Studies on Isoindoline Derivatives and Related Compounds. I Synthesis and Reduction of 1,3-Dicarboethoxymethyleneisoindoline

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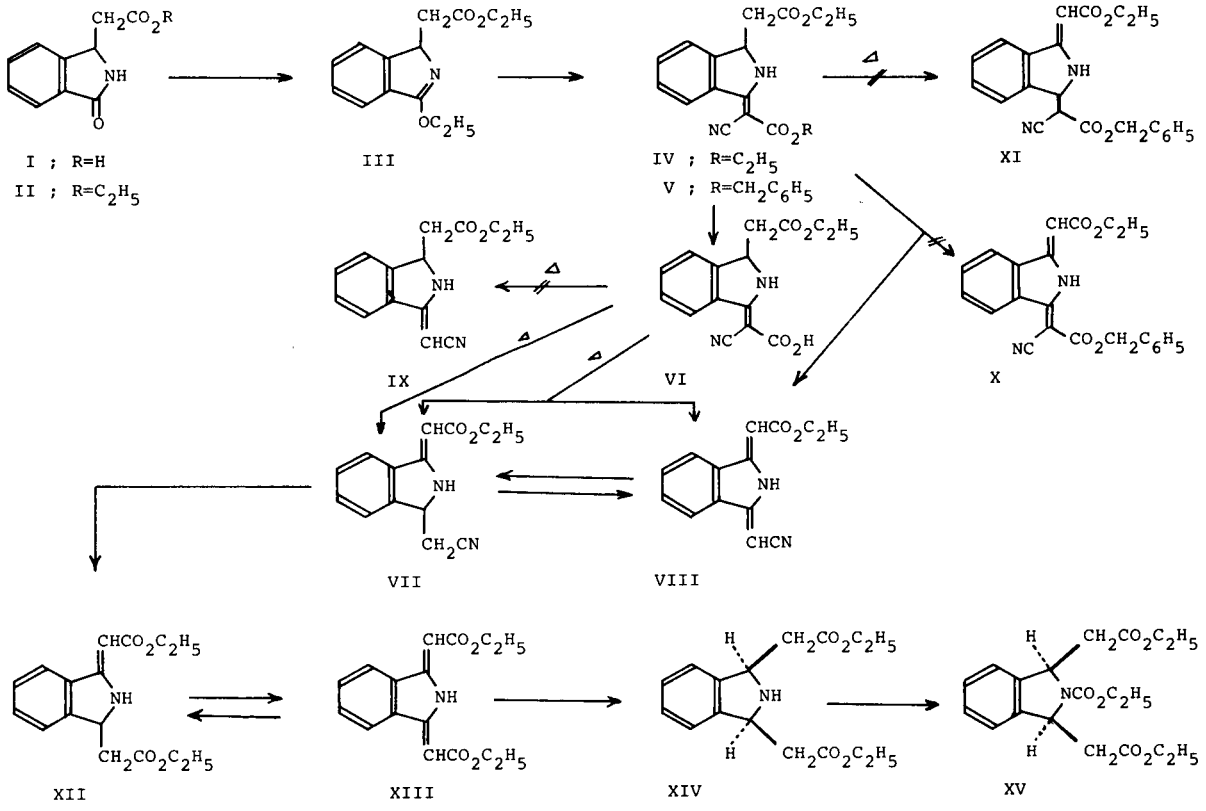
The reaction of iminoether III with benzyl cyanoacetate gave ethyl 1-(α-cyanocarbobenzyloxymethylene)isoindoline-3-acetate (V) in a 26% yield. Decarboxylation of ethyl 1-(α-cyanocarboxymethylene)isoindoline-3-acetate (VI), obtained by hydrogenolysis of V, gave a mixture of 1-carboethoxymethyleneisoindoline-3-acetonitrile (VII) as major component and 1-carboethoxymethylene-3-cyanomethyleneisoindoline (VIII) as minor component, which were reconvertible into each other. On the other hand, decarboxylation of VI was successfully carried out to give VII as a single product under a nitrogen atmosphere. Ethanolysis and autoxidation of VII gave crystalline diethyl 1,3-dicarboethoxymethyleneisoindoline (XIII). Catalytic hydrogenation of of XIII over platinum oxide gave diethyl isoindoline-*cis*-1,3-diacetate (XIV) in a yield of 92%. The uv spectra of these 1,3-disubstituted isoindoline derivatives are summarized in Table I.

Although isoindoline itself can be isolated, neither it nor its derivatives are characterized by great instability unless a stabilizing resonating group is present (1). There are many methods for the preparation of these substances (1,2). Among them, Sugasawa (3) reported the synthesis and electrolytic reduction of benzylphthalimidine, and

Scheme I



Heidenbluth (4) reported the catalytic reduction of 1,3-*bis*benzalisoindoline to 1,3-dibenzylisoindoline. We now wish to report the synthesis and reduction of 1,3-dicarboethoxymethyleneisoindoline (XIII) which has the interesting *bis*-vinylogous urethane system (5).

Treatment of ethyl 1-ethoxyisoindolenine-3-acetate (III), readily obtained from ethyl phthalimidine-3-acetate (II) (6,7), with excess triethyloxonium fluoroborate (8), with ethyl and benzyl cyanoacetates in benzene in the presence of ammonium acetate (9) under reflux for 8 hours gave 32% and 26% yields of ethyl 1-(α-cyanocarboethoxymethylene)isoindoline-3-acetate (IV) and ethyl 1-(α-cyanocarbobenzyloxymethylene)isoindoline-3-acetate (V) respectively. Debenzylation of V by hydrogenolysis yielded ethyl 1-(α-cyanocarboxymethylene)isoindoline-3-acetate (VI), m.p. 153-154°, which was subsequently decarboxylated at ~ 170° to give a 83% yield of a mixture of two components, whose ir spectrum showed no absorption due to $CH_2CO_2C_2H_5$ group. Fractional recrystallization of this mixture gave 1-carboethoxymethyleneisoindoline-3-acetonitrile (VII) as the major product and 1-carboethoxymethylene-3-cyanomethyleneisoindoline (VIII) as the minor product. The ir spectrum of VII exhibited a saturated nitrile band at 2240 cm^{-1} and vinylogous amide bands at 1658, 1618 and 1595 cm^{-1}, whereas that of VIII exhibited an unsaturated nitrile band at 2200 cm^{-1}. Both compounds (VII and VIII) can be easily differentiated by means of their uv spectra as shown in Table I.

Upon heating at 170°, the saturated nitrile VII changed partially to an unsaturated nitrile VIII. Decarboxylation of VI was successfully carried out under a nitrogen atmosphere at ~ 170° to give a saturated nitrile VII as a single product, which was readily dehydrogenated in the presence of 10% palladium-carbon in toluene to VIII. Moreover, since the expected decarboxylation product IX could not be isolated after a careful search, this result demonstrated the proof of migration of the double bond during decarboxylation. It is proposed that the mechanism of formation of VII is by initial formation of IX followed by prototropy to the isoindole IX′ and again by prototropy to form the more stable VII as outlined in Scheme II.

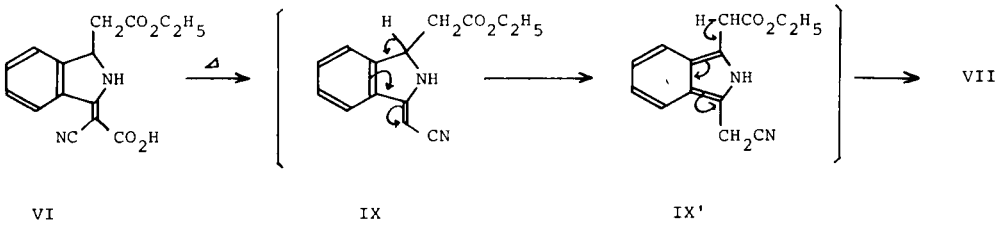
Dehydrogenation of V over large excess of 10% palladium-carbon in refluxing xylene for 10 hours gave VIII in 92% yield with hydrogenolysis and decarboxylation, but 1-(α-cyanocarbobenzyloxymethylene)-3-carboethoxymethyleneisoindoline (X) was not detected. An attempt to prepare 1-(α-cyanocarbobenzyloxymethyl)-3-carboethoxymethyleneisoindoline (XI) from V upon heating at 200° was unsuccessful. The starting material was recovered quantitatively. From these results it can be concluded that compound V is more stable than the structure XI, and compound VII is more stable than the structure IX.

Ethanolysis of VII gave a 85% yield of the oily ethyl 1-carboethoxymethyleneisoindoline-3-acetate (XII), which was gradually dehydrogenated on standing to give crystalline 1,3-dicarboethoxymethyleneisoindoline (XIII), m.p. 134-135°, exhibiting ir absorption bands at ν max (potassium bromide) 3370 cm^{-1} due to the NH group and 1695, 1675, and 1630 cm^{-1} due to the *bis*-vinylogous urethane system, nmr signals (deuteriochloroform) at δ 5.63 (2H, singlet, vinyl protons) 11.46 (1H, broad singlet, NH). The uv spectral data of these 1,3-disubstituted isoindoline derivatives are summarized in Table I.

Next, the behaviors of the reduction of 1,3-*bis*-exomethylene derivatives (VIII and XIII) were investigated. As Heidenbluth (4) had reported, catalytic hydrogenation of 1,3-*bis*-benzalisoindoline gave 1,3-dibenzylisoindoline. Catalytic hydrogenation of VIII over 5% palladium-carbon in methanol gave the saturated nitrile VII selectively in good yield. Accordingly when compound XIII was reduced under the same condition as VIII, the monosaturated ester XII was obtained during a short reaction time. On the other hand, catalytic hydrogenation of XII or XIII over platinum oxide in a mixture of acetic acid and ethanol (1:1) afforded diethyl isoindoline-1,3-diacetate (XIV) as a viscous oil in 92% yield.

1,3-Disubstituted isoindolines have been shown to yield predominantly the *cis*-1,3-disubstituted isoindolines by reduction (10). Bender and Bonnett have reported (11) that *cis* and *trans* isomers of symmetrically 1,3-disubstituted isoindolines such as 1,3,4,7-tetramethylisoindoline can be differentiated by means of nmr spectra of

Scheme II



VI IX IX′

Table I

Absorption Spectra λ max nm (ε x 10^{-3}) in Ethanol

V	251 (3.57)	313 (3.86, sh)	324 (4.16)	339 (3.62, sh)		
VI	248 (3.65)	313 (3.92)	324 (3.99)	340 (3.66, sh)		
VII	241 (3.93)	314 (4.17)	326 (4.19)	341 (3.76, sh)		
VIII	261 (3.48)	271 (3.62)	281 (3.86)	293 (3.86)	360 (4.23)	378 (4.22)
XIII	260 (3.44)	273 (3.75)	282 (4.09)	294 (4.10)	366 (4.24)	386 (4.29)

the 2-benzyl derivative. The 1,3-*cis* isomer shows a singlet for the two methylene protons of the benzyl group, while, the 1,3-*trans* isomer display an AB quartet. To determine the configuration of XIV, we tried to synthesize the corresponding *N*-benzyl derivative, but this was unsuccessful. When XIV was treated with ethyl chloroformate in the presence of triethylamine in tetrahydrofuran, a good yield of diethyl 2-ethoxycarbonylisoindoline-1,3-diacetate (XV) was obtained as a viscous oil. The nmr spectrum of XV provided the necessary information to provide the configurational assignment as the 1,3-*cis* isomer. The nmr spectra of XV have been recorded in deuteriochloroform and are shown in Figure I: δ 1.26 (6H, triplet) and 4.20 (4H, quartet) due two symmetrical $CO_2CH_2CH_3$ groups, δ 1.33 (3H, triplet) and 4.25 (2H, quartet) due to $>N\text{-}CO_2CH_2CH_3$, δ 2.46-3.32 (4H, multiplet, AB part of ABX pattern) and δ 5.45 (2H, quartet, X part of ABX pattern) due to two symmetrical $CHCH_2$ group.

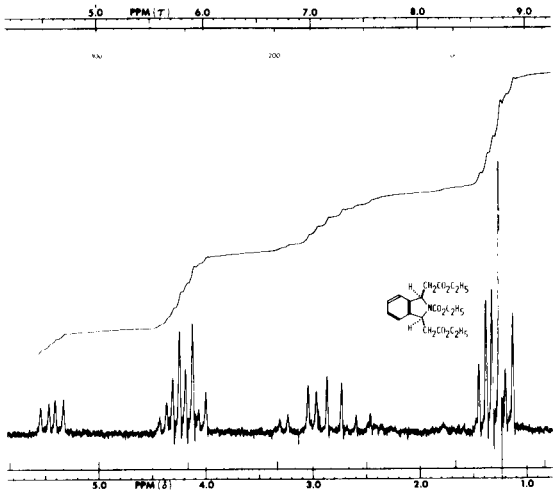
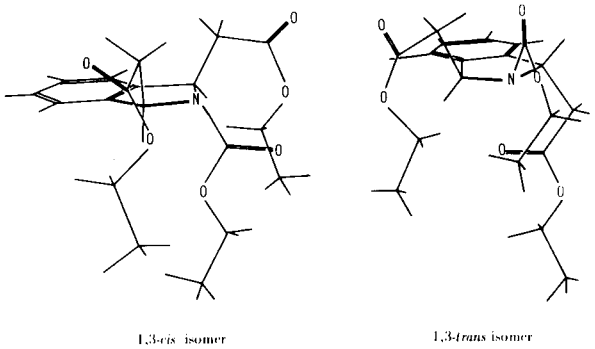


Figure I. 60 MHz of XV in deuteriochloroform solution.

Since the 1,3-*cis* isomer has a plane of symmetry, the observed nmr spectrum can be rationalized. If a 1,3-*trans* configuration were to be assigned, the two $CH_2CO_2C_2H_5$ groups become chemically nonequivalent, because by a study of the Dreiding models the $>N\text{-}CO_2C_2H_5$ group has an effect on the methyl or the methine protons situated on the same side (distance *ca.* 2.3 Å) as shown in Figure II.



1,3-*cis* isomer 1,3-*trans* isomer

Figure II. Stereostructure of 1,3-*cis* and *trans* Diethyl 2-Etoxycarbonylisoindoline-1,3-diacetate.

EXPERIMENTAL

All melting and boiling points are uncorrected. The ir and uv spectra were taken with JASCO Model IRA-1 and Schimadzu UV-200 spectrophotometers. The nmr spectra were measured, using tetramethylsilane as the internal standard, with Varian A-60 spectrometer. The mass spectrometric analyses were determined with Hitachi Mass Spectrometer RMU-7L.

Ethyl 1-Ethoxyisoindolenine-3-acetate (III).

To a solution of ethyl phthalimidine-1-acetate (II) (87.6 g., 0.3 mole) in dichloromethane (400 ml.) was added dried triethyloxonium tetrafluoroborate, prepared from epichlorohydrin (75 g.) and borontrifluoride etherate (150 g.) in anhydrous ether (200 ml.) under ice cooling. The clear solution was heated at 45° for 10 hours and then made basic by the addition of 5*N* potassium carbonate solution under ice cooling. The dichloromethane solution was separated and the aqueous layer was extracted with dichloromethane. The combined extracts were washed with water, dried (magnesium sulfate) and evaporated. The residual oil was distilled under reduced pressure to give pale yellow oil (85 g.) (86%) of III, b.p. 140-143°/3 mm; ir ν max (chloroform): 1730 ($CO_2C_2H_5$), 1622, 1600, 1595 cm^{-1}; nmr δ (deuteriochloroform): 1.26 and 1.46 (each 3H, each t, J = 8 Hz, CH_3), 2.3-3.2 (2H, m, AB part of ABX pattern, CH_2), 4.23 and 4.53 (each 2H,

each q, J = 8 Hz, CH_2), 5.12 (1H, q, X part of ABX pattern, C_3-H).

Anal. Calcd. for $C_{14}H_{17}NO_3$: C, 67.99; H, 6.93; N, 5.66. Found: C, 68.11; H, 7.07; N, 5.36.

Ethyl 1-(α-Cyanocarboethoxymethylene)isoindoline-3-acetate (IV).

A mixture of III (4.94 g., 0.02 mole), ethyl cyanoacetate (4.5 g., 0.04 mole) and ammonium acetate (1.0 g.) in benzene (30 ml.) was refluxed for 8 hours. After cooling, the mixture was washed with water, dired (magnesium sulfate) and evaporated. The residual oil was dissolved in methanol (5 ml.) and the solution was allowed to stand in a refrigerator for two days. The needles which separated were collected by filtration, washed with cold methanol and dried (2.01 g.) (32%). Recrystallization from ethanol gave pale brown needles, m.p. 135-137°; ir ν max (potassium bromide): 3390 (NH), 2200 (CN), 1730 ($CO_2C_2H_5$), 1660, 1600 and 1585 cm^{-1}; nmr δ (deuterichloroform): 2.20-3.30 (2H, m, AB part of ABX pattern), 5.20 (1H, m, X part of ABX pattern); mass spectrum: m/e 314 (M^+).

Anal. Calcd. for $C_{17}H_{18}N_2O_4$: C, 64.95; H, 5.77; N, 8.91. Found: C, 64.92; H, 5.58; N, 8.69.

Ethyl 1-(α-Cyanocarbobenzyloxymethylene)isoindoline-3-acetate (V).

The reaction of III (49.4 g., 0.2 mole) with benzyl cyanoacetate (70.0 g., 0.4 mole) in the presence of ammonium acetate (10 g.) in benzene (300 ml.) in a similar manner as in the case of IV afforded an oil, which was dissolved in methanol (50 ml.). After standing in refrigerator for two days, the needles which separated were collected by filtration, washed with cold methanol and dried (16.7 g.) (22%). Concentration of the filtrate to half volume and allowing to stand in the refrigerator for a few days gave an additional crop of V (3.1 g.) (4%). The total yield was 26%. Recrystallization from methanol gave pale yellow needles, m.p. 126-127°; ir ν max (potassium bromide): 3390 (NH), 2200 (CN), 1725 ($CO_2C_2H_5$), 1665, 1600 and 1580 cm^{-1}; nmr δ (deuteriochloroform): 1.30 (3H, t, J = 8 Hz, CH_3), 1.65 (1H, s, NH exchanged with deuteriowater), 2.73 (2H, m, AB part of ABX pattern, CH_2), 4.26 (2H, q, J = 8 Hz, CH_2), 5.15 (1H, q, X part of ABX pattern, C_3-H), 5.31 (2H, s, Ph-CH_2), 8.68 (1H, broad d, J = 7 Hz, C_7-H); mass spectrum: m/e 376 (M^+).

Anal. Calcd. for $C_{22}H_{20}N_2O_4$: C, 70.20; H, 5.36; N, 7.44. Found: C, 70.09; H, 5.41; N, 7.39.

Ethyl 1-(α-Cyanocarboxymethylene)isoindoline-3-acetate (VI).

To a solution of V (3.76 g., 0.01 mole) in methanol (600 ml.) was added 10% palladium-carbon (0.8 g.) and the mixture was subjected to catalytic hydrogenation at atmospheric pressure. After shaking for 15 hours, the catalyst was filtered off and the filtrate was evaporated to dryness under reduced pressure to give a brown solid, which was decolorized by washing with a small amount of cold chloroform. The yield of crude material was 83%. Recrystallization from methanol afforded colorless needles of VI, m.p. 153-154° dec.; ir ν max (potassium bromide); 3390 (NH), 2200 (CN), 1740 ($CO_2C_2H_5$), 1645, 1595 cm^{-1}; nmr δ (deuteriodimethylsulfoxide): 1.18 (3H, t, J = 7 Hz, CH_3), 2.70-3.40 (2H, m, AB part of ABX pattern, CH_2), 4.11 (2H, q, J = 7 Hz, CH_2), 5.26 (1H, m, X part of ABX pattern, C_3-H), 10.30 (1H, broad s, NH exchanged with deuteriowater).

Anal. Calcd. for $C_{15}H_{14}N_2O_4$: C, 62.93; N, 4.93; N, 9.79. Found: C, 62.82; H, 5.10; N, 9.73.

Decarboxylation of VI.

(a)

The flask containing VI (2.86 g., 0.01 mole) was heated in an oil bath at 160-170° until foaming ceased. The resultant resinous material was digested with ethanol to give a pale yellow solid, which was recrystallized from ethanol affording colorless needles of 1-carboethoxymethyleneisoindoline-3-acetonitrile (VII) (1.48 g.) (61%), m.p. 153-154°; ir ν max (potassium bromide): 3390 (NH), 2240 (CN), 1658, 1618 and 1595 cm^{-1}; nmr δ (deuteriochloroform): 1.30 (3H, t, J = 8 Hz, CH_2), 2.50-3.20 (2H, m, AB part of ABX pattern, CH_2), 4.20 (2H, q, J = 8 Hz, CH_2), 5.10 (1H, m, X part of ABX pattern, C_3-H), 7.62 (1H, s, C = CH); mass spectrum: m/e 242 (M^+).

Anal. Calcd. for $C_{14}H_{14}N_2O_2$: C, 69.40; H, 5.87; N, 11.56. Found: C, 69.13; H, 5.87; N, 11.81.

From the filtrate was obtained 1-carboethoxymethylene-3-cyanomethyleneisoindoline (VIII) (0.51 g.) (21%), m.p. 178-180°, as pale yellow needles, which were recrystallized from ligroin; ir ν max (potassium bromide): 3390 (NH), 2200 (CN), 1670 and 1625 cm^{-1}; nmr δ (deuteriochloroform): 1.35 (3H, t, J = 8 Hz, CH_3), 4.26 (2H, q, J = 8 Hz, CH_2), 4.95 (1H, s, CHCN), 5.65 (1H, s, $CHCO_2C_2H_5$).

Anal. Calcd. for $C_{14}H_{12}N_2O_2$: C, 69.99; H, 5.03; N, 11.66. Found: C, 70.16; H, 5.27; N, 11.93.

(b) Under a Nitrogen Atmosphere.

The decarboxylation of VI (2.86 g., 0.01 mole) under a nitrogen atmosphere at ~ 170° gave resinous material (showed one spot on tlc), which was digested with ethanol to give a pale yellow solid. Recrystallization from ethanol gave colorless needles of VII (1.70 g.) (86%), which was identical with the authentic VII by comparison of their ir spectra and mixed melting point determination.

Dehydrogenation of VII to VIII.

To a solution of VII (121 mg., 0.0005 mole) in toluene (10 ml.) was added 10% palladium-carbon (150 mg.) and the mixture was refluxed for 3 hours. After the palladium-carbon was filtered off, the filtrate was evaporated under reduced pressure to give a brown solid. Recrystallization from ligroin afforded VIII (98 mg.), m.p. 178-180°, which was identical with authentic VIII by comparison of their ir spectra and mixed melting point determination.

Catalytic Hydrogenation of VIII to VII.

To a solution of VIII (120 mg., 0.0005 mole) in ethanol (10 ml.) was added 5% palladium-carbon (50 mg.) and the mixture was subjected to catalytic hydrogenation and worked up in the usual manner to give VII (84 mg.), m.p. 153-154°, which was identical with the authentic VII by comparison of their ir spectra and the mixed melting point determination.

Treatment of V with 10% palladium-carbon in Xylene.

To a solution of V (125 mg., 0.00033 mole) in xylene (10 ml.) was added 10% palladium-carbon (0.5 g.) and the mixture was refluxed for 12 hours. After the palladium-carbon was filtered off, the filtrate was evaporated under reduced pressure to give solid VIII (73 mg.) (92%), which was identical with authentic VIII by comparison of their ir spectra and mixed melting point determination.

1,3-Dicarboethoxymethyleneisoindoline (XIII).

To a solutionof VII (2.42 g., 0.01 mole) dissolved in absolute ethanol (200 ml.) was dry hydrogen chloride gas saturated under ice cooling. The mixture was allowed to stand over night and then refluxed until the evolution of gas had ceased. After evaporation

of the solvent, the residual oil was dissolved in chloroform. The chloroform solution was washed with saturated sodium carbonate solution, water, dried (magnesium sulfate) and evaporated to give a pale pink oil of XII (2.37 g.) (82%); ir ν max (chloroform): 3420 (NH), 1730 ($CO_2C_2H_5$), 1660, and 1610 cm^{-1}; nmr δ (deuteriochloroform): 2.20-3.20 (2H, m, AB part of ABX pattern, CH_2), 5.20 (1H, m, X part of ABX pattern), 7.45 (1H, s, C = CH), 8.48 (1H, broad s, NH exchanged with deuteriowater); mass spectrum: 289 (M^+). This compound was gradually autoxidized on standing to yield crystalline XIII. Recrystallization from ligroin gave dark violet needles (2.14 g.) (74% from VII), m.p. 134-135°; ir ν max (potassium bromide): 3370 (NH), 1695, 1675, and 1630 cm^{-1}; nmr δ (deuteriochloroform): 1.63 (6H, t, J = 8 Hz, 2 x CH_3), 4.31 (4H, q, J = 8 Hz, 2 x CH_2), 5.63 (2H, s, 2 x C = CH), 11.46 (1H, broad s, NH); mass spectrum: m/e 287 (M^+).

Anal. Calcd. for $C_{16}H_{17}NO_4$: C, 66.88; H, 5.96; N, 4.88. Found: C, 66.83; H, 6.13; N, 5.10.

Catalytic Hydrogenation of XIII.

(a) Over 5% palladium-Carbon

To a solution of XIII (140 mg.) (0.0005 mole) in ethanol (10 ml.) was added 5% palladium-carbon (50 mg.) and the mixture was hydrogenated and worked up in the usual manner to give an oil, which was identical with authentic XII by comparison of their ir spectra.

(b) Over Platinum Oxide.

To a solution of XIII (2.87 g.) (0.01 mole) in 50 ml. of the mixture of acetic acid and ethanol (1:1) was added platinum oxide (0.5 g.) and the mixture was subjected to catalytic hydrogenation at an initial pressure of 10 pounds in the Paar apparatus. After shaking for 5 hours, the catalyst was filtered off and the filtrate was evaporated under reduced pressure to yield an oil, which was distilled to give a colorless oil of diethyl isoindoline-1,3-diacetate (XIV) (2.65 g.) (92%), b.p. 130-135° (bath temperature)-2 mm, which failed to give a crystalline salt; ir ν max (chloroform): 1730 ($CO_2C_2H_5$) cm^{-1}; nmr δ (deuteriochloroform): 1.35 (6H, t, J = 8 Hz, 2 x CH_3), 2.35-3.20 (2H, m, AB part of ABX pattern, 2 x CH_2), 2.90 (1H, s, NH exchanged with deuteriowater), 4.27 (4H, q, J = 8 Hz, 2 x CH_2), 4.90 (2H, X part of ABX pattern 2 x CH).

Anal. Calcd. for $C_{16}H_{21}NO_4$: C, 65.95; H, 7.27; N, 4.81. Found: C, 66.22; H, 7.40; N, 4.90.

Diethyl 2-Ethoxycarbonylisoindoline-1,3-diacetate (XV).

A mixture of XIV (2.91 g., 0.01 mole), ethyl chloroformate (2.16 g., 0.02 mole) and triethylamine (2.0 g., 0.02 mole) in anhydrous tetrahydrofurane (10 ml.) was kept at room temperature for two days. The mixture was made basic by the addition of 10% sodium carbonate solution and extracted with chloroform. The extract was washed with water, dried (magnesium sulfate) and evaporated under reduced pressure to yield viscous oil, which was distilled to give colorless oil of XV (2.7 g.) (74%), b.p. 150-155° (bath temperature)/1 mm; ir ν max (chloroform): 1735 ($CO_2C_2H_5$), 1695 (N-$CO_2C_2H_5$) cm^{-1}; mass spectrum: m/e 363 (M^+).

Anal. Calcd. for $C_{19}H_{25}NO_6$: C, 62.79; H, 6.93; N, 3.85. Found: C, 62.94; H, 7.25; N, 4.01.

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