Sterically-Crowded Pyrroles (1)

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The syntheses in good yields of a considerable number of moderately to severely sterically-crowded 1,2,5-trisubstituted pyrroles by means of modifications of the Knorr-Paal condensation are described. Notwithstanding reports to the contrary, the classical procedure succeeded in moderately sterically-crowded cases, *e.g.*, R^2 = R^5 = Me, R^1 = i-Pr, $Me_2CHMeCH$-, Me_2N-, Ph_2N-, 9-carbazolo, subst. 4-morpholino, 1-piperazino, 1-piperidino, etc. A product-water azeotroping procedure succeeded in more severely sterically-crowded cases *e.g.*, R^2 = R^5 = Et, R^1 = i-Pr; R^2 = R^5 = Me, R^1 = Me_3CCH_2-, R^2 = R^5 = i-Pr, R^1 = $PhCH_2$-. Highly sterically-crowded pyrroles, *e.g.*, R^2 = R^5 = Me, R^1 = *t*-Bu, adamantyl, $PhCH_2CMe_2$; R^2 = R^5 = Et, R^1 = *t*-Bu; R^1 = R^2 = R^5 = i-Pr; R^2 = R^5 = *t*-Bu, R^1 = Me, Et, $PhCH_2$-, were obtained using titanium tetrachloride as a Lewis acid catalyst and as a water scavenger. Infrared spectra of the reacting mixtures provided evidence pertinent to the mechanism of the reaction, which is discussed.

It has become increasingly evident in recent years that a simple basic nitrogen atom as the sole functional group attached to a relatively large, but sterically compact, hydrocarbon moiety may confer pharmacologically potent and valuable properties on a molecule, *e.g.*, mecamylamine (3-β-methylamino-2,2,3-trimethylbicyclo[2.2.1]heptane) and pempidine (1,2,2,6,6-pentamethylpiperidine), both potent drugs for the treatment of hypertension, and amantadine (1-aminoadamantane), the first FDA approved antiviral agent. These developments emphasize the need for improved methods of synthesizing sterically-crowded amines.

Published reports to the contrary notwithstanding (3), the Knorr-Paal synthesis of pyrroles by the condensation of primary amines with γ-diketones seemed to us to offer attractive possibilities as a route (*via* subsequent reduction of the pyrroles) to sterically-crowded tertiary amines. This paper describes the synthesis of a considerable number of moderately to severely sterically-crowded 1,2,5-trisubstituted pyrroles by means of variations on the Knorr-Paal condensation. Observations pertinent to the detailed mechanism of the cyclization were obtained from infrared spectra of the reacting mixtures intermediate to the final products.

Although many of the cyclic hydrazines used in this work have become commercially available during the past four years, they were not available when this study was begun and consequently were synthesized in our laboratory. Reduction of the nitrosamine compounds with lithium aluminum hydride (Method A) in anhydrous tetrahydrofuran gave the hydrazines in good yield. When lithium aluminum hydride of rather poor quality was used, very little N-N cleavage resulted, even upon addition of the nitrosamine to excess hydride. However, if this procedure was employed using newly purchased lithium aluminum hydride, a large percentage of the product underwent N-N cleavage to give the starting amine. The *unsym*-disubstituted hydrazines and their properties are listed in Table I. The nitrosamine compounds were obtained by nitrosation of the parent amines in glacial acetic acid (Method B) or aqueous hydrochloric acid (Method C) or sulfuric acid (Method D) with a saturated aqueous solution of sodium nitrite.

Even the classical Knorr-Paal procedure in which the amine and the diketone were heated together in equimolar quantities in the presence of a trace of catalyzing acid, either neat or in alcoholic solution (Method E), gave 40-90% yields of a variety of pyrroles exhibiting steric crowding of intermediate severity. Examples derived from *unsym*-disubstituted hydrazines (Table I) and 2,5-hexanedione are the 1-diphenylamino-, 1-(*N*-phenyl-*N*-methylamino)-, 1-(*N*-phenyl-*N*-benzylamino)-, 1-(4-methylpiperazino)-, and 1-(4-nitroso-2,5-dimethylpiperazino)-2,5-dimethylpyrroles (Table II). Other examples are 1-isopropyl- and 1-(1,3-dimethylbutyl)-2,5-dimethylpyrroles and a series of α,ω-polymethylene-1,1′-bis (2,5-dimethyl-

TABLE I

Cyclic *N*-Amino Compounds Used in the Synthesis of 1-(Substituted amino)-2,5-dimethylpyrroles, Prepared by Method A.

	B.P. °/torr	M.P.°	% Yield
1-Amino-4-nitroso-*trans*-2,5-dimethylpiperazine (a)		65-70	22
1-Amino-2-methylpiperidine (b)	62-64/13		51 (c)
1-Aminocarbazole		146-148	80
1-Amino-4-methylpiperazine (d)	76-80/25		50
4-Aminomorpholine (e)	159-165/650		46
1-Amino-2,6-dimethylmorpholine (f)	80-82/23		63

(a) Optimum rate of addition of *N*-nitroso compound caused THF to reflux. Infrared (KBr), cm^{-1}: 3311(m), 3115(m), 2967(m), 2793(m), 1639(m), 1464(m), 1408(s), 1389(s), 1353(m), 1325(s), 1235(s), 1200(m), 1159(m), 1136(m), 1096(s), 1070(m), 1012(m), 958(m), 921(s), 833(m), 760(m), 660(w). (b) Ref. (10), 156-160°/760 torr. (c) Ethyl ether was used as solvent in this reaction. Ref. (11), 50%; m.p. 147°. (d) Ref. (12), 172-175°/760 torr. (e) Ref. (13), 53%, 168°/767 torr. (f) See Experimental.

pyrroles) (Table III) which were derived from the corresponding primary amines and 2,5-hexanedione.

This method failed to yield pyrroles from *tert*-butylamine, α,α-dimethylphenethylamine, 1,1,3,3-tetramethylbutylamine and similar systems. Unaccountably, 1-*tert*-butyl-2,5-dimethylpyrrole was obtained in 40% yield on the very first attempt to condense the amine and 2,5-hexanedione together by the classical procedure, yet the preparation failed completely in dozens of subsequent attempts by this and many different water-entrainment procedures including a novel "self-entrainment", "self-generating" technique employing 2,2,5,5-tetraethoxyhexane as simultaneous water scavenger and source of the γ-diketone.

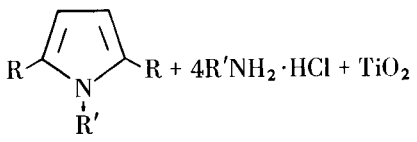
A second Knorr-Paal type cyclization procedure (Method F) more powerful than the classical method for the synthesis of sterically-crowded pyrroles involved the use of a water-azeotroping solvent (4) such as toluene, benzene, or heptane and a Dean-Stark, Molecular Sieve, calcium carbide or other water-scavenging scheme to provide a continously anhydrous environment for the primary amine and γ-diketone reactants. By this means 1-isobutyl-, 1-*sec*-butyl-, 1-(1,1-dimethyl-2-hydroxyethyl)-, and 1-neopentyl-2,5-dimethylpyrroles; 2,2-dimethyl-1,3-propane-bis(2,5-dimethyl-1-pyrrole), 1-cyclododecyl-2,5-dimethylpyrrole, and others with the more bulky groups (ethyl and isopropyl) in the 2,5- positions were prepared (Table IV).

Especially remarkable was the formation of 2-(2,5-dimethyl-1-pyrryl)-1-aryl-1,3-propanediols using chloramphenicol-type bases as starting amines. The pyrroles were accompanied in these cases by more than 50% yields of derivatives of a new heterotricyclic system of unique geometry, 2,6-dioxa-10-azatricyclo[5.2.1.$0^{4,10}$]decane. 2-Alkyl-2-amino-1,3-propanediols gave the corresponding heterotricycles exclusively (5).

A third, still more powerful, procedure for the synthesis of sterically-crowded pyrroles (Methods G and H) was adapted from the enamine synthesis of White and Weingarten (6) in which titanium tetrachloride is used both as a Lewis acid to enhance the electrophilicity of the carbonyl carbon atom and as a scavenger of product water. By this means even very highly sterically-crowded pyrroles have been synthesized, such as 1-*tert*-butyl-, 1,1,3,3-tetramethylbutyl-, 1-(α,α-dimethylphenylethyl)-, and 1-adamantyl-2,5-dimethylpyrroles; 1-*tert*-butyl-2,5-diethylpyrrole; 1,2,5-triisopropylpyrrole; and 1-methyl- and 1-ethyl-2,5-di-*tert*-butylpyrroles. Yields ranged from 25-80% (Table V).

The stoichiometry of the titanium tetrachloride-catalyzed Knorr-Paal condensation appears to be as follows:

$$RCOCH_2CH_2COR + 5R'NH_2 + TiCl_4 \longrightarrow$$



$$+ 4R'NH_2 \cdot HCl + TiO_2$$

It was found that addition of a solution of titanium tetrachloride in benzene or toluene to a cold solution of the γ-diketone and primary amine in benzene, toluene, or ethyl ether was the simplest of all addition schemes and gave the best yields. This scheme is described in Method G in Experimental. However, initial addition of the titanium tetrachloride solution to the solution of only the diketone and subsequent addition of a solution of the amine gave comparable yields. Benzene, toluene, and ethyl ether were used as solvents for the reaction; acetonitrile and *p*-dioxane produced faster and slower rates of reaction, respectively, but lower yields in both cases.

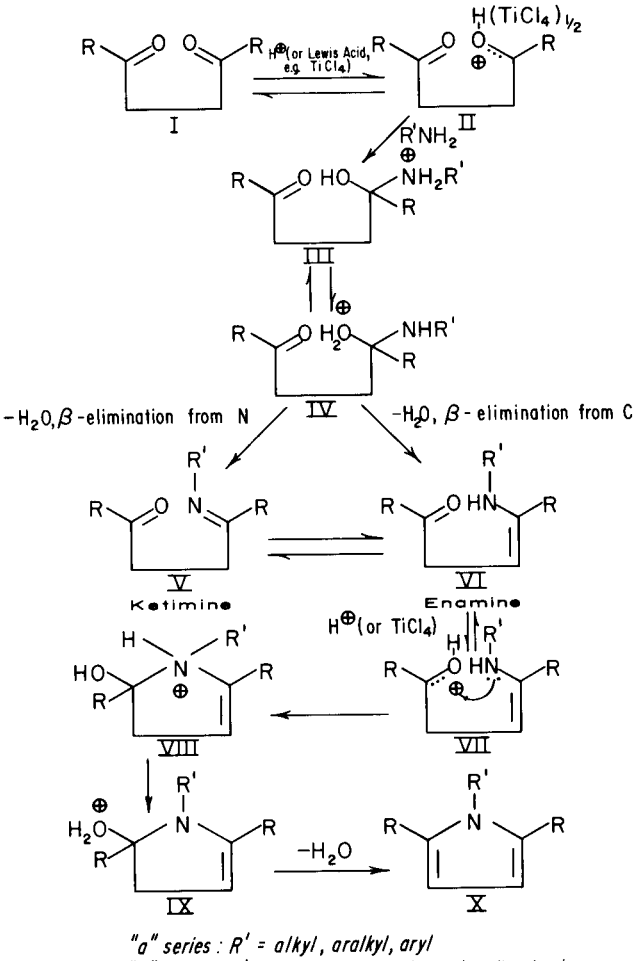
The progress of the titanium tetrachloride-assisted reaction was followed by observing the rate of formation of the pyrrole. This was done by periodically removing aliquots from the reaction mixtures, contrifuging to remove insoluble material, pipetting the supernatant liquid onto a pair of salt plates, evaporating the solvent and observing the infrared spectrum of the residue (if the residue were a crystalline solid, the solvent was evaporated in a watch glass and a potassium bromide disc was prepared). The 1,2,5-tri-substituted pyrroles exhibited very strong infrared absorption bands at about 750 cm^{-1} (13.2 μ) which have been assigned to the out-of-plane bending modes of the hydrogen atoms in the 3- and 4-positions of the pyrrole nucleus. The growth in intensity of this band was followed until it had reached a maximum and then the reaction was terminated.

A great deal of tarry material was left in the flask after the final distillation of the liquid pyrroles. (*cf.* Method G, under Experimental). This problem, which could possibly be due to titanium tetrachloride-catalyzed polymerization of the pyrroles during the reaction and work-up process, could not be overcome by quenching the reaction with water or aqueous sodium bicarbonate in order to dispose of any excess titanium tetrachloride. The bulk of the polymer is probably formed in the reaction flask concurrently with the synthesis of the pyrrole.

Inasmuch as 4/5 of the amine reactant functions only as an acid-scavenger and is not incorporated into the pyrrole molecule, it appeared likely that an inexpensive, tertiary amine might fulfill the acid-scavenging role quite as well as the primary amine condensing with the diketone. This would spare the primary amine for the condensation function which it alone could serve. The foregoing surmise was partially realized by substituting triethylamine for four of the five equivalents of primary amine in the system (Method H). This substitution, however, caused a substantial decrease in reaction rates and a *ca.* 50% decrease in yields compared to cases where only primary amine was used both as reactant and acid-scavenger. When used in an attempt to synthesize 1-*tert*-butyl-2,5-dimethylpyrrole by the scheme of addition wherein one mole of titanium tetrachloride in benzene solution was added to four moles of the tertiary amine with subsequent addition of one mole of primary amine plus one mole of γ-diketone, triethylamine and pyridine deactivated the titanium tetrachloride completely and no pyrrole was obtained even after refluxing the mixtures for 12 hours. Any time pyridine was used in any scheme as a hydrogen chloride scavenger, no pyrrole was obtained.

Even the powerful titanium tetrachloride-method is limited in the degree of steric crowding which can be achieved by its application. 1-Isopropyl-2,5-di-*tert*-butylpyrrole, 1-isobutyl-2,5-di-*tert*-butylpyrrole, and 1-*tert*-butyl-2,4-diisopropylpyrrole could not be synthesized by this method. The method was also unsuccessful with carboxamides. None of the expected product was obtained from benzamide and 2,5-hexanedione. The titanium tetrachloride-assisted reaction of benzenesulfonamide and 2,5-hexanedione yielded, however, 1-benzenesulfonyl-2,5-dimethylpyrrole.

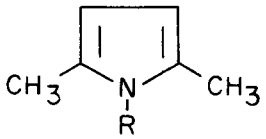
FIGURE 1

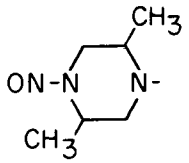
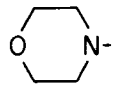
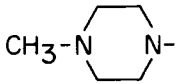
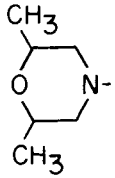
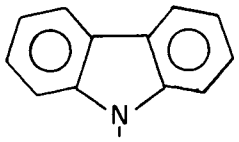


"a" series : R' = alkyl, aralkyl, aryl
"b" series : R' = dialkylamino, aralkylamino, diarylamino

TABLE II

1-(Substituted amino)-2,5-dimethylpyrroles

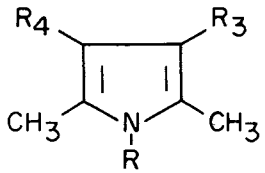


R	M.P.°	B.P.°/torr	% Yield	Synthetic Method	Analyses, % Calcd. C	H	N	Found C	H	N
$(C_6H_5)_2N$- (a)	86-87		45	E	82.40	6.92	10.68	82.10	6.94	10.96
(C_6H_5) $(C_6H_5CH_2)N$- (b)	102-103		61	E	82.57	7.29		82.78	7.48	
$(CH_3)_2N$- (c)		58-66/650	47	F			20.30			19.82
(C_6H_5) $(CH_3)N$-(d,e)	40-41		78	E	77.96	8.05	13.99	77.95	8.07	14.18
 (f)	84-85		35	E	60.99	8.53	23.71	61.23	8.79	24.17
 (g)	111-112		50	E	66.63	8.95	15.54	66.65	9.11	15.25
 (h)	55-56		75	E	68.35	9.91	21.74	67.95	10.26	21.61
 (i)	62-63		29	E			13.45			13.20
 (j)	147-148		94	E	83.04	6.20		82.97	6.33	

(a) Infrared (potassium bromide), cm^{-1}: 3049(m), 2933(m), 1587(s), 1486(s), 1330-1276 (four bands, m), 1222(m), 759(s), 745(vs), 689(s). (b) Infrared (potassium bromide), cm^{-1}: 3030(w), 2899(m), 1597(s), 1495(s), 1451(m), 1271(m), 755(s), 747(s), 737(s), 690(s). (c) Infrared (Film), cm^{-1}: 3125(w), 2924(m), 1453(s), 1439(s), 1393(s), 1020(s), 927(s), 744(vs). (d) Infrared (potassium bromide), cm^{-1}: 3077(m), 2915(m), 1597(s), 1495(s), 1403(m), 1399(m), 1285(m), 1218(m), 1133(m), 1093(m), 1030(m), 1014(m), 744(vs), 688(s). (e) See Ref. (11) for another synthesis. (f) Infrared (potassium bromide), cm^{-1}: 3077(w), 2959(m), 2907(m), 2849(m), 1408(s), 1387(s), 1353(w), 1326(m), 1289(w), 1225(s), 1205(s), 1149(m), 1133(m), 1089(m), 1071(m), 1025(m), 745(vs.). (g) Infrared (potassium bromide), cm^{-1}: 3096(w), 2967(m), 2890(m), 2841(m), 1451(m), 1441(m), 1399 (m), 1264(s), 1107(s), 1013(s), 911(s), 842(s), 754(s). (h) Infrared (potassium bromide), cm^{-1}: 2924(m), 2833(m), 2770(m), 1456(m), 1443(m), 1399 (m), 1374(m), 1314(w), 1280(s), 1264(m), 1195(w), 1148(s), 1086(m), 1074(m), 1010(m), 909(w), 785(w), 743(vs). (i) Infrared (potassium bromide), cm^{-1}: 3040(w), 2933(m), 2882(m), 1513(m), 1443(m), 1381(m), 1361(m), 1312(m), 1225(m), 1167(m), 1131(s), 1074(s), 1016(m), 962(m), 749(s), 741 (s). (j) Infrared (potassium bromide), cm^{-1}: 3058(m), 2924(m), 1603(m), 1484(m), 1447(m), 1418(m), 1316(m), 1255(m), 1230(s), 1021(m), 748(vs), 734(s), 721(s).

TABLE III

1-Substituted-2,5-dimethylpyrroles Prepared by the Classical Knorr-Paal Procedure (Method E).



R	R_3	R_4	M.P. °C	B.P.°C/torr	% Yield	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
$(CH_3)_2CHCH_2CH(CH_3)$	H	H		130-134/50	60	80.38	11.81	7.81	80.18	11.84	7.57
$(CH_3)_2CH$-	H	H		75-75.5/17	70	78.77	11.02		78.98	10.90	
-$(CH_2)_4$-	H	H	154-155		60	78.63	9.90	11.46	79.00	9.77	11.85
-$(CH_2)_5$-	H	H		134-145/0.075	58	79.02	10.14	10.84	79.15	10.23	10.71
-$(CH_2)_7$-	H	H	48-49		71	79.66	10.56	9.78	79.23	10.67	9.44
-$(CH_2)_8$-	H	H		158-162/0.15	40			9.32			9.51
$(CH_3)_2CH$-	-$CO_2C_2H_5$	-$CO_2C_2H_5$		163-164/0.45	65	64.03	8.21	4.98	64.32	8.29	5.03
$(CH_3)_2CH$-	-CH_2OH	-CH_2OH		152-154/0.45	3.5	67.0	9.64		67.0	9.15	

TABLE IV

1,2,5-Trisubstituted Pyrroles Prepared by the Water-Azeotroping Modificaton of the Knorr-Paal Procedure (Method F)

R_1	R_2	R_5	M.P. °C	B.P. °C/torr	% Yield	Solvent	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
$(CH_3)_2(CH_2OH)C$-	CH_3-	CH_3-		91-93/0.5	56	benzene	71.83	10.25	8.38	71.74	10.34	8.38
$CH_3CH_2CHCH_3$	CH_3-	CH_3-		67/8	67	benzene	79.40	11.34		79.13	11.09	
$(CH_3)_2CH_2CH_2$-	CH_3-	CH_3-		47-48/2	65	benzene	79.40	11.34		79.25	11.19	
$(CH_3)_3CCH_2$-	CH_3-	CH_3-		52-53/1.5	82	benzene	79.94	11.59		80.02	11.72	
-$CH_2C(CH_3)_2CH_2$-	CH_3-	CH_3-	69-70 (a)		42	toluene	79.02	10.14	10.84	79.20	10.14	10.77
Cyclododecyl-	CH_3-	CH_3-	72-73.5 (a)		16	toluene			5.36			5.31
$(CH_3)_2CH$-	C_2H_5-	C_2H_5-		*ca.* 90/10 (b)	73	benzene			8.48			8.24
$C_6H_5CH_2$-	$(CH_3)_2CH$-	$(CH_3)_2CH$-	81.5-81.6 (a)		70	toluene			5.80			5.90
p-$NO_2C_6H_4$CH(HO)CH(CH_2OH)- (c)	CH_3-	CH_3-	151-151.5		14	toluene	62.1	6.21	9.66	61.9	6.37	9.50

(a) from 95% ethanol. (b) This distillation was done with a Craig concentric tube column (Ref. 7) which had a 2 ml. bulb. The true boiling point is probably 3-5 degrees lower than indicated. (c) Infrared (potassium bromide) cm^{-1}: 3436(s), 3106(w), 2941(m), 2874(m), 1605(m), 1517(s), 1395(s), 1348(vs), 1292(m), 1193(m), 1072(m), 1047(s), 863(m0, 827(m), 749(s), 734(m), 704(m), 697(m).

TABLE V

Highly Sterically Hindered 1,2,5-Trialkylpyrroles Obtained by the Titanium Tetrachloride-Assisted Knorr-Paal Reaction (Method G)

					Analyses, %					
					Calcd.			Found		
R_1	R_2,R_5	M.P. °C	B.P. °C/torr	% Yield	C	H	N	C	H	N
$(CH_3)_3C$-	CH_3-		34-36/0.025	40 20 (a)	79.40	11.34		79.44	11.41	
1-adamantyl	CH_3-	126.4-127.5 (b)		20	83.78	10.11		83.65	10.12	
$C_6H_5CH_2C(CH_3)_2$	CH_3-		89-90/0.25	38 18 (a)	84.53	9.31		84.72	9.26	
$(CH_3)_3C$-	CH_3CH_2-		*ca.* 50/0.05 (c)	34	80.38	11.81		80.10	11.55	
$(CH_3)_2CH$-	$(CH_3)_2CH$-		68-70/1.75	36	80.76	11.99		80.66	12.06	
CH_3CH_2-	$(CH_3)_2CH$-		*ca.* 60/0.5 (c)	79	80.38	11.81		80.52	12.02	
CH_3-	$(CH_3)_2CH$-		*ca.* 60/0.05 (c)	82	79.94	11.59		79.74	11.81	
CH_3-	$(CH_3)_3C$- (d)	32.5-33.0 (b)	54-55/0.05	50	80.76	11.99		80.51	12.01	
CH_3CH_2-	$(CH_3)_3C$- (d)		49-51/0.025	64	81.09	12.15		81.07	12.42	
$C_6H_5CH_2$-	$(CH_3)_3C$-	120.5-121.5 (e)		43	84.70	10.10		84.59	10.00	
Cyclododecyl-	CH_3-	75.0-75.5 (b)		30			5.36			5.31
$(CH_3)_3CCH_2C(CH_3)_2$	CH_3-		64-65/0.05	25	81.09	12.15		81.16	12.35	
$C_6H_5SO_2$-	CH_3-	104-104.5 (b,f)		40	61.27	5.57		61.45	5.61	

(a) Triethylamine was substituted for 4/5 of the primary amine (Method H). (b) Recrystallized from 95% ethanol and sublimed. (c) These distillations were done with a Craig concentric column (Ref. 7) which has a 2 ml. bulb. The true boiling points are probably 3-5 degrees lower than indicated. (d) Refluxed for 12 hours after 12 hours stirring at room temperature. (e) Recrystallized from absolute ethanol and sublimed. (f) Stirred 56 hours at room temperature using 50% ethyl ether in toluene as solvent.

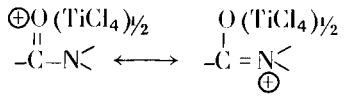
Most of the pyrroles mentioned in this paper have been hydrogenated to the corresponding pyrrolidines. Correlation of the proton affinities of the pyrrolidines with the degree of steric crowding in the vicinity of the basic nitrogen is under study.

DISCUSSION

It has been proposed (8) that the Knorr-Paal condensation of primary aliphatic or aromatic amines and γ-diketones proceeds by the formation of the enamine intermediate (VIa) (Figure 1) which ring closes with the γ-keto group to form the pyrrole (Xa). Considering the lower nucleophilicity of nitrogen in the imine form (Va), this mechanism would seem reasonable. However, if the condensation reaction were to be carried out with an *unsym*-disubstituted hydrazine rather than a primary amine, the hydrazone form (Vb) might be expected to predominate over the enamine (VIb) to a great extent in the equilibrium, Vb ⇄ VIb.

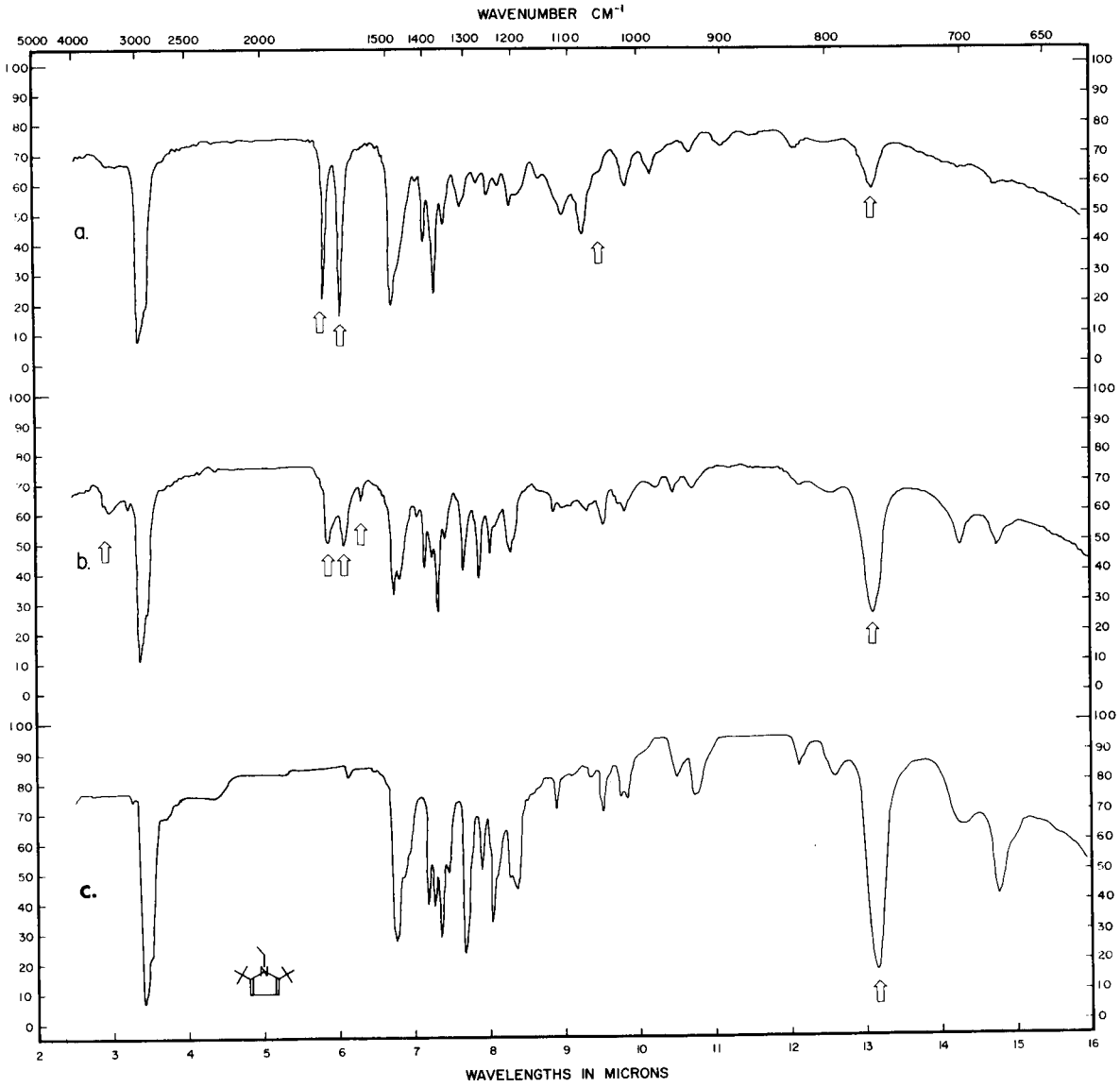
Thus there would appear to be two possible paths by which the Knorr-Paal reaction of *unsym*-disubstituted hydrazines proceeds--one through the enamine intermediate (VIb) and the other through the hydrazone (Vb). This problem was first clarified during our work leading to the synthesis of 1-dimethylamino-2,5-dimethylpyrrole. When a 20% solution of 1,1-dimethylhydrazine in benzene was refluxed with an equimolar quantity of 2,5-hexanedione and 0.1 molar equivalent of glacial acetic acid, according to Method F, one molar equivalent of water collected in the Dean-Stark trap. An impure compound was isolated which exhibited a strong infrared absorption band at 1715 cm^{-1} (5.83 μ) as well as a band of intermediate intensity at 1641 cm^{-1} (6.09 μ). These bands were assigned to the carbonyl and imino groups, respectively. After elimination of one mole of water in a repetition of the reaction, most of the benzene was removed leaving just enough of the solvent to serve as a continuous azeotroping system for the removal of product water. Under these conditions a second mole of water was eliminated. After neutralization and steam distillation of the mixture, a 40% yield of the 1-dimethylamino-2,5-dimethylpyrrole was obtained. From these observations that the monohydrazone can be first formed in the reaction mixture and then, under more vigorous conditions be made to cyclize, it appears that the reactive intermediate in this condensation may not be the monohydrazone. It is probable that the reactive form of the intermediate is the isomeric enamine, which may not be directly observable since the equilibrium between the two (Vb ⇄ VIb) heavily favors the hydrazone form (Vb) (*cf.* below).

The fact that a pyrrole derivative of benzenesulfonamide was successfully synthesized by the titanium tetrachloride-assisted procedure while none was obtained from benzamide may be explained by considering that coordination of the titanium tetrachloride with the carbonyl oxygen enhances the contribution of the canonical resonance form involving "back-polarization" delocalization of the extra electron pair on the nitrogen of the carboxamide more than would be expected with titanium tetrachloride coordinated to the oxygen of the sulfonamide moiety:



Thus the nucleophilicity of the carboxamide amino group is decreased below that of the sulfonamide amino group in their corresponding transition states.

Infrared spectra of aliquots of the titanium tetrachloride-assisted reaction of 2,2,7,7-tetramethyl-3,6-octanedione (9) and ethylamine provide evidence for the mechanism of the reaction (*cf.* spectra). As the reaction progresses, bands due to the diketone at 1700 cm^{-1} and 1060 cm^{-1} rapidly diminish in intensity while the intensity of the band (760 cm^{-1}) due to out-of-plane bending of the 3,4-hydrogens on the pyrrole ring gradually increases to a maximum (spectra a, b, and c). A new, strong band, absent in the reactants *and* products, appears in the C=N stretching region at 1640 cm^{-1} and diminishes in intensity with increasing reaction time (spectra a and b). After refluxing the toluene solution of the reactants for 24-48 hours, a band develops in the C=C stretching region (1580 cm^{-1}, spectrum b) which is accompanied by the development of a band in the N-H stretching region at about 3460 cm^{-1} (spectrum b) and by further loss in intensity of the bands at 1700 cm^{-1} and 1640 cm^{-1}. By this time the pyrrole band (760 cm^{-1}) has increased to its maximum. Distillation of the crude product gives a colorless distillate and a yellow residue. The infrared spectrum of the distillate also shows sharp bands at 3460, 1580, and 760 cm^{-1}. Only the 760 cm^{-1} band remains in the spectrum of the recrystallized product, 1-ethyl-2,5-di-*tert*-butylpyrrole (spectrum c). These observations suggest that the reaction proceeds *via* initial formation of the ketimine (Va, Figure 1), tautomerization to the enamine form (VIa, Figure 1), and subsequent rapid cyclization to the pyrrole (VIIa ⟶ Xa). The infrared bands in the N-H stretching region (3460 cm^{-1}) and the C=C stretching region (1580 cm^{-1}) may be accounted for by considering that the ketimine-enamine quasi-equilibrium is such that the enamine (unable to cyclize due to the unavailability of titanium tetrachloride late in the reaction) reaches concentrations which allow detection.



EXPERIMENTAL

Cyclic *N*-Amino Compounds.

Method A. 4-Amino-2,6-dimethylmorpholine.

A suspension of lithium aluminum hydride (16 g., 0.42 mole) in anhydrous tetrahydrofuran (200 ml.) was added in small increments over a one hour period to a stirred solution of *N*-nitroso-2,6-dimethylmorpholine (60 g., 0.42 mole) in tetrahydrofuran (200 ml.) while cooling in ice. Stirring was continued for another hour, during which the mixture was allowed to warm to room temperature.

After cooling to 15°, the adduct was decomposed by the careful addition of 19 ml. of water with stirring, 22 ml. of 10% NaOH solution and then 52 ml. of water in that order, and the mixture was allowed to come to room temperature. The slurry was filtered and the filter cake pulverized and stirred well in ether with anhydrous potassium carbonate. Filtration and evaporation yielded a brown oil which was vacuum distilled to yield 34 g. (63%) of the hydrazine, b.p. 80-82°/23 torr. Infrared (capillary film), cm^{-1}: 3289(w), 2959(m), 2849(m), 2778(m), 1595(w), 1372(m), 1319(m), 1175(m), 1140(s), 1075(s), 832(s).

Properties and references for other compounds are given in Table I.

N-Nitrosamines.

1-Nitroso-2-methylpiperidine (10).

This compound was prepared by Method E in 72% yield, b.p. 116-117°/12 torr (ref. (10) 123°/31 torr).

N-Nitrosocarbazole.

This compound was prepared by the method of Wieland and Susser (11) (Method B) in 81% yield, m.p. 80° (ref. (15) 82.5°).

1-Nitroso-4-methylpiperazine (12).

This compound was prepared by Method D in 70% yield, b.p. 124-126.5°/33 torr (ref. (12) 118-120°/25 torr).

1-Nitrosododecahydrocarbazole.

This compound was prepared by Method B in 85% yield, m.p. 80-83°: infrared (potassium bromide) cm^{-1}; 2907(s), 2841(m), 1447(m), 1399(s), 1348(w), 1319(m), 1299(m), 1266(s), 1248(s), 1238(s), 1185(m).

Anal. Calcd. for $C_{12}H_{20}N_2O$: N, 13.45. Found: N, 13.36.

N-Nitrosodicyclohexylamine (16).

This compound was prepared by Method B in 65% yield, m.p. 103° (ref. (16) 105-106°).

1,4-Dinitroso-*trans*-2,5-dimethylpiperazine (17).

This was prepared by Method D in 81% yield, m.p. 176.5-177.5° (ref. (17) 173°).

1-Nitrosomorpholine (18).

This was prepared by Method D in 96% yield, m.p. 29°, b.p. 223°/650 torr (ref. (18) m.p. 29°, b.p. 224°/747 torr).

4-Nitroso-2,6-dimethylmorpholine.

This compound was prepared by Method D in 59% yield, b.p. 112-114°/23 torr: infrared (liq. film) cm^{-1}; 2985(m), 2924(m), 2786(m), 1451(s), 1429(s), 1355(s), 1297(m), 1269(m), 1205(w), 1161(s), 1136(s), 1080(s), 967(w), 942(w), 835(w).

Anal. Calcd. for $C_6H_{12}N_2O_2$: N, 19.43. Found: N, 19.43.

1-(Substituted-amino)-2,5-dimethylpyrroles.

N-(2,5-dimethyl-1-pyrryl)carbazole. Method E.

A mixture of 9-aminocarbazole (13.2 g., 0.0750 mole) and 2,5-hexanedione (10.5 g., 0.0922 mole) was refluxed for 24 hours in 200 ml. anhydrous methanol containing 1.0 ml. of glacial acetic acid. Upon cooling to room temperature the pyrrole precipitated as cream-colored plates, which were removed by filtration and air dried. The filtrate was evaporated to half the original volume and again refluxed for 24 hours and worked up as before. Repetition gave still another batch of crystals. The combined material was washed with cold methanol and dried to yield 14 g. (72%) of the pyrrole, m.p. 147-148°. Infrared (potassium bromide) cm^{-1}: 3058(m), 2924(m), 1603(m), 1484 (m), 1447(m), 1418(m), 1316(m), 1255(m), 1230(m), 1022(m), 748(vs), 734(s), 721(s).

Properties and elemental analyses of this and other 1-(substituted-amino)-2,5-dimethylpyrroles are given in Table II.

1,2,5-Trialkylpyrroles.

1-Isopropyl-2,5-dimethyl-3,4-dicarbethoxypyrrole.

Diethyl diacetylsuccinate (20 g., 0.077 mole), isopropylamine (4.7 g., 0.08 mole), and glacial acetic acid (1.5 g., 0.025 mole) were refluxed together for 17 hours. The mixture was then neutralized with saturated sodium bicarbonate, and the organic layer was taken up in ether and dried over sodium sulfate. Removal of the ether followed by vacuum distillation yielded 14 g. (65%) of a yellow oil, b.p. 162-164°/0.45 torr.

(*Anal., cf.* Table III).

1-Isopropyl-2,5-dimethyl-3,4-bis(hydroxymethyl)pyrrole.

1-Isopropyl-2,5-dimethyl-3,4-dicarbethoxypyrrole (3.9 g., 0.014 mole) in anhydrous ether (40 ml.) was added dropwise to a suspension of lithium hydride (0.53 g., 0.014 mole) in anhydrous ether (50 ml.) while stirring. Hydrolysis was effected by dropwise addition of water and dilute NaOH. The mixture was filtered, the filtrate was dried over sodium sulfate, and again filtered. Evaporation of the ether and vacuum distillation yielded 0.1 g. (3.5%) of a yellow oil, b.p. 152-154°/0.45 torr.

(*Anal., cf.* Table III).

1-Neopentyl-2,5-dimethylpyrrole. Method F.

A solution of neopentylamine (13.7 g., 0.15 mole), 2,5-hexanedione (17.0 g., 0.15 mole), and 9 ml. glacial acetic acid in 50 ml. benzene was refluxed until no more water collected in a Dean-Stark trap. The solvent was distilled off and the residue was neutralized with cold, saturated potassium carbonate solution, extracted with ether, dried with anhydrous potassium carbonate. The ether was evaporated and the residue distilled to yield 13.6 g. (82%) of the pyrrole boiling at 52-53°/1.5 torr. The infrared spectrum was typical of 1,2,5-trisubstituted pyrroles.

Other pyrroles prepared by Method F are listed in Table IV.

1-*tert*-Butyl-2,5-dimethylpyrrole. Method G.

To a solution of 2,5-hexanedione (28.5 g., 0.25 mole), and *tert*-butylamine (110 g., 1.5 moles) in 1250 ml. benzene maintained under dry nitrogen gas, a solution of titanium tetrachloride (52.5 g., 0.275 mole) in 250 ml. benzene was added dropwise with stirring over a 2-hour period while maintaining the temperature of the mixture below 10°. Stirring was continued for 10 hours at room temperature while periodically examining aliquots of the mixture to follow the reaction. After filtration and evaporation, the residue was distilled yielding 15.3 g. (40%) of product boiling at 34-36°/0.025 torr. Infrared (capillary film), cm^{-1}: 3058(w), 2941(s), 1515(m), 1460(s), 1381(s), 1370(s), 1325(m), 1282(s), 1222(s), 1029(w), 749.1(s).

This and other pyrroles prepared by Method G are described in Table V.

1-(α,α-Dimethylphenethyl)-2,5-dimethylpyrrole. Method H.

2,5-hexanedione (5.9 ml., 5.7 g., 0.05 mole) and α,α-dimethylphenethylamine (19) (11.2 g., 0.075 mole) and triethylamine (28 ml., 20.2 g., 0.2 mole) were dissolved in 350 ml. benzene and cooled under dry nitrogen to 5°. Titanium tetrachloride (10.5 g., 0.055 mole) in 50 ml. benzene was then added dropwise while maintaining the temperatures of the mixture below 10°. The mixture was stirred at room temperature for six days. After filtration and evaporation of the benzene, the crude product was distilled to give 2.0 g., (18%) of the pyrrole, b.p. 89-90°/0.25 torr. Infrared (capillary film), cm^{-1}; 2985(m), 2924(s), 1511(w), 1490(m), 1449(s), 1377(s), 1279(s), 1252(m), 1200(m), 1170(w), 1072(w), 1028(m), 751.9(sh), 743.5(s), 722(w), 700.8(s).

(*Anal., cf.* Table V).

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