Heterocyclic Studies. 49. Preparation and Reactions of Dihydro-3,5,7-trimethyl-6-phenyl-1,2-diazepin-4-ones[1]

Chris A. Veale, Arnold L. Rheingold, and James A. Moore*

Department of Chemistry, University of Delaware, Newark, Delaware 19716

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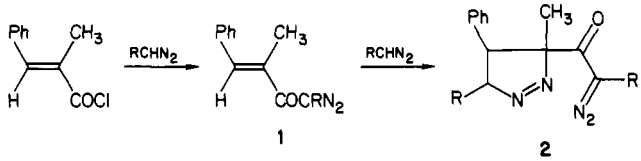
The reaction of diazoethane with α-methylcinnamoyl chloride or mixed anhydrides leads to a 3-(diazopropionyl)pyrazoline **5**, which is converted to the 1,5- or 2,3-dihydrodiazepinone (**11** and **12**). The chemistry of these diazepinones and the 3,5,7-trimethyl-1,2-diazabicyclo[3.2.0]-3-heptenone **15** is compared to that of the monomethyl series. The aza-2,5-cyclohexadienone **25** is described.

Previous studies in this series have dealt with (diazoacetyl)pyrazolines and dihydrodiazepinones stemming from reactions of unsaturated acid derivatives and diazomethane.[2,3] In this paper we describe the products resulting from the corresponding reactions with diazoethane. The (diazoacetyl)pyrazolines **2** (R = H) can be prepared in two steps by formation of the unsaturated diazo ketone **1** (R = H) from α-methylcinnamoyl chloride followed by cycloaddition of further diazomethane to give **2** (eq 1). In



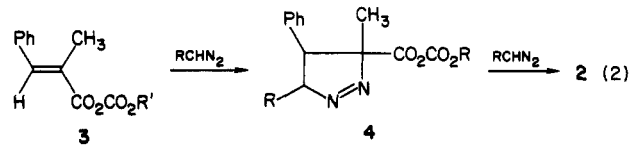
(1)

principle the use of diazoethane in the sequence of eq 1 should permit the introduction of methyl groups as either or both of the R substituents in **2**, depending on the order of steps.

Wilds and Meader have shown that diazoethyl ketones can be prepared in good yields from acid chlorides and diazoethane at −20 °C.[4] Unstable products containing a further C_2H_4 increment were obtained with excess diazoethane. On repeating this work we could not isolate the latter products, but NMR spectra of reaction mixtures showed that a slow reaction did occur on treatment of either diazomethyl or diazoethyl *p*-tolyl ketone with diazoethane.

Attempts to obtain the pyrazolines **2** with one additional methyl group failed. Reaction of diazoethane with the unsaturated diazomethyl ketone **1** (R = H) gave either unreacted starting material or unstable mixtures whose spectra indicated reaction of the $COCHN_2$ group with diazoethane. An attempt to obtain the unsaturated diazoethyl ketone **1** ($R = CH_3$) from α-methylcinnamoyl chloride and 2.2 mol of diazoethane gave only small amounts of the pyrazoline **2** ($R = R = CH_3$); if any unsaturated diazoethyl ketone was present, we were unable to find it.

These results suggest that the sequence of steps leading to the pyrazoline from the acid chloride and diazoethane is cycloaddition prior to acylation rather than the steps shown in eq 1, which obtain with diazomethane. This same "reverse" sequence, i.e., eq 2, was implicated earlier in the



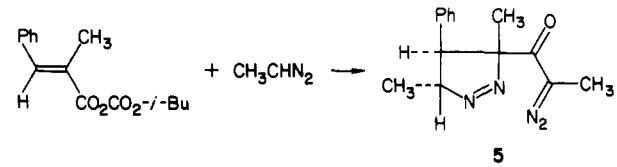
(2)

reaction of diazomethane with unsaturated carboxylic–carbonic anhydrides.[3] This method leads directly to the (diazomethyl)pyrazolines **2** in one step and provides a more convenient and efficient process for these products. In the case of (*Z*)-α-phenylcinnamic acid, the (diazoacetyl)pyrazoline could be obtained only from the anhydride; the unsaturated diazo ketone prepared from the acid chloride was unreactive.[5]

To test this point directly, an NMR comparison was made of the rate of pyrazoline formation from the unsaturated diazo ketone **1** (R = H) and the mixed anhydride **3** ($R' = C_2H_5$) with diazomethane. This experiment confirmed a significantly faster reaction with the anhydride. Although the pyrazoline anhydride **4** must be an intermediate in the reaction of **3**, no NMR peaks corresponding to **4** were observed. Qualitative comparison of several other compounds with the general structure (*E*)-$C_6H_5CH{=}C(CH_3)COR$ in the reaction with diazomethane indicated that the rate of pyrazoline formation decreased for R in the order $OCO_2Et \simeq CH_2Cl > CHN_2 \simeq CH_3 > OCH_3$.

With the acid chloride (R = Cl) cycloaddition of diazomethane would probably be at least as rapid as that of the anhydride, but the much more rapid acylation prevents a comparison [the unsaturated diazo ketone (**1**, R = H) is isolated in 70% yield with 2 equiv of diazomethane]. With diazoethane, however, which undergoes cycloaddition with methyl methacrylate about 9 times faster than diazomethane,[6] cycloaddition is apparently faster than acylation, even with the acid chloride, and therefore the (diazoacyl)pyrazoline is the product.

For preparative purposes the (diazopropionyl)pyrazoline **5** was obtained in 54% yield as bright yellow crystals by reaction of (*E*)-α-methylcinnamic isobutoxycarbonyl anhydride with 3 mol of diazoethane. The pyrazoline was a single stereoisomer; the *trans*-4-phenyl-5-methyl structure is assumed from simple steric considerations; *J* (4-H,5-H) was 8.5 Hz.



Conversion of (diazoacetyl)-1-pyrazolines **6** to dihydrodiazepinones **9** involves three steps: isomerization to the 5-pyrazoline **7**, acid-catalyzed cyclization to a [3.2.0]bicyclic ketone **8**, and ring opening to **9** (Scheme I). These steps have been carried out separately and the intermediates **7**

(1) Part 48: Moore, J. A.; Rothenberger, O. S.; Fultz, W. C.; Rheingold, A. L. *J. Org. Chem.* **1984**, *49*, 1261.
(2) Moore, J. A. *J. Org. Chem.* **1955**, *20*, 1607.
(3) Nabeya, A.; Culp, F. B.; Moore, J. A. *J. Org. Chem.* **1970**, *35*, 2015.
(4) Wilds, A. L.; Meader, A. L. *J. Org. Chem.* **1948**, *13*, 763.
(5) Nabeya, A., unpublished observations, 1970.
(6) Ledwith, A.; Parry, D. *J. Chem. Soc. C* **1966**, 1408.
(7) Ratcliffe, R. W.; Salzmann, T. N.; Christensen, B. G. *Tetrahedron Lett.* **1980**, *21*, 31.
(8) McClure, D. E.; Lumma, P. K.; Arison, B. H.; Jones, J. H.; Baldwin, J. J. *J. Org. Chem.* **1983**, *48*, 2675.

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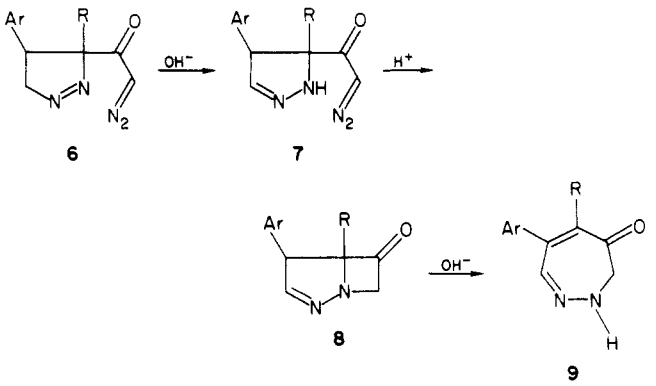
Scheme I



and 8 isolated.[9] The sequence has usually been accomplished more efficiently in one step by heating 6 in glacial acetic acid, although the latter procedure leads to extensive decomposition in some cases, and this occurred also with 5.

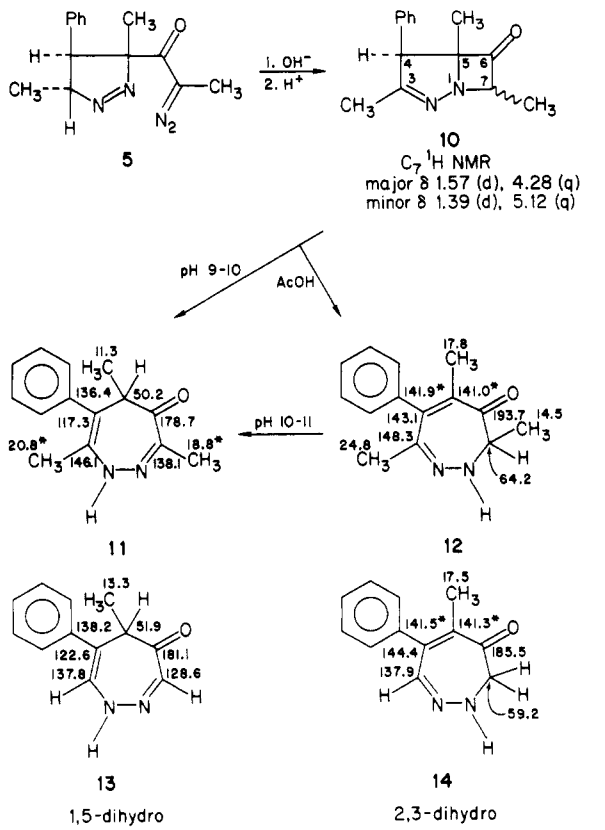
Another very effective approach that has been used recently to effect C–N bond formation is the rhodium-catalyzed carbenoid insertion of α-diazo-β-keto esters into NH bonds.[7] Most examples of this process involve diazodicarbonyl systems, but metal-catalyzed α-diazoamide insertion into an OH bond has been reported.[8] We have tried this carbenoid method in the (diazoacetyl)pyrazoline series, under the crystalline Δ^5-pyrazoline 7 (Ar = Ph, R = CH_3).[9] Under the usual conditions and amounts of catalyst, very little reaction occurred. In refluxing toluene with 20 wt % $Rh_2(OAc)_4$, a mixture of 8 and 9 was obtained, which with base gave a 27% yield of diazepinone 9 (Ar = Ph, R = CH_3). Decomposition of the sensitive pyrazoline is a limiting factor, and the carbenoid approach clearly has no advantage over the acid-catalyzed diazonium method in this series.

In the trimethyl series, heating the (diazopropionyl)-pyrazoline 5 in glacial acetic acid gave a black tar. A one-pot stepwise procedure was then devised which has been found to be generally useful and quite convenient. The 1-pyrazoline is treated in methanol–water solution with base to isomerize the pyrazoline double bond, and the solution is then acidified to pH 1 to effect cyclization. Neutralization permits isolation of the bicyclic ketone 8, or the diazepinone 9 is obtained by raising the pH to 10.

The bicyclic ketone obtained at pH 5.5 from pyrazoline 5 was an oil whose NMR spectrum showed the presence of two epimers of 10 in about 2:1 ratio (Scheme II). These isomers could not be crystallized nor could they be separated by chromatography. The chemical shifts of the 7-CH_3 doublet and 7-H quartet peaks in the two epimers differed considerably, but no enhancements were obtained in NOE experiments, and assignment of exo and endo configurations to the major and minor isomers would be speculative.

Ring opening of the bicyclic ketone mixture at pH 6–8 led to the rapid formation of two yellow compounds which were very difficult to separate. One of these compounds, shown to be the 2,3-dihydro-3,5,7-trimethyldiazepinone 12, was isolated in 20% yield by treatment of the bicyclic ketones with glacial acetic acid for 2 h at 20 °C. Longer treatment led to a mixture. The second product was obtained in low yield from the bicyclic ketone at pH 9 and was characterized as the 1,5-dihydro-3,5,7-trimethyldiazepinone 11.

Scheme II



The structures of 11 and 12 are based on comparisons of spectral data with those of the corresponding 1,5-dihydro- and 2,3-dihydrodiazepinones in the 5-methyl series (13 and 14). ^{13}C NMR values (indicated in Scheme II) are consistent for the two 2,3-dihydro and the two 1,5-dihydro compounds. A very clear distinction between the two tautomeric series is found in the congruent mass spectral fragmentation pathways of the 1,5-dihydro compounds 11 and 13 and of the 2,3-dihydro isomers 12 and 14.[10] In the 1,5-dihydro series the two most abundant fragment ions from 11 and 13 appear to arise from loss of a (RCN, CO, H) fragment or from loss of the 5-CH_3 group followed by loss of CO and then RCN. A peak 14 (CH_2) or 28 ($2CH_2$) mass units higher in the spectrum of 11 matches in relative intensity each of the six highest mass peaks of 13. The spectrum of the 2,3-dihydro compounds are more complex, and the congruence of the trimethyl and monomethyl spectra is less complete. Prominent fragmentation appears to be loss of ketene from C3–C4 or loss of RCH=NH from C3–N2. Both 12 and 14 gave a very strong *m/e 116* ion due to $PhC{\equiv}CCH_3^{+\cdot}$. The latter was small in the 1,5-dihydro spectra. All four compounds gave a *m/e* 115 ion (phenylcyclopropenium).

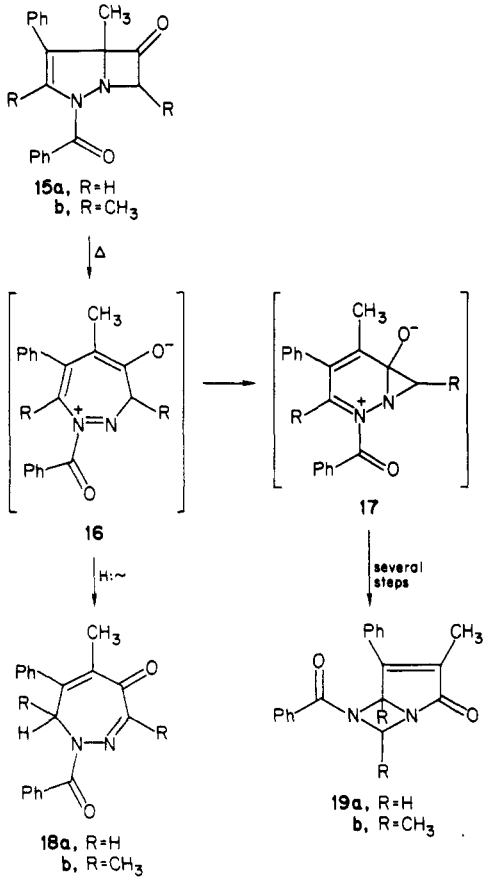
The formation of the 1,5-dihydrotrimethyldiazepinone from 10 in aqueous alcohol at pH 8–9 was shown to be due to rapid isomerization of the initially formed 2,3-dihydro tautomer 12. The 2,3 → 1,5 conversion occurs also in the 5-methyl series (14 → 13)[11] and leads to an equilibrium containing the more stable 1,5-dihydro isomer as the major component (~5:1). However, in the monomethyl series this process requires much more drastic conditions (3 days in 2.5 N NaOH–Me_2SO at 60 °C). The very facile 2,3 →

(9) Moore, J. A.; Marascia, F. J.; Medeiros, R. W.; Wineholt, R. L. *J. Org. Chem.* **1966**, *31*, 34.

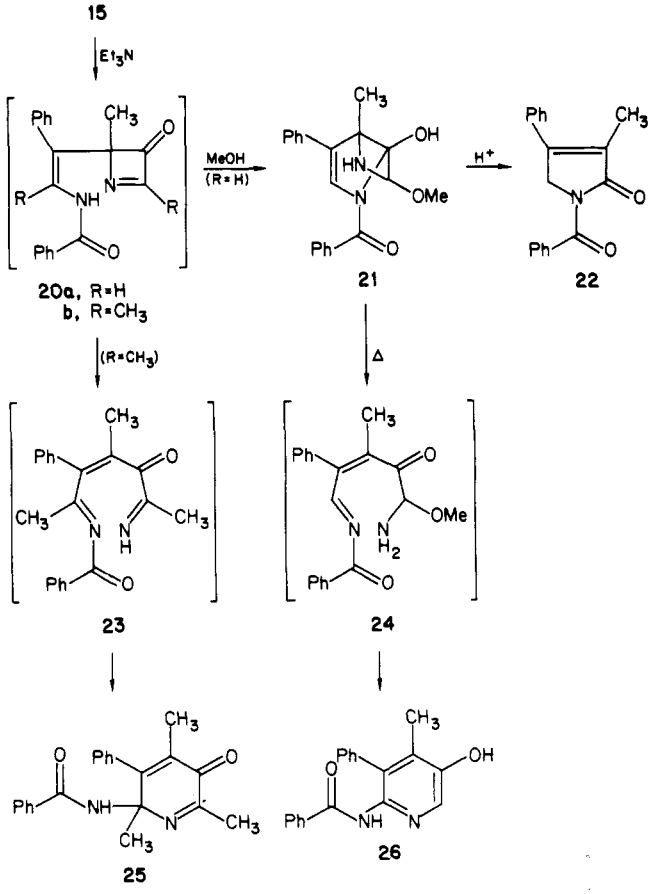
(10) Fragment ion formulas were confirmed by precise mass measurements; full data and suggested structural assignments are given in the supplementary material (see paragraph at end of paper).

(11) Pleiss, M. G.; Moore, J. A. *J. Am. Chem. Soc.* **1968**, *90*, 1369.

Scheme III



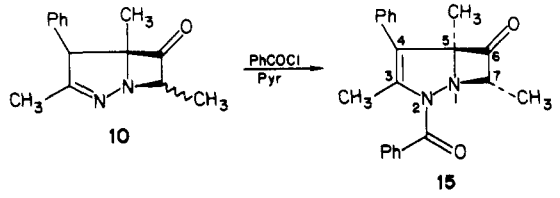
Scheme IV



1,5 shift in the trimethyl series is attributed to relief of strain in the sterically congested trisubstituted C5–C7 segment of **12**.

Some of the most interesting chemistry in this series has been found in reactions of the 2-acyl-Δ^3-1,2-diazabicyclo-[3.2.0]heptenones obtained by acylation of the Δ^2-bicyclic ketones or the 2,3-dihydrodiazepinones. The preferred method in the monomethyl series is acylation of the diazepinones **14**,[9] but because of the difficulty in isolating the pure trimethyl-2,3-dihydrodiazepinone **12**, the most practical route to the trimethyl compound was from the bicyclic precursor **10**.

Benzoylation of the epimeric mixture of ketones **10** gave the crystalline 2-benzoylbicyclo-3-hepten-6-one **15** in 50% yield. This product was sterically homogeneous, indicating either that only the major epimer of the Δ^2-bicyclic ketone **10** reacted in >80% yield or much more probably that enolization occurs during the acetylation, leading to the thermodynamically favored ketone. The same product was obtained also by benzoylation of the diazepinone **12**.



The 7-*exo*-methyl configuration of **15** was defined by crystallography. The two rings in the bicyclic system of **15** are nearly planar, with the average deviation from the mean plane of the ring bonds being 0.074 Å in the four-membered ring and 0.046 Å in the five-membered ring. The angle between planes is 111.9°, close to the tetrahedral bond angle for the C4–C5–C6 backbone.

The 2-acyl bicyclic ketones **15** undergo rather complex reactions on heating. At 80–90 °C, the monomethyl compound **15a** (Scheme III) gives a mixture of the 1,7-dihydrodiazepinone **18a** and the 1,6-diazabicycloheptenone **19a** in a ratio of 1:10. The former (**18a**) has been shown to arise via the diazepinium betaine **16**.[12] Formation of the major product **19a** (~80% yield) is thought to involve **17a** and subsequent intermediates.[13] Thermolysis of the trimethyl ketone **15b** led to a mixture from which only one product (15%) was characterized. The bicyclic structure **19b** is ruled out by the presence of only one ^{13}C signal (d, 58.6 ppm) between 21 and 125 ppm (**19a** shows 68.9 (t) and 70.7 (d) ppm). The spectra were generally consistent for **18b**, and this 1-benzoyl-1,7-dihydrodiazepinone structure is assigned for the thermal rearrangement product in the trimethyl series. No product resembling **19b** was seen. The factors influencing the partition between the two pathways observed in the monomethyl series are not well understood. Although the yield of **18b** is very low it is nevertheless 3 times higher than that of **18a** in the monomethyl case. The predominance of **18** vs. **19** in the trimethyl series may again reflect the greater relief of steric compression in **16**, R = CH_3.

Another set of complex reactions of the 2-acyl-1,2-diazabicyclo ketone **15a** occurs on heating in methanol, which leads to a mixture of the pyrrolinone **22** and pyridine **26** (Scheme IV). This process occurs by an initial β-elimination, presumably giving **20a**; an intermediate **21** resulting from methanol addition and cyclization of **20a** can be isolated by very mild treatment (10 min, 35 °C) of **15a** with methanol–1% triethylamine.[14] Thermal rearrangement

(12) Rothenberger, O. S.; Moore, J. A. *J. Org. Chem.* **1972**, *37*, 2796.
(13) Moore, J. A.; Staskun, B.; Blount, J. F. *J. Org. Chem.* **1976**, *41*, 3156.

of **21** gives **26**, and acid-catalyzed solvolysis gives **22**. The same reactions with the trimethyl ketone **15b** could lead to a 5-methyl derivative of **22** but not to an aromatic pyridine homologous to **26**. No reaction occurred on heating **15b** in methanol. The reaction with methanol–Et_3N was much slower than that of **15a**, but more vigorous conditions (4 h, 50 °C) gave a single isomeric product (70%) which was found by crystallographic analysis to be the azacyclohexadienone **25**. Thus although the final aromatization step is blocked by methyl substitution, the reaction of **15b** otherwise parallels that in the monomethyl series. The α-methoxyamine **24** was assumed to be an intermediate in the formation of **26** from **21**, but the formation of **25** can be most directly represented as occurring by cyclization of the diimine **23**.

Experimental Section

NMR spectra were obtained on a Bruker WM-250 spectrometer. Melting points were determined on a Fisher-Johns block. Column chromatography was carried out as described by the "TLC mesh" procedure[15] using 30% ethyl acetate–70% petroleum ether unless other specified.

3-(α-Diazopropionyl)-3,5-dimethyl-4-phenyl-Δ¹-pyrazoline (5). To a solution (590 mL) of 0.22 mol of diazoethane in ether (prepared in 60% yield from ethyl *N*-nitroso-*N*-ethylcarbamate[4]) was added an ether solution of 18 g (0.069 mol) of the mixed anhydride prepared from 12.2 g of α-methylcinnamic acid, 9.7 mL of isobutyl chloroformate, and 10.4 mL of Et_3N. The original orange color faded to yellow after 1 h. After 24 h of standing at 0 °C the solution was filtered through Celite and evaporated to an oil, which crystallized to give 6.85 g of **5**, mp 85–86 °C. Successive evaporation and crystallization gave a second crop of 1.05 g (mp 84–88 °C) and a third crop of 0.76 g (mp 83–85 °C); total yield, 54%. A sample crystallized from MeOH had mp 86–88 °C: IR (KBr) 2080, 1610, 1555 cm^{-1}; ^1H NMR δ 1.13 (s, 3, 3-CH_3), 1.51 (d, 3, J = 7.0 Hz, 5-CH_3), 2.07 (br s, 3, CH_2CH_3), 3.47 (d, 1, J = 8.5 Hz, 4-H), 4.78 (dq, 1, 5 lines, H-5), 7.26 (m, 5); mass spectrum, no M^+, m/e 185 (100%).

Anal. Calcd for $C_{14}H_{16}N_4O$: C, 65.60; H, 6.29; N, 21.86. Found: C, 65.42; H, 6.34; N, 21.65.

4-Phenyl-3,5,7-trimethyl-1,2-diazabicyclo[3.2.0]-2-hepten-6-one (10). A solution of 2.0 g of the 1-pyrazoline **5** in 25 mL of methanol was treated with 4 mL of 1 N methanolic KOH. After 30 min at 5 °C, TLC showed complete conversion to a lower R_f compound (5-pyrazoline). The solution was diluted with 100 mL of water (oil separated), and 1 N aqueous HCl was added with stirring to pH 1. Vigorous gas evolution occurred, and all but a trace of oil redissolved. After 20 min the pH was adjusted to 5.5 by addition of $NaHCO_3$ solution. The methanol was evaporated, and the mixture was extracted with CH_2Cl_2; the organic phase was a brilliant emerald green color. After drying and evaporation a yellow oil was obtained: IR (film) 1790 cm^{-1}. The ^1H NMR spectrum showed only peaks for the products and residual solvent. The NMR peaks in the mixture were assigned on the basis of the relative peak areas for the two sets of signals.

Epimer A (major): ^1H NMR δ 1.14 (s, 3, 5-CH_3), 1.57 (d, 3, J = 7.7 Hz, 7-CH_3), 1.89 (s, 3, 3-CH_3), 4.28 (q, 1, J = 7.7 Hz, 7-H), 4.40 (s, 1, 4-H), 7.0–7.4 (m, 5).

Epimer B (minor): ^1H NMR δ 1.19 (s, 3, 5-CH_3), 1.39 (d, 3, J = 7.2 Hz, 7-CH_3), 1.91 (s, 3, 3-CH_3), 4.20 (s, 4-H), 5.12 (q, J = 7.2 Hz, 7-H), 7.0–7.4 (m, 5).

2,3-Dihydro-6-phenyl-3,5,7-trimethyl-1,2-diazepin-4-one (12). The mixture of epimeric Δ²-bicyclic ketones **10** obtained from 1.0 g of pyrazoline **5** as described above was dissolved in 4 mL of glacial acetic acid at 25 °C. TLC showed rapid development of a yellow product of higher R_f than **10**. After 2 h the solution was poured into 30 mL of saturated $NaHCO_3$ solution, and the products were extracted with ether. The washed and dried ether solution was evaporated to an oil, which was chromatographed on 50 g of silica gel (20% EtOAc–petroleum ether). The first fractions obtained provided 190 mg of yellow crystals (one spot on TLC) of **12** and unreacted bicyclic ketone. Recrystallization from methanol–water gave 125 mg of yellow needles, mp 108–109 °C. From another run, crystallization from ether gave bright yellow crystals, mp 109–110 °C: IR (KBr) 3260, 1640, 1450 cm^{-1}; ^1H NMR δ 1.49 (d, 3, J = 6.9 Hz, 3-CH_3), 1.76 (s, 3, 5- or 7-CH_3), 1.78 (s, 3, 7- or 5-CH_3), 3.35 (q, 1, J = 6.9 Hz, 3-H), 5.79 (br s, 1, NH), 7.06–7.10 (m, 2), 7.34–7.45 (m, 3); mass spectrum, m/e (% intensity) 228 (12), 187 (14), 186 (76), 185 (71), 172 (47), 144 (39), 116 (100), 115 (86); m/e calcd for $C_{14}H_{16}ON_2$ 228.126, found 228.129.

Anal. Calcd for $C_{14}H_{16}ON_2$: C, 73.65; H, 7.06; N, 12.27. Found: C, 73.17; H, 6.88; N, 11.56.

In another experiment (from 1 g of **5**) a second TLC spot for the 1,5-dihydro isomer **11** developed after 2.5 h of treatment in AcOH. The oil obtained after workup crystallized to give 85 mg of yellow crystals, mp 97–103 °C; chromatography gave an additional 230 mg, mp 95–100 °C; total 36% of 2,3-dihydrodiazepine containing 5–10% of 1,5-dihydro isomer.

1,5-Dihydro-6-phenyl-3,5,7-trimethyl-1,2-diazepin-4-one (11). Δ¹-Pyrazoline **5** (300 mg) was added to 1 mL of 1 N methanolic KOH. After 40 min at 25 °C, 3 mL of 1 N HCl was added (gas evolved). After 1 h the pH was adjusted to 9.0 with aqueous KOH. After 1 h at 25 °C the solution was neutralized and extracted with CH_2Cl_2. The oil obtained after evaporation was chromatographed on 10 g of silica gel (30% EtOAc–petroleum ether). The yellow band that was eluted was evaporated to give 20 mg of crystals. After recrystallization from ether the melting point was 167–168 °C: IR (KBr) 3300, 1625 cm^{-1}; ^1H NMR δ 1.02 (d, 3, J = 7 Hz 5-CH_3), 1.89 (s, 3), 2.25 (s, 3), 3.20 (q, 1, J = 7 Hz, 5-H), 7.05–7.1 (m, 2), 7.24–7.35 (m, 3), 8.30 (s, 1, NH); mass spectrum, m/e (% intensity) 228 (35), 185 (38), 158 (100), 144 (95); m/e calcd for $C_{14}H_{16}ON_2$ 228.126, found 228.129.

Anal. Calcd for $C_{14}H_{16}N_2O$: C, 73.65; H, 7.06; N, 12.27. Found: C, 73.52; H, 7.18; N, 12.18.

Conversion of 2,3-Dihydro to 1,5-Dihydro. A mixture of 2,3- and 1,5-dihydrodiazepinones (mp 95–100 °C) (375 mg), containing most 2,3-dihydro, was allowed to stand in methanolic KOH at pH 13. After 4 days, the solution was acidified to pH 5. Evaporation and addition of water gave 160 mg of pale yellow solid, mp 151–154 °C; recrystallization from methanol–water gave fine yellow needles of **11**, 110 mg, mp 166–167 °C.

2-Benzoyl-4-phenyl-3,5,7-trimethyl-1,2-diazabicyclo-[3.2.0]-3-hepten-6-one (15). (a) From Bicyclic Ketone. Pyrazoline **5** (2.0 g) was converted to the epimeric mixture of Δ²-bicyclic ketones (**10**) as described above. The bicyclic ketone mixture in 20 mL of CH_2Cl_2 was treated with 1.8 mL (15 mmol) of benzoyl chloride and 1.3 mL of pyridine. After 2 h the solution was poured into iced 1 N HCl. After ether was added, the organic phase was extracted thoroughly with HCl and then $NaHCO_3$. Evaporation of the dried solution gave an oil, which crystallized to give 0.85 g of **15**. Chromatography of the mother liquor on 50 g of silica gel gave an additional 0.40 g of **15**, total 1.25 g (49%), mp 124–125 °C. Recrystallization from methanol gave a sample with mp 125–127 °C: IR (KBr) 1800, 1645 cm^{-1}; ^1H NMR δ 1.03 (d, 3, J = 7.3 Hz, 7-CH_3), 1.38 (s, 3, 5-CH_3), 2.48 (s, 3, 3-CH_3), 4.55 (q, 1, J = 7.3 Hz, 7-H), 7.35 (m, 9), 7.73 (m, 1); m/e calcd for $C_{21}H_{20}N_2O_2$ 332.152, found 332.153.

Anal. Calcd for $C_{21}H_{20}N_2O_2$: C, 75.88; H, 6.07; N, 8.43. Found: C, 75.89; H, 6.13; N, 8.36.

Later fractions of the chromatography gave 70 mg of colorless crystals of another product, mp 149–151 °C.

(b) From 2,3-Dihydrodiazepinone. To a solution of 150 mg of **12** in 3 mL of CH_2Cl_2 were added 0.2 mL of benzoyl chloride and 0.5 mL of *N,N*-dimethylaniline. After 2 h at 25 °C the solution was poured into iced HCl and worked up as above to give 90 mg (40%) of colorless crystals, recrystallized from methanol, mp 126–126 °C; spectra were identical with those above.

1-Benzoyl-6-phenyl-3,5,7-trimethyl-1,7-dihydro-2,3-diazepin-4-one (18b). A solution of 1.0 g of bicyclic ketone **15** in 20 mL of toluene was heated at reflux for 3.5 h. TLC showed the presence of three new compounds. The oil obtained after evaporation was chromatographed on 60 g of silica gel (10% ethyl

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(16) Crystal data for **15**: $C_{21}H_{20}N_2O_2$, $P\bar{1}$, a = 8.835 (4) Å, b = 10.320 (5) Å, c = 11.313 (6) Å, α = 108.91 (4)°, β = 109.00 (4)°, γ = 96.29 (4)°, V = 895.6 (8) Å³, Z = 2. Crystal data for **25**: $C_{21}H_{20}N_2O_2$, $Pbca$, a = 9.606 (3) Å, b = 36.092 (11) Å, c = 10.580 (3) Å, V = 3668 (2) Å³, Z = 8.

acetate–petroleum ether). The first fractions eluted gave 150 mg of white solid, which was recrystallized from ether to give 100 mg of **18b**, mp 123–124 °C: IR 1695, 1640, 1602, 1590 cm^{-1}; UV max 270 nm; ^1H NMR δ 1.71 (d, 3, J = 6.9 Hz, 7-CH_3), 1.95 (s, 6, 3- and 5-CH_3), 6.46 (q, 1, J = 6.9 Hz, 7-H), 7.44 (m, 7), 8.01 (m, 2); ^{13}C NMR 14.1 (q), 15.3 (q), 21.0 (q), 58.6 (d), 127.8–128.9 (5 lines) 133.0 (d), 135.6 (s), 135.8 (s), 136.4 (s), 143.3 (s), 144.2 (s), 160.5 (s), 196.8 (s); m/e calcd for $C_{21}H_{20}N_2O_2$ 332.1524, found 332.152.

Further elution of the column with 100% ethyl acetate and finally ethanol gave 125 mg of very insoluble material and 210 mg of soluble material which was recrystallized to give 45 mg of colorless crystals, mp 241–243 °C, which was not further investigated.

4-Benzamido-5-phenyl-2,4,6-trimethyl-3-aza-2,5-cyclohexadienone (25). A solution of 310 mg (0.93 mmol) of bicyclic ketone **15** (mp 126–127 °C) in 7 mL of $CHCl_3$–MeOH–Et_3N (5:10:0.4) was heated for 3.7 h at 50 °C. TLC showed nearly complete disappearance of starting material and formation of a single, less polar product. Solvent was removed in vacuo, and the residue was evaporated twice with CCl_4 and then crystallized from ether to give 245 mg of yellow solid. Recrystallization from methylene chloride–petroleum ether gave 210 mg of large greenish yellow crystals, mp 157–158 °C, and a second crop of 30 mg, mp 155–156 °C (75% yield): IR (KBr) 3320 (NH), 1675, 1655, 1640 cm^{-1}; ^1H NMR δ 1.68 (s, 6), 2.38 (s, 3), 6.80 (br, 1), 7.1–7.9 (m, 10); ^{13}C NMR 12.3 (q), 20.1 (q), 28.6 (q), 70.2 (s), 127–128 (aryl), 131.8 (d), 132.2 (s), 134.1 (s), 136.8 (s), 162.4 (s), 163.5 (s), 167.4 (s), 176.9 (s); m/e calcd for $C_{21}H_{20}N_2O_2$ 332.153, found 332.154.

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Registry No. (*E*)-**3** (R′ = $CH_2CH(CH_3)_2$), 96213-69-3; **5**, 96213-61-5; **10**, 96213-62-6; **11**, 96213-63-7; **12**, 96213-64-8; **13**, 19971-06-3; **14**, 1706-26-9; **15a**, 5109-45-5; **15b**, 96213-65-9; **18a**, 96213-66-0; **18b**, 96213-67-1; **19a**, 10137-20-9; **25**, 96213-68-2.

Supplementary Material Available: Tables of mass spectral data for diazepinones **11**–**14** and crystallographic data and tables of atomic coordinates, bond lengths, and bond angles for compounds **15** and **25** (17 pages). Ordering information is given on any current masthead page.

Regioselective Para Chlorination of Activated Aromatic Compounds

William David Watson[1]

Organic Chemicals Research, The Dow Chemical Company, Midland, Michigan 48640

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A series of 2-alkylphenols were chlorinated with chlorine, sulfuryl chloride, and sulfuryl chloride catalyzed with a divalent sulfur compound and a metal halide. The latter chlorinating system is the most regioselective for both para chlorination and for the degree of chlorination, i.e., monochlorination. The selectivity is also demonstrated for 2-halophenols, 3-substituted phenols, and aromatic ethers. The reactive intermediate is proposed to be $[R_2SCl^+][MCl_4^-]$ which explains the selectivity to the para isomer due to the bulkiness of the chlorinating agent. The observed differences in isomer distribution with the studied phenols are explained by the degree of hydrogen bonding of the phenol as seen in the IR and NMR as well as the differences in reactivity.

It has long been the desire of organic chemists to control isomer distributions in electrophilic aromatic substitution reactions. Techniques used in the chlorination of activated aromatic compounds such as phenols include reagents,[2] solvents,[3] catalysts,[4] concentrations,[5] and temperature.[6] Previous work in this laboratory on the chlorination of phenols has demonstrated techniques to enhance ortho chlorination.[7] For example, the chlorine chlorination of a 5% solution of phenol in refluxing carbon tetrachloride yields a maximum of 68% 2-chlorophenol. After this work our attention turned to methods to enhance para chlorination. A preliminary paper[8] has reported the regioselective para chlorination of 2-methylphenol using sulfuryl chloride catalyzed by diphenyl sulfide and aluminum chloride.

It is the purpose of this work to report the generality of the regioselective para-chlorinating system by reporting data on various substituted phenols and aromatic ethers and to compare these results with data generated when chlorine and sulfuryl chloride are used. Chlorine is a strong electrophile and reacts rapidly with neat aromatic compounds. Sulfuryl chloride[9] is a relatively weak electrophile[10] and monochlorinates activated compounds slowly at room temperature. A metal halide catalyst with sulfuryl chloride does not significantly increase the rate of reaction but does improve selectivity to the *p*-chloro isomer.[11]

(1) Current address: Polycarbonate Research, Dow Chemical Co., B-3817 Building, Freeport, TX 77541.

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