Formation of Pyrazoles from 3,3-Disubstituted 2,4-Pentanediones and 2-Hydroxyethyl Hydrazines. Coproduction of 3,3a,5,6-Tetrahydropyrazolo[3,2-*b*]oxazoles

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Condensation of various 3,3-disubstituted 2,4-pentanediones with 2-hydroxyethylhydrazines affords 3,3a,5,6-tetrahydropyrazolo[3,2-*b*]oxazoles resulting from an intramolecular alcohol–enamine reaction of the initially formed 5-methylene-2-pyrazolines. Nuclear magnetic resonance studies of these nonplanar heterobicycles which have been isolated indicate that phenyl, when attached to C-5, generally occupies a single preferred configuration. When one or both of the starting diketone substituents is allylic, a rearrangement, evidently of the Claisen–Cope type, occurs producing isomeric pyrazoles as coproducts. Tetrahydropyrazolo[3,2-*b*]oxazoles bearing one or more allyl groups at C-3 undergo isomerization to their pyrazole coproducts under thermal conditions (*ca.* 200°) or upon simple refluxing in ethanol solution. This latter transformation of 3-allyltetrahydropyrazolo-[3,2-*b*]oxazoles suggests that they are kinetically favored products which give rise to their thermodynamically stable pyrazole isomers during the course of the condensation reaction.

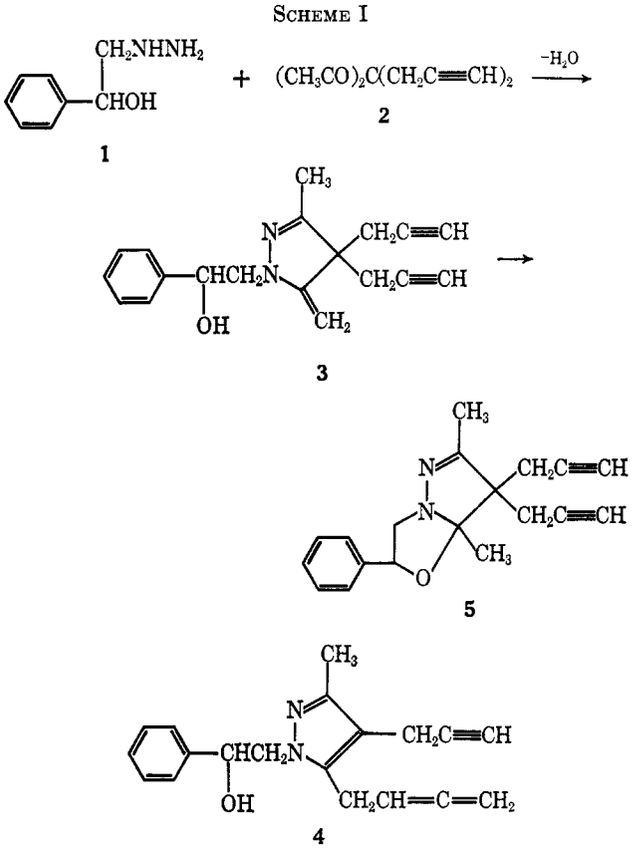
Earlier we noted that 3,3-disubstituted 2,4-pentanediones having allylic or propargylic groups at C-3 react with monosubstituted hydrazines forming rearranged pyrazoles *via* a Claisen–Cope type of rearrangement.[1] By means of an exceptionally facile propargylic rearrangement, the reaction enables preparation, in good yields, of pyrazoles having C-5 allenic substitution. The aim of obtaining such unsaturated pyrazoles with additional pharmacophoric β-phenylethyl substitution suggested α-(hydrazinomethyl)benzyl alcohol (**1**) as an appropriate carbonyl reactant.

Results and Discussion

Treatment of 3,3-di(2-propynyl)-2,4-pentanedione (**2**) with **1** was performed in refluxing ethanol under conditions typical[1] for formation of **4** by propargylic rearrangement (Scheme I). The product, obtained in 59% yield, displayed none of the expected spectroscopic features of **4**, however, but was a nonhydroxylic isomer with strong C–O–C (9.95 μ) absorption. The nmr spectrum showed two methyl groups and three AMX protons as pairs of doublets at δ 3.07, 3.99, and 4.65. These data, along with mass spectral studies, led to formulation of the new product as 3,3a,5,6-tetrahydro-2,3a-dimethyl-5-phenyl-3,3-di(2-propynyl)pyrazolo-[3,2-*b*]oxazole (**5**) representing a heterobicyclic system described only recently by Gillis and Weinkam.[2]

Formation of **5** may be viewed as an intramolecular nucleophilic interception of the Claisen–Cope precursor **3** by an alcohol–enamine addition related to the oxidative cyclization of 2-pyrrolidinoethanols reported by Leonard and Musker.[3] We had observed that allylic groups at the pyrazoline C-4 of intermediates such as **3** rearrange more rapidly than do propargylic groups.[1]

SCHEME I



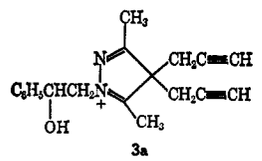
Thus it was not unexpected that in the reaction of 3,3-diallyl-2,4-pentanedione (**6**) with **1** rearrangement competed with enamine cyclization giving both the pyrazole **10** and the tetrahydropyrazolo[3,2-*b*]oxazole **9** in crude yields of 54 and 24%, respectively (Scheme II). The relatively nonpolar **9** was readily separated from **10** by column chromatography.

Condensation of **1** with **6** to give the carbinol **7** is a reasonable first step and the ability to form enamines such as **8** under these reaction conditions has been demonstrated.[1] Compound **9** may then arise *via* paths A or B. The ability of **9** to serve as the precursor of **10**

(1) D. T. Manning, H. A. Coleman, and R. A. Langdale-Smith [*J. Org. Chem.*, **33**, 4413 (1968)] describe the general background of and lead references pertinent to this new variant of the Claisen–Cope rearrangement.

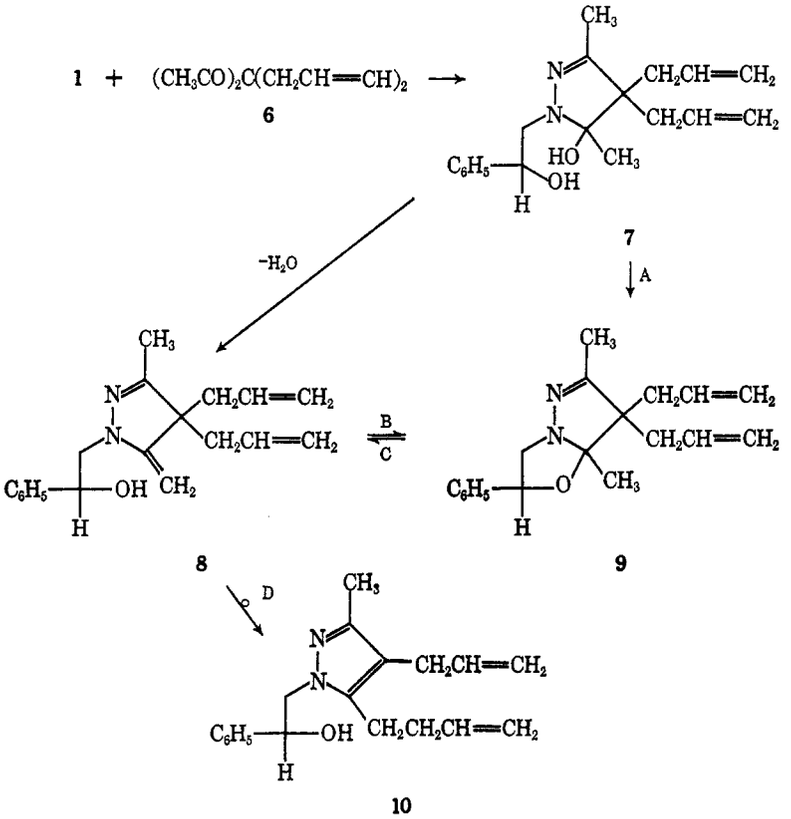
(2) B. T. Gillis and R. Weinkam, *ibid.*, **32**, 3321 (1967).

(3) N. J. Leonard and W. K. Musker, *J. Amer. Chem. Soc.*, **82**, 5148 (1960). By analogy with the oxidative cyclization of these authors the protonated iminium species **3a** may be considered to be the precursor of the bicyclic system.



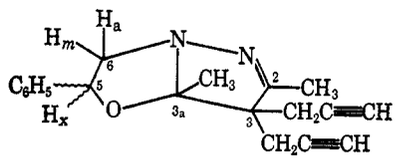
3a

Scheme II



was shown by refluxing **9** with ethanol under simulated reaction conditions. An approximately 85% conversion of **9** into **10** occurred suggesting that 3-allylic tetrahydropyrazolo[3,2-*b*]oxazoles are kinetically controlled products which are converted into their thermodynamically stable pyrazole isomers during the reaction by paths C and D. Similarly, synthesis of the 3-allyl-3-propargyl derivative **11** resulted in coproduction of **12** along with a small amount of the product (**13**) of propargylic rearrangement (Scheme III). Attempted vacuum distillation of **11** also gave **12**, containing a trace of **13**, in high yield. Tetrahydropyrazolo[3,2-*b*]oxazoles were the only products observed upon reaction of hydroxyethylhydrazines with 3,3-dimethyl-2,4-pentanedione.

Inferences from Nmr Spectral Data.—The rigid tetrahydropyrazolo[3,2-*b*]oxazole system is butterfly shaped with magnetically nonequivalent "concave" and "convex" surfaces. This accounts for the δ 2.55–2.82 resonance range of the propargyl methylenes of **5** (at C-3) and for the appearance of two C-3 methyl singlets for the tetramethyl derivative **14**. With two



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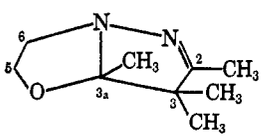

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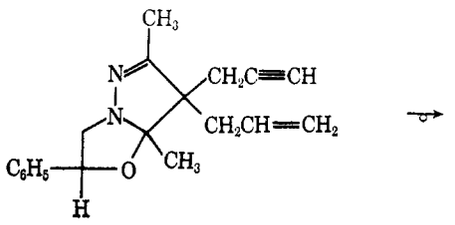
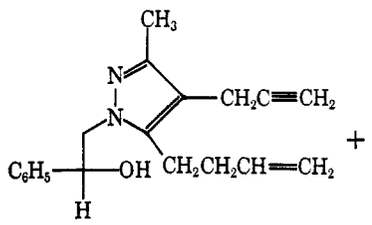
Scheme III



11



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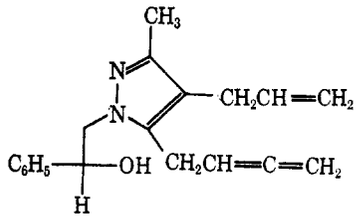

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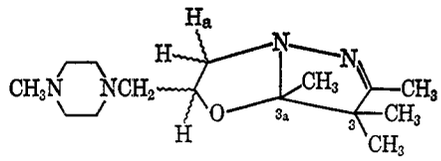
centers of asymmetry **5** can exist, theoretically, as two stereoisomers. The appearance of both the C-2 and C-3a methyl resonances of **5** as sharp singlets indicates that either (a) a mixture of *cis* and *trans* isomers exists but this variation in phenyl position is without effect on the chemical shift of the methyl protons, or (b) the C-5 phenyl group exists in a single preferred configuration.

Consideration of the above-mentioned AMX patterns of the 5-phenyltetrahydropyrazolo[3,2-*b*]oxazoles enables a choice between these alternatives. While we are not able to give configurational assignments to H_a, H_m, H_x, and phenyl, the appearance of three sharp pairs of doublets, with no second AMX sets apparent, indicates that the phenyl group occupies one preferred configuration and **5** is therefore a single stereoisomer. In the case of **11** the unlike allyl and propargyl groups at C-3 form a *ca.* 50:50 *cis–trans* mixture with the C-2 and C-3a methyls consequently showing pairs of singlets of approximately equal area. Unlike phenyl substitution, **15**, having an aminomethyl group at C-5, was isolated as an isomer mixture of *ca.* 2:1 as estimated from the in-



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tegrals of the two C-3a methyl signals. Here, the usual AMX pattern was obscured by the apparent presence of isomers and by additional coupling with the methylene protons attached at C-5. Surprisingly, the apparent isomer mixture melted relatively sharply at 55.8–58°. Two additional recrystallizations changed the isomer ratio, indicated by the C-3a methyl integrals, to 3–5:1, but with only a small change in melting point. Despite the nmr evidence of stereoisomerism, both **11** and **15** behaved as single compounds upon thin layer chromatography (tlc). An nmr examination of **15** in a second solvent produced an identical spectrum following which the unchanged compound was recovered. This result seems to eliminate the possibility that a single isomer of **15** is converted into two isomers by ring opening–reclosing in the nmr solvent system.[4] In the tetramethyl derivative **14**, as expected, the AMX system was replaced by an ABCD multiplet representing the CH_2CH_2 groups at positions 5 and 6.

Experimental Section

All melting points are corrected. Nmr spectra were obtained with Varian A-60 and HA-100 instruments employing tetramethylsilane as the internal standard. An Aerograph Model 202B dual-column gas chromatograph was used for vpc analysis. 3,3-Di(2-propynyl)-2,4-pentanedione (**2**),[1,5] 3-allyl-3-(2-propynyl)-2,4-pentanedione,[1] 3,3-diallyl-2,4-pentanedione (**6**),[6] and 3,3-dimethyl-2,4-pentanedione[7] were prepared as previously described.[7,8]

α-(Hydrazinomethyl)benzyl Alcohol (**1**).—To a stirred solution of 186.9 g (5.84 mol) of hydrazine in 500 ml of butanol, held at 86–92° by a steam cone, was added 60 g (0.5 mol) of styrene oxide over a 45-min period. After continued heating and stirring for 17 hr, 150 ml of water was carefully added and volatiles removed under reduced pressure. Distillation gave 54.0 g (71.0%) of product, bp 162–165° (4 mm) [lit.[9] 165° (4 mm)].

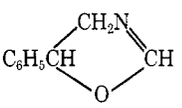
1-Glycidyl-4-methylpiperazine.—Was prepared from epichlorhydrin and 1-methylpiperazine by a method similar to that of Heywood and Phillips.[10] The dihydrochloride, mp 212–216° dec, was analyzed.

Anal. Calcd for $C_8H_{18}N_2OCl_2$: N, 10.50. Found: N, 10.32.

α-(Hydrazinomethyl)-4-methylpiperazine-1-ethanol.—1-Glycidyl-4-methylpiperazine (78.1 g, 0.5 mol) and anhydrous hydrazine (165.0 g, 5.0 mol) were allowed to react under conditions similar to those employed in the preparation of **1**. Distillation and redistillation gave 55.8 g of product, bp 132–135° (0.35 mm), whose nmr spectrum was confirmatory but showed the presence of some remaining butanol solvent.

Anal. Calcd for $C_8H_{20}N_4O$: N, 29.76. Found: N, 28.13.

3,3a,5,6-Tetrahydro-2,3a-dimethyl-5-phenyl-3,3-di(2-propynyl)pyrazolo[3,2-*b*]oxazole (**5**).—To a mixture of **1** (7.6 g, 0.05 mol) and **2** (8.8 g, 0.05 mol) in 200 ml of ethanol was added 15 ml of 5% acetic acid and the resulting mixture was then refluxed for a period of 3.5 hr. Evaporation of volatiles gave an oil which crystallized on standing. The crude product was dissolved in methanol and precipitated with water giving 7.05 g of cream-colored crystals, mp 99–101°. An impure fraction (1.55 g, mp 72–95°) brought the total yield to 58.9%: ir (KBr) 3.04 (C≡CH), 6.16 (C=N), 7.24 (CCH_3), 9.95 (COC), 13.25 and 14.32 μ (monosubstituted phenyl); mass spectrum [70 eV (49°)] *m/e* 292 (parent), 186 (loss of $C_6H_5CHCH_2$ ion), 147 (ion a), 104 ($C_6H_5CHCH_2$ ion), 91 (benzyl ion), 77 (phenyl ion),



a

43 (CH_3CO ion), 39 (propargyl ion); nmr (deuterioacetone) δ 1.63 (s, 3, CH_3CO), 2.0 (s, 3, CH_3C=N), 2.46 (t, 2, HC≡C), 3.07 (doublet pair, 1, J_{am} = 13 Hz, J_{ax} = 10 Hz, H_aCN), 3.99 (doublet pair, 1, J_{ma} = 13 Hz, J_{mx} = 5.5 Hz, H_mCN), 4.65 (doublet pair, 1, J_{xm} = 5.5 Hz, J_{xa} = 10 Hz, H_xCO), 7.32 (s, 5, C_6H_5).

Anal. Calcd for $C_{19}H_{20}N_2O$: C, 78.05; H, 6.90; N, 9.58. Found: C, 78.15; H, 6.95; N, 9.72.

3,3-Diallyl-3,3a,5,6-tetrahydro-2,3a-dimethyl-5-phenylpyrazolo[3,2-*b*]oxazole (**9**).—A mixture of **6** (14.9 g, 0.083 mol), **1** (12.6 g, 0.083 mol), 5% acetic acid (30 ml), and ethanol (400 ml) was refluxed for 4 hr and then stripped under reduced pressure to give 24.4 g of an oil. The latter was diluted with ether and the resulting solution was chromatographed (alumina) giving four fractions, obtained by anhydrous ethyl ether elution, having a combined composition (estimated by ir) of 5.9 g of **9** (24.1% crude yield) along with the isomeric rearranged pyrazole **10** and ketonic impurities. Rechromatographing (ether elution) fractions rich in **9** followed by recrystallization of the residue from isopropyl alcohol gave 1.5 g of **9** as white crystals: mp 71–72°; ir (KBr) 6.1 (C=C), 7.21 (CCH_3), 8.19 (CN), 9.71 (COC), 10.58, 10.91, and 11.84 μ (CH=CH_2); nmr ($CDCl_3$) δ 1.54 (s, 3, CH_3CO), 1.89 (s, 3, CH_3C=N), 2.10–2.80 (m, 4, 2 CH_2-C=C), 3.12 (doublet pair, 1, J_{am} = 12.5 Hz, J_{ax} = 10 Hz, H_aCN), 4.04 (doublet pair, 1, J_{ma} = 12.5 Hz, J_{mx} = 5 Hz, H_mCN), 4.71 (doublet pair, 1, J_{xa} = 10 Hz, J_{xm} = 5 Hz, H_x-CO), 5.14–6.25 (m, 6, 2 CH=CH_2), 7.34 (s, 5, C_6H_5).

Anal. Calcd for $C_{19}H_{24}N_2O$: C, 76.99; H, 8.16; N, 9.45. Found: C, 77.37; H, 8.14; N, 9.41.

4-Allyl-5-(3-butenyl)-3-methyl-α-phenylpyrazole-1-ethanol (**10**). **A. As Coproduct of 9.**—Infrared examination of the chromatographed fractions from the preparation (above) of **9** indicated an approximate content of 13.2 g (53.9% crude yield) of **10** showing OH at 3.0 μ (NaCl). An ether solution of the fractions was rechromatographed, eluting with ether to remove impurities. The alumina column was then washed with methanol releasing 7.6 g of moderately pure **10**. Recrystallization from petroleum ether gave 1.65 g of crystals: mp 47.5–50°; ir (KBr) 3.14 (OH), 6.1 (C=C), 9.38 μ (COH); nmr ($CDCl_3$) δ 2.05 (m, 2, CH_2CH_2CH=CH_2), 2.17 (s, 3, CH_3), 2.43 (t, J = 3.5 Hz, CH_2CH_2CH=CH_2), 3.08 (m, 2, allyl CH_2), 4.09 (m, 2, CH_2N), 5.0 (m, 5, 2C=CH_2 and C_6H_5CH), 5.27 (s, 1, OH), 5.45–6.20 (m, 2, CH=C<), 7.32 (s, 5, C_6H_5).

Anal. Calcd for $C_{19}H_{24}N_2O$: C, 76.99; H, 8.16, N, 9.45. Found: C, 76.71; H, 8.11; N, 9.46.

(4) A possible rationale of the melting point behavior suggested by a referee.

(5) E. K. Schulte, J. Reisch, and A. Mock, *Arch. Pharm.*, **295**, 627 (1962).

(6) R. B. Davis and P. Hurd, *J. Amer. Chem. Soc.*, **77**, 3284 (1955).

(7) J. J. Bloomfield, *J. Org. Chem.*, **26**, 4112 (1961).

(8) A. W. Johnson, E. Markham, and R. Price, *Org. Syn.*, **42**, 75 (1962).

(9) G. Benoit, *Bull. Soc. Chim. Fr.*, **6**, 708 (1939).

(10) D. L. Heywood and B. Phillips, *J. Amer. Chem. Soc.*, **80**, 1257 (1958).

B. By Isomerization of 9.—A solution of 0.15 g of **9** in 200 ml of ethanol containing 3 drops of water (pH ~6) was refluxed for 3.5 hr after which the solvent was removed under reduced pressure. Infrared analysis of the residual colorless syrup (0.15 g) produced a spectrum essentially identical with that of **10** obtained in part A (above). The nmr spectrum showed the product to be predominantly **10** (≥85%) containing some unconverted **9**.

3-Allyl-3,3a,5,6-tetrahydro-2,3a-dimethyl-5-phenyl-3-(2-propynyl)pyrazolo[3,2-*b*]oxazole (11).—A mixture of 3-allyl-3-(2-propynyl)-2,4-pentanedione (12.6 g, 0.0708 mol), **1** (10.75 g, 0.0708 mol), 5% aqueous acetic acid (20 ml), and ethanol (300 ml) was refluxed for an 8-hr period after which volatiles were evaporated leaving an oil. This was dissolved in ether, dried ($MgSO_4$), and chromatographed on alumina giving 8.7 g (41.7%) of crude **11**, recovered by ether elution. Two recrystallizations from hexane gave pure material: mp 66–68°; ir (KBr) 3.01 and 3.06 (C≡CH), 7.25 (CCH_3), 9.75–9.80 μ (COC); nmr ($CDCl_3$) δ 1.51 and 1.60 (two singlets, 3, CH_3CO, *cis* and *trans*), 1.90 and 2.01 (two singlets, 3, $CH_3C{=}N$, *cis* and *trans*), 2.10 (m, 1, HC≡C), 2.34–2.70 (m, 4, $CH_2CH{=}CH_2$, and $CH_2C{\equiv}CH$), 3.11 (doublet pair, 1, J_{am} = 12.6 Hz, J_{ax} = 10.5 Hz, H_aCN), 4.03 (doublet pair, 1, J_{ma} = 12.6 Hz, J_{mx} = 5.5 Hz, H_mCN), 4.68 (doublet pair, 1, J_{xm} = 5.5 Hz, J_{xa} = 10.5 Hz, H_xCO), 4.9–6.4 (m, 3, $CH{=}CH_2$), 7.32 (s, 5, C_6H_5).

Anal. Calcd for $C_{19}H_{22}N_2O$: C, 77.52; H, 7.53; N, 9.52. Found: C, 77.83; H, 7.67; N, 9.55.

Separation of the apparent allyl–propargyl *cis–trans* isomers was attempted by tlc but the various systems examined revealed only a single product spot.

5-(3-Butenyl)-3-methyl-α-phenyl-4-(2-propynyl)pyrazole-1-ethanol (12). A. As Coproduct of 11.—Following ether elution of **11** from the above-described chromatography the column was flushed with methanol to give, on evaporation, 10.8 g (51.8% crude yield) of syrupy **12**: ir (NaCl) 2.95–3.10 μ (OH and C≡CH). A weak allene band at 5.1 μ was due to the isomeric **13**, an impurity which could not be separated from the product.

B. By Thermolysis of 11.—A 10.76-g sample of **11** was distilled through a short-path system employing a pot temperature of 193–215° (0.25 mm). The distillate, bp 154–166° (8.93 g), crystallized in the receiver. Two recrystallizations of the solid from hexane gave 4.2 g of **12**, mp 80–82°. The infrared spectrum was essentially identical with that of the coproduct of **11** (part A, above) and showed, in addition to weak allene absorption, bands at 3.01 (C≡CH), 3.15 (OH), 4.7 (C≡C), 6.1 and 6.42 (C=C, C=N), 7.21 (CCH_3), 9.37 (COH), 10.05 and 10.95 (=CH, $=CH_2$), 13.0 and 14.25 μ (monosubstituted phenyl).

Anal. Calcd for $C_{19}H_{22}N_2O$: C, 77.52; H, 7.53; N, 9.52 Found: C, 77.79; H, 7.66; N, 9.52.

3,3a,5,6-Tetrahydro-2,3,3,3a-tetramethylpyrazolo[3,2-*b*]oxazole (14).—A mixture of 3,3-dimethyl-2,4-pentanedione (12.9 g, 0.10 mol), 2-hydroxyethylhydrazine (8.37 g, 0.11 mol), 5% aqueous acetic acid (26 ml), and ethanol (200 ml) was refluxed for a 3.5-hr period and then evaporated free of volatiles under reduced pressure. The residual oil was dissolved in ethyl ether and the solution was chromatographed on alumina. Elution with ether gave fractions of crude product totaling 11.0 g. These were distilled giving 10.3 g (61.2%) of **14**: bp 50° (1.1 mm); 100% pure by vpc; ir (KBr) 3.4 and 3.5 (CH_3, CH_2), 6.15 (C=N), 7.24 and 7.32 (CCH_3), 8.55 (CN), 9.77 (COC); nmr ($CDCl_3$) δ 1.03 and 1.13 (two singlets, 6, CH_3CCH_3), 1.25 (s, 3, CH_3CO), 1.83 (s, 3, $CH_3C{=}N$), 3.17–3.94 (ABCD multiplet, 4, CH_2-CH_2).

Anal. Calcd for $C_9H_{16}N_2O$: C, 64.25; H, 9.59; N, 16.65. Found: C, 64.71; H, 9.69; N, 16.69.

3,3a,5,6-Tetrahydro-5-(4′-methylpiperazin-1′-ylmethyl)-2,3,-3,3a-tetramethylpyrazolo[3,2-*b*]oxazole (15).—A solution of α-(hydrazinomethyl)-4-methylpiperazine-1-ethanol (20.6 g, 0.11 mol), 3,3-dimethyl-2,4-pentanedione (12.9 g, 0.1 mol), and 5% aqueous acetic acid (26 ml) in ethanol (300 ml) was refluxed for 4.5 hr after which volatiles were removed under reduced pressure. The residue was distilled through a short-path system giving 19.3 g (69.0%) of **15**, bp 116–118° (0.2 mm), which solidified on standing. Crystallization from petroleum ether at −80° gave white crystals: mp 55.5–58°; ir (KBr) 3.35 and 3.55 (CH_3, CH_2), 6.15 (C=N), 7.25 (CCH_3), 8.57 (CN), 9.83 (COC); nmr ($CDCl_3$) δ 1.02 and 1.12 (two singlets, 6, CH_3CCH_3), 1.26 (s, 0.33 × 3, CH_3CO of isomer "A"), 1.29 (s, 0.67 × 3, CH_3CO of isomer "B"), 1.82 (s, 3, $CH_3C{=}N$), 2.26 (s, 3, $CH_3N<$), 2.34–2.70 (m, 10, 5 CH_2), 3.01–4.30 (series of multiplets, 3, NCH_2CHO).

Anal. Calcd for $C_{15}H_{28}N_4O$: C, 64.25; H, 10.06; N, 19.98. Found: C, 64.27; H, 10.25; N, 19.72.

Two additional recrystallizations (pentane) of the product gave material, mp 54.5–55.5°, whose nmr spectrum showed the apparent isomer "A" (CH_3CO at δ 1.26) content reduced to 20–25%. A similar spectrum was obtained in deuterioacetonitrile and the sample, recovered from the solution, was unchanged **15** (melting point and mixture melting point). Various tlc systems were investigated in an attempt to separate the apparent isomers. The various product fractions, including those recovered from nmr determinations, behaved identically and in no case was separation of a second component evident. Best results were obtained by elution with methanol–diethylamine (3%) on silica gel which produced single, well-defined spots.

Registry No.—1-Glycidyl-4-methylpiperazine dihydrochloride, 20238-14-6; α-(hydrazinomethyl)-4-methylpiperazine-1-ethanol, 20238-15-7; **5**, 20238-16-8; **9**, 20238-17-9; **10**, 20238-18-0; **11**, 20238-19-1; **12**, 20238-20-4; **14**, 20238-21-5; **15**, 20238-22-6.

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