further 30 h. Extractive workup as described gave the 1-carboxy complex (19.8 g, 95%).

Resolution of the 1-CO_2H Complex (2, R = H or ^2H, R′ = H). (−)-1-Phenylethylamine (9.5 mL, 75 mmol) was added dropwise to a stirred solution of the acid (19 g, 72 mmol) in chloroform and acetone (3:1, 400 mL). After 30 min the precipitate was collected and washed with chloroform. The washings and filtrate were set aside. Recrystallization twice from chloroform of the precipitate gave a pure diastereomer (7.4 g), $[\alpha]^{25}_D$ +68° (acetone, *c* 1). The combined washings and filtrate were concentrated and cooled at 0 °C overnight to give a second crop (6.2 g), $[\alpha]^{25}_D$ −95° (acetone, *c* 0.1), which after a further recrystallization from chloroform provided a second pure diastereomer (3.3 g), $[\alpha]^{25}_D$ −126° (acetone, *c* 0.1). Repetition of the above crystallization procedure on combined washings and filtrates provides a further 0.4 g of pure (+)-isomer and 2.6 g of pure (−)-isomer.

The separated diastereomeric phenylethylammonium salts were each dissolved in EtOH containing 2 M HCl (aq). The solution was partitioned between ether and water, the organic phase was separated and washed with 2 M HCl (aq) and water, and then dried and evaporated to give the corresponding acids in quantitative yield. The (−)-salt gave the (−)-acid $[\alpha]^{25}_D$ −136° (*c* 0.1, acetone). Spectral data were as already reported.[11] The absolute configuration of this isomer is as shown in the text and is 1*S*.

((1*S*)-1-Carbomethoxycyclohexadienylium)iron Hexafluorophosphate (3, R = H). An ether solution of the (−)-acid (2.2 g in 20 mL) was treated with diazomethane (0.5 g) in ether (30 mL) at room temperature for 30 min. Formic acid (0.5 mL) was added to destroy any excess CH_2N_2. Evaporation gave the 1*S* ester as a yellow oil which was purified by column chromatography (silica gel, 10% EtOAc in hexane): 2.3 g (100%); $[\alpha]^{25}_D$ −115° (*c* 0.3, $CHCl_3$). Spectral data were as reported for the racemic material.[11]

A solution of this ester (2.2 g) in dry hexane (10 mL) was added dropwise with constant swirling to a solution of trityl hexafluorophosphate (4 g) in dry CH_2Cl_2 (35 mL). Any precipitate forming during the addition was redissolved by using a minimum volume of CH_2Cl_2. After standing 3 h the orange precipitate was collected and washed with reagent-grade ether. The solid was purified by precipitation with ether of an acetone solution to give the pure salt: 2.4 g (73%); $[\alpha]^{25}_D$ −162° (*c* 0.3, acetone). Unreacted starting material (ca. 16%) was recovered.

[(1*S*,5*S*)-1-Carbomethoxy-5-[(*tert*-butoxycarbonyl)amino]cyclohexadiene]iron (4, R = H). To a stirred mixture of the (−)-1-CO_2Me salt (2 g) and *tert*-butyl carbamate (1.21 g) in CH_2Cl_2 (10 mL) at 0 °C was added dropwise diisopropylethylamine (0.86 mL). The resultant clear yellow solution was stirred for 5 min and then diluted with hexane (20 mL). Filtration then solvent removal left an oily solid which was heated in vacuo (50–60 °C, 0.1 torr) to remove excess *tert*-butyl carbamate. Chromatography over silica gel (15% EtOAc in hexane) gave the complex as a yellow oil, 1.5 g (81%). A sample was recrystallized from hexane: mp 116–118 °C; ^1H NMR ($CDCl_3$) 6.2 (d, *J* = 4 Hz, 1 H), 5.4 (t, *J* = 4 Hz, 1 H), 4.3 (m, 2 H), 3.68 (s, 3 H), 3.3 (m, 1 H), 2.82 (dd, *J* = 16, 10 Hz), 1.22 (s, 9 H), 1.1 (br d, *J* = 16 Hz, 1 H); IR ($CHCl_3$) 2065, 2000, 1710 cm^{-1}; MS, *m/e* (relative intensity) 393 (M^+) (2), 365 (5), 337 (16), 309 (39), 253 (45), 193 (82), 134 (89), 105 (100); $[\alpha]^{25}_D$ −52° (*c* 0.2, $CHCl_3$). Anal. Found: C, 48.7; H, 4.8; N, 3.4; Fe, 14.0. Calcd for $C_{16}H_{19}FeNO_7$: C, 48.9; H, 4.9; N, 3.6; Fe, 14.2%.

(5*S*)-5-[(*tert*-Butoxycarbonyl)amino]cyclohexadienecarboxylic Acid (5, R = R′ = H). The complex from above (1 g) was dissolved in dimethylacetamide (10 mL) and the solution was cooled to −10 °C before adding trimethylamine *N*-oxide dihydrate (3 g). The mixture was stirred at this temperature for 3 h and then at 0 °C overnight. The crude diene ester was obtained following filtration (Celite) and extractive workup. ^1H NMR of the product showed the presence of about 10–15% aromatic material. Methanol (5 mL) and 2 M NaOH (2.5 mL) were added to this compound without further purification. After being stirred for 2.5 h, the solution was acidified with 2 M HCl and the acid collected. The acid was obtained as a white solid after recrystallization from ether–hexane: 0.4 g (66%); mp 147–149 °C (lit.[5] 147–148 °C); ^1H NMR ($CDCl_3$) 7.15 (m, 1 H), 6.16 (m, 2 H), 4.55 (br, ca. 2 H, [NH]), 2.68 (dd, *J* = 7, 2 Hz, 2 H), 1.45 (s, 9 H); MS, *m/e* (relative intensity) 237 (M^+ − 2) (5), 183 (20), 137 (28), 122 (35), 57 (100); IR ($CHCl_3$) 1720 cm^{-1}; $[\alpha]^{25}_D$ −249° (*c* 0.1, $CHCl_3$).

(5*S*)-5-Aminocyclohexa-1,3-dienecarboxylic Acid (Natural Gabaculine; 6, R = H). This was prepared from the *t*-BOC derivative above as previously described.[5] The spectral data were exactly as described in the literature: $[\alpha]^{25}_D$ −395° (*c* 0.05, H_2O)[20] [(lit. $[\alpha]$ −454° (*c* 1, H_2O)].

Preparation of Deuterated Compounds. Deuterium was incorporated specifically into the 6β-position of the (±)-1-CO_2Me complex as described.[11] However, in the case of the resolved complex some racemization was observed (ca. 15% at 70% $^2H_1$ incorporation). Fully resolved, deuterium-labeled gabaculine was therefore obtained by performing the optical resolution on the (±)-6β-^2H-acid obtained from the corresponding ester (2, R′ = Me, R = ^2H) by D_2SO_4/D_2O hydrolysis.[11] Deuterium levels at the 6β-position could be raised to about 95% by carrying out the sequence two or more times, but this procedure led to increased (up to 35%) ^2H incorporation at C-5β. Deuterium levels were assessed from ^1H NMR and MS spectra, after allowing for natural abundance contributions. A large isotope effect operates in the deuterium sequence and attempts were made to exclude proton sources. Key differences in the ^1H NMR spectra of the labeled compounds are as follows: **2**, see ref 11; **4**, δ 2.82 reduced and 1.1 now a broad singlet; **5**, δ 2.68 now a broad singlet with reduced integration value; **6**, δ 2.7 now a broad singlet with reduced integration value.

Registry No. **2** (R = R′ = H), 51539-46-9; **2** (R = D, R′ = H), 90149-63-6; (+)-**2** (R = R′ = H) (−)-1-phenylethylamine salt, 90242-12-9; (−)-**2** (R = R′ = H) (−)-1-phenylethylamine salt, 75800-57-6; (−)-**2** (R = R′ = H), 75765-30-9; (+)-**2** (R = R′ = H), 75765-29-6; (−)-**2** (R = H, R′ = Me), 90242-13-0; (−)-**3** (R = H), 90242-15-2; (−)-**4** (R = H), 90149-64-7; (−)-**4** (R = D), 90149-65-8; (−)-**5** (R = R′ = H), 90242-16-3; (−)-**5** (R = D, R′ = H), 90171-27-0; (−)-**6** (R = H), 59556-29-5; (−)-**6** (R = D), 90171-28-1; H_2NCO_2-*t*-Bu, 4248-19-5; tricarbonyl(2-carbomethoxycyclohexa-1,3-diene)iron, 51539-41-4.

(20) Contaminated with 6–7% *m*-anthranilic acid.

2 + 2 Cycloaddition of 4-Substituted-1,2,4-triazoline-3,5-diones to Diphenylketene

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Staudinger reported over 70 years ago that diphenylketene under went 2 + 2 cycloaddition with azobenzene.[1,2] It was found that the reaction with the trans isomer was very slow even at elevated temperature, but the *cis* isomer reacted rapidly at room temperature to give 1,2,4,4-tetraphenyl-1,2-diazetidine-3-one.[3] The reaction has been investigated by a number of other workers[3-7] and it has been postulated that it proceeds by a $_2\pi_s + _2\pi_a$ concerted pathway. The main evidence seems to be the almost total lack of regioselectivity in the addition of unsymmetrically

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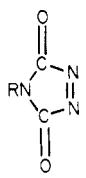
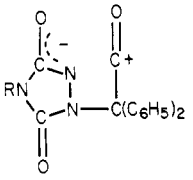
substituted azobenzenes to diphenylketene and the rather small solvent effect on the reaction.[7] Taylor found the *cis*-azobenzene also reacted with ketene and dimethylketene.[8] Arylazo cyanides[10] and arylazo esters[4,9] also undergo rapid 2 + 2 cycloaddition to diphenylketene. Isomerization to the cis isomer is apparently not necessary in these cases. In contrast, the addition of azodicarboxylate esters,[4,11] vinylazobenzenes,[12] and acetylazobenzenes[13] all give mixtures of 2 + 2 and 2 + 4 cycloaddition. In those cases where the geometry of the azo group has been held cis and reacted with ketenes, 1:2 (azo:ketene) adducts have usually been formed. For example dimethylketene gives a 1:2 adduct with cinnolines,[14] and diphenylketene and dimethylketene give 1:2 adducts with 2,3-diazabicyclo-[2.2.1]hept-2-ene.[8] The above cases contrast with the report of Reid and Kahr[15] that benzodiazines give 2 + 2 cycloadducts.

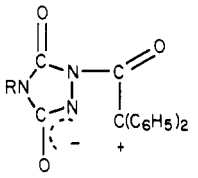
The above results on azo compounds with cis geometry suggested to us that it might interesting to examine the reaction of 4-substituted-1,2,4-triazoline-3,5-diones **1** (R-TAD's) with diphenylketene to see if 2 + 2 cycloaddition



1a, R = CH_3
b, R = C_2H_5
c, R = n-C_3H_7
d, R = n-C_4H_9
e, R = C_6H_5



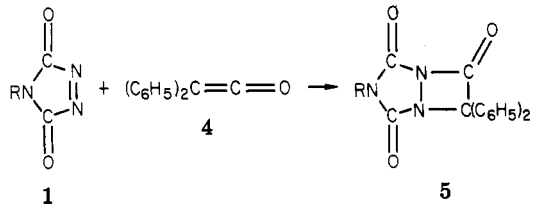
2



3

is observed or whether 1:2 adducts are formed. Since the 1:2 adducts cannot be formed by a concerted pathway, the observation of such an adduct is proof of an open-chain intermediate. Also, since R-TAD's are known to react with electron-rich alkenes to give 1,4-dipolar intermediates,[16] there seemed to be a good possibility that intermediates such as **2** or **3** might be involved in the reaction.

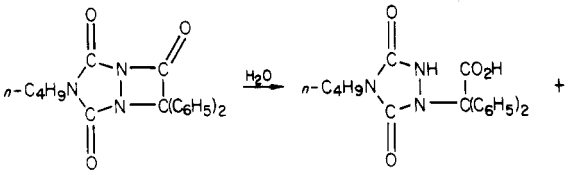
Methyl-TAD (**1a**) dissolved in methylene chloride was added dropwise to a solution of diphenylketene in methylene chloride at 0 °C. With this mode of addition, the chance for formation of 1:2 adducts would be maximized since the diphenylketene would be in excess during the reaction. As the azo compound was added, the red color was discharged instantaneously. One mole of diphenylketene decolorized exactly 1 mol of the R-TAD, indicating clearly a 1:1 stoichiometry. Evaporation of the solvent gave a solid which was purified by recrystallization from nitroethane to give pure solid **5a**. The elemental analysis indicated clearly that the product was a 1:1 adduct. The IR gave the expected peaks for the urazole carbonyls at 1735 and 1785 cm^{-1} and a peak at 1852 cm^{-1} for the 1,2-diazetidin-3-one carbonyl. The ^1H NMR showed a singlet for the methyl group at 2.96 ppm and sharp peak at 7.3 ppm for the ten aromatic protons. Examination of the ^1H



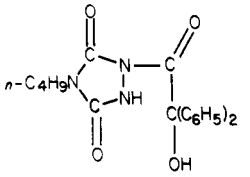
1 **4** **5**

NMR of the crude product in the reaction and comparison with the ^1H NMR of the purified material indicated clearly that **5a** was the only product in the reaction; i.e., the reaction was essential quantitative.

The above procedure was repeated by using ethyl-TAD and *n*-propyl-TAD with essentially the same result. When *n*-butyl-TAD was used, the ^1H NMR indicated that **5d** was formed quantitatively. However, it was a viscous oil, so it was allowed to stand at room temperature and exposed to the air for 4 months in hope that it might decide to crystallize. Instead, it absorbed moisture from the air and hydrolyzed to give a mixture of **6** and **7**, isolated in 25% and 6% yields, respectively. The structure of **6** was based



5d **6**



7

on it elemental analysis, its solubility in 5% sodium bicarbonate, its IR which exhibited a broad band at 3150 cm^{-1} (NH, OH) and carbonyl bands at 1770 and 1728 cm^{-1} (urazole C=O's) and at 1711 and 1664 cm^{-1} (carboxyl C=O free and H bonded), and its ^1H NMR which had peaks at δ 0.81, (3 H, t), 1.0–1.5 (4 H, m), 3.32 (2 H, t), 7.2–7.6, (10 H, m), 8.9 (1 H, v br), and 10.2 (1 H, v br). The structure of **7** was based on elemental analysis, its insolubility in sodium bicarbonate, its solubility in 5% sodium hydroxide, its IR which showed the expected peaks at 3295 (OH, NH) and at 1810, 1785, and 1712 (C=O's), and its ^1H NMR which exhibited peaks at δ 0.77 (3 H, t), 1.2 (4 H, m), 3.26 (3 H, t), and 7.26 (10 H, m). The NH and OH in the NMR are apparently too broad to be seen, but the IR peak and base solubility clearly indicate their presence.

When phenyl-TAD was reacted with diphenylketene, the methylene chloride solution of diphenylketene was added dropwise to the phenyl-TAD solution. As the last drop was added the phenyl-TAD solution changed from red to colorless, once again showing an exact 1:1 molar ratio, the reaction being quantitative. The expected carbonyl peaks at 1860 cm^{-1} (diazetidinone C=O) and at 1730 and 1782 cm^{-1} (urazole C=O's) were observed. The ^{13}C NMR showed the carbonyls at 148.7 ppm (diazetidinone) and at 157.1 and 164.7 ppm (urazole) as well as the carbon next to the diazetidine carbonyl at 95.8 ppm.

The lack of 1:2 adducts in these reactions does of course not exclude dipolar intermediates **2** or **3**. Since 1,4-dipoles derived from R-TAD's and alkenes have been trapped by acetone,[16] we tried running the reaction in acetone. However, none of the acetone was incorporated in the product. We also tried running the reaction in anisole in

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an effort to trap the acylium ion **2**. This was also unsuccessful. No ketones were formed in the reaction.

The formation of the two hydrolysis products **6** and **7** is rather intriguing. Although **6** probably results from direct nucleophilic attack of water on the carbonyl of **5d**, the formation of **7** by an S_N2 pathway seems unlikely due to the fact that backside attack is highly hindered. It seems most likely that **7** arises from the dipolar intermediate **3**, i.e., perhaps the diazetidinone **5** may be in equilibrium with trace amounts of the 1,4-dipole **3**.

Experimental Section

All melting and boiling points are uncorrected. The infrared spectra were recorded on a Perkin-Elmer 197 spectrophotometer. The ^1H NMR spectra were recorded on a Perkin-Elmer R32 (90 MHz) spectrometer. The ^{13}C NMR spectra were recorded on a Nicolet NT-200 FT-NMR spectrometer. Microanalysis were performed by Gailbraith Laboratories, Knoxville, TN.

The 4-substituted-1,2,4-triazoline-3,5-diones were prepared by oxidation of the corresponding urazoles with *N*-bromosuccinimide.[18] The 4-alkyl-TAD's were purified by sublimation prior to use and the phenyl-TAD was recrystallized from methylene chloride at −10 °C.

General Procedure. In 10 mL of spectroscopic grade methylene chloride was dissolved 0.002 mol of the R-TAD. This was added dropwise with stirring to a solution of 0.002 mol of diphenylketene in methylene chloride at 0–5 °C. In the case of phenyl-TAD, the reverse addition was used. After the addition was complete, the solvent was removed under vacuum. The reaction was essentially quantitative. Analytical samples were prepared by recrystallization with recovered yields in the range of 49–54%. The product from diphenylketene and *n*-butyl-TAD was a viscous oil. IR, ^1H NMR, melting points, recrystallization solvent, and ^{13}C NMR data are given below. Satisfactory elemental analyses were obtained for **5a**, **5b**, **5c**, and **5e**; **5d** was not analyzed.

Compound **5a**: IR (Nujol) 1852, 1785, 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.96 (s), 7.3 (m); mp 155–156 °C (from nitroethane); ^{13}C NMR ($CDCl_3$) δ 149.8 (C_1), 94.5 (C_2), 164.5 (C_3), 158.3 (C_4), 133.0, 130.1, 129.0, 127.3 (aryls), 26.6 (CH_3).

Compound **5b**: IR (Nujol) 1860, 1789, 1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.08 (t), 3.48 (q), 7.41 (m); mp 114–115 °C (from ether); ^{13}C NMR ($CDCl_3$) δ 149.7 (C_1), 94.8 (C_2), 164.9 (C_3), 158.2 (C_4), 133.0, 130.1, 129.0, 127.4 (aryls), 13.0 (CH_3), 36.3 (CH_2).

Compound **5c**: IR (Nujol) 1855, 1785, 1725 cm^{-1}; ^1H NMR δ 0.65 (t), 1.47 (m), 3.37 (t), 7.42 (m); mp 101–102 °C (from ether); ^{13}C NMR ($CDCl_3$) δ 149.8 (C_1), 94.7 (C_2), 164.8 (C_3), 158.4 (C_4), 133.1, 130.0, 129.1, 127.1 (aryls), 11.1 (CH_3), 20.8 (CH_2), 42.8 (CH_2N).

Compound **5d**: IR (neat) 1852, 1780, 1732 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 0.84 (t), 1.4 (m), 3.41 (t), 7.40 (m); viscous ligand.

Compound **5e**: IR (Nujol) 1860, 1782, 1730 cm^{-1}; ^1H NMR ($CHCl_3$) δ 7.45 (m); mp 170–172 °C dec (from ethyl acetate); ^{13}C NMR ($CHCl_3$) δ 148.7 (C_1), 95.8 (C_2), 164.7 (C_3), 157.1 (C_4), 133.5, 132.7, 130.3, 128.3, 128.0, 127.2, 125.6 (aryls).

Hydrolysis of 5d. The viscous oil obtained from the above reaction between *n*-butyl-TAD and diphenylketene was allowed to stand open to the air for 4 months. Treatment of this oil with anhydrous ether gave a precipitate, mp 180–181 °C (5.7% yield). It was soluble in 5% sodium hydroxide but insoluble in 5% sodium bicarbonate. It was identified as 1-[2,2-diphenyl-2-(hydroxyacetyl)]-4-*n*-butylurazole: IR (Nujol, cm^{-1}) 3295, 1810, 1785, 1712; ^1H NMR ($CDCl_3$) δ 0.77 (3 H, t), 1.2 (4 H, m), 3.26 (3 H, t) NH and OH too broad to observe, 7.26 (10 H, m).

Anal. Calcd for $C_{20}H_{21}N_3O_4$: C, 65.38; H, 5.76; N, 11.44. Found: C, 66.01; H, 5.75; N, 11.20.

Removal of the ether from the above filtrate gave an oil. Treatment of this oil with nitromethane gave a second solid. It was dissolved in 5% sodium bicarbonate. The solution was filtered and the filtrate was acidified to give a 25% yield of 2-[1-(4-*n*-butylurazolyl)]-2,2-diphenylacetic acid: mp 170–182 °C dec; IR (Nujol, cm^{-1}) 3150, 1770, 1728, 1711, 1664; ^1H NMR ($CDCl_3$) 0.81 (3 H, t), 1.0–1.5 (4 H, m), 3.32 (2 H, t), 7.2–7.6 (10 H, m), 8.9 (1 H, v br), 10.2 (1 H, v br).

Anal. Calcd for $C_{20}H_{21}N_3O_4$: C, 65.38; H, 5.76; N, 11.44. Found: C, 65.44; H, 5.79; N, 11.36.

Registry No. **1a**, 13274-43-6; **1b**, 40609-72-1; **1c**, 90046-99-4; **1d**, 13482-57-0; **1e**, 4233-33-4; **4**, 525-06-4; **5a**, 90047-00-0; **5b**, 90047-01-1; **5c**, 90047-02-2; **5d**, 90047-03-3; **5e**, 90047-04-4; **6**, 90047-05-5; **7**, 90047-06-6.

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Synthesis of 1-(*p*-Carbomethoxyphenyl)-3-pyrrolidinone by a Diels–Alder Route[1]

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In connection with studies directed toward the synthesis of various annulated methotrexate and aminopterin derivatives as potential antimitotic agents, we required a convenient synthesis of 1-(*p*-carbomethoxyphenyl)-3-pyrrolidinone (**1**). This compound had previously been prepared in our laboratory either by Dieckmann cyclization of methyl *p*-[*N*-(carbomethoxymethyl)-*N*-(carbomethoxyethyl)amino]benzoate, followed by decarbomethoxylation, or by arylation of 3-pyrrolidinol with methyl *p*-fluorobenzoate, followed by oxidation.[3] We now describe a third synthesis of this key intermediate that represents a novel exploitation of our recently described conversion of primary amino groups to nitroso compounds.[4]

Treatment of methyl *p*-aminobenzoate with dimethyl sulfide, followed immediately by the addition of *N*-chlorosuccinimide in CH_2Cl_2 at −25 °C, gave a white slurry, which, upon extraction with 5% sodium hydroxide, gave a solution of the sulfilimine **2** (Scheme I). Oxidation of **2** in situ at 0 °C to methyl *p*-nitrosobenzoate (**3**) was accomplished by addition of 1.2 equiv of *m*-chloroperbenzoic acid. Diels–Alder reaction of **3** with 2-methoxy-1,3-butadiene at 0 °C then led to separation of the dihydro-2*H*-1,2-oxazine **4** in 76% yield.

Initial attempts to effect hydrogenolysis of the N–O bond in **4** were disappointing. Zinc in acetic acid, which has been used successfully to cleave the N–O bond in many related dihydrooxazines,[5] failed to give the desired amino alcohol **5**. Aluminum amalgam, reputed to be the most effective of available reducing agents for such N–O bond cleavages,[6] gave **5** in very low yield, and the product proved to be both difficult to purify and resistant to cyclization to the pyrroline **6**. The dihydro-2*H*-1,2-oxazine enol ether **4** was therefore hydrolyzed in 1 N hydrochloric acid at room temperature to the tetrahydro-2*H*-1,2-oxazinone **7**. Although neither zinc in acetic acid nor aluminum amal-

(1) This work was supported by the National Cancer Institute (Grant No. R01 CA 28351), and by a grant-in-aid from Eli Lilly & Co.
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