[CONTRIBUTION FROM THE DEPARTMENTS OF CHEMISTRY, UNIVERSITY COLLEGE, CORK AND UNIVERSITY OF CALIFORNIA AT LOS ANGELES]

Studies in the Pyrazole Series. VIII.[1] Aminolyses of Some 3,5-Dimethyl-1-acylguanylpyrazoles

F. L. SCOTT[2]

Received February 18, 1957

The aminolytic deguanylations of four types of 1-acylguanylpyrazole, wherein the acyl group varies from *N*-*p*-toluenesulfonyl to *N*-benzoyl to *N*-phenylthiocarbamyl to *N*-α-naphthylcarbamyl, has been examined. The comparative unreactivity of the first three of these types toward bases in ethanol is consistent with a BAc2 mechanism of deguanylation. The fourth type of acyl derivative behaved anomalously. Use of the displacing amines as both solvents and reactants did effect ready deguanylation, mono- and di-substitutions being detected therein. Evidence was obtained from the scissions of some substituted *S*-methylpyrazolyl thioureides that the pyrazolide leaving group can have a greater mobility than the labile thiomethoxide ion. The detection of this difference depended upon the aminolysis temperature; above a certain temperature level both pyrazolide and thiomethoxide were eliminated to form trisubstituted biguanides. Reaction conditions were devised, *viz.*, with dialkyl cyanamides in chloroform, wherein some substituted 1-guanylpyrazole free bases underwent eliminations to yield dicyandiamide. This elimination process was not encountered with comparable acyclic systems.

In some previous papers in this series,[1,3] we have examined the reactions of certain substituted 1-acylpyrazoles (*e.g.* Ia, Ib and Ic) with nucleophiles, the over-all reaction observed therein being a fragmentation of the substituted (I) substrate with the liberation of 3,5-dimethylpyrazole (Id) and the formation of the nucleophilic adduct of the articulated acyl group (X). The possible mechanisms of these deacylations have also received some consideration. One of these mechanisms, the equivalent of a carbonyl addition-elimination process, a so-called BAc2 reaction,[4] has been established by kinetic methods[5] as the operative mode of decarbamylation of a variety of 1-carbamylpyrazoles in neutral ethanolic solution, and as the sole mode of deacylation of 3,5-dimethyl-1-(*N*,*N*-diphenylcarbamyl)pyrazole (Ie), even in basic media, because of the structural prohibition this substance offers toward other types of heterolytic cleavage.[3a] The other available heterolytic mechanisms for the general 1-pyrazolyl deacylations involve an intermediate anion and may consist of either a simple elimination process[6] or a base-catalyzed modification of the $B_{Ac}2$ reaction.[7] The present work, amidst its consideration of a diversity of pyrazolyl aminolyses, has some further pertinence with regard to the possibility of the intrusion of such an anionic intermediate.

Thus if such an intermediate were involved in the base-induced deacylations then an increase in the acidity of the 1-carbamyl- or 1-guanyl-pyrazolyl substituents should greatly increase the population of intermediate anion and thereby result in an overall facilitation of the deguanylation process.[8] Such (small) acidity increases were incorporated into the 1-guanylpyrazole system with four types of acyl substitution therein. With three of the resulting compounds, *viz.* 3,5-dimethyl-1-[*N*-*p*-toluenesulfonyl (If)-, *N*-benzoyl (Ig)-, and *N*-(*N'*-phenyl)-thiocarbamyl (Ih)]guanylpyrazoles, the relative reactivities towards aminolytic deacylations were greatly below that of the parent 1-guanylpyrazole (Ij).[9,10] That is, refluxing If, Ig or Ih in ethanolic solution for 3- to 6-hour periods in the presence of equimolar quantities, or an excess, of such nucleophiles as aniline, *n*-butylamine, cyclohexylamine, morpholine, phenylhydrazine or piperidine resulted in the substituted pyrazoles being recovered in *ca.* 80–95% yields. With the fourth pyrazole derivative used, *viz.* 3,5-dimethyl-1-(*N*-α-naphthylcarbamyl)guanylpyrazole (Ik) the aminolytic reactions detected under these conditions were anomalous–a facile scission occurring at the naphthyl-proximate carbonyl group therein, perhaps *via* the anion (II).[8] Thus, when refluxed with phenylhydrazine or cyclohexylamine for 1 hour in ethanolic solution, Ik afforded 4-α-naphthyl-1-phenyl-

(1) Part VII, F. L. Scott, D. G. O'Donovan, M. R. Kennedy, and J. Reilly, *J. Org. Chem.*, **22**, 820 (1957).

(2) Present address, Pennsalt Chemical Corp., Whitemarsh Research Labs., Box 4388, Phila. 18, Pa.

(3) (a) Part IX, This Series, F. L. Scott, A. Ahearne, and J. Reilly, to be submitted for publication; (b) F. L. Scott, M. T. Kennedy, and J. Reilly, *J. Am. Chem. Soc.*, **75**, 1294 (1953).

(4) Compare C. K. Ingold, *Structure and Mechanism in Organic Chemistry*, Cornell University Press, Ithaca, N. Y., 1953, pp. 752 *et seq.*, in which the symbolism BAc2 is used to represent a base-induced bimolecular hydrolysis of an ester with acyl scission.

(5) F. L. Scott, *Chimia* (*Switz.*), **11**, 163 (1957).

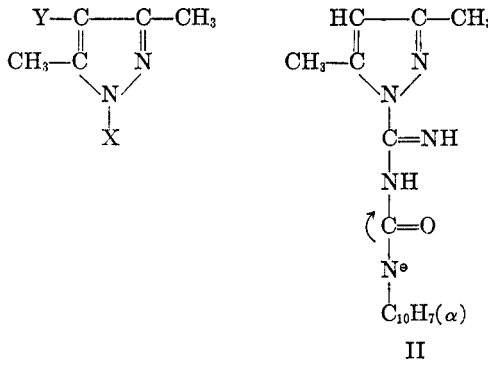
(6) See p. 420 *et seq.* of Ingold, *op. cit.*

(7) *Cf.* D. G. Crosby and C. Niemann, *J. Am. Chem. Soc.*, **76**, 4458 (1954).

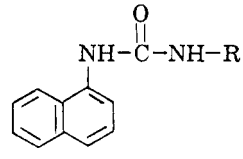
(8) For some related kinetic data see F. L. Scott, R. E. Glick, and S. Winstein, *Experientia*, **13**, 183 (1957).

(9) Compare the data in (a) F. L. Scott and J. Reilly, *J. Am. Chem. Soc.*, **74**, 4562 (1952), and (b) F. L. Scott, D. G. O'Donovan, and J. Reilly, *J. Am. Chem. Soc.*, **75**, 4053 (1953).

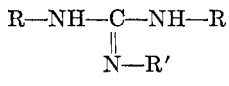
(10) Strictly speaking, one should compare the reactivities of If, Ig and Ih *versus* the 3,5-dimethyl-1-guanylpyrazole free base (Ip) rather than Ij. This does not change the reactivity sequence as Ip is even more prone to solvolytic deguanylation than Ij.

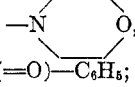
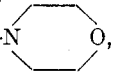
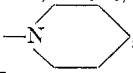
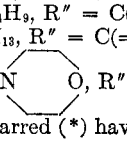
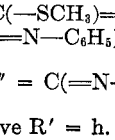


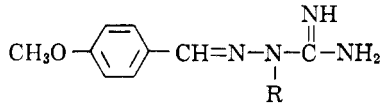
I, a*, X = $CONH_2$;
b*, X = $CSNH_2$;
c*, X = $C(=NH)NHNO_2$;
d*, X = H;
e*, X = $CON(C_6H_5)_2$;
f*, X = $C(=NH)NHSO_2C_6H_4CH_3(p)$;
g*, X = $C(=NH)NHCOC_6H_5$;
h*, X = $C(=NH)NHCSNHC_6H_5$;
j*, X = $C(=NH)NH_2 \cdot HNO_3$;
k*, X = $C(=NH)NHCONHC_{10}H_7(\alpha)$;
l*, X = $C(=NH)NHC(SCH_3)=N-C_6H_5$;
m Y = Cl, X as in l;
n, Y = Br, X as in l;
p*, X = $C(=NH)NH_2$;
q, Y = Cl, X as in p;
r, Y = Br, X as in p;
Those symbols starred (*) have Y = h.



III, a, R = $-NH-C_6H_5$;
b, R = C_6H_{13};
c, R = $C(=O)-NH_2$



IV, a*, R″ = $SO_2-C_6H_4-CH_3(p)$;
b*, R = n-C_4H_9,
R″ = $C(=O)-C_6H_5$;
c*, R = C_6H_{13},
R″ = $C(=O)-C_6H_5$;
d, R = R′ = C_6H_{13},
R″ = $C(=O)-C_6H_5$;
e*, RNH =  ,
R″ = $C(=O)-C_6H_5$;
f, RNH = NHR′ =  ,
R″ = $C(=O)-C_6H_5$;
g*, RNH =  , R″ = $C(=O)-C_6H_5$;
h*, R = C_6H_5,
R″ = $-C(-SCH_3) = N-C_6H_5 \cdot HI$;
j*, R = n-C_4H_9, R″ = $C(-SCH_3)=N-C_6H_5$;
k*, R = C_6H_{13}, R″ = $C(=N-C_6H_5)-NHC_6H_{13}$;
l*, RNH =  , R″ = $C(=N-C_6H_5)-$  ;
Those symbols starred (*) have R′ = h.



V, A, R = H;
b, R = $C(=NH)N(CH_3)_2$;

semicarbazide (IIIa) or 1-cyclohexyl-3α-naphthylurea (IIIb) in 85 or 90% yields respectively. In that connection, it is interesting to note that under acidic conditions, *i.e.* on refluxing Ik for 90 minutes with an excess of 10% hydrochloric acid solution, its cleavage resembles that normally detected with the 1-guanylpyrazoles,[9] the product of the acidolysis being an 80% yield of 1-α-naphthyl biuret (IIIc).

The experiments conducted with If, Ig and Ih, clearly indicating that their rates of aminolytic deacylation were much slower than that obtaining for the parent 1-guanyl compound (Lj),[10] strongly suggest that the base-induced deacylations of at least the substituted 1-guanylpyrazoles do not involve an intermediate anion. This in turn would again point to the $B_{AC}2$ mechanism. Now the detailed formulation of such a $B_{AC}2$ process reveals it has 2 stages: (1) addition of the displacing nucleophile to the carbonyl site, with some retrogression of the adduct, and (2) elimination of the (anionic) leaving group from the resulting adduct.[11] Acyl substitution in Ip should increase the electrophilicity of its guanyl moiety and thereby favor step (1) in its ($B_{AC}2$) mode of deguanylation. Such electrophilicity increase should also inhibit the dissociation step (2) therein. The present results suggest therefore that with the compounds examined, step (2) is more important in formulating the transition state of the over-all $B_{AC}2$ displacement than is step (1). This point[5] is elaborated on in a subsequent report on the kinetics of such 1-pyrazolyl deacylations.[12-14]

In an effort to overcome the lack of reactivity of the pyrazoles If, Ig, and Ih their reaction conditions were modified, *i.e.*, to the use of the displacing amine in large excess as both reactant and solvent. Under these conditions the aminolyzing pyrazolyl substrate was enveloped in a medium of displacing nucleophile, the nuances of mechanism discussed earlier were essentially obscured, and the over-all reaction was reduced to that of a pseudo first order solvolysis. The modified conditions did, however,

(11) *Cf.* C. A. Bunton, T. A. Lewis, and D. R. Llewellyn, *Chemistry & Industry*, 1154 (1954).

(12) F. L. Scott and R. Rubin, forthcoming paper in this series.

(13) For some earlier discussion on the varying importances of bond-formation *versus* bond rupture in the transition states of related acyl halide solvolyses, see the interesting paper of E. W. Crunden and R. F. Hudson, *J. Chem. Soc.*, 501 (1956).

(14) For a more complete discussion of the solvolysis mechanisms at a reactive carbonyl function, and the solvent-dependency of such mechanisms, see S. Winstein and A. H. Fainberg, forthcoming publication.

lead to 1-deguanylations. Thus, If, when refluxed without further solvent other than an excess of the amines aniline, *n*-butylamine, cyclohexylamine, morpholine, or piperidine, for 30-minute periods, formed the appropriate 1-*p*-toluenesulfonyl-3-substituted guanidines (IVa) in 70–100% yields. While aniline reacted anomalously when similarly refluxed with Ig, *n*-butylamine cleaved this substituted pyrazole to form 3-benzoyl-1-*n*-butylguanidine (IVb) in 98% yield. Dual substitution reactions were encountered between Ig and both cyclohexylamine, which afforded not only 1-benzoyl-3-cyclohexylguanidine (IVc) but also 1-benzoyl-2,3-dicyclohexylguanidine (IVd), and morpholine, which similarly resulted in 4-(*N*-benzoyl)guanylmorpholine (IVe) and *N*-benzoyl-(4,4′-dimorpholino)keto-imine (IVf). With piperidine as base the sole product isolated under these forcing conditions with Ig was 1-(*N*-benzoyl)guanylpiperidine (IVg). With Ik, even under these conditions, the anomalous scission pattern encountered in the earlier ethanolic reactions of this material was duplicated. For example, *n*-butylamine and cyclohexylamine when refluxed with Ik in the absence of further solvent resulted in the formation of the appropriate 3-substituted-1-α-naphthylureas (III). With an excess of morpholine and piperidine, in addition to the formation of compounds of type (III), Ik also yielded both 1-guanylmorpholine and -piperidine, respectively, in small yields. Finally, with aniline Ik appeared to afford a double displacement, the final product isolated being 1,3-diphenylurea in high yield. In all of the above experiments, accompanying the main products cited, 3,5-dimethylpyrazole was formed in good yield.

Thioureide systems are prone to base-induced eliminations and desulfurizations[15] and hence an effort was made to avoid these complications with Ih, and related molecules, in the aminolyses attempted with these substances. This attempt consisted of replacing the acidic thiol function of Ih by an *S*-ether grouping; in the case of Ih, the *S*-methyl derivative (Il) being so prepared. Despite this the aminolysis reactions of Il were generally complex and have not as yet been completely clarified. However, some data have been obtained. Thus, when Il, as its hydriodide, was refluxed for 1 hour with one equivalent of either cyclohexylamine, morpholine, or piperidine in ethanolic solution, the free base Il was the only solid recovered, and that in only 40–60% yield. The 4-chloro (Im)- and 4-bromo (In)-analogs of Il behaved similarly. However, with aniline, Il did yield a displacement reaction, 40% Id being isolated as well as a 30% yield of 1-(phenylamidino)-2-methyl-3-phenylthiouronium hydriodide (IVh). This result suggested that even under these mild conditions the pyrazolide leaving group has at least comparable lability with the labile thiomethoxide ion.[16] When some reactions were attempted between Il, Im, and In in the displacing amines as solvent, this lability comparison was further supported. Thus, when either Il, Im, or In was refluxed in 10 equivalents of *n*-butylamine for 30 minutes, the same compound, *viz.* 1-(*n*-butylamidino)-2-methyl-3-phenylthiourea (IVj), was formed in *ca.* 95% yield in all 3 experiments, together with the respective derivatives of Id. These results would imply that, in the given competitive situation at least, the pyrazolide ion has a *greater* affinity for separation than the thiomethoxide group. Incidentally, if one combines this observation with other data,[17] the following lability sequence might be predicted: azide $\geq$ pyrazolide > thioalkoxide > nitramide. Finally, when these thioureidopyrazoles were treated with both cyclohexylamine and morpholine, again at reflux temperatures in the amines as solvent, the higher reaction temperatures involved (134° and 126° as compared to 78° with *n*-butylamine) obscured the discrimination in leaving tendency just commented on and the main products isolated were 1,4-dicyclohexyl-5-phenylbiguanide (IVk) and 1,4-di(tetramethyleneoxy)-5-phenylbiguanide (IVl), respectively, corresponding to a replacement of both pyrazolide and thiomethoxide groups by base. In addition to describing more fully the reactions just discussed the Experimental Section has some further data on the synthesis of thioureido substituted pyrazoles similar to Ih and Il.

The above deguanylations, as already mentioned, occur by the $B_{AC}2$ mechanism. However, in some cognate experiments, a set of deguanylation conditions were realized in which the operative mechanism appeared to be unequivocally of the elimination type.[6] Thus, when 4-unsubstituted (Ip)-, 4-chloro (Iq)-, and 4-bromo (Ir)- 3,5-dimethyl-1-guanylpyrazole free bases were refluxed in anhydrous chloroform solution with either dimethyl or diethyl cyanamides as potential (but weak) nucleophiles, no incorporation of the dialkyl cyanamide molecule within the guanylpyrazole system resulted. Instead, deguanylation to yield dicyandiamide in good yield was the sole process detected. Under these conditions no form of solvolytic displacement was possible, no products were isolated to suggest the operation of any $B_{AC}2$ displacements, and hence the observed reaction would appear to correspond to an initial (E_2)[6] elimination of cyanamide from Ip, Iq, and Ir, followed by dimerization of the cyana-

(15) Compare (a) F. L. Scott, D. G. O'Donovan, M. Paye, and J. Reilly, to be submitted for publication; (b) F. L. Scott, *Chemistry & Industry*, 1350 (1956); (c) W. H. R. Shaw and D. G. Walker, *J. Am. Chem. Soc.*, **78**, 5769 (1956) and references therein; (d) F. L. Scott, *Experientia*, **13**, 275 (1957).

(16) Compare for example F. L. Scott, D. A. O'Sullivan, and J. Reilly, *J. Appl. Chem.*, **2**, 184 (1952) and references therein.

(17) *Cf.* F. L. Scott, A. J. Kocjarski, and J. Reilly, to be submitted for publication; L. Fishbein and G. A. Gallaghan, *J. Am. Chem. Soc.*, **76**, 1877 (1954).

mide to dicyandiamide.[18] No formation of this latter material occurred when these reactions were attempted in ethanolic solution, ethanolysis evidently being far superior to the elimination mechanism as a deguanylating process. Again no elimination, or displacement, was detected when Ij, *i.e.* Ip-nitrate, was refluxed for 2 hours without further solvent other than an excess of diethyl cyanamide. To emphasize the labilizing effect of the readily displayed pyrazolide ion[1] on such guanyl systems as Ip, *et al.*, some cognate reactions with acyclic systems were investigated. Some of the results obtained were as follows. When aminoguanidine nitrate was refluxed in an excess of dimethyl cyanamide for 3 hours, or with diethyl cyanamide in aqueous ethanolic solution for 6 hours, it was recovered in 90% yield. A similar unreactivity was demonstrated under comparable conditions by triaminoguanidine nitrate. An anomalous reaction was detected when aminoguanidine free base was refluxed for 3 hours in aqueous solution with an equimolar proportion of diethyl cyanamide. Finally, although *p*-methoxybenzylidene aminoguanidine (Va) when refluxed with dimethyl cyanamide for 3 hours in either ethanolic or chloroform solution was recovered in 97% yield, when this reaction was conducted in the dialkyl cyanamide itself as solvent only 30% Va was isolated, together with a 17% yield of *p*-methoxybenzylidene 1-amino-4,4-dimethyl-2-guanyl-guanidine (Vb).[19] In all of the above reactions no evidence of dicyandiamide was detected; hence, within the material balances indicated, the pyrazolyl elimination mechanism was not reproduced by comparable acyclic systems.

EXPERIMENTAL[20]

The substituted 3,5-dimethyl-1-acylguanylpyrazoles, If to Ik, and Ip, Iq, and Ir, were prepared by the methods of Scott and Reilly.[9a] The melting points of these compounds found in the present work agreed with those reported previously.

Aminolysis experiments with If, Ig, and Ih. (1) *In ethanolic solution.* The following is typical of the runs attempted. To 1.0 g. of Ig dissolved in 20 ml. of ethanol was added 0.3 ml. of cyclohexylamine and the whole was refluxed for 2 hr. On allowing the solution to cool some Ig separated. After addition of an excess of water to the ethanolic filtrate a further quantity was obtained. These crops, added to the trace of Ig obtained on ethereal extraction (5 × 50 ml.) of the aqueous ethanolic mother-liquor, corresponded to a 98% recovery of starting material. A similar result was obtained when Ig was refluxed, again in ethanol, with even a 10-molar excess of aniline for a 6-hr. period. Variation of the base employed had but little effect on the comparative aminolytic unreactivity of Ig, under these conditions. The results were similar with If, it being recovered in 95–98% yields after 6 hr. refluxing with either aniline or morpholine in ethanol.

As mentioned earlier, Ik did react under these conditions though not in the expected manner. Thus, when 0.5 g. of Ik dissolved in 20 ml. of ethanol was refluxed with 0.17 ml. of phenylhydrazine, after 10 min., a heavy separation of solid was detectable. Refluxing was continued for a further 35 min. and the solution was then allowed to cool overnight. The solid which had deposited (0.22 g., 48% yield), had a m.p. of 215–218°, and after the substance had been recrystallized from aqueous ethanol, it melted at 224°. It corresponded to 4-α-naphthyl-1-phenylsemicarbazide (IIIa).

Anal. Calcd. for $C_{17}H_{15}N_3O$: C, 73.6; H, 5.4; N, 15.2. Found: C, 73.5; H, 5.7; N, 15.2.

From the original ethanolic filtrate was isolated, on further work-up, 0.23 g. (48% yield) of unchanged Ik. Cyclohexylamine when treated with Ik under analogous conditions yielded 37% starting material and 56% of 1-cyclohexyl-3-α-naphthylurea (IIIb),[21] m.p. 237–239°.

Anal. Calcd. for $C_{17}H_{20}N_2O$: C, 76.1; H, 7.5; N, 10.4 Found: C, 76.1; H, 7.4; N, 10.0.

The following experiment is an acidolysis cognate to the above. To 0.5 g. of Ik was added 30 ml. of 10% hydrochloric acid solution and the resulting mixture was then refluxed for 90 min. The residual solid, 300 mg., 80% yield, with m.p. 214° (it re-solidified and then sublimed after melting), was recrystallized from aqueous ethanol as a white paperlike amorphous solid, m.p. 217–218° (again with re-solidification and sublimation). This was 1-α-naphthylbiuret (IIIc), reported[22] m.p. 217.3–217.6°.

Anal. Calcd. for $C_{12}H_{11}N_3O_2$: C, 62.9; H, 4.8: N, 18.3. Found: C, 63.2; H, 4.8; N, 18.1.

(2) *In various amines as solvents.* The following is typical of this series of experiments. To 1.21 g. of Ig was added 4.5 ml. of morpholine. The resulting solution was then refluxed for 30 min., during which time the reaction liquor adopted a mauve tint and a faint odor of ammonia developed. The liquor was allowed to stand for 24 hr. and was then poured into 100 ml. of water. A white solid, 0.40 g., m.p. 145–148°, was immediately precipitated and on standing a further 0.30 g. of this same substance also separated. This crystallized from 95% ethanol as a gelatinous solid which dried to a white amorphous powder, m.p. 148°. It proved to be 4-(*N*-benzoyl)guanylmorpholine (IVe).

Anal. Calcd. for $C_{12}H_{15}N_3O_2$: C, 61.8; H, 6.4; N, 18.0. Found: C, 61.6; H, 6.0; N, 18.3.

Ethereal extraction of the original filtrate afforded a further 0.25 g. of the above substance, the total yield obtained was 81%, as well as 0.29 g. (60% yield) of 3,5-dimethylpyrazole (Id).[23] The residual aqueous mother liquor was concentrated to small bulk. To it was then added an excess of aqueous picric acid solution, and the oily material which separated was filtered off and washed with a little ethanol and water. After recrystallization from ethanol, the picrate (0.22 g., 8% yield) was obtained as small rhombic crystals, m.p. 165°, and it corresponded to the salt of *N*-benzoyl-(4,4′-dimorpholino)keto-imine (IVf).

(18) An alternative to a direct elimination process is an initial $B_{AC}2$ displacement *e.g.* of the type: 2 Py—C(=NH)—NH_2 → PyH + Py—C(=NH)—NH—C(=NH)—NH_2 (A), where Py represents a substituted pyrazolyl group. However, (A) still has to undergo elimination to yield dicyandiamide. The possibility of a homolytic reaction rather than a heterolytic process cannot still be discounted.

(19) Compare the observations of A. D. Ainley, F. H. S. Curd, and F. L. Rose, *J. Chem. Soc.*, 98 (1949) and previous papers in that series.

(20) All melting points are uncorrected and all microanalyses are by Drs. Wieler and Strauss, Oxford, England.

(21) This compound was formed in 93% yield when Ik was refluxed in an excess of cyclohexylamine, without further solvent, for 30 min.

(22) T. L. Davis and K. C. Blanchard, *J. Am. Chem. Soc.*, 51, 1801 (1929).

(23) In all of the aminolysis experiments conducted in an excess of the amine as sole solvent, Id was isolated in from 60–70% yields. It was identified in each case not only by mixture m.p. with an authentic sample but also by mixture m.p. of its picrate with an authentic sample.

Anal. Calcd for $C_{22}H_{24}N_6O_{10}$: C, 49.6; H, 4.5; N, 15.8. Found: C, 49.8; H, 4.1; N, 16.0.

Most of the remaining aminolyses effected with this trio of 1-acylguanylpyrazoles are summarized in Table I.

Aminolyses of Ih and related compounds. (1) *In ethanol.* The following represents a typical experiment. To 1.37 g. of Ih dissolved in 20 ml. of ethanol was added 0.45 ml. of aniline. The resulting solution was then refluxed for 1 hr. and allowed to cool overnight. On the addition of an excess of water 0.97 g. of Ih were precipitated and a further 0.30 g. of this substance was recovered on work-up of the aqueous mother liquor. The total recovery of Ih was 95%. Analogous results were obtained when the base employed was either cyclohexylamine or morpholine. For reasons discussed earlier, Ih, and the analogous 4-chloro- and 4-bromo-3,5-dimethyl-1-(*N*-phenylthiocarbamyl)guanylpyrazoles, were then methylated. The following illustrates how this was effected. A solution of 1.0 g. of Ih in 25 ml. of methyl iodide was refluxed for 30 min. The pale yellow liquor was then poured into a large excess, *ca.* 300 ml., of anhydrous ether. A white oil was immediately precipitated but this solidified on scratching. This substance, 1.50 g., 99% yield, m.p. 84–85°, was recrystallized from a mixture of ethanol and ether as a fine white powder which turned yellow on prolonged exposure to light, m.p. 87–88°. It proved to be 3,5-dimethyl-1-(*N*-phenyl-*S*-methyl-thiocarbamyl)guanylpyrazole (Il) hydriodide.

Anal. Calcd. for $C_{14}H_{18}N_5SI\cdot H_2O$: C, 38.8; H, 4.6; N, 16.2; S, 7.4. Found: C, 38.4: H, 4.6; N, 15.7; S, 7.7.

The other methiodides, and their free bases Il, Im, and In, together with a number of related aryl- and alkylthiocarbamylguanylpyrazoles have their properties summarized in Table II.

When the pyrazolyl substrate aminolyzed was either Il, Im or In hydriodide, and the reaction conditions consisted of 1 hr.'s refluxing in ethanolic solution with either cyclohexylamine, morpholine, or piperidine, in each reaction some methyl mercaptan was evolved but the only solids isolated were the respective free bases Il, Im or In, in *ca.* 40–60% yields. There was only one exception to this pattern and that was as follows. To 4.16 g. of Il, as its hydriodide, dissolved in 50 ml. of ethanol, was added 1.86 ml. of aniline. The mixture was refluxed for 1 hr. during which time a little methyl mercaptan was evolved. The solution was then allowed to cool and was evaporated in a stream of air. On work-up of the resulting oil, both 3,5-dimethylpyrazole, 0.38 g., 40% yield[23] and crystals of m.p. 145–150° (1.20 g., 30% yield) were obtained. This latter substance after further crystallization from aqueous ethanol proved to be 1-(*N*-phenylamidino)-2-methyl-3-phenylthiouronium hydriodide (IVh), m.p. 158°.

Anal. Calcd. for $C_{15}H_{17}N_4SI$: C, 43.7; H, 4.1; N, 13.6; S, 7.8; I, 30.8 Found: C, 44.1; H, 3.9; N, 13.6; S, 7.8; I, 31.1.

(2) *In various amines as solvents.* These reactions were generally quite complex but some definite products have been identified therefrom. The following illustrates a comparatively clean-cut aminolysis within this group. To 1.0 g. of Il was added 3 ml. of *n*-butylamine and the resulting solution was then refluxed for 30 min. During this time, a slight evolution of methyl mercaptan was detected from the liquor. After it had been allowed to cool the solution was poured into 50 ml. of distilled water. An oil separated immediately but after a short while, with vigorous scratching, this crystallized. The white powder thus obtained, 0.90 g., 98% yield, had a m.p. of 70–75°. After recrystallization from 50% aqueous ethanol it proved to be 1-(*n*-butylamidino)-2-methyl-3-phenylthiourea (IVj), m.p. 78–80°.

Anal. Calcd. for $C_{13}H_{20}N_4S$: C, 59.1; H, 7.6; N, 21.2; S, 12.1. Found: C, 58.8, 59.5; H, 7.4, 7.7; N, 21.6, 21.6; S, 11.5, 11.8.

This same compound was also obtained, and in good yield, from the similar aminolyses of Im and In. In each case 3,5-dimethylpyrazole, or the appropriate 4-chloro- or 4-bromo-derivative thereof,[24] was isolated in *ca.* 60–70% yields from the aqueous mother liquors.

While all three pyrazoles Il, Im, and In, under the above conditions, afforded unworkable oils with both aniline and benzylamine, with cyclohexylamine they afforded the same compound in *ca.* 70% yields, together with some methyl mercaptan evolution. This common product, m.p. 135° after 3 recrystallizations from aqueous ethanol, proved to be 1,4-dicyclohexyl-5-phenylbiguanide (IVk).

Anal. Calcd. for $C_{20}H_{31}N_5$: C, 70.4; H, 9.1; N, 20.5. Found: C, 70.3; H, 9.0; N, 20.4.

With morpholine as the basic medium, Il afforded a strong evolution of methyl mercaptan and a white solid, insoluble in ether and very soluble in ethanol, with m.p. 105°, which is still unidentified.

Anal. Calcd. for $C_{10}H_{16}N_3O_2$: C, 57.1; H, 7.6; N, 20.0. Found: C, 57.2; H, 7.4; N, 20.4.

Also isolated from this reaction was a picrate in 70% yield, m.p. 204° (Il-picrate melts at 123–125°), which proved to be the salt of 1,4-di(tetramethyleneoxy)-5-phenylbiguanide (IVe).

Anal. Calcd. for $C_{22}H_{26}N_8O_9$: C, 48.4; H, 4.8; N, 20.5. Found: C, 48.0; H, 5.0; N, 19.9.

This same picrate was isolated from the analogous experiments with Im and In, and morpholine, again in *ca.* 75% yield. However, in neither of these last two experiments was the white solid, m.p. 105°, re-encountered.

Some dialkyl cyanamide reactions. (1) *With Ij.* Equimolar quantities of 3,5-dimethyl-1-guanylpyrazole nitrate (Ij) and dimethyl cyanamide were refluxed in ethanolic solution for 5 hr. On allowing the solution to cool unchanged Ij separated in 64% yield. The filtrate was then evaporated to dryness in a stream of air and the residual solid washed with ether. Unexpectedly, the ethereal washings afforded not only a 5% yield of Id[24] but a 14% yield of the free base Ip. This latter substance, after careful crystallization from benzene, melted at 70°, reported[9a] m.p. 70–71°.

Anal. Calcd. for $C_6H_{10}N_4$: C, 52.7; H, 7.2; N, 40.6. Found: C, 52.6; H, 7.4; N, 40.5.

The ether-insoluble solid was a further quantity (16%) of unchanged Ij. When the substituted cyanamide employed in this experiment was the diethyl compound, with a 6-hr. reflux period, 38% Id and 60% Ij were isolated, and no formation of Ip was detected. Finally, when Ij was dissolved in a 10-molar proportion of diethyl cyanamide and refluxed under anhydrous conditions for 2 hr., it crystallized out in 41% yield on standing. After the removal of the major portion of the dialkyl cyanamide "solvent" by distillation *in vacuo*, the residual viscous liquor was taken up in aqueous ethanol, and excess saturated aqueous picric acid solution was added to it. A 30% yield of Ij-picrate, m.p. 207–209°, reported[9a] 207–208.5°, separated.

Anal. Calcd. for $C_{12}H_{13}N_7O_7$: C, 39.2; H, 3.5; N, 26.7. Found: C, 39.1; H, 3.5; N, 27.0.

(2) *With the substituted 1-guanylpyrazole free bases, Ip, Iq, and Ir.* (a) When Ip was refluxed in ethanolic solution for 6 hr. with an equimolar proportion of diethyl cyanamide it yielded Id in 48% yield and Ip was recovered to the extent of 46%. No dicyandiamide was detected With dimethyl cyanamide under identical conditions the deguanylation effect was less, 59% Ip being isolated and 38% Id. (b). When Iq was refluxed in chloroform solution with an equimolar proportion of either dimethyl or diethyl cyanamides for 3 hr. it was recovered in 42 and 40% yields, and also formed in 20 and 57% yields, respectively, dicyandiamide, m.p. 208°, which did not depress a mixture m.p. with an authentic sample, reported[25] m.p. 207–209°.

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(24) These were identified by mixture m.p. with authentic samples, which in turn were prepared by the methods of G. T. Morgan and I. Ackermann, *J. Chem. Soc.*, 1308 (1923).

(25) I. Heilbron and H. M. Bunbury, *Dictionary of Organic Compounds*, 4th edition, Eyre and Spottiswoode, London, 1953, p. 177.

TABLE I

AMINOLYSES OF SOME SUBSTITUTED 1-ACYLGUANYLPYRAZOLES

Amine	Product	Molecular Formula	M.P., °C.	Yield, %	Analyses: Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
Aniline[a,b]	1-Phenyl-3-*p*-toluenesulfonylguanidine[c]	$C_{14}H_{15}N_3SO_2$	185–186	70	58.1	57.8	5.2	5.0	14.5	14.4[d]
n-Butylamine[a]	1-*n*-Butyl-3-*p*-toluenesulfonylguanidine	$C_{12}H_{19}N_3SO_2$	118–120	99	53.5	53.8	7.1	6.6	15.6	15.4[e]
Cyclohexylamine[a]	1-Cyclohexyl-3-*p*-toluenesulfonyl-guanidine	$C_{14}H_{21}N_3SO_2$	170	72	57.0	57.1	7.1	6.8	14.2	14.0[f]
Morpholine[a]	4-(N-*p*-Toluenesulfonyl) guanyl-morpholine	$C_{12}H_{17}N_3SO_3$	163–164	84	50.9	51.4	6.0	5.8	14.8	15.4[g]
Piperidine[a]	1-(N-*p*-Toluenesulfonyl) guanyl-piperidine	$C_{13}H_{19}N_3SO_2$	148	91	55.5	55.8	6.8	6.4	14.9	14.9[h]
Aniline[i,b]	Unidentified[j,k]	$(C_8H_7N_2)_x$	208–210[l]	36[m]	73.3	73.7	5.3	5.2	21.3	20.8
n-Butylamine[i]	1-Benzoyl-3-*n*-butylguanidine	$C_{12}H_{17}N_3O$	114	98	65.8	66.4	7.8	7.8	—	—
	+									
	1-Benzoyl-3-*n*-butylguanidine picrate	$C_{18}H_{20}N_6O_8$	126[n]	–	48.2	48.5	4.5	4.2	18.8	19.3
Cyclohexylamine[i]	1-Benzoyl-3-cyclohexylguanidine	$C_{14}H_{19}N_3O$	131–132	63	68.6	69.1	7.8	7.7	17.1	16.7
	+									
	1-Benzoyl-2,3-dicyclohexylguanidine	$C_{20}H_{29}N_3O$	155–156	15	73.4	73.3	8.9	8.7	12.8	12.2
Piperidine[i]	1-(N-Benzoyl)guanylpiperidine	$C_{13}H_{17}N_3O$	142–143	95	67.5	67.8	7.4	6.9	—	—
Aniline[o,b]	1,3-Diphenylurea	$C_{13}H_{12}N_2O$	236[p]	84	73.6	73.7	5.7	5.6	13.2	12.8
n-Butylamine[o]	1-*n*-Butyl-3-α-naphthylurea	$C_{15}H_{18}N_2O$	146–147	98	74.4	74.3	7.4	7.2	11.6	11.2
Morpholine[o]	1-(N-α-Naphthyl) carbamylmorpholine	$C_{15}H_{16}N_2O_2$	195[q]	95	70.3	70.4	6.3	6.1	10.9	10.9
	+									
	1-Guanylmorpholine[r]	$C_{11}H_{14}N_6O_5$	229–230[s]	*ca.* 4	36.9	37.5	3.9	3.8	23.5	23.9
Piperidine[o]	1-(N-α-Naphthyl) carbamylpiperidine	$C_{16}H_{18}N_2O$	159[t]	98	75.6	75.3	7.1	6.9	11.0	10.4
	+									
	1-Guanylpiperidine[r]	$C_{12}H_{16}N_6O_7$	244[u]	*ca.* 6	40.4	41.0	4.4	4.3	23.6	23.3

[a] These represent reactions with If. [b] General reaction conditions consist of 30 min. refluxing of the substituted 1-acylguanylpyrazole in a nine-fold excess of amine. [c] This was accompanied by some evolution of ammonia. [d] Calcd.: S, 11.1. Found: S, 11.4. [e] Calcd.: S, 11.9. Found: S, 12.1. [f] Calcd.: S, 10.8. Found: S, 10.2. [g] Calcd.: S, 11.3. Found: S, 11.0. [h] Calcd.: S, 11.4. Found: S, 11.5. [i] These represent reactions with Ig. [j] This substance was accompanied by another of m.p. 91–92° in 30% yield. *Anal.* Calcd. for $C_{13}H_6N_2O$: C, 75.7; H, 2.9; N, 13.6. Found: C, 76.0; H, 2.4: N, 13.1. [k] During this reaction a copious evolution of ammonia was detected. [l] The m.p. of 3-benzoyl-1-phenylguanidine has been reported as 199° by F. Arndt and B. Rosenau, *Ber.*, **50**, 1248 (1917). [m] This was calculated on the basis of a molecular formula of $C_{16}H_{14}N_4$. [n] The m.p. of 1-*n*-butylguanidine picrate is 154.5°, as reported by T. L. Davis and R. C. Elderfield, *J. Am. Chem. Soc.*, **54**, 1499 (1932). [o] These correspond to reactions with Ik. [p] Reported m.p. 238°, R. L. Shriner, R. C. Fuson, and D. Y. Curtin, *The Systematic Identification of Organic Compounds*, John Wiley and Sons, Inc., New York, N. Y., 1948, p. 287. [q] Reported m.p. 197–198°, by R. A. Henry and W. M. Dehn, *J. Am. Chem. Soc.*, **71**, 2297 (1949). [r] The data reported are for the picrate salt. [s] Reported m.p. 230°, Scott, O'Donovan, and Reilly, *loc. cit.* [t] Reported m.p. 160.5–161.5°, Henry and Dehn, *loc. cit.* [u] Reported m.p. 245°, by Davis and Elderfield, *loc. cit.* and as 244°, by Scott, O'Donovan and Reilly, *loc. cit.*

TABLE II

SOME DERIVATIVES OF TYPE R—C(=NH)—NH—C(X)=N—R′

R	X	R′	Molecular Formula	M.P., °C.	Analyses							
					Carbon		Hydrogen		Nitrogen		Sulfur	
					Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
Py[a]	SCH_3	C_6H_5[b]	$C_{14}H_{17}N_5S$	94	58.5	58.4	5.9	5.7	24.4	24.8	11.1	11.5
Py′[c]	SCH_3	C_6H_5	$C_{14}H_{16}N_5SCl$	113–114	52.3	52.3	5.0	4.8	21.8	21.2	—	—
Py″[d]	SCH_3	C_6H_5	$C_{14}H_{16}N_5SBr$	123	45.9	46.4	4.4	4.5	19.1	19.7	8.7	8.4
Py[a]	SH	CH_2=CH—CH_2—	$C_{10}H_{15}N_5S$[e]	83–84	50.6	50.7	6.3	6.5	29.5	29.0	13.5	13.3
Py[a]	SCH_3	CH_2=CH—CH_2—	$C_{11}H_{18}N_5SI$[f]	118	34.8	35.1	4.7	5.1	18.5	18.0	8.4	7.9
Py[a]	SH	n-C_3H_7	$C_{10}H_{17}N_5S$[e]	79–80	50.2	50.4	7.1	7.0	29.3	29.0	13.4	13.2
Py[a]	SCH_3	n-C_3H_7	$C_{11}H_{20}N_5SI$[f]	114.5–115	34.6	34.8	5.2	5.4	18.4	18.5	8.4	8.5[g]
Py[a]	SH	n-C_4H_9	$C_{11}H_{19}N_5S$[e]	78–79	52.2	51.8	7.5	7.3	27.7	28.1	12.6	13.0
Py[a]	SCH_3	n-C_4H_9	$C_{12}H_{22}N_5SI$[f]	119–120	36.5	36.5	5.6	5.4	17.7	17.9	8.1	8.0[h]
Py[a]	SH	1-$C_{10}H_7$	$C_{17}H_{17}N_5S$[e]	130–131	63.2	62.7	5.3	5.1	21.7	21.2	9.9	10.0
Py[a]	SCH_3	1-$C_{10}H_7$	$C_{18}H_{20}N_5SI$[f]	143–145	46.5	46.4	4.3	4.6	15.1	14.9	6.9	6.7[i]

[a] Py represents 3,5-dimethyl-1-pyrazolyl. [b] This is II. It and the other free bases Im and In were prepared from the corresponding hydriodides by first dissolving the salts in ethanol and then adding an excess of cold 20% sodium hydroxide solution to the ice-cold salt solution. The free bases were thus quantitatively precipitated They were appreciably less soluble in ethanol than the corresponding hydriodide salts. They crystallized well and did not exhibit any tendency towards phototropism. [c] Py′ represents 4-chloro-3,5-dimethyl-1-pyrazolyl. [d] Py″ corresponds to 4-bromo-3,5-dimethyl-1-pyrazolyl [e] These thiocarbamylguanylpyrazoles were prepared by the method of Scott and Reilly, *loc. cit.*, *viz.* by warming gently a solution of the appropriately substituted 1-guanylpyrazole free base in ethanol with the respective aryl or alkyl isothiocyanate. The addition products separated in from 80–90% yields [f] The data recorded are for the hydriodide salt of an S-methyl ether This was prepared by the general technique described in the text and was usually isolated in quantitative yield. [g] Calcd.: I, 33.3. Found: I, 33.2, 33.4. [h] Calcd.: I, 32.2. Found: I, 31.8, 32.2. [i] Calcd.: I, 27.3 Found: I, 26.9.

Anal. Calcd. for $C_2H_4N_4$: C, 28.9; H, 4.8; N, 66.0. Found: C, 28.6; H, 4.8; N, 66.5.

(c) When Ir was analogously refluxed with either of the above 2 cyanamides in chloroform it was recovered in 92 and 70% yields, respectively, and formed dicyandiamide in 25% yield in the latter experiment. (d) Finally, when Id was refluxed with either dialkyl cyanamide in ethanolic solution for 6 hr. it was recovered in 70–80% yields.

(3) *With substituted aminoguanidines.* (a) When aminoguanidine nitrate was refluxed, without further solvent, in either a small or large excess of dimethyl cyanamide for 3 hr. it was recovered in 90% yield. However, when aminoguanidine, as its free base, was refluxed with an equimolar proportion of diethyl cyanamide for 3 hr., fumes of ammonia were readily detectable from the reaction liquor and a white solid, m.p. 88°, was isolated, total yield 50% (on the basis of a provisional molecular weight of 140). This has not been identified as yet.

Anal. Calcd. for $C_6H_{12}N_4$: C, 51.4; H, 8.6; N, 40.0. Found: C, 51.5; H, 8.3; N, 39.7.

The aminoguanidine free base incidentally was used in the form of its aqueous solution and this was obtained by titration of aminoguanidine sulfate in water with a barium solution. (b) When triaminoguanidine nitrate was refluxed with an excess of dimethyl cyanamide in ethanol or without further solvent, for 3-hr. periods, it was recovered in 95 and 92% yields, respectively. (c) When *p*-methoxybenzylidene aminoguanidine (Va) was refluxed with dimethyl cyanamide either in ethanol or in chloroform solution for 3 hr. it was recovered in 95 and 92% yields, respectively. However, when Va was refluxed in dimethyl cyanamide, without further solvent and under anhydrous conditions, again for 3 hr., it yielded 30% unchanged Va and *ca.* 17% of a cream-colored substance, m.p. 248–250°, which proved to be *p*-methoxybenzylidene 1-amino-4,4-dimethyl-2-guanylguanidine (Vb).

Anal. Calcd. for $C_{12}H_{18}N_6O$: C, 55.0; H, 6.9; N, 32.1. Found: C, 54.7; H, 7.0; N, 32.2.

Acknowledgment. The author is indebted to C. L. McCarthy, M.S., and particularly to Dr. M. F. Cashman, for experimental assistance with portions of this work.

CORK, IRELAND
LOS ANGELES 24, CALIF.

[CONTRIBUTION NO. 1454 FROM THE STERLING CHEMISTRY LABORATORY, AND FROM THE BINGHAM OCEANOGRAPHIC LABORATORY, YALE UNIVERSITY]

Contributions to the Study of Marine Products. XLIII. The Nucleosides of Sponges. V. The Synthesis of Spongosine[1]

WERNER BERGMANN AND MARTIN F. STEMPIEN, JR.

Received June 9, 1957

Spongosine has been synthesized by two different methods and shown to be 9-β-D-ribofuranosyl-2-methoxyadenine.

Spongosine, one of the unusual nucleosides obtainable from the Caribbean sponge, *Cryptotethia crypta*, has recently been shown[2] to be the ribofuranoside of 2-methoxy-6-aminopurine.[3] The present communication deals with two syntheses of spongosine which establish beyond doubt the point and configuration of the junction between the purine and ribose moieties. In the first synthesis 2-methoxyadenine, prepared by a modification of the method previously reported,[2] was converted to its chloromercuri salt[4] which was treated with 2,3,5-tri-*O*-acyl-D-ribosyl chloride. In this reaction the triacetyl derivative[5] afforded a mixture of products difficult to separate. The tribenzoate, however, which has recently been used with conspicuous success by Kissman, Pidacks, and Baker,[6] reacted smoothly to give a product which after *O*-debenzoylation with catalytic amounts of sodium methoxide afforded the glycoside in a 30% yield. The identity of the reaction product with spongosine was shown by a comparison of the melting points, rotations, and the chromatographic, electrophoretic,

(1) This investigation was supported by a research grant (G-3789) from the National Institutes of Health, Public Health Service.

(2) W. Bergmann and D. C. Burke, *J. Org. Chem.*, **21**, 226 (1956).

(3) It was pointed out in the previous publication[2] that spongosine not only appears to be the first methoxypurine to be found in nature, but also one of the first *O*-methyl compounds to be isolated from animal tissues. It should be mentioned in this connection that prior to this observation the occurrence of some phenolic methylethers had been noted in animals, such as methanethol in the sponge, *Spheciospongia vesparia* [W. Bergmann and W. J. McAleer, *J. Am. Chem. Soc.*, **73**, 4969 (1951)], and of quinol monomethylether, chavicol, *p*-methoxyacetophenone, and 5-methoxysalicylic acid in the scent gland of the beaver [E. Lederer, *J. Chem. Soc.*, 2120 (1949)]. Ferulic acid, *m*-methoxybenzoic acid, and vanillic acid have been isolated from the urine of horses [E. Lederer and J. Polonski, *Biochim. et Biophys. Acta*, **2**, 431 (1948)] and men [M. D. Armstrong, K. N. F. Shaw, and P. E. Wall, *J. Biol. Chem.*, **218**, 293 (1956)]. These compounds may well have been derived from methyl ethers in dietary plant material. More recent observations, however, show that *O*-methylations may occur within the animal, *cf.* N. F. MacClagan and J. H. Wilkinson, *Biochem. J.*, **56**, 2111 (1954); J. M. Price and L. W. Dodge, *J. Biol. Chem.*, **223**, 699 (1956); S. Kraychy and T. F. Gallagher, *J. Am. Chem. Soc.*, **79**, 754 (1957); and F. DeEds, A. N. Booth, and F. T. Jones, *J. Biol. Chem.*, **225**, 615 (1957).

(4) J. Davoll and B. A. Lowy, *J. Am. Chem. Soc.*, **73**, 1650 (1951).

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(6) H. M. Kissman, C. Pidacks, and B. R. Baker, *J. Am. Chem. Soc.*, **77**, 18 (1955).