR spectra were obtained at 60 MHz in pyridine, at 0.5 to 1 molar concentration, with a Varian A-60 spectrometer. Chemical shifts are given as shielding (p.p.m.) relative to internal TMS (tetramethyl silane), at ~1 to 2% concentration.

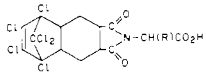
The spectra of the protons assigned to the central cyclohexane ring are essentially the same in all cases. Four absorptions are distinguishable, each of equal area, and consistent with the proposed structures. The structure and placement of the NCH < proton are consistent with the proposed substitution. The absorptions may be described as follows; specific values are listed for the benzyl derivative, where structure was seen best, and there is no interference from the R protons.

Absorption	Chem. Shift, P.P.M. from TMS	Chem. Shift for Benzyl Derivative
A	−1.40 to −1.45	−1.40 ± 0.03
B	−2.50 to −2.53	−2.50 ± 0.03
C	−3.0 ± 0.1	−3.1 ± 0.1
D	−3.21 to −3.46	−3.21 + 0.02
NCH	−4.75 to −5.55	−5.55 ± 0.02

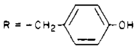
Group A is a triplet (J = 12 to 14 Hz, 13.4 ± 0.4 Hz for benzyl) of broad lines with intensity distorted toward lower field. In some cases, each line is weakly resolved as a doublet (J = 3 to 5 Hz, 3.5 Hz for benzyl). Group B is a doublet (14 to 15 Hz, 14.8 ± 0.2 Hz for benzyl) of broad lines with intensity distorted toward A. Each line usually is resolved weakly as a nominal doublet (3.5 to 6 Hz, 3.8 Hz for benzyl). Group C is a broad multistructured absorption not well defined because the lower shift side is obscured by D. Group D is a single broad line (5 to 7 Hz wide at half peak height) which shows slight tendency toward structure. NCH structure reflects anticipated splitting patterns owing to vicinal protons in all cases. The lines are sharp (≦ 1 Hz wide at half maximum). For R = *sec*-butyl the diastereoisomers are shifted 0.05 p.p.m. apart, each appearing as a 7 Hz doublet. For R = isobutyl the NCH absorption is a pair of doublets, reflecting preferred rotational isomers about the NCH—CH$_2$ bond favorable to moderately different vicinal H—H couplings.

The spectra of the R groups are as anticipated. All methyls are recognized readily, and nonequivalence is seen

Table II. Infrared Absorption Maxima

	$\nu_{C=O}$, Cm.^{1}							
Substituent, R	Imide		Acid	Olefin	Carbon-Chlorine[a], Cm.$^{-1}$			
CH_3—	1774	1712	1697	1607	868m	859wm	773m	689m
iso-C_3H_7—	1780	1709	1697	1607	865m	854w	769m	686m
iso-C_4H_9—	1778	1707	1707	1607	864m	850w	773m	685m
sec-C_4H_9—	1781	1710	1710	1609	868m	853w	771m	688m
$CH_3SCH_2CH_2$—	1776	1707	1707	1603	863m	850w	769m	684m
$C_6H_5CH_2$—	1777	1706	1706	1599	860m	850w	769m	685m
p-$HOC_6H_4CH_2$—	1778	1700	1692	1600	862m	851ww	769m	684m

where anticipated (the shift between α-methyls is 0.31 p.p.m. for isopropyl and 0.26 p.p.m. for *sec*-butyl; the shift between β-methyls is $\sim$0.1 p.p.m. for *sec*-butyl and 0.07 p.p.m. for isobutyl; S—CH_3 is a sharp singlet at −2.00 p.p.m. The benzylic CH_2 protons are a moderately sharp doublet (8.1 ± 0.2 Hz at −3.92 p.p.m.) for benzyl and broad doublet (7 Hz at −3.90 p.p.m.) for *p*-hydroxy benzyl. Other CH and CH_2 protons in the *R* groups are not seen well because of interference by the ring protons. The acid OH proton was seen in the range −13 to −15 p.p.m. For



the combined OH and COOH proton line was at −13.17 p.p.m.

The spectra of the cyclohexane ring protons give strong evidence for trans placement of the rings fused to it and one strongly preferred conformation. This assignment is based on the general first-order splitting features of groups *A* and *B*, and limits may be placed on other intergroup couplings. The poor resolution of these patterns is attributed readily to high complexity arising from strong coupling between vicinal protons at the ring junctures and weaker long range couplings. A complete analysis of the system was not performed; it is unlikely to be very exact and should not affect the resulting structure assignment.

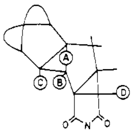
Groups *A* and *B* may be assigned to the CH_2 protons at the prow of the boat form. The distortion of their patterns and common splitting of $\sim$14 Hz is typical of geminal placement, and chemical shifts are reasonable. The *A* protons are assigned as predominantly axial on the basis of their higher shift and implied couplings to *C* and *D* protons—a large coupling to *C* ($\sim$ 12 Hz) and smaller coupling to *D* ($\sim$2 to 4 Hz) suggests trans placement of *C* to *A* and gauche placement of *D* to *A*. This assignment is consistent with the broad pattern of *C* and "narrow" pattern of *D*. Predominantly equatorial placement of *B* is consistent with its lower shift and smaller couplings to both C and *D*.

Protons *C* and *D* are assigned to those at the junctures with the fused rings, but no choice can be made on the basis of their chemical shifts. The placement of protons *C* trans to *A* and gauche to *B*, while protons *D* are gauche to both *A* and *B* implies that the fused ring to which proton *C* belongs must be predominantly equatorial while the fused ring to which protons *D* belongs must be predominantly axial. Therefore, the rings fused to the central cyclohexane ring must be placed trans to one another.

One would anticipate equatorial placement of the bicycloheptene and axial placement of the anhydride rings rather than the converse, because transannular interaction by the planar imide being axial should be less than having the more bulky chlorinated bicycloheptene ring axial. By this argument, protons *C* would be assigned to being at the juncture with the equatorial bicycloheptene ring and protons *D* at the juncture with the imide ring.

No decision is made with respect to placement of the cyclohexane ring on the bicycloheptene ring—i.e., endo or exo to the double bond. The relative constancy of the ring proton pattern throughout this series of compounds is good indication that this placement is the same for all.

In conclusion the tentative structure assignment is



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Some Derivatives of 1,4-Diazabicyclo(2.2.2)octane (Triethylenediamine)

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TRIETHYLENEDIAMINE, or 1,4-diazabicyclo(2.2.2)-octane, was first synthesized in 1942 in low yields by Hromatka (*16*) from the hydrochlorides of the ethanolamines. This cage-type ditertiary amine is characterized by high symmetry, globular structure, high melting point, and contains two exposed nitrogen atoms whose unshared electron pairs are free of steric hindrance. From the unique structure of triethylenediamine stems a number of its interesting chemical, physical, and thermodynamic properties (*13*). The unhindered "lone pair" electrons of the nitrogen atoms of triethylenediamine are responsible for its high nucleophilicity and its catalytic activity in base-catalyzed reactions. With the advent of economical methods of synthesis (*2, 7-9, 17, 18*), triethylenediamine became one of the most efficient (*3, 12, 14, 15, 22*) and most widely used catalysts for the production of urethane foams. The present paper is concerned with some derivatives of triethylenediamine that show the changes in properties and the reactivity of the exposed nitrogen atoms on introducing a methyl group into the triethylenediamine structure.

2-METHYLTRIETHYLENEDIAMINE

Introduction of a methyl group into triethylenediamine destroys its symmetry and produces an asymmetric carbon atom. Thus, 2-methyltriethylenediamine is a liquid in contrast to the more symmetrical triethylenediamine, which is a solid (m.p. 159.8° C.).

2-Methyltriethylenediamine has been synthesized by the catalytic cyclodehydration of hydroxyethylated 2-methylpiperazine (*5, 6*). Purification was accomplished by fractional distillation followed by gas chromatographic separation.

The physical and chemical properties of triethylenediamine and its methyl derivative are compared in Table