1,3-Bridged Aromatic Systems. I. A New Synthesis of Pyrazoles[1]

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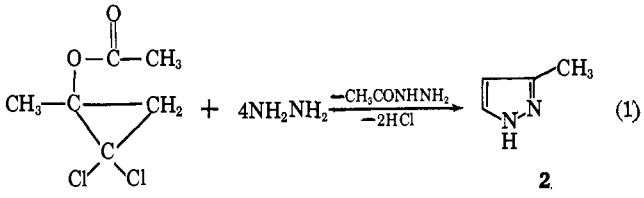
Abstract: The reaction of *gem*-dihalocyclopropyl acetates, which are readily available by reaction of enol acetates with phenyl(trichloromethyl)mercury or phenyl(dichlorobromomethyl)mercury, with hydrazine or phenylhydrazine constitutes a new and convenient synthesis of pyrazoles. The mechanism of reaction is discussed, and preparations of 3-methylpyrazole (92% yield), 3,5-diphenylpyrazole (90% yield), 3,5-[10]-pyrazolophane (>49% yield), and 1-phenyl-3-methylpyrazole (33% yield) are reported.

The ready availability of *gem*-dihalocyclopropyl acetates, obtained by condensation of enol acetates with phenyl(trichloromethyl)mercury or phenyl(dichlorobromomethyl)mercury,[2] prompted us to explore the application of these compounds as intermediates for the synthesis of heterocyclic systems. It was of particular interest to us to develop a convenient synthesis of heterocyclic metacyclophanes of type **11**.

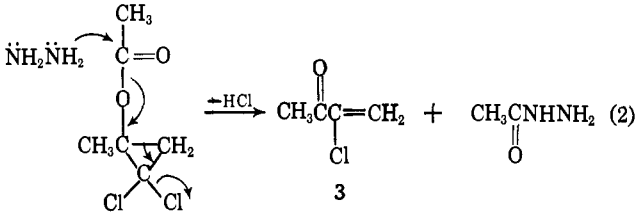
The reaction of isopropenyl acetate with phenyl(trichloromethyl)mercury in refluxing benzene gave 2,2-dichloro-1-methyl-1-cyclopropyl acetate (**1**) in 78% yield. Reaction of this cyclopropane with 4 equiv of hydrazine was exothermic at room temperature and afforded 3-methylpyrazole (**2**) in 92% yield (eq 1).



(1)

1 **2**

The pyrazole **2** could logically be formed by two reaction paths. Nucleophilic attack by hydrazine on the carbonyl group of **1** could be followed by ring opening, with loss of hydrogen chloride, to give the α,β-unsaturated ketone **3**. Loss of hydrogen chloride



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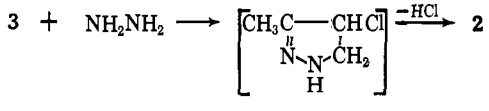
1 **3**



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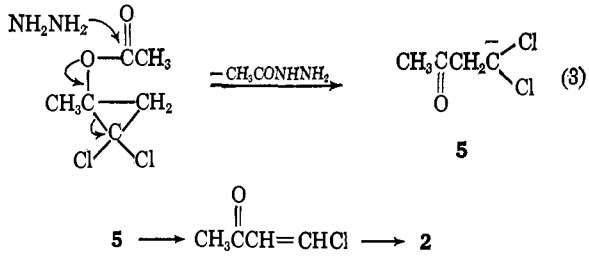
from **4** would give **2** as shown in eq 2. An alternative reaction path is shown in eq 3. Protonation of **5**,



(3)

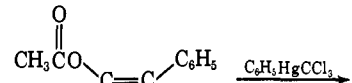
5

5 → $CH_3CCH{=}CHCl$ → **2**

6

with subsequent loss of hydrogen chloride, could give **6**, a logical precursor of **2**.

A study of the cyclopropanes derived from *trans*-α-stilbenol acetate (**7**) and *cis,trans*-cyclododecenyl acetate has provided direct evidence for the reaction sequence shown in eq 2. Reaction of cyclopropane **8**, obtained in 74% yield from **7**, with hydrazine gave acetylhydrazide, hydrazine hydrochloride, and 3,5-diphenylpyrazole (**9**, 90% yield). These products are consistent with the reaction sequence shown in eq 2, but inconsistent with that shown in eq 3. The latter would lead to 3,4-diphenylpyrazole instead of the observed 3,5-diphenylpyrazole.



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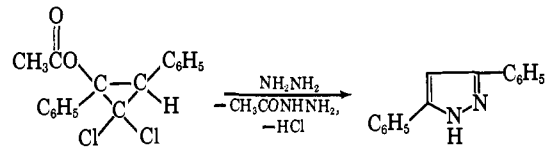
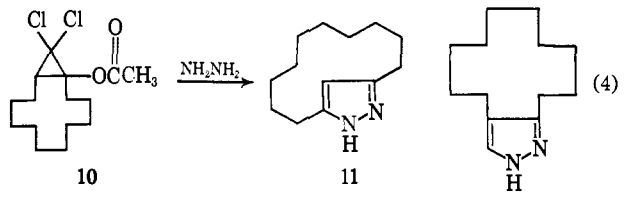


8 **9**

This synthesis of pyrazoles have provided a convenient route to the metacyclophane **11** (eq 4). *cis,trans*-



(4)

10 **11** **12**

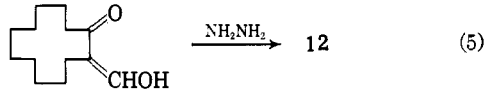
Cyclododecenyl acetate, prepared in 81% yield from cyclododecanone, was converted to the corresponding

(1) Supported by the National Science Foundation Grant GP-3357 and GP-6169X.

(2) D. Seyferth, J. M. Burlitch, R. J. Minasz, J. Yick-Pui Mui, H. D. Simmons, Jr., A. J. H. Treiber, and S. R. Dowd, *J. Am. Chem. Soc.*, 87, 4259 (1965).

cyclopropane **10** in 57% yield by reaction with phenyl(trichloromethyl)mercury. Reaction of **10** with 4 equiv of hydrazine gave 3,5-[10]-pyrazolophane (**11**) in >49% yield. The solid pyrazole **11** (mp 92–93°) was characterized by its composition, its spectra, and conversion to its crystalline nitrate salt. The structure of **11** was established by oxidation to 3,5-pyrazoledicarboxylic acid (49% yield) by reaction with neutral permanganate.

The formation of **11** is consistent with the reaction sequence shown in eq 2. However, the nmr spectrum of the residue, obtained subsequent to removal of acetyl hydrazide and most of **11**, indicated the presence of two pyrazoles. One was identified as additional **11** (*CH*=, τ 3.71), and the other (*CH*=, τ 2.78) corresponded to the isomeric pyrazole **12**. The second pyrazole was formed in low yield (~5%) and attempts to separate it from **11** by liquid chromatography or by gas chromatography were unsuccessful. The pyrazole **12** was unknown and was prepared as shown in eq 5. The nmr spectrum of authentic **12** (*CH*, τ 2.78) corresponded exactly to the second pyrazole in the mixture obtained from **10**. While the identification



(5)

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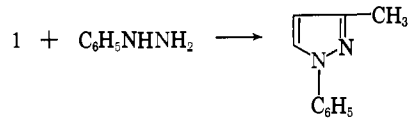
of **12** as a product derived from **10** cannot be considered as conclusive, the results do provide evidence that halocyclopropanes derived from enol acetates may also undergo reaction as shown in eq 3, and further studies directed to this point are under investigation.

This new synthesis of pyrazoles appears to be general. Reaction of 2,2-dichloro-1-methyl-1-cyclopropylacetate (**1**) with phenylhydrazine gave a mixture of



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phenylhydrazine and 1-phenyl-3-methylpyrazole (**14**). 1-Phenyl-3-methylpyrazole was isolated pure in 43% yield. We are currently examining the effect of ring size on the yield and course of the metacyclophane synthesis, and the possible extension of this reaction to the synthesis of other heterocyclic systems.

Experimental Section[3]

2,2-Dichloro-1-methyl-1-cyclopropyl Acetate (1). Isopropenyl acetate (21.4 g, 0.21 mole) and phenyl(trichloromethyl)mercury[4] (102.0 g, 0.26 mole) were added to 200 ml of dry benzene under an atmosphere of dry nitrogen. The mixture was heated at the reflux temperature for 52 hr, cooled to room temperature, and filtered to give 74.5 g (93% yield) of phenylmercuric chloride (mp 256°). Benzene was removed from the filtrate, and the residue was distilled to give 29.72 g (78% yield) of 2,2-dichloro-1-methyl-1-cyclopropylacetate[5] [bp 84–85° (27 mm), n^{24}D 1.4528].

Anal. Calcd for $C_6H_8Cl_2O_2$: C, 39.38; H, 4.37; Cl, 38.76. Found: C, 39.24; H, 4.48; Cl, 38.84.

The infrared spectrum of **1** showed: the absence of olefin absorption, $\nu_{C=O}$ (1750 cm^{-1}), ν_{C-O-C} (1200, 1075–1055 cm^{-1}), and ν_{C-Cl} (850, 799, and 762 cm^{-1}). The nmr spectrum (neat) showed: CH_2 (AB quartet, τ 8.30, J = 9.0 cps), C-*CH*$_3$ (singlet, τ 8.25), and C(O)*CH*$_3$ (singlet, τ 7.93).

Reaction of 2,2-Dichloro-1-methyl-1-cyclopropylacetate (1) with Hydrazine. Hydrazine (95%, 5.36 g, 0.16 mole) dissolved in absolute ethanol (20 ml) was added dropwise to a solution of **1** (5.68 g, 0.03 mole) in absolute ethanol (20 ml). An exothermic reaction occurred, and the solution turned milky white. The mixture was heated at the reflux temperature for 15 min and allowed to stand at room temperature for 24 hr. Sodium hydroxide (1.66 g) was added, and the mixture was heated at the reflux temperature for 1 hr. Hydrogen peroxide (30%, 8.30 g) was added to the cooled reaction to destroy excess hydrazine. After the vigorous evolution of nitrogen had ceased, the mixture was treated with sodium bisulfite solution (5 ml, saturated) to decompose excess peroxide. The resulting mixture was diluted with water (20 ml) and extracted with three 50-ml portions of ether. The dried ($MgSO_4$) ether extract was concentrated on a rotary evaporator and distilled to give 2.34 g (92% yield) of 3-methylpyrazole [**2**, bp 72° (1.0 mm), n^{26}D 1.4872].

Anal. Calcd for $C_{10}H_9N_5O_7$, as the picrate: C, 38.59; H, 2.92; N, 22.51. Found: C, 38.86; H, 2.68; N, 22.16.

The nmr spectrum of **2** showed: *CH*$_3$ (singlet, τ 7.66, wt 3), C=*CH*—C (singlet, τ 3.96, wt 1), *C*—*CH*—NH (singlet, τ 2.50, wt 1), and *NH* (singlet, τ −2.88, wt 1). The mass spectrum[6] of **2** exhibited a molecular ion peak at *m/e* 82 and prominent peaks at the following mass numbers: 83, 82, 81, 67, 66, 54, 42, 32, 28, 18, and 15.

The 3-methylpyrazole described above had properties (boiling point, refractive index, infrared and nmr spectra) identical with those of an authentic sample,[7] prepared (60% yield) from sodium acetoacetaldehyde. The picrate (mp 143–144° from ethanol) caused no depression in melting point when admixed with the picrate (mp 144–146°) prepared from an authentic sample of 3-methylpyrazole.

1-Phenyl-3-methylpyrazole (12). 2,2-Dichloro-1-methyl-1-cyclopropylacetate (9.10 g, 0.05 mole) and freshly distilled phenylhydrazine (16.20 g, 0.150 mole) were dissolved in 95% ethanol (40 ml), and the solution was heated for 12 hr. The cooled mixture was filtered to remove precipitated phenylhydrazine hydrochloride (3.50 g, 29% yield, mp 243°) and the filtrate was concentrated on a rotary evaporator. The residue was chromatographed on silica gel (80 g, 300 mesh) using benzene as eluent. Five 250-ml fractions were collected and monitored by gas chromatographic retention time (Silicone DC 710 on Chromosorb W, 80–100 mesh, at 200°). The first fraction contained ethanol, the second and third fractions phenylhydrazine, and the fourth and fifth fractions 1.34 and 2.58 g, respectively, of an oil which was a mixture of phenylhydrazine and 1-phenyl-3-methylpyrazole. Fractional distillation of the last two fractions gave 1-phenyl-3-methylpyrazole [3.44 g, 43% yield, bp 76–78° (0.25 mm)].

The nmr spectrum of the pyrazole **12** showed: *CH*$_3$ (singlet, τ 7.62, wt 3), =*CH* (doublet centered at τ 3.71, J = 3.0 cps, wt 1), aromatic *H* and =C—H (complex multiplet centered at τ 2.4, wt 6). The mass spectrum[7] of the pyrazole showed a molecular ion peak at *m/e* 158 and prominent peaks at *m/e* 130, 90, 81, 77, 32, and 28. The ultraviolet spectrum showed $\lambda_{max}^{95\%\ alc}$ 260 mμ (ϵ 18,600) with strong end absorption.

The pyrazole described above was identical (boiling point, infrared spectrum, and nmr spectrum) with an authentic sample of 1-phenyl-3-methylpyrazole prepared (48% yield) from sodium formylacetone.[8]

trans-**α-Stilbenol Acetate (7).** α-Stilbenol acetate (mp 97–98° cor, lit.[9] 101°) was prepared (56% yield) from desoxybenzoin as previously described.[9] The nmr spectrum of 7 showed: *CH*$_3$ (singlet, τ 7.82, wt 3), =CH (singlet, τ 3.50, wt 1), and aromatic *H* (complex centered at τ 2.75, wt 10); the ultraviolet spectrum showed $\lambda_{max}^{95\%\ alc}$ 222.0 mμ (ϵ 12,700) and λ_{max} 286.7 mμ (ϵ 27,800).

The α-stilbenol acetate was assigned the *trans* structure on the

(3) Melting points are corrected. Unless otherwise specified, infrared spectra were determined neat.

(4) T. J. Logan, *J. Org. Chem.*, **28**, 1129 (1963).

(5) The cyclopropane **1** was reported (20% yield) by reaction of isopropenyl acetate and sodium trichloroacetate in hot dimethoxyethane; however, the composition and properties of the product were not described. C. E. Cook and M. E. Wall, *Chem. Ind.* (London), 1927 (1963).

(6) Mass spectra (Hitachi, Model RMU-6D) were obtained using an all glass inlet maintained at 70° using an ionizing voltage of 50 ev.

(7) L. Knorr, *Ann.*, **279**, 219 (1894).

(8) L. Claisen and N. Stylos, *Ber.*, **21**, 1144 (1888).

(9) R. P. Barnes and S. R. Cooper, *J. Org. Chem.*, 8, 153 (1943).

basis of comparison of its ultraviolet spectrum with *cis*- and *trans*-cinnamic acid and *cis*- and *trans*-stilbene.[10]

***trans*-1,1-Dichloro-2,3-diphenyl-2-acetoxycyclopropane (8).** The reaction of *trans*-α-stilbenol acetate (8.00 g, 0.0335 mole) with phenyl(trichloromethyl)mercury (17.22 g, 0.0435 mole) was carried out for 2 days as described for isopropenyl acetate. Evaporation of the benzene (100 ml), obtained subsequent to removal of phenylmercuric chloride, gave an oil which was dissolved in a minimum amount of hot petroleum ether (bp 60–68°). 1,1-Dichloro-2,3-diphenyl-2-acetoxycyclopropane (8.00 g, 74% yield) precipitated as a white solid (mp 94°).

Anal. Calcd for $C_{17}H_{14}Cl_2O_2$: C, 63.57; H, 4.39; Cl, 22.08. Found: C, 63.29; H, 4.49; Cl, 22.13.

The cyclopropane showed end absorption ($\lambda_{max}^{95\%\ alc}$ 221 mμ (ε 20,400) in the ultraviolet and the following nmr spectrum: CH_3 (singlet, τ 8.10, wt 3), cyclopropyl *H* (singlet, τ 6.72, wt 1), and aromatic *H* (complex centered at τ 2.65, wt 10).

3,5-Diphenylpyrazole (9). Hydrazine (95%, 40 mg, 1.25×10^{-4} mole), dissolved in absolute ethanol (1 ml), was added dropwise to a stirred solution of **8** (100 mg, 3.12×10^{-4} mole) in absolute ethanol (4 ml), and the solution was heated at the reflux temperature for 3 hr. The reaction mixture was cooled and filtered to remove hydrazine hydrochloride (18.2 mg, 43% yield, mp 89°). The filtrate was cooled to give 67.3 mg (89.6% yield) of white crystalline 3,5-diphenylpyrazole (mp 200°). The mother liquor was concentrated and 20.2 mg (88% yield) of acetylhydrazide (mp 66–67°, lit.[11] mp 67°) was obtained.

The pyrazole was identical (melting point, mixture melting point, and infrared spectrum) with an authentic sample of 3,5-diphenylpyrazole prepared (57% yield)[12] from dibenzoylmethane and hydrazine.

***cis,trans*-1-Cyclododecenyl Acetate.** Cyclododecenyl acetate [bp 94–96° (25 mm), 81% yield, $n^{25}D$ 1.4802; lit.[13] bp 65° (0.10 mm), $n^{25}D$ 1.4810, 67% yield] was prepared from cyclododecanone as previously described.[13]

Anal. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 74.73; H, 10.77.

The nmr spectrum of the product showed: CH_2 (broad near τ 8.62), C(O)CH_3 (two singlets at τ 7.99 and 7.93), CH_2—CH= (broad τ 7.50–8.30), =CH— (triplet with second-order splitting centered at τ 4.93, J = 7.0 cps). Gas chromatography of the enol acetate (Apiezon L on Chromosorb W, 80–100 mesh at 200°, He flow rate 20 cc/min) showed two symmetrical peaks for the *cis* and *trans* isomers at 468 and 603 sec in the ratio ~51/49; the infrared spectrum showed only one carbonyl peak at 1755 cm^{-1}.

1-Acetoxy-2,2-dichlorobicyclo[10.1.0]tridecane (10). A mixture of cyclododecenyl acetate (13.05 g, 0.059 mole) and phenyl(trichloromethyl)mercury (30.01 g, 0.076 mole) in dry benzene (100 ml) was heated at the reflux temperature under an atmosphere of nitrogen for 48 hr. The reaction mixture was cooled and filtered to remove phenylmercuric chloride (17.65 g, 75% yield) and then concentrated at atmospheric pressure. An additional 2.43 g of phenylmercuric chloride precipitated and was removed. The red oil (13.92 g) thus obtained was chromatographed on silica gel (200 g) using petroleum ether (1250 ml, bp 60–68°) as eluent. Removal of solvent from the eluate gave 10.42 g (58% yield) of reasonably pure **10** ($n^{23}D$ 1.4858) which was used in subsequent reactions.

A pure sample of **10** was obtained by additional chromatography of the product on silica gel (100 g) using benzene (65%)–petroleum ether (35%) as eluent. The product had $n^{23}D$ 1.4981 and decomposed upon attempted distillation.

Anal. Calcd for $C_{15}H_{24}Cl_2O_2$: C, 58.64; H, 7.87; Cl, 23.08. Found: C, 58.94; H, 7.58; Cl, 22.91.

The infrared spectrum of **10** showed the absence of olefin absorption and had the following characteristic bands: $\nu_{C=O}$ (1758 cm^{-1}), ν_{C-O-C} (1200, 1040–1030 cm^{-1}), and ν_{C-Cl} (850 cm^{-1}). The nmr spectrum of **10** showed: CH_2 (broad, τ 8.62), C(O)CH_3 (singlet, τ 7.99, and singlet τ 7.93).

3,5-[10]-Pyrazolophane (11). A. A solution of hydrazine (95%, 11.5 g, 0.34 mole) in 95% ethanol (60 ml) was added dropwise to a solution of 1,1-dichloro-2-acetoxy[10.1.0]tridecane (23.26 g, 0.076 mole) dissolved in 60 ml of 95% ethanol, and the resulting mixture was heated at the reflux temperature for 12 hr. A solution of sodium hydroxide (13.62 g, 0.341 mole) in water (30 ml) was added, and the mixture was heated at the reflux temperature for 1 hr to hydrolyze the acetylhydrazide. The solution was cooled to 30°, and the solid (2.53 g) which precipitated was removed by filtration and shown to be primarily sodium chloride. The filtrate was diluted with water (200 ml) and extracted with four 50-ml portions of ether. The dry ($MgSO_4$) ether extract was concentrated (rotary evaporator) to give 11.09 g (71% yield) of impure, yellow 3,5-[10]-pyrazolophane (mp 75–78°). The product was washed with pentane (40 ml) to give white crystals (7.64 g, 49% yield) of **11** melting at 90–91.5°. The melting point was raised to 92.5–93.0° by further recrystallization from petroleum ether (bp 60–68°).

Evaporation of the pentane washings gave 3.34 g of an orange oil. The nmr spectrum of the oil showed the following absorptions: CH_2 (broad, τ 0.95 and 1.32), CH_2—C=CH (complex multiplet, τ 2.58), C=C—*H* (singlet, τ 4.17), =*CH*—N (singlet, τ 2.78), *N*—H (broad, τ 2.00). The values for CH_2 (τ 0.95) and =CH—N (τ 2.78) were assigned to the isomeric 2H-cyclododecapyrazole on the basis of comparison with the spectrum of an authentic sample. Using the integrated peak areas of the aromatic protons the over-all yield of 2H-cyclododecapyrazole was estimated to be about 5%.

Anal. Calcd for $C_{13}H_{22}N_2$: C, 75.67; H, 10.75; N, 13.58. Found: C, 75.95; H, 10.71; N, 13.43.

3,5-[10]-Pyrazolophane showed: $\lambda_{max}^{95\%\ alc}$ 216 mμ (ε 4890); infrared (*NH* at 3100–3200 cm^{-1}, =*CH* at 3010 cm^{-1}, and pyrazole at 1585 cm^{-1}); nmr (CH_2, broad at τ 8.0–9.3, wt 16; CH_2CH=CH, complex multiplet at τ 7.16–7.62, wt 4; =*CH*, singlet, τ 4.19, wt 1; *NH* broad at τ −2.75, wt 1).

B. The reaction was carried out using impure (unchromatographed) **10** (5.00 g, 0.016 mole) and hydrazine (95%, 1.56 g, 0.048 mole) at reflux for 1 hr, and the hydrolysis step with aqueous sodium hydroxide was omitted. Chromatography of the orange oil (2.80 g), obtained subsequent to filtration and concentration, on silica (200 g) using methanol (50%)–ethyl acetate (50%) as eluent gave 2.21 g of a partially crystalline material. Recrystallization of this product from methanol gave bis(dicyclododecyl)hydrazone (mp and mmp 113–114.5°) and (from the mother liquor) 3,5-[10]-pyrazolophane (mp 92–93°).

Bis(dicyclodecyl)hydrazone. Hydrazine (95%, 0.372 g, 0.011 mole), dissolved in absolute ethanol (5 ml), was added dropwise to a solution of cyclododecanone (4.00 g, 0.022 mole) in absolute ethanol (10 ml), and the clear solution was heated at the reflux temperature for 1 hr. The mixture was cooled and filtered to give 3.2 g (82%) of bis(dicyclododecyl)hydrazone (82% yield) as white plates (mp 113–114.5°).

Anal. Calcd for $C_{24}H_{48}N_2$: C, 79.69; H, 12.02; N, 7.62; mol wt, 364. Found: C, 79.93; H, 12.30; N, 7.77; mol wt (freezing point lowering in benzene), 392.

The bishydrazone showed end absorption with shoulders at $\lambda_{max}^{95\%\ alc}$ 222 mμ (ε 22,000) and 234 mμ (ε 6000); nmr CH_2 (broad, τ 8.0–9.2, wt 36), and CH_2—CH= (complex multiplet, τ 7.37–7.80, wt 8).

3,5-[10]-Pyrazolophonium Nitrate. A suspension of **11** (0.20 g, 0.001 mole) in a solution of 20% nitric acid (10 ml) was heated at the reflux temperature for 2 hr. The solution was cooled and filtered to give 0.165 g (60% yield) of white crystalline solid (mp 138–148°). This material was recrystallized from petroleum ether (bp 60–68°) and vacuum sublimed to give pure 3,5-[10]-pyrazolophonium nitrate (mp 149.5–150.5°).

Anal. Calcd for $C_{13}H_{23}N_3O_3$: C, 57.97; H, 8.61; N, 15.60. Found: C, 57.61; H, 8.55; N, 15.86.

The product showed: infrared (NH at 3020 cm^{-1}, $\nu_{C=C}$ stretch at 1610 cm^{-1}, and ν_{N-O} at 1535 and 1315 cm^{-1}); nmr (CH_2, τ 8.0–9.5, wt 17.5; CH_2C=, complex centered at τ 7.10, wt 4; *CH*=, singlet, τ 3.71, wt 1); mass spectrum[7] (molecular ion at *m/e* 206; calcd for **11**, 206).

Oxidation of 3,5-[10]-Pyrazolophane. Potassium permanganate (3.16 g, 0.02 mole) was added to a suspension of **11** (0.20 g, 0.001 mole) in 10 ml of water, and the mixture was heated to the reflux temperature and a vigorous reaction occurred. The resulting mixture was heated at the reflux temperature for 3 hr, the mixture was cooled and filtered, and the filtrate was treated with activated charcoal (~2 g). The resulting mixture was filtered and concentrated to a volume of *ca.* 10 ml. This solution was acidified (acetic acid) and evaporated to dryness. The residual white salt was dissolved in 0.5 *N* hydrochloric acid (10 ml) which gave on cooling a tan solid (mp >375°). Evaporation of the mother liquor gave 3,5-pyrazoledicarboxylic acid (76.6 mg, 49% yield, mp 289–295°).

(10) J. R. Dyer, "Applications of Absorption Spectroscopy of Organic Compounds," Prentice-Hall, Inc., Englewood Cliffs, N. J., 1965, p 20.
(11) G. Schöfer and N. Schvan, *J. Prakt. Chem.*, [2] **51**, 185 (1895).
(12) L. Knorr and P. Duden, *Ber.*, **26**, 111 (1893).
(13) N. J. Leonard and F. H. Owens, *J. Am. Chem. Soc.*, **80**, 6039 (1959).

This material was identical with authentic[14] 3,5-pyrazoledicarboxylic acid (mp 289–295°, mmp 289–295°, lit.[14] mp 289°).

2H-Cyclododecapyrazole (12). To a solution of 2-hydroxymethylenecyclododecanone (6.46 g, 0.03 mole), prepared in 43% yield as previously described,[15] dissolved in ethanol (15 ml) was added dropwise to a solution of hydrazine (95%, 1.44 g, 0.04 mole) dissolved in ethanol (5 ml). The clear solution was heated at the reflux temperature for 12 hr, then cooled, and poured into water (50 ml). The resulting mixture was extracted with five 50-ml portions of ether. The combined ether extracts were dried ($MgSO_4$), and the solvents were removed on a rotary evaporator to give 12.73 g of a green oil, $n^{27}D$ 1.4309. Distillation of the oil gave 2H-cyclododecapyrazole (2.00 g, 32%) as a clear viscous oil, bp 160° (0.025 mm), $n^{28}D$ 1.5305. The oil crystallized upon standing overnight to give a white solid melting at 81.5–83.5°. Recrystallization of this product from petroleum ether (bp 60–68°) gave essentially a quantitative recovery of 2H-cyclododecapyrazole, mp 88.5–89.0°. The mixture melting point of 2H-cyclododecapyrazole and 3,5-[10]-pyrazolophane (mp 92.5–93.0°) was depressed (mp 49–63°).

Anal. Calcd for $C_{13}H_{22}N_2$: C, 75.67; H, 10.75; N, 13.58. Found: 75.72; H, 10.47; N, 13.42.

2H-Cyclododecapyrazole showed: infrared (NH at ν 3180–3110 cm^{-1}, C=C stretch at ν 1690 and 1620 cm^{-1}); nmr (CH_2, broad, τ 0.95, CH_2—C=CH, complex multiplet, τ 2.58, =C(H)—N, singlet, τ 2.78, N—H, broad, τ 3.40).

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Sequence Peptide Polymers. I. Polymers Based on Aspartic Acid and Glycine[1,2]

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Abstract: This is the first of a series of papers giving particulars of the "active" ester method of making sequence peptide polymers. Polymerization of HBr-H-Asp(OCH_3)-Gly-Gly-ONP and TosOH-H-Asp(Im)-Gly-Gly-ONP give the respective sequence peptide polymers poly Asp(OCH_3)-Gly-Gly and poly Asp(Im)-Gly-Gly. Polymerization was carried out in dimethyl sulfoxide or in dimethylformamide solutions by mixing the salt with triethylamine. Number-average molecular weights are 5000–10,000 and the aspartic acid residue is entirely L. Improved methods have been developed for characterizing the optical purity of aspartic acid peptides. The problems of synthesizing sequence peptide polymers are principally those of making the requisite highly reactive "monomers" in chemically and optically pure form. Efficient syntheses are described as are important limitations of certain possible routes.

The development of efficient methods of preparing homopolymers and of random copolymers of amino acids has led to extensive studies of these polypeptides as protein models.[3-5] The next step, the preparation of random peptide polymers with known repeating sequences, has also been studied for many years. Early examples have been reviewed by Bamford, Elliott, and Hanby[4] and more comprehensively by Katchalski.[3] In most cases the approaches used were suitable only for sequences without reactive side chains. More recently poly Gly-Pro-Hypro(H)[6] was prepared by polymerization of the free tripeptide with tetraethylpyrophosphite[7] and poly Gly-Ser(H)-Ala was prepared by action of N-bromosuccinimide on the acid hydrazide.[8] The use of dicyclohexylcarbodiimide as polymerization reagent has also been studied.[3,4,9]

Some time ago we reported several examples of the "active" ester synthesis of sequence peptide polymers.[2] The present paper is the first of a series which provides the details. The generality of the method has been further illustrated by recent publications.[10-12] The

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(6) The conventional amino acid abbreviations are used in a special way: the symbols stand for the stem alone. Glycine is H-Gly-OH; aspartic acid is H-Asp(OH)-OH; the β-methyl ester of aspartic acid is H-Asp(OCH_3)-OH. This procedure permits the precise description of all derivatives. In addition **Z** is used for benzoyloxycarbonyl, Bz always stands for benzoyl, Bl stands for benzyl, HONP for *p*-nitrophenol, HOPCP for pentachlorophenol, DCC for dicyclohexylcarbodiimide, DCU for dicyclohexylurea, DPC is diisopropylcarbodiimide, DPU is the urea, and CMC is cyclohexyl(2-morpholinoethyl)carbodiimide metho-*p*-toluenesulfonate. See M. Goodman and G. W. Kenner, *Advan. Protein Chem.*, **12**, 488 (1957); and R. Schwyzer, J. Rudinger, E. Wünsch, and G. T. Young, "Peptides," G. T. Young, Ed., Pergamon Press Ltd., London, 1963, p 261.

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