Heterocyclic Studies. 42. Transformation of a Diazoacetylpyrazoline to a 2,3-Diazabicyclo[4.1.0]-3-hepten-5-one. A New Valence Isomer in the 1,2-Diazepin-4-one System[1]

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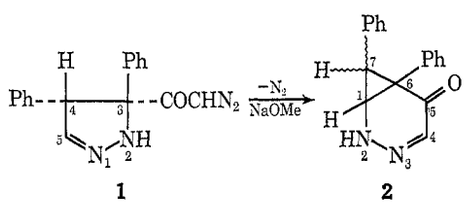
Treatment of diazoacetylpyrazoline **1** with base gives the 2,3-diazabicyclo[4.1.0]heptenone **2**. The structure of **2** was established by photoisomerization and substitution reactions leading to derivatives of 2,3-dihydro- and 1,5-dihydro-5,6-diphenyl-1,2-diazepin-4-one. Compound **2** readily undergoes dimerization. The formation of **2** is suggested to occur *via* a tetrazonine intermediate.

The base-catalyzed fragmentation of 3-diazoacetylpyrazolines to pyrazoles plus hydrazonoacetic ester *via* intermediate pyrazolo[1,5-*c*]-*v*-triazines was described in the accompanying papers.[2] This reaction occurs with several pyrazolines having different substituents and steric configurations at C-3–C-4. A striking exception was observed, however, in the reaction of the *trans*-3,4-diphenylpyrazoline **1**. Under the same conditions (1 equiv of NaOMe at 20°), **1** (or the Δ^1-pyrazoline) liberates *nitrogen*, and a product comprising the remainder of the molecule is isolated in 70–80% yield; diphenylpyrazole was not detected. The main product has been shown to be the diazabicyclo[4.1.0]heptenone **2**; evidence for the structure and a suggestion concerning the reaction pathway are presented here.

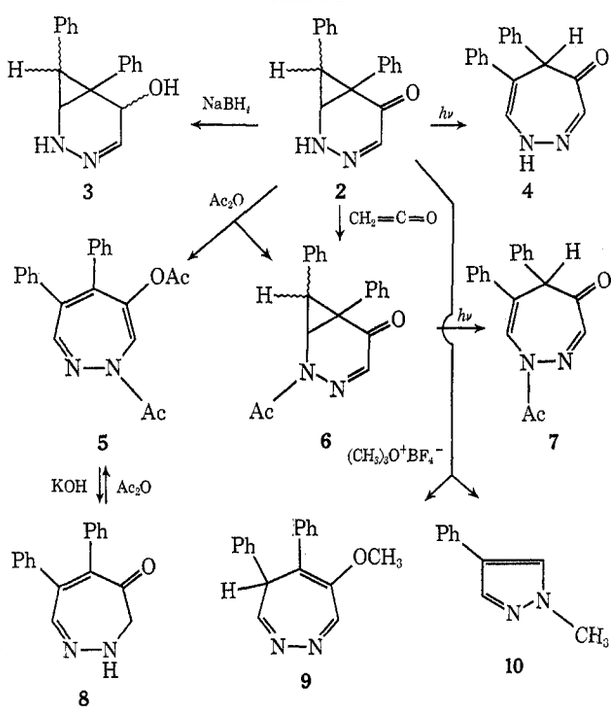


1 **2**

The ir spectrum (ν 3250 and 1630 cm^{-1}) indicates the presence of NH and conjugated carbonyl groups in **2**, and the uv spectrum [λ_{max} 327 nm (ϵ 5100)] is consistent with the cyclic –NHN=C—C=O chromophore.[2a] The nmr spectrum contains a doublet of doublets, δ 3.19 and 4.75 (J = 5 Hz), and a singlet at 6.63 ppm. The latter signal is absent in the spectrum of material prepared in CH_3OD, and this proton in **2** thus arises from the CHN_2 in **1**. The presence of a cyclopropane system in **2** was first considered in order to account for the relatively high-field doublets. Chemical shift effects for phenyl and CO_2H substituents in cyclopropane have been derived,[3] and rough application of these values to **2**, equating the C-5 CO group to CO_2H and assuming $\Delta\delta$ for *gem*-N as 2.0 and β_c-N as zero,[4] leads to chemical shifts of about δ 3 and 4, respectively, for H-7 and H-1 in **2** (or the endo-phenyl epimer). Neither chemical shift or coupling constant permits conclusions on the configuration at C-7.

For chemical characterization of the functional groups, **2** was reduced with $NaBH_4$ to alcohol **3** (Chart I) ($\delta_{H\text{-}7}$ 3.00, $\delta_{H\text{-}1}$ 3.49, $J_{1,7}$ = 4.5 Hz) and acylated

CHART I



with ketene at 0° to give **6** ($\delta_{H\text{-}7}$ 3.10, $\delta_{H\text{-}1}$ 5.63, $J_{1,7}$ = 5.5 Hz). Acetylation with Ac_2O provided the first correlation of **2** with a known structure. In addition to a small amount of **6**, a yellow diacetyl compound was obtained in 40% yield. This product was recognized as the acetoxydiazepine **5** by hydrolysis to the 2,3-dihydro ketone **8** and reacetylation.[5,6] Compounds **5** and **6** were also obtained from **2** in low yields with acetyl chloride.

A further instructive correlation with the diazepinone system was provided by the irradiation (350 nm) of **2** and the *N*-acetyl derivative **6**, which gave rise to the 1,5-dihydrodiazepinone **4** and the 1-acetyl-1,5-diazepinone **7**, respectively. The structures of these products were confirmed by comparison with samples prepared independently *via* **8**.

(1) Supported in part by the National Science Foundation and the Unidel Foundation.

(2) (a) F. B. Culp, A. Nabeya, and J. A. Moore, *J. Org. Chem.*, **38**, 2949 (1973); (b) F. B. Culp, K. Kurita, and J. A. Moore, *ibid.*, **38**, 2945 (1973).

(3) T. A. Wittstruck and E. N. Trachtenberg, *J. Amer. Chem. Soc.*, **89**, 3810 (1967).

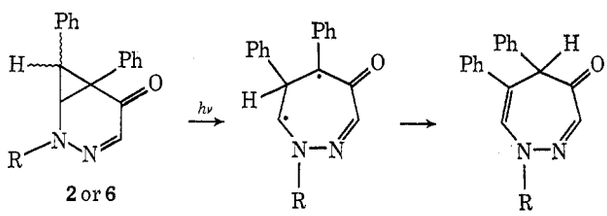
(4) These estimates are based on the spectrum of cyclopropylamine (No. 37 in Varian Associates Spectral Catalog, Palo Alto, Calif., 1962), in which H_α has δ 2.30 and H_β has δ 0.35.

(5) A. Nabeya, F. B. Culp, and J. A. Moore, *J. Org. Chem.*, **35**, 2015 (1970).

(6) J. A. Moore, W. J. Freeman, K. Kurita, and M. G. Pleiss, *ibid.*, **37**, 2939 (1972).

An additional link with the 1,5-dihydrodiazepinone system was established by methylation of **2** with trimethyloxonium fluoroborate. This reaction was complex and erratic, but it was possible to isolate three products on one occasion. One of these was a dimer of **2** with one *N*-methyl group and is related to other dimers mentioned below. The second contained an OCH_3 group and nmr signals at δ 4.09 (d) and 6.81 (d, J = 5 Hz); it is tentatively assigned the 6*H*-methoxydiazepine structure **9**. The third product was identified as 1-methyl-4-phenylpyrazole (**10**). The origin of this compound is clearly analogous to the formation of 1-acylpyrazoles from the bicyclic ketones derived from the 1,5-dihydrodiazepinone **4**.[6]

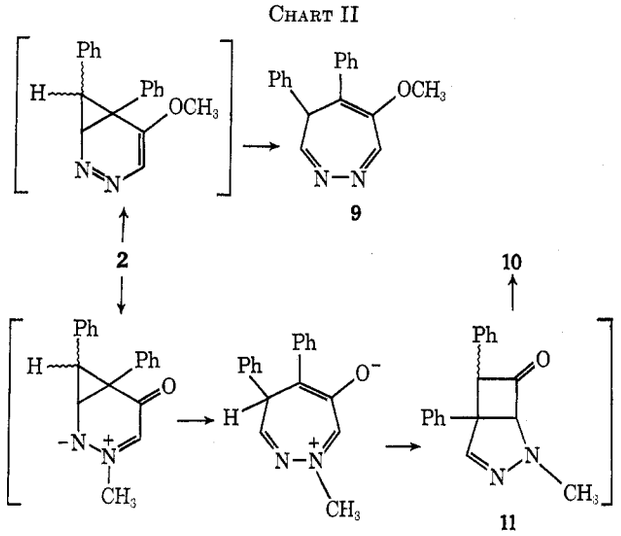
The conversion of **2** to representatives of the two dihydrodiazepinone tautomers (which are not interconverted under conditions in which either is formed from **2**) requires a structure from which both diazepines can arise by accessible methanisms. All of the products described can be formulated by breaking the 1,6 bond in **2** or its derivatives. The photochemical rearrangements involve hydrogen migration, probably from a diradical.



2 or 6

The methylation products **9** and **10** (Chart II) can arise following attack on **2** at the two sites that would

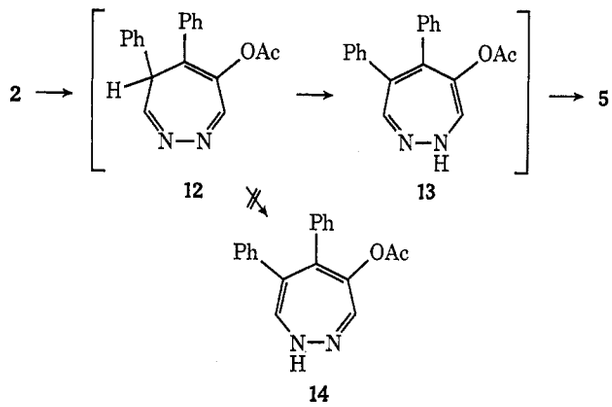
CHART II



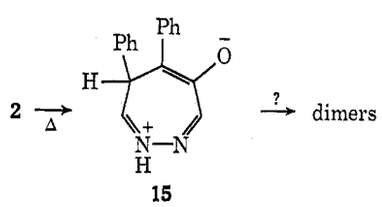
11

be expected for the trimethyloxonium reagent, namely carbonyl oxygen and N-3, respectively. In the first case, valence isomerization to a diazepine leads directly to **9**. In the second, further rearrangement to the bicyclo[3.2.0]ketone **11** and fragmentation would give **10**. The acyl counterparts of **11** lose phenylketene at room temperature to give 1-acyl-4-phenylpyrazoles.[6]

The acetylation of **2** leading to the 2,3-dihydro enol acetate **5** can be formulated in several ways depending on the sequence of introduction of the acetyl groups. One possibility is initial O-acylation followed by rearrangement to the 2,3-dihydro enol ester **13** and further acetylation. The factors that direct reactions of **2** to the 1,5-dihydro series (**11**) in the methylation and to the 2,3-dihydro series (**5**) in the acetylation cannot be defined.



The study of **2** was severely complicated by the formation of a number of dimeric compounds under unpredictable and inexplicable conditions. Thus a dimer of **2** (dimer A) was obtained more or less consistently on heating **2** in methanol, but *not* in ethanol. A different dimer B was obtained from **2** or from dimer A in acetic acid. On heating in toluene, **2** or dimer A gave an anhydro dimer. A monoacetyl dimer was obtained on one occasion from acetylation of **2**; a methyl dimer was noted above. Several of these compounds were partially characterized, but no structural suggestions can be made. We assume that these dimers and derivatives arise from $_4\pi_s + _6\pi_s$ cycloadditions of a valence tautomeric form such as **15** or a derivative (*e.g.*, **9** or **12**), perhaps with a second molecule of **2**. Such additions are well known in the 1*H*-azepine series, and the initial dimers are prone to further rearrangement.[7-9]

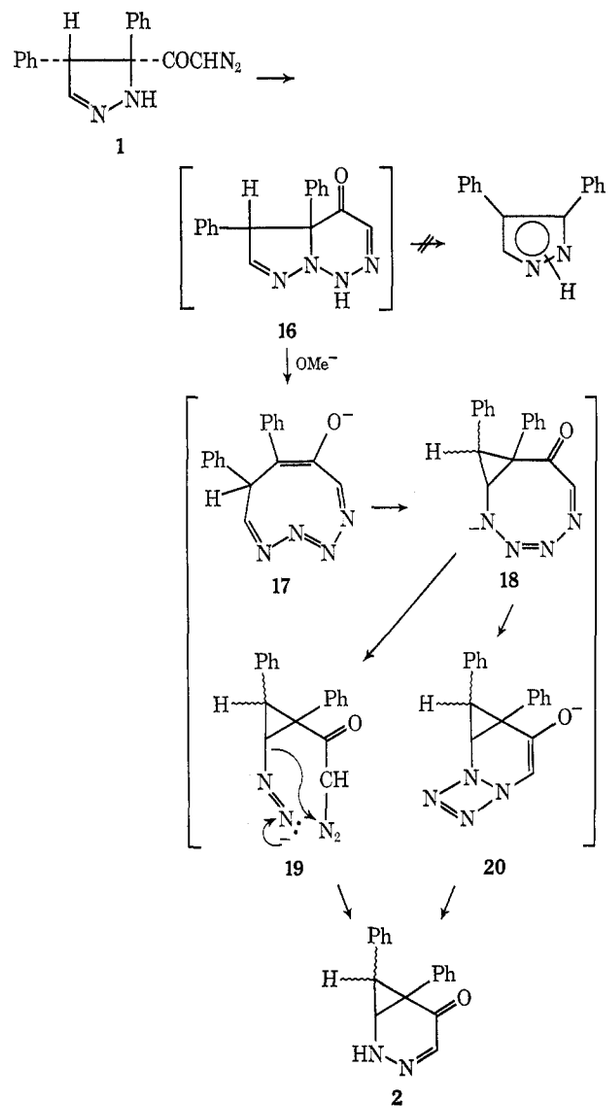


15

Formation of 2.—In considering the pathway by which **2** is formed from the diazoacetylpyrazoline **1** in base, the first step is assumed to be cyclization to the pyrazolo-*v*-triazinone **16**, as postulated for the cis-diphenyl epimer and both isomeric 3-methyl-4-phenyl compounds.[2a,b] To arrive at a precursor of **2** which can lose nitrogen at room temperature, we suggest that **16** undergoes opening at the central bond to a tetrazonine enolate **17**. If **16** has a trans ring fusion,

(7) K. Hafner and A. Mondt, *Angew. Chem., Int. Ed. Engl.*, **5**, 839 (1966).
(8) L. Paquette and J. H. Barrett, *J. Amer. Chem. Soc.*, **88**, 2590 (1966).
(9) A. Johnson and H. E. Simmons, *ibid.*, **89**, 3191 (1967).

this step would lead to the trans N=N double bond in **17**, permitting 8-π-conrotatory cyclization to a *cis*-bicyclo[6.1.0] system (**18**). Subsequent steps could involve opening to a diazoacetyl diazene, loss of nitrogen, and cyclization to **2** or, perhaps more fancifully, cyclization to a fused tetrazete system (**20**) and elimination of nitrogen. These suggestions invoke some unfamiliar species and are, of course, totally speculative.



Experimental Section

6,7-Diphenyl-2,3-diazabicyclo[4.1.0]-3-hepten-5-one (2). A. From 1.—To a solution of 870 mg of the 5-pyrazoline **1** in 15 ml of methanol was added 4 ml of 1 *N* KOH in methanol. The solution was allowed to stand at 20° for 2 hr. (When the reaction was carried out in a sealed system, 1 mol of gas was evolved per mole of **1** in about 1 hr.) Addition of Dry Ice to the solution caused separation of a pale yellow solid which was collected, washed, and dried to give 370 mg (47%) of **2**, mp 175° dec. Crystallization from methanol (note, however, the dimerization in methanol described below!) gave a colorless solid: mp 175° dec; ν^{KBr} 3250, 1630 cm^{-1}; λ_{max}^{MeOH} 327 nm (ϵ 5100); δ^{CDCl_3} 3.19 (d, 1, J = 5 Hz, H-7), 4.75 (d, 1, J = 5 Hz, H-1), 6.63 (s, 1, H-4), 6.8–7.5 (m, 10).

Anal. Calcd for $C_{17}H_{14}N_2O$: C, 77.84; H, 5.38; N, 10.68. Found: C, 78.29; H, 5.64; N, 10.56; *m/e* 262.1106.

B.—A solution of 0.58 g of 3-diazoacetyl-*trans*-3,4-diphenyl-1-pyrazoline in 10 ml of methanol and 10 ml of tetrahydrofuran was treated with 2 ml of 1 *N* methanolic KOH. After standing for 5 hr at 30° the orange solution was treated with Dry Ice and evaporated *in vacuo*. The residual yellow solid was triturated with water and then collected and dried to give 0.51 (94%) of crude powder. Recrystallization from ethanol–water gave 0.40 g (76%) of **2**, ir same as that from A.

6,7-Diphenyl-2,3-diazabicyclo[4.1.0]-3-hepten-5-ol (3).—A solution of 520 mg of **2** in 40 ml of a mixture of EtOH–tetrahydrofuran (1:1) was treated with 100 mg of $NaBH_4$. After 5 hr the reaction mixture was diluted with water, made distinctly basic with NaOH, and extracted with ether. After washing, drying, and evaporation the ether was evaporated and the solid colorless residue was recrystallized from methanol–water to give 240 mg (40%) of **3**, mp 165°. Further recrystallization from ether–pentane gave material with mp 168–170°; ν^{KBr} 3220, 1600, 1496 cm^{-1}; δ^{CDCl_3} 2.6 (s, 1, OH), 3.00 (d, 1, J = 4.5 Hz, H-7), 3.49 (d, 1, J = 4.5 Hz, H-1), 4.18 (br s, 1, -CHOH), 5.95 (s, 1, NH), 6.5–7.3 (m, 11).

Anal. Calcd for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10; N, 10.60. Found: C, 76.98; H, 6.10; N, 10.62.

The 2-acetyl derivative of **3** was obtained by treatment of 211 mg of **3** in CH_2Cl_2 with 2 equiv of acetyl chloride in pyridine. After addition of water, etc., the CH_2Cl_2 was evaporated to give 60 mg of white solid which was recrystallized from $CHCl_3$–pentane: mp 225°; ν^{KBr} 1650, 1605, 3330 cm^{-1}; δ^{DMSO-d} 2.31 (s, 3), 2.83 (d, 1, J = 5 Hz, H-7), 4.17 (br s, 1, CHOH), 4.85 (d, 1, J = 5 Hz, H-1), 7.0–7.2 (m, 11).

Anal. Calcd for $C_{19}H_{18}N_2O_2$: C, 74.49; H, 5.92; N, 9.15. Found: C, 74.30; H, 5.95; N, 8.87.

Excess acetyl chloride gave a noncrystalline diacetyl derivative: δ^{CDCl_3} 2.20 (s, 3), 2.40 (s, 3), 2.87 (d, 1, J = 5.5 Hz, H-7), 5.04 (d, 1, J = 5.5 Hz, H-1), 5.50 (d, 1, J = 1.7 Hz, H-5), 6.78 (d, 1, J = 1.7 Hz, H-4), 7.1 (m, 10).

Reaction of 2 with Acetic Anhydride.—A solution of 0.79 g of **2** in 3 ml of Ac_2O and 5 ml of pyridine was allowed to stand for 4 hr and was then added to water. The mixture was shaken with ether and some white insoluble solid was collected by filtration and dried to give 60 mg (7%) of the 2-acetyl bicyclic compound **6**. Recrystallization from chloroform–hexane gave colorless crystals: mp 245°; ν^{CHCl_3} 1710, 1675 cm^{-1}; δ^{CDCl_3} 2.50 (s, 3), 3.10 (d, 1, J = 5.5 Hz, H-7), 5.63 (d, 1, J = 5.5 Hz, H-1), 6.7–7.3 (m, 11).

Anal. Calcd for $C_{19}H_{16}N_2O_2$: C, 74.98; H, 5.30; N, 9.21. Found: C, 74.49; H, 5.54; N, 9.04.

The ether solution from above was washed, dried, and evaporated to a yellow residue. After the residue was redissolved in ether and the solution was filtered to remove a small amount of **6**, the solution was again concentrated to give 380 mg (37%) of orange solid, mp 150°. Recrystallization from chloroform–hexane gave the enol acetate **5** as yellow needles: mp 152–154; ν^{KBr} 1775, 1690, 1370, 1320, 1210, 1170 cm^{-1} (all strong); δ^{CDCl_3} 1.65 (s, 3), 2.29 (s, 3), 6.62 (s, 1),[10] 6.8–7.3 (m, 10). The ir spectrum matched (positions and relative intensities of 23 peaks) that of a sample prepared by acetylation of the 2,3-dihydrodiazepinone.[5,6]

Anal. Calcd for $C_{21}H_{18}N_2O_3$: C, 72.82; H, 5.24; N, 8.09. Found: C, 72.64; H, 5.34; N, 7.99.

To a solution of 100 mg of the yellow crystals in 3 ml of methanol was added 2 ml of 1 *N* KOH. After 1 hr the solution was diluted with ice water and made acidic with HCl, and the resulting yellow solid was collected, washed, and dried to give 75 mg (88%) of **8**, mp 200° dec; ir identical with that of authentic sample.[5]

5,6-Diphenyl-1,5-dihydro-4*H*-1,2-diazepin-4-one (4) from 2.—A solution of 150 mg of **2** in 140 ml of benzene was irradiated in a Rayonet photochemical reactor with 16 75-W 3500-Å lamps; the solution was cooled to 13° with a circulating water jacket. After 30 min, tlc showed the formation of a yellow, faster moving compound; after 2 hr this appeared to be the major component. After 2.5 hr of irradiation the solution was evaporated *in vacuo* to a solid residue which was chromatographed on silicic acid in $CHCl_3$ solution. The material in the yellow band was treated with charcoal to remove some dark color and was then chromatographed again. Crystallization from benzene–cyclohexane

(10) This signal was absent in the spectrum of a sample prepared by acetylation of **2-4-*d*** obtained from **1** in CH_3OD–NaOD.

gave 30 mg (20%) of bright yellow crystals of **4**, mp 133–134°; the ir spectrum was identical with that of a sample prepared by base-catalyzed isomerization of the 2,3-dihydrodiazepinone.[6]

Photoisomerization of 6.—A solution of 100 mg of the 2-acetyl compound **6** in 100 ml of benzene was irradiated as described above for **2**. After 3 hr the yellow solution was evaporated and the residual oil was chromatographed on silica gel to give 65 mg of yellow oil. The ir spectrum was identical with that of a noncrystalline sample of the 1-acetyl-5,6-diphenyl-1,5-dihydrodiazepinone (**7**) obtained from **4** plus ketene.[5] (Crystalline **7** was obtained subsequent to this photoisomerization experiment.) For further characterization the irradiation product was acetylated with Ac_2O to obtain the crystalline enol acetate, mp 150–151°, identical (ir) with a sample prepared from **4**.[6]

Methylation of 2.—A suspension of 262 mg of **2** in 5 ml of acetone at 0° was treated with 443 mg (3 mequiv) of trimethyloxonium fluoroborate. The solid **2** rapidly dissolved. After 30 min, 0.7 ml of triethylamine was added and acetone was evaporated. The orange oil was dissolved in $CHCl_3$ and the solution was washed with dilute NaOH and then water, dried, and evaporated. The amber oil crystallized from $CHCl_3$–hexane to give 30 mg of white solid: mp 175°; ν^{KBr} 1660, 1610 cm^{-1}; δ^{CDCl_3} 3.55 (s, 3), 3.6–4.3 (m, 3), 4.96 (m, 1), 6.47 (m, 3), 6.9–7.4 (m, 20) (analysis showed retention of $CHCl_3$); mass spectrum *m/e* 538 (dimer of **2** + CH_2) (10),[11] 453 (38), 276 (**2** + CH_2) (80), 219 (100).

The mother liquor from the methyl dimer was chromatographed in $CHCl_3$ on silicic acid. The resulting light amber oil, obtained in one fraction, crystallized from benzene–pentane to give 30 mg of tan solid. Recrystallization from $CHCl_3$–hexane gave 20 mg of white crystals of **9**: mp 192–193°; ν^{KBr} 1640, 1560 cm^{-1} (these are assumed to be C=N stretching); δ^{CDCl_3} 3.66 (s, 3), 4.09 (d, 1, J = 5 Hz), 6.81 (d, 1, J = 5 Hz), 7.0–7.5 (m, 11); λ_{max}^{MeOH} 263 nm (ϵ 9500), 303 (8300), 334 (9000).

Anal. Calcd for $C_{15}H_{16}N_2O$: C, 78.23; H, 5.84; N, 10.14. Found: C, 78.32; H, 5.81; N, 10.19.

The mother liquor from **9** was concentrated and the residual oily solid was sublimed [70° (1 mm)] to give 25 mg of pale yellow solid. Recrystallization from hexane gave white plates of the methylpyrazole **10**: mp 101–102°; δ^{CDCl_3} 3.91 (s, 3), 7.15–7.5 (m, 5), 7.55 (s, 1), 7.75 (s, 1).

Anal. Calcd for $C_{10}H_{10}N_2$: C, 75.92; H, 6.37; N, 17.71. Found: C, 75.39, H 6.81; N, 17.61.

An authentic sample of **10** was obtained by treating a suspension of 70 mg of 4-phenylpyrazole in acetone with 220 mg of $(CH_3)_3O\cdot BF_4$ at 9° for 1 hr. After addition of Et_3N, and the usual isolation, the product mixture was chromatographed to remove some unreacted starting material and 35 mg of **10** was obtained, mp 100–101°, ir identical with that of sample described above.

Dimerization of 2 in Methanol (Dimer A).—**2** (600 mg) was warmed with 100 mg of methanol until solution was complete and the solution was then concentrated and allowed to crystallize. A first crop of 150 mg of colorless needles of dimer A was obtained. Addition of water to the mother liquor gave an additional 300 mg of tan crystals. Tlc of the first crop showed one spot, faster moving than **2**; the second crop contained mainly dimer and a small amount of **2**. Recrystallization of the combined material from methanol gave colorless needles: mp 196° dec; ν^{KBr} 3350, 3200, 1720, 1660 cm^{-1}; δ^{CDCl_3} 4.11 (t, 1), 4.7 (d, 1, J = 5 Hz), 4.8 (s, 1), 4.95 (d, 1, J = 5.7 Hz), 5.48 (m, 1, in D_2O → d, J = 5.7 Hz), 6.7 (s, 1), 6.8–7.3 (m, 21), 8.5 (br, in D_2O exchanges).

Anal. Calcd for $C_{34}H_{28}N_4O_2$ (mol wt 524): C, 77.84; H, 5.38; N, 10.68. Found: C, 77.62; H, 5.47; N, 10.33.

Anhydro Derivative of 2.—A solution of 150 mg of **2** in 2 ml of toluene was refluxed for 4 hr. On cooling, 40 mg of tan powder separated. Tlc showed a major component at slightly higher R_f value than **2**. Recrystallization of this solid from methanol gave 20 mg of light tan crystals: mp 209° dec; ν^{KBr} 3350, 1710, 1640, 1560 cm^{-1}; δ^{DMSO} 3.84 (d, 1, J = 7 Hz), 6.0 (dd, 1, J = 3 and 7 Hz), 6.80 (s, 1), 7.0–7.5 (m, 20–23); *m/e* 506 (dimer of **2** − 18) (65),[11] 479 (84), 460 (84), 436 (56), 244 (63), 206 (100).

Anal. Calcd for $C_{34}H_{26}N_4O$ (mol wt 506): C, 80.61; H, 5.17; N, 11.06. Found: C, 80.66; H, 4.89; N, 11.13.

A somewhat higher yield, and more easily purified sample of this compound, was obtained by heating dimer A in toluene for 4 hr.

Dimerization of Acetic Acid.—A solution of 200 mg of **2** (or dimer A) in 10 ml of glacial acetic acid was heated at 60° for 10 hr. After a small amount of undissolved solid was removed the acetic acid was evaporated (benzene added and evaporated) to give a brown powder. Several recrystallizations from methanol gave colorless rods: mp 235° dec; ν^{KBr} 3250, 1730, 1650 cm^{-1}; δ^{DMSO} 4.22 (d, 1, J = 8 Hz), 5.38 (dd, 1, J = 4 and 13 Hz), 5.80 (dd, 2, J = 4 and 8 Hz, in D_2O → d, J = 8 Hz), 6.5 (m, 2), 6.7 (apparent d, J = 6 Hz), 7.2 (br s, 15); *m/e* 524 (4),[11] 505 (7), 496 (6), 478 (24), 467 (20), 451 (17), 437 (18), 436 (18), 363 (20), 334 (21), 308 (23), 262 (40), 247 (42), 235 (100), 234 (55).

Anal. Calcd for $C_{34}H_{28}N_4O_2$ (mol wt 524): C, 77.84; H, 538; N, 10.68. Found: C, 78.06; H, 4.81; N, 10.86.

Registry No.—**1**, 24302-17-8; **2**, 40635-72-1; **3**, 40635-73-2; **3** 2-acetyl derivative, 40635-74-3; **3** diacetyl derivative, 40635-75-4; **4**, 40635-76-5; **5**, 40635-77-6; **6**, 40635-78-7; **8**, 24301-66-4; **9**, 40635-80-1; **10**, 10199-69-6; dimer A, 40633-49-6; 4-phenylpyrazole, 10199-68-5; $(CH_3)_3O\cdot BF_4$, 420-37-1.

(11) Numeral in parentheses is per cent intensity of base peak (100).