chloroform to 9.45 ppm in DMSO and 10.3 ppm in pyridine. These shifts in the N–H resonance probably reflect the differences in hydrogen bonding of **1** with these solvents.

TABLE I

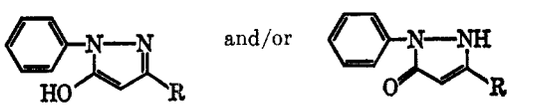
THE NMR SPECTRA[a] OF 3-ANILINO-1-PHENYL-2-PYRAZOLIN-5-ONE

Solvent	Temp, °C	δ,[b] ppm CH₂	δ,[b] ppm NH	Relative area[c] of NH peak	J ^{15}NH
Unlabeled Compound (1)					
$CDCl_3$[d]	50	3.63	6.40	...	
Pyridine-d_5	38	3.7	10.3	0.854	
Pyridine-d_5	100[e]	3.7 ± 0.05	9.5 ± 0.1	...	
DMSO-d_6	38	3.85	9.45	1.0	
Labeled Compound (1a)					
$CDCl_3$[d]	30	3.61	6.35[f]	1.0	92 ± 1
$CDCl_3$[d]	50	3.63	6.45	...	91.5 ± 0.5
Pyridine-d_5	38	3.74	10.3	0.88	91.5 ± 0.5
Pyridine-d_5	100[e]	3.70 ± 0.03	9.6 ± 0.1	...	91 ± 1
DMSO-d_6	38	3.87	9.43	0.96	92 ± 0.5

[a] Recorded on the Varian A-60 nmr spectrometer. [b] δ is parts per million downfield from internal TMS. [c] The CH_2 area is assigned the value 2.0. [d] Spectra in $CDCl_3$ were recorded at 100 MHz on the Varian HA-100. [e] At 100° the peaks had broadened considerably and are less exact. [f] Center of gravity positions.

TABLE II

THE PER CENT TAUTOMER CONTENT[a] OF SOME 3-SUBSTITUTED PYRAZOLIN-5-ONES IN DMSO-d_6



R	Tautomer, %	δ, ppm =CH-	δ, ppm -CH₂-
CH_3	74[b]	5.43	3.55
$NHCCH_3$ (O)	70	6.03	4.08
$NHCC_6H_5$ (O)	67	6.32	4.30
NHC_6H_5	0	...	3.85

[a] These values were obtained by integration of the respective olefinic proton peaks. [b] An accuracy within ±5% is expected.

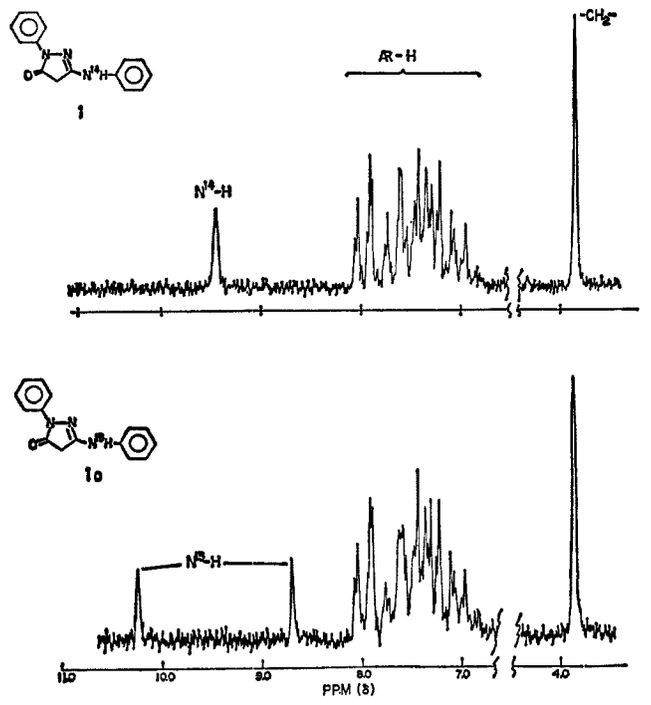


Figure 2.—Nmr spectra of **1** and **1a** in *ca.* 10% (w/v) DMSO-d_6 solution.

The large ^{15}N–H coupling constant (91–92 Hz) in pyridine remained relatively unchanged when the solution was heated to 100°, although at this temperature the resonance peaks had broadened considerably. However, when this heated solution was cooled to 38°, the nmr spectrum was identical with that of a freshly prepared solution.

The lack of detectable tautomerization in DMSO-d_6 for compound **1** and **1a** is contrary to what we have observed for some other pyrazolinones in this solvent. As shown in Table II, some other pyrazolin-5-ones, which differ from **1** in the nature of the 3-substituent, exist substantially in another tautomeric form(s).

In summary, we have synthesized **1a** with a labeled nitrogen exclusively at the 3-anilino site and shown by mass spectrometry a decomposition path for this compound under electron impact. By means of nmr spectroscopy we have shown that **1** and **1a** exist in only one detectable tautomeric form in chloroform, pyridine, and DMSO solutions.

Experimental Section

All melting points are uncorrected. Infrared spectra were obtained with a Beckman IR-12 grating spectrophotometer. Samples were examined as potassium bromide pressings. The solutions of **1** and **1a** were *ca.* 10% (w/v) in DMSO and pyridine and about 5% in chloroform. A 60° sector type of mass spectrometer fitted with an all-glass inlet system was operated at 230°. The exact masses were measured on a Consolidated Electrodynamics 21-110-B high-resolution mass spectrometer.

3-^{15}N-Anilino-1-phenyl-2-pyrazolin-5-one (1a).—A solution of 0.94 g (5.4 mmol) of 3-amino-1-phenyl-2-pyrazolin-5-one (EK 3841) in 10 ml of acetic acid containing 1 ml of concentrated hydrochloric acid and 0.5 g (5.3 mmol) of ^{15}N-aniline[8] was refluxed for 1 hr. On standing, the solution deposited a white solid which, after it had been washed with water and recrystallized from acetonitrile, gave 0.4 g (30%) of **1a** as a white solid, mp 218–219°. Unlabeled **1** melted at 218–219° (lit.[3] mp 219–221°). The infrared spectrum of **1a** was identical with that of **1**.

Isolation of Ammonium Chloride.—The filtrate from the reaction mixture was drowned in 100 ml of water. After the resulting solids were removed, 3 ml of concentrated hydrochloric acid was added, and the solution was evaporated under reduced pressure to a gummy solid. Trituration of this material with ethanol gave 0.05 g (0.9 mmol) of a white solid, mp >320°. The infrared and mass spectrograms of the residual material were identical with those of an authentic unlabeled sample of ammonium chloride.

Registry No.—**1**, 7186-66-5; **1a**, 16774-23-5.

(8) Obtained from Merck Sharpe and Dohme of Canada, Ltd.

The Synthesis of *o*-Di-*t*-butyl Heteroaromatics

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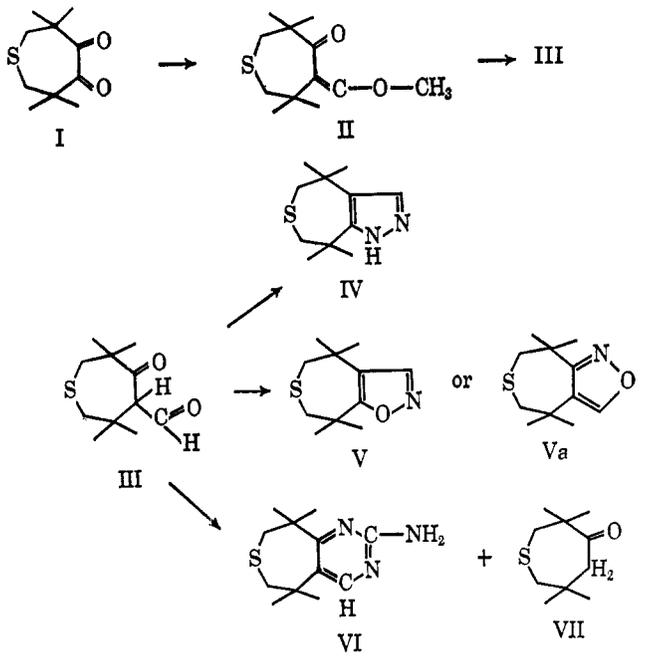
The use of 3,3,6,6-tetramethyl-1-thiacycloheptane-4,5-dione (I) as the starting compound in the synthesis of several *o*-di-*t*-butyl heteroaromatics has been reported.[1,2] A Wittig reaction with diketone I gave 5-methoxymethylene-3,3,6,6-tetramethyl-1-thiacyclo-

(1) Ae. de Groot and Hans Wynberg, *J. Org. Chem.*, **31**, 3954 (1966).
(2) Ae. de Groot, Ph.D. Thesis, Groningen, 1967.



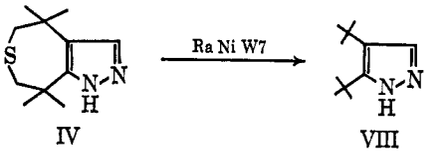
heptan-4-one (II) which upon hydrolysis yielded 5-formyl-3,3,6,6-tetramethyl-1-thiacycloheptan-4-one (III). This keto aldehyde III is also a suitable starting material for several ring-closure reactions to aromatic compounds.

Methoxymethylene ketone II was prepared in 75% yield by reaction of diketone I with (methoxymethylene)triphenylphosphorane in dimethyl sulfoxide as solvent and with the corresponding anion as base.[3] The ultraviolet spectrum of II showed a maximum at λ 242 mμ (ϵ 720) and a shoulder at λ 308 mμ (ϵ 87). This suggests that there is little resonance between the double bond and the carbonyl function in II. The same feature can be noticed in diketone I (λ_{max} 333 mμ) and in 4,5-dimethylene-3,3,6,6-tetramethyl-1-thiacycloheptane (λ_{max} < 185 mμ). The abnormally low absorption maxima in the ultraviolet spectra of these compounds indicate that here too normal conjugation is lacking.[4]

Methoxymethylene ketone II was hydrolyzed with perchloric acid[5] to keto aldehyde III in 93% yield. The infrared spectrum of III showed no enol absorption at 1600 cm^{-1}; a strong carbonyl absorption was present at 1720 cm^{-1}. The ultraviolet spectrum of III, taken in cyclohexane and in ethanol, showed maxima at λ 240 mμ (ϵ 850), 302 (60), and 312 (70), and at 243 (760), 301 (84), and 310 (82), respectively. Keto aldehyde III gave no color with ferric chloride solution. These facts indicate that enolization of this 1,3-dicarbonyl compound is prevented by steric inhibition of resonance.

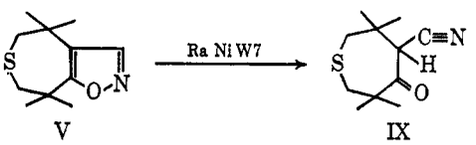
A reaction of keto aldehyde III with hydrazine in boiling acetic acid gave 4,4,8,8-tetramethyl-4,5,7,8-tetrahydro-6-thiacyclohepta[*c*]pyrazole (IV) in 90% yield. The reaction of keto aldehyde III with hydroxylamine gave 4,4,8,8-tetramethyl-4,5,7,8-tetrahydro-6-thiacyclohepta[*d*]isoxazole (V) in 75% yield. The formation of two isomeric isoxazole derivatives V and Va is possible in this reaction. However, the hydroxylamine will probably react with the aldehyde function first. In addition, the greater steric hindrance around the keto function will be important in preventing initial reaction at this point. It is very likely, therefore, that the isoxazole V is the only product in this reaction. The 2-amino-5,5,9,9-tetramethyl-5,6,-8,9-tetramethyl-5,6,8,9-tetrahydro-7-thiacyclohepta[*e*]-pyrimidine (VI) is formed in only 35–40% yield when keto aldehyde III and guanidine carbonate are heated to 160–170° in absolute ethanol in a sealed tube. This low yield is due to the competing ketone cleavage reaction, which occurs under the basic reaction conditions. The 3,3,6,6-tetramethyl-1-thiacycloheptan-4-one (VII) is formed in ~50% yield in this reaction.

Desulfurization of the pyrazole derivative IV with Raney nickel W7 in boiling dioxane as solvent gave 3,4-



di-*t*-butylpyrazole (VIII) in 45% yield. 3,4-Di-*t*-butylpyrazole is a stable white crystalline solid, mp 129–130°.

Isoxazole and derivatives normally give ring opening when treated with Raney nickel[6] or with base.[7] Thus, desulfurization of V with retention of the isoxazole ring cannot be expected. Indeed, one experiment in which isoxazole V was treated with Raney nickel W7 in boiling acetone gave at least three reaction products. The only product which was isolated and identified was keto nitrile IX.[7] The other two products still contained sulfur and showed strong carbonyl absorption in the infrared spectrum, indicating that again no desulfurization but ring opening had occurred.



Attempts to desulfurize pyrimidine derivative VI were unsuccessful. The reason for the failure of this desulfurization is not clear. In seven experiments, carried out with variation in solvent, reaction temperature, and pH, only small amounts of starting material VI were recovered. No desulfurized products were isolated.

Experimental Section

Infrared spectra were determined in CCl_4, in KBr disks, or neat on a Perkin-Elmer Infracord Model 137 or on a Unicam SP 200. Ultraviolet spectra were recorded on a Zeiss spectrophotometer, Model PMQ II; the solvents are indicated. Nuclear magnetic resonance (nmr) spectra were taken on a Varian A-60 spectrometer with tetramethylsilane as internal standard and are reported in τ values (parts per million); the solvents are indicated. Melting points and boiling points are uncorrected. Microanalysis were performed by the Analytical Department of this laboratory under the supervision of Mr. W. M. Hazenberg.

5-Methoxymethylene-3,3,6,6-tetramethyl-1-thiacycloheptan-4-one (II).—A dispersion of sodium hydride in mineral oil, containing 2.9 g (0.06 mol) of sodium hydride, was washed three times with dry pentane. Then 50 ml of dimethyl sulfoxide was added with a syringe and the mixture was heated for 45 min at 75–80°. At that time the solution was clear and no gas evolution was observed. After cooling to room temperature a solution of 20.5 g (0.06 mol) of (methoxmethyl)triphenylphosphonium chloride in 100 ml of dimethyl sulfoxide was injected and the deep

(3) R. Greenwald, M. Chaykovsky, and E. J. Corey, *J. Org. Chem.*, **28**, 1128 (1963).
(4) Ae. de Groot, B. Evenhuis, and Hans Wynberg, *ibid.*, in press.
(5) S. G. Levine, *J. Amer. Chem. Soc.*, **80**, 6150 (1958).
(6) G. Stagno D'Alcontres, *Gazz. Chim. Ital.*, **80**, 441 (1950).
(7) L. Claisen and R. Stock, *Chem. Ber.*, **24**, 130 (1891).

dark red solution was stirred for 15 min. Then a solution of 8.0 g (0.04 mol) of diketone I in 30 ml of dimethyl sulfoxide was injected and the reaction mixture was stirred for 16 hr at room temperture and for 2 hr at 50–60°. The reaction mixture was poured on 200 g of crushed ice and the water–dimethyl sulfoxide mixture was extracted with pentane. The pentane solution was washed with aqueous dimethyl sulfoxide (1:1) and with a saturated salt solution and dried ($MgSO_4$). The dried pentane solution was chromatographed on neutral alumina to remove all of the triphenylphosphine oxide and the pentane was evaporated. The solid residue was recrystallized from petroleum ether (bp 40–60°). The yield of methoxymethylene ketone II, mp 109–110°, was 60–77%: ir (CCl_4) 1690, 1640, and 1100 cm^{-1}; uv max (95% ethanol) 242 mμ (ε 720), 308 (87); nmr (CCl_4), τ 8.87 and 8.84 s (ring methyl protons), 7.60 and 7.48 s (ring methylene protons), 6.47 s (ether methyl protons), 4.21 s (vinyl proton).

Anal. Calcd for $C_{12}H_{20}O_2S$ (228.35): C, 63.11; H, 8.82; S, 14.04. Found: C, 62.7, 63.0; H, 8.8, 8.8; S, 13.9, 14.0.

5-Formyl-3,3,6,6,6-tetramethyl-1-thiacycloheptan-4-one (III).—A solution of 4.0 g (0.017 mol) of methoxymethylene ketone II and 10 ml of perchloric acid in 50 ml of ether was refluxed for 30 min. The reaction mixture was poured into water and the ether layer was separated and washed with water and with sodium bicarbonate solution. The ethereal extract was dried (Na_2SO_4) and concentrated. The residue was recrystallized from petroleum ether (bp 40–60°). The yield of keto aldehyde III was 3.4 g (93%): mp 97–99°; ir (CCl_4) 1705 and 1735 cm^{-1}; uv (see discussion); nmr (CCl_4), τ 8.96, 8.84, and 8.78 s (methyl protons), 7.40 7.82, 7.58, 7.40, and 7.17 q (methylene protons), 6.58 and 6 .50d (proton at C_4), 0.30 and 0.22 d (aldehyde proton).

Anal. Calcd for $C_{11}H_{18}O_2S$ (214.32): C, 61.64; H, 8.47; S, 14.96. Found: C, 61.6, 61.5; H, 8.5, 8.3; S, 15.0, 15.0.

4,4,8,8-Tetramethyl-4,5,7,8-tetrahydro-6-thiacyclohepta[*c*]pyrazole (IV).—A solution of 1.0 g (0.0047 mol) of keto aldehyde III, 3 ml of hydrazine hydrate, and 1 drop of hydrochloric acid in 15 ml of acetic acid was refluxed for 1 hr. The reaction mixture was poured on ice and the precipitated compound was separated and washed with water. After recrystallization from aqueous methanol (1:1), 0.86 g (90%) of pyrazole IV was obtained: mp 186–188°; ir (KBr) 3200, 1570, and 1505 cm^{-1}; nmr (CCl_4), τ 8.63 s (methyl protons), 7.54 s (methylene protons), 2.80 s (C–H aromatic proton), 2.42 s (N–H proton).

Anal. Calcd for $C_{11}H_{18}N_2S$ (210.32): C, 62.81; H, 8.63; N, 13.32; S, 15.24. Found: C, 62.5, 62.6; H, 8.6, 8.7; N, 13.4, 13.4; S, 14.8, 14.8.

4,4,8,8-Tetramethyl-4,5,7,8-tetrahydro-6-thiacyclohepta[*d*]isoxazole (V).—A solution of 1.5 g (0.007 mol) of keto aldehyde III and 1.5 g (0.022 mol) of hydroxylamine hydrochloride in 25 ml of acetic acid was refluxed for 1 hr. The reaction mixture was poured on ice and the precipitated compound was separated and washed with water. Recrystallization from aqueous methanol (1:1) yielded 1.1 g (75%) of isoxazole V: mp 111–112°; ir (KBr) 1590 cm^{-1}; nmr (CCl_4), τ 8.65 and 8.55 s (methyl protons), 7.37 and 7.35 s (methylene protons), 2.12 s (aromatic proton).

Anal. Calcd for $C_{11}H_{17}NOS$: C, 62.51; H, 8.11; N, 6.63; S, 15.18. Found: C, 62.7, 62.6; H, 8.3, 8.2; N, 6.7, 6.5; S, 14.7, 15.0.

2-Amino-5,5,9,9-tetramethyl-5,6,8,9-tetrahydro-7-thiacyclohepta[*e*]pyrimidine (VI).—A mixture of 2.0 g (0.009 mol) of keto aldehyde III, 2.0 g (0.017 mol) of guanidine carbonate, and 25 ml of absolute ethanol was heated in a sealed tube at 160–170° for 8 hr. The tube was opened and the contents were washed with water and ether. The water layer was separated and extracted with ether. The combined ether layers were extracted with dilute hydrochloric acid. The ethereal extract was dried ($CaCl_2$) and concentrated. The organic residue proved to be 3,3,6,6-tetramethyl-1-thiacycloheptan-4-one (VII). The yield of VII was 900 mg (52%). The hydrochloric acid extracts were neutralized with sodium hydroxide solution and extracted with ether. The ether solution was washed with water, dried ($CaCl_2$), and concentrated. The residue was recrystallized from petroleum ether (bp 60–80°). The yield of pyrimidine VI was 900 mg (42%): mp 109–110.5°; ir (KBr) 3400, 3230, 1645, 1580, and 1530 cm^{-1}; nmr ($CDCl_3$), τ 8.54 s (methyl protons), broad 7.25 s (methylene protons), broad 4.73 s (NH_2 protons), 1.72 s (aromatic proton).

Anal. Calcd for $C_{12}H_{19}N_3S$ (237.35): C, 60.72; H, 8.04; N, 17.70. Found: C, 61.0, 60.9; H, 8.2, 8.1; N, 17.8, 17.8.

3,4-Di-*t*-butylpyrazole (VIII).—A suspension of 20 g of Raney nickel W7 and 1.6 g (0.008 mol) of pyrazole IV in 150 ml of dioxane was stirred and refluxed for 5 hr. The reaction mixture was cooled to room temperature and filtered. The Raney nickel was refluxed twice with 200 ml of dioxane to remove the absorbed pyrazole. The dioxane was evaporated and 800 mg of residue was obtained. Recrystallization from aqueous methanol (1:1) yielded 500 mg (45%) of white crystalline 3,4-di-*t*-butylpyrazole: mp 129–130°; ir (KBr) 3200 and 1550 cm^{-1}; nmr (CCl_4), τ 8.63 and 8.58 s (*t*-butyl protons), 2.75 s (C–H aromatic proton), 2.03 s (N–H proton).

Anal. Calcd for $C_{11}H_{20}N_2$ (180.28): C, 73.28; H, 11.18; N, 15.54. Found: C, 73.4, 73.3; H, 11.1, 11.1; N, 15.6, 15.7.

5-Cyano-3,3,6,6-tetramethyl-1-thiacycloheptan-4-one (IX).—A suspension of 10 g of Raney nickel W7 and 1.1 g (0.005 mol) of isoxazole V in 200 ml of acetone was stirred and refluxed for 5 hr. After cooling to room temperature the mixture was filtered and the Raney nickel was refluxed twice with 200 ml of acetone to remove all of the absorbed materials. The combined acetone solutions were concentrated and the residue was dissoved in petroleum ether (bp 40–60°). The warm petroleum ether solution was filtered and upon cooling 300 mg of cyanide IX crystallized: mp 114–116°; ir (KBr) 2280 and 1720 cm^{-1}; nmr ($CDCl_3$), τ 8.83 and 8.75 s (methyl protons), 7.38 s and 7.61, 7.38, 7.28, and 7.00 q (methylene protons), 6.15 s (proton at C_5).

Anal. Calcd for $C_{11}H_{17}NOS$ (211.32): C, 62.51; H, 8.11; N, 6.63; S, 15.18. Found: C, 62.6, 62.7; H, 8.3, 8.2; N, 6.6, 6.6; S, 15.3, 15.3.

Concentration of the petroleum ether solution gave 200 mg of a solid. It was shown by tlc that at least three products were present. The infrared spectrum of this mixture showed a strong absorption at 1690 cm^{-1}.

Registry No.—II, 16867-90-6; III, 16867-91-7; IV, 16867-92-8; V, 16867-93-9; VI, 16867-94-0; VIII, 16867-95-1; IX, 16867-96-2.

Pteridines. XIII.[1] Aromatization during the Attempted Synthesis of a 6,6-Disubstituted 5,6-Dihydropteridine

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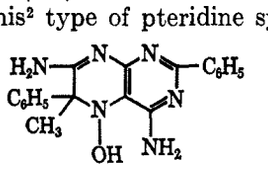
Received December 26, 1967

In the course of our work on the diuretic pteridines we wished to prepare 4,7-diamino-5-hydroxy-6-methyl-2,6-diphenyl-5,6-dihydropteridine (I) as an example of a pteridine in which a 5,6-dihydro form has been fixed by the presence of two stable substituents at position 6. In an approach to this, 2-phenylpropionitrile was condensed with 4,6-diamino-5-nitroso-2-phenylpyrimidine (III) in ethanol in the presence of alkali in a Timmis[2] type of pteridine synthesis. The



I

only product isolated (in 16% yield) was 4-amino-7-ethoxy-2,6-diphenylpteridine (IV). The structure of

(1) Previous paper in this series: J. Weinstock, J. W. Wilson, V. D. Wiebelhaus, A. R. Maass, F. T. Brennan, and G. Sosnowski, *J. Med. Chem.*, **11**, 573 (1968).

(2) G. M. Timmis, *Nature*, **164**, 139 (1949).