GUANIDINE COMPOUNDS

IV. ACETYLATION OF SOME ALKYL-SUBSTITUTED GUANIDINES WITH ACETIC ANHYDRIDE AND ETHYL ACETATE[1,2]

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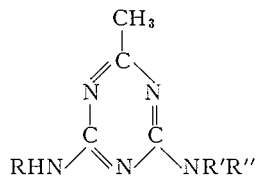
ABSTRACT

The acetylation of some mono-, N,N-, and N,N′-dialkylguanidines was studied using ethyl acetate and acetic anhydride. Except for the N,N-dialkylguanidines, the action of ethyl acetate on the free bases gave monoacetyl derivatives. Acetic anhydride with the acetate salts gave diacetyl derivatives with monoalkylguanidines, acetamido-1,3,5-triazines with N,N-dialkylguanidines, and unstable di- and tri-acetyl derivatives with N,N′-dialkylguanidines. The assignment of symmetrical structures to the mono- and tri-acetyl derivatives and an asymmetrical structure to the diacetyl derivatives was supported by nuclear magnetic resonance spectra. The ultraviolet spectra of the monoacetyl derivatives exhibited one peak in the region 230–235 mμ whilst the diacetyl derivatives showed two peaks in the regions 220–230 mμ and 253–263 mμ. Some comments are made on the infrared spectra of these compounds.

In an earlier paper in this series Cockburn and Bannard (1) reported the formation of amino- (I) and acetamido-*s*-triazines (II) on acetylation of alkylguanidine salts under vigorous conditions.



I. R = H; R′, R″ = H or alkyl
II. R = CH_3CO; R′, R″ = H or alkyl
III. R = CH_3CO; R′, R″ = CH_3

Ryabinin (2) had previously shown that the products obtained on acetylation of guanidine acetate were dependent on the conditions used. Under mild conditions, an acetylated guanidine derivative was obtained rather than an *s*-triazine derivative. The present study, in which the acetylation of several mono-, N,N-, and N,N′-dialkylguanidines with ethyl acetate and acetic anhydride was examined, revealed that the type of alkyl substitution also influenced the product obtained. The opportunity was taken to examine the infrared and ultraviolet spectra of the acetylated guanidines isolated.

Various conditions for the acetylation of *trans*-2-guanidocyclohexanol with acetic anhydride were examined to determine which gave the highest yield of acetylated products. The addition of sodium acetate did not influence the yields and was therefore omitted, since it merely complicated isolation of the products. It was found that a shorter time of heating at 100° than that previously employed for the acetylation of guanidine (3) was beneficial, since even the relatively stable diacetyl derivatives were degraded or cyclized on prolonged heating with acetic anhydride at this temperature.

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[2]*Part III, Can. J. Chem.* **37**, *1810 (1959).*

The use of the readily soluble acetate salts rather than the more insoluble hydrochlorides, nitrates, or sulphates enabled a reaction period of 30 minutes to be used.

Acetylation of the monoalkylguanidines under these conditions gave the diacetyl derivatives in yields exceeding 79%, together with small amounts of the corresponding acetylated amino compounds. The latter products were shown to result from degradation of the diacetyl derivatives by acetic anhydride, since on warming of diacetyl cyclohexylguanidine for 1 hour at 100° with acetic anhydride, acetyl cyclohexylamine was isolated in 50% yield.

The N,N-dialkylguanidines gave, in general, acetamido-*s*-triazines, although in the case of N,N-dimethylguanidine a diacetyl derivative was also isolated. The results given in Table I show that the amount of diacetyl derivative (IV) decreases as the amount of acetamido-*s*-triazine (III) increases when the heating period is prolonged. It thus appears that diacetyl derivatives are intermediates in the formation of triazines from N,N-dialkylguanidines. This behavior contrasts with that of the diacetyl derivatives of the monoalkylguanidines, which, on being heated with acetic anhydride, are degraded rather than cyclized. The formation of triazines from monoalkylguanidine acetates or monoacetyl derivatives has been reported (4) but more drastic conditions were involved (0.5 hour at 200°).

TABLE I

Variation of product composition on heating N,N-dimethylguanidine with acetic anhydride at 100° for various periods of time

Heating period (min)	Percentage yield of products	
	III	IV
15	24	46
30	32	31
60	49	23

NOTE: III = 2-dimethylamino-4-acetamido-6-methyl-1,3,5-triazine. IV = diacetyl N,N-dimethylguanidine.

With N,N′-dialkylguanidines, the products obtained were very dependent on the individual structure of the guanidine. Both six-membered ring compounds gave unstable diacetyl derivatives which could only be isolated by vacuum distillation. Attempts to purify them by chromatography on alumina, or recrystallization from alcohol gave the more stable monoacetyl derivatives. N,N′-Dimethylguanidine together with 2-iminoimidazolidine gave compounds whose analysis indicated a triacetyl derivative. Because of the peculiar spectral and chemical properties of triacetyl 2-iminoimidazolidine it is discussed more fully later in the paper.

Acetylation of alkylguanidines with ethyl acetate was studied with the object of preparing monoacetyl derivatives. Ostrogovich (5) reported the acetylation of aminotriazines by boiling them with ethyl acetate or acetic acid. The reaction most likely occurs by nucleophilic attack of the π electrons of the guanidine on the ester, similar to the mode of action formulated by Gordon *et al.* (6) for the ammonolysis of esters. Simons and Weaver (4) showed that ethyl acetate reacts with monoalkylguanidine free bases in the cold to give the monoacetyl derivatives. We modified their procedure by using Amberlite IRA-400 (OH) resin prepared in absolute alcohol to generate the free base. This procedure had the advantage over the usual one in which the hydrochloride

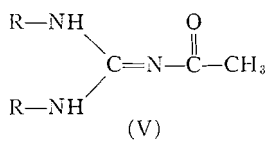
is treated with sodium ethoxide in that it gave quantitative conversion to the pure free base, uncontaminated with inorganic material. The type of alkyl substituents again affected the type of product obtained. With the exception of the N,N-dialkylguanidines all the alkylguanidines gave monoacetyl derivatives by this method. Since Angyal and Warburton (7) and Neivelt *et al.* (8) have shown that methyl guanidines, regardless of the type and degree of alkyl substitution have a pK_a greater than 13.4, basicity is obviously not the reason for lack of reactivity. It is interesting to note that 2-imino-5-hydroxyhexahydropyrimidine gave only a mono-N-acetyl derivative, indicating that the method could be used to selectively monoacetylate a guanidine moiety in a molecule also possessing a hydroxyl function. Acetylation of guanidine itself gave a monoacetyl derivative which is still basic (pK_a 8.2) but would not form a diacetyl derivative on further treatment with ethyl acetate.

TABLE II

Ultraviolet absorption of monoacetyl guanidines in absolute alcohol

Compound	λ_{max} (mμ)	log ϵ_{max}
Acetyl guanidine	230	4.24
Acetyl methylguanidine	234	4.31
Acetyl cyclohexylguanidine	232	4.30
N-Acetyl guanidocyclohexanol	234	4.26
Acetyl N,N′-dimethylguanidine	234	4.23
Acetyl 2-iminoimidazolidine	230	4.24
Acetyl 2-iminohexahydropyrimidine	234	4.23
Acetyl 2-imino-5-hydroxyhexahydropyrimidine	235	4.31
Acetyl guanidine acetate	230	3.92

The ultraviolet spectra of the monoacetyl guanidines, when measured in ethanol, all exhibit one peak in the range 230–235 mμ as shown in Table II. This absorption is independent of the type of alkyl substitution possessed by the guanidine moiety. A similar observation was reported by McKay *et al.* (9) for alkyl nitroguanidines.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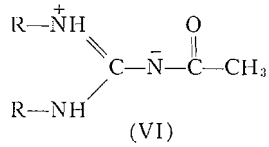
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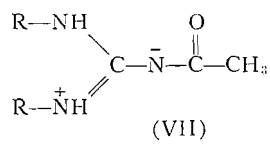
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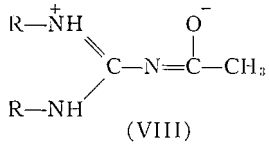
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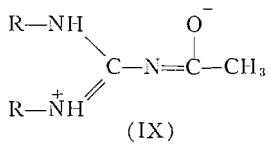

(IX)

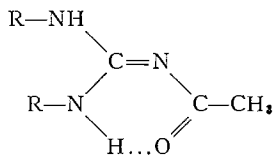
Since neither guanidine nor primary or secondary amides absorb strongly above 210 mμ, the absorption indicates conjugation of the acetyl carbonyl group with the guanidine moiety. It was therefore concluded that monoacetyl guanidines exist in the acetylimino form (V, R = alkyl or H) and this was confirmed in the case of acetyl 2-iminoimidazolidine by measurement of its nuclear magnetic resonance spectrum.

Some contribution to the structure from the other canonical forms of the guanidine moiety (VI) and (VII), together with a small contribution from forms (VIII) and (IX)

would also be expected. Bryden *et al.* (10), from crystallographic studies, showed this to be the case for nitroguanidine, which is best formulated as a resonance hybrid which combines both the forms postulated by McKay *et al.* (9) and by Kirkwood and Wright (11).

The infrared spectra of monoacetyl guanidines would be expected to show two bands in the region 1700–1500 cm^{-1} corresponding to the stretching vibrations of the C=N and the C=O of the acetyl group (amide I (12)). Table III shows the results obtained.

The spectra mainly show one very strong broad band at 1620–1580 cm^{-1} with shoulders on the high and low frequency sides. This strong band is presumably due to the unresolved vibrations of the C=N and C=O groups. Two bands are observed only in the cases of the monoacetyl derivatives of 2-iminoimidazolidine and 2-imino-5-acetoxyhexahydropyrimidine. The stronger band, at 1580 cm^{-1} and 1595 cm^{-1} respectively, was assigned to amide I vibrations, since it is doubtful whether the intensity of the C=N vibration, even though it is known to increase on conjugation (13), would approach that of an amide I. Also, the amide I is known to be more susceptible to displacement than the C=N vibration. The large shift found for the amide I band can be attributed partly to intramolecular hydrogen bonding as shown in X and partly to conjugation. Examination of the spectrum of triacetyl 2-iminoimidazolidine, a compound which contains no NH bond shows a normal amide I vibration with no absorption around 1600 cm^{-1}.



(X)

The second band found in the spectra of both monoacetyl 2-iminoimidazolidine and monoacetyl 2-imino-5-acetoxyhexahydropyrimidine occurs at 1620 cm^{-1} and is assigned to the C=N stretching vibration, the shift to lower frequency resulting from conjugation with the acetyl group. In the literature, the C=N vibration for substituted nitroguanidines is variously assigned, Leiber *et al.* (14) give 1680–1661 cm^{-1}, Randall *et al.* (15) 1695–1639 cm^{-1}, and Kumler (16) 1689–1618 cm^{-1}. Kumler's assignment for the C=N vibration in 2-nitriminoimidazolidine at 1618 cm^{-1} agrees closely with that of the acetyl analogue, but his assignment of a band at 1664 cm^{-1} in nitroguanidine itself seemed high. Monoacetyl guanidine also shows a band at 1660 cm^{-1} which we thought was most likely due to the NH_2 deformation vibrations as suggested by Jones (17) for guanidine. Attempts to deuterate acetyl guanidine resulted in hydrolysis, but deuteration of nitroguanidine caused the band at 1664 cm^{-1} to disappear whilst another band appeared at 1290 cm^{-1}. Hence Kumler's assignment of the 1664 cm^{-1} band in nitroguanidine to the C=N appears to be in error and it must appear at lower frequencies together with the vibration for the nitro group.

The diacetyl guanidines possess characteristic ultraviolet spectra by means of which they can be readily distinguished from mono- or tri-acetyl guanidines. All the diacetyl guanidines show two peaks in the regions 212–225 mμ and 243–263 mμ as shown in Table V.

In all cases examined the extinction coefficient of the low wavelength peak was just

TABLE III

Infrared absorption of some monoacetyl guanidines in the region 1700–1550 cm^{-1}

Compound	Absorption (cm^{-1})				Type of spectrum
Acetyl guanidine	1660 (m)	1605 (sh)	1600 (vs)	—	KBr pellet
Acetyl cyclohexylguanidine	—	1615 (sh)	1590 (vs)	1565 (sh)	KBr pellet
	—	1640 (sh)	1595 (vs)	1575 (sh)	Chloroform solution
Acetyl *trans*-2-guanidocyclohexanol	—	1640 (sh)	1600 (vs)	1580 (sh)	KBr pellet
Acetyl 2-iminohexahydropyrimidine	—	1620 (sh)	1595 (vs)	1560 (sh)	KBr pellet
	—	1620 (sh)	1595 (vs)	1570 (sh)	Chloroform solution
Acetyl 2-iminoimidazolidine	1660 (w)	1620 (sh)	1595 (vs)	1565 (sh)	KBr pellet
	—	1620 (s)	1580 (vs)	—	Chloroform solution
Acetyl 2-imino-5-acetoxyhexahydropyrimidine	—	1620 (s)	1595 (vs)	1575 (sh)	KBr pellet

TABLE IV

Infrared absorption of some diacetyl guanidines in the region 1750–1550 cm^{-1}

Compound	Absorption frequencies (cm^{-1})					Type of spectrum
Diacetyl guanidine	—	1700 (s)	1625 (s)	1585 (vs)	1550 (m)	KBr pellet
Triacetyl *trans*-2-guanidinocyclohexanol	1740 (s)	1705 (s)	1620 (sh)	1595 (vs)	1570 (m)	KBr pellet
Diacetyl cyclohexylguanidine	—	1700 (s)	1615 (sh)	1600 (vs)	1565 (m)	KBr pellet
Diacetyl N,N-dimethylguanidine	—	1705 (m)	1620 (sh)	1595 (vs)	1550 (m)	KBr pellet
Diacetyl 2-iminohexahydropyrimidine	—	1670 (m)	—	1595 (s)	—	KBr pellet
	—	1680 (m)	—	1605 (s)	—	Chloroform solution
Diacetyl 2-imino-5-acetoxyhexahydropyrimidine	1725 (s)	1680 (m)	1620 (m)	1595 (vs)	—	KBr pellet

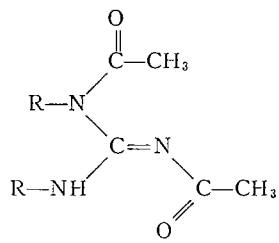
TABLE V

Ultraviolet absorption of diacetyl guanidines

Compound	λ_{max} (mμ)	log ϵ_{max}	λ_{max} (mμ)	log ϵ_{max}	Solvent
Diacetyl guanidine	212	3.95	243	4.25	Abs. ethanol
Diacetyl guanidocyclohexanol	222	3.99	255	4.23	Abs. ethanol
Diacetyl cyclohexylguanidine	221	4.03	254	4.25	Abs. ethanol
Diacetyl methylguanidine	218	4.01	254	4.24	Cyclohexane
Diacetyl N,N'-dimethylguanidine	225	3.87	263	4.29	Abs. ethanol
Octa-acetyl streptidine	220	4.27 (3.99)*	254	4.55 (4.25)*	Abs. ethanol
Diacetyl 2-iminohexahydropyrimidine	223	3.95	256	4.24	Cyclohexane
Diacetyl 2-imino-5-acetoxyhexahydropyrimidine	225	3.97	254	4.17	Cyclohexane

*Log ϵ_{max}/guanidine moiety.

about half that for the peak at higher wavelength. Unlike monoacetyl guanidines, alkyl substitution does affect the chromophore for the diacetyl guanidines, resulting in a variation of 13 mμ for the first peak and 20 mμ for the second. The bathochromic shift observed in the ultraviolet spectra in going from mono- to di-acetyl derivatives is compatible with a further lengthening of the π electron path. An asymmetrical structure XI was assigned to the diacetyl derivatives based on nuclear magnetic resonance studies with the diacetyl derivative of 2-iminohexahydropyrimidine.



(XI)

Korndorfer (18) postulated the existence of both symmetrically and asymmetrically substituted diacetyl guanidines. Later Ryabinin (2) established that only one isomer exists, but did not specify which one. The infrared spectra of the diacetyl guanidines also give ample evidence for the asymmetric structure, the results being given in Table IV.

The spectra exhibit a very strong broad band in the region 1620–1585 cm^{-1} together with a strong band in the region 1705–1670 cm^{-1}. The first band is similar to that exhibited by the monoacetyl guanidines and, as in that case, is ascribed to the unresolved stretching frequencies of the C=N and the C=O of the acetylimino group. The second band is assigned to the amide I vibration of the second acetyl group by analogy with the absorption observed for the acetamido group in 6-methyl-2-cyclohexylamino-4-acetamido-1,3,5-triazine at 1680 cm^{-1}, 6-methyl-2-dimethylamino-4-acetamido-1,3,5-triazine at 1685 cm^{-1}, and 6-methyl-2-piperidino-4-acetamido-1,3,5-triazine at 1690 cm^{-1}. The shift to higher frequencies of the amide I band of the second acetyl group is expected, since Richards and Thompson (19) showed that substitution of an amide nitrogen with an electrophilic group produces this effect. We found the amide I band above 1700 cm^{-1}

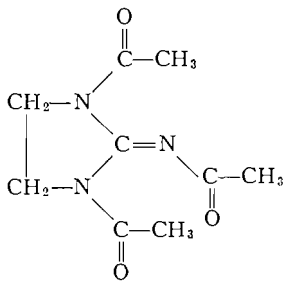
if the second acetyl group is present as a secondary amide and below if present as a tertiary amide, e.g. diacetyl N,N-dimethylguanidine absorbs at 1705 cm^{-1} (KBr) and diacetyl hexahydropyrimidine at 1670 cm^{-1} (KBr). Since the main difference between the amides is in the nature of the third group attached to the amide nitrogen, i.e. either a hydrogen or an alkyl group, the spectral data can be explained in terms of the electron-donating power of the third group. The alkyl group is able to contribute a greater share of its electrons to the amide nitrogen than the hydrogen, thus reducing the demand placed on the nitrogen by the acetyl and acetylimino groups. Hence the increase in frequency is not as great for the tertiary amide. In diacetyl guanidines possessing a secondary amide group, a third band in the range 1575–1560 cm^{-1} is found, due to the amide II vibration.

The ultraviolet spectra of the triacetyl derivatives obtained from N,N′-dimethylguanidine and 2-iminoimidazolidine were similar, showing only one peak at 232 mμ and 234 mμ respectively. This absorption is similar to that obtained with the monoacetyl derivatives, although it seems unlikely that the same chromophore is involved. The infrared spectra showed no absorption above 3000 cm^{-1} or near 1600 cm^{-1} in either case, and this was interpreted as evidence for intramolecular hydrogen bonding between the N—H and acetylimino groups in mono- and di-acetyl guanidines. The spectra differed in that triacetyl N,N′-dimethylguanidine shows two strong bands at 1690 and 1620 cm^{-1} (film), whereas triacetyl 2-iminoimidazolidine shows three in chloroform solution at 1745, 1690, and 1645 cm^{-1} and four for a KBr pellet at 1725, 1690, 1680, and 1620 cm^{-1}. The band at lowest frequency is thought to be due to the amide I of the non-hydrogen-bonded acetylimino group, whilst bands at 1690 cm^{-1} are due to the amide I of the tertiary amides. The band found at 1745 cm^{-1} (chloroform) and 1725 cm^{-1} (KBr) in triacetyl 2-iminoimidazolidine appears to be associated with the C=N, since it is missing from the methanol adduct of triacetyl 2-iminoimidazolidine where addition has taken place across the C=N bond. Since it is also missing from triacetyl N,N′-dimethylguanidine, it appears to be associated with the cyclic structure. The shift in the amide I frequently observed for the lactam group in ethylene urea from 1652 cm^{-1} to 1752 cm^{-1} (KBr) in the diacetyl ethylene urea lends credence to this idea.

The proof that triacetyl 2-iminoimidazolidine has a symmetrical structure (XII) was obtained from its nuclear magnetic resonance spectrum, which showed three peaks at 3.41, 4.96, and 5.12 p.p.m. upfield from chloroform with relative intensities 4:6:3. The first peak was assigned to the methylene hydrogens and as no splitting was apparent, it was taken as evidence that they were equivalent. The two remaining peaks were assigned to the methyl hydrogens of the acetyl groups, the intensities indicating that two of the three methyl groups were similar. Formation of an addition product on warming of triacetyl 2-iminoimidazolidine with alcohol is of interest in view of the fact that dinitro-2-iminoimidazolidine also exhibits such a property with alcohols and amines (20). The cyclic structure (XIII) was assigned to it on the basis of its analysis and infrared spectrum. The presence of bands at 3142(m), 1650(s), and 1525(m) cm^{-1} (KBr pellet) was taken as indicative of the formation of a secondary amide. The absence of the C=N group was indicated by the stability of the addition product to boiling water, since under these conditions triacetyl 2-iminoimidazolidine readily yields diacetyl ethylene urea.

To summarize, this work has shown that the products obtained on acetylation of alkylguanidines depend on the degree and position of alkyl substitution, as well as the

conditions used. Analogies have been shown to exist between the chemistry of the nitro and acetyl derivatives of alkylguanidines. This is to be expected, since a similarity does exist between the inductive and mesomeric effects of the two groups, although it is of a qualitative nature. However, the extent to which a guanidine moiety is nitrated or acetylated is not necessarily the same, e.g. 2-iminoimidazolidine forms a dinitro (20) but a triacetyl derivative.



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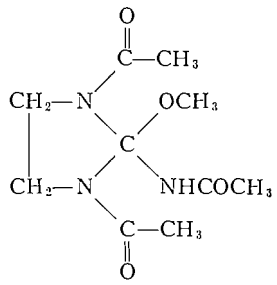

(XIII)

The difference in reactivity of the five- and six-membered cyclic N,N′-dialkylguanidines on acetylation must be attributed to the effect of the geometry of the ring on the guanidine moiety, since no difference exists in the basicity of these guanidines.

EXPERIMENTAL

All melting points are uncorrected unless otherwise stated. Microanalyses are by Micro-Tech Laboratories, Skokie, Ill., and J. Helie of these laboratories. Ultraviolet spectra were measured on a Cary Model 14 P.M. recording spectrophotometer, while the infrared spectra were measured on a Baird double beam recording spectrophotometer.

Starting Materials

Methylguanidine was purchased from Mann Research Laboratories. Cyclohexylguanidine, 2-guanidocyclohexanol, N,N-dimethylguanidine, guanylpyrrolidine, and guanylpiperidine were prepared from the corresponding amines by the action of 1-guanyl-3,5-dimethylpyrazole nitrate as described by Bannard *et al.* (21). The method of Mold *et al.* (22), employing cyanogen bromide and methylamine, was used to prepare N,N′-dimethylguanidine. Synthesis of 2-iminoimidazolidine, 2-iminohexahydropyrimidine, and 2-imino-5-hydroxyhexahydropyrimidine involved first preparation of the corresponding cyclic nitrimines as described by McKay and Wright (23), followed by treatment of the nitrimines with liquid ammonia as reported by Stefanye and Howard (24). We isolated these compounds as the acetate salts, which are described in Table VI.

All the other alkylguanidines were converted into the acetate salts by ion exchange and dried prior to acetylation with acetic anhydride.

Acetylation of Guanidine Free Bases with Ethyl Acetate

An Amberlite IRA-400 (OH^-) resin column (15 ml) was prepared in the usual manner, then washed for 24 hours with absolute ethanol excluding carbon dioxide. Guanidine hydrochloride (500 mg, 5.2 millimoles) was dissolved in absolute ethanol (15 ml) and the solution passed through the column, after which the column was washed with absolute ethanol, a total of 100 ml eluate being collected. Evaporation of the latter to dryness

TABLE VI

Cyclic guanidine acetates

Compound	Formula	m.p.	C		H		N	
			Calc.	Found	Calc.	Found	Calc.	Found
2-Iminoimidazolidine acetate	$C_5H_{11}O_2N_3$	186–188°	41.37	41.51	7.64	7.81	28.95	28.66
2-Iminohexahydropyrimidine acetate	$C_6H_{13}O_2N_3$	141–143°	45.27	45.32	8.37	8.30	26.30	26.17
2-Imino-5-hydroxyhexahydropyrimidine acetate	$C_6H_{13}O_3N_3$	134–135°	41.13	40.90	7.48	7.65	23.99	23.91

TABLE VII

Monoacetyl guanidines

Compound	Formula	m.p.	C		H		N		Yield (%)
			Calc.	Found	Calc.	Found	Calc.	Found	
Acetyl guanidine	$C_3H_7ON_3$	188–190°	35.63	35.62	6.95	7.07	41.56	41.56	89
Acetyl methylguanidine	$C_4H_9ON_3$	158–160°	41.72	41.45	7.88	7.62	36.50	36.63	73
Acetyl 2-iminoimidazolidine	$C_5H_9ON_3$	227–229°	47.23	47.05	7.13	7.11	33.05	32.93	84
Acetyl cyclohexylguanidine	$C_9H_{17}ON_3$	163–165°	59.98	59.96	9.35	9.28	22.93	23.10	92
Acetyl 2-guanidinocyclohexanol	$C_9H_{17}O_2N_3$	183–185°	54.25	54.34	8.60	8.57	21.09	21.26	80
Acetyl 2-imino-5-hydroxyhexahydropyrimidine	$C_6H_{11}O_2N_3$	213–215°	45.85	45.84	7.05	7.25	26.74	26.82	87
Acetyl 2-iminohexahydropyrimidine	$C_6H_{11}ON_3$	189–191°	51.04	51.07	7.85	8.00	29.77	29.55	71

in vacuo gave a colorless oil which was dissolved in absolute alcohol (0.5 ml), to which solution freshly distilled ethyl acetate (0.5 ml, 5.2 millimoles) was slowly added. Although colorless crystals formed instantly, the solution was allowed to stand overnight at room temperature before they were filtered off, washed with ethyl acetate/ethanol and finally recrystallized from ethanol/acetone to give 475 mg (89%) of monoacetyl guanidine as colorless prisms, m.p. 188–190°. The compound was characterized by its acetate, m.p. 178–180°, lit. 180° (3), picrate m.p. 237–239°, lit. 238° (2).

All the other monoacetyl derivatives shown in Table VII were prepared in a similar manner.

Acetylation of Guanidine Acetate Salts with Acetic Anhydride

Cyclohexylguanidine

Cyclohexylguanidine hydrochloride (500 mg) was converted to the acetate salt by ion exchange using Amberlite IRA-400 (OAc) resin. The acetate salt was thoroughly dried *in vacuo* (0.05 mm) at room temperature before addition of acetic anhydride (5 ml). The mixture was heated at 100° for 1/2 hour, after which the acetic anhydride was removed *in vacuo* leaving 493 mg of brown oil. The oil was chromatographed on Woelm IV neutral alumina and gave two fractions. Elution with 2:1 hexane/benzene yielded a crystalline material, which, after recrystallization from pentane, gave colorless prisms, m.p. 71–72°, and analyzed for diacetyl cyclohexylguanidine. Calc. for $C_{11}H_{19}O_2N_3$: C, 58.64; H, 8.50; N, 18.65. Found: C, 58.87; H, 8.64; N, 18.36%. Yield: 445 mg (86%). Further elution with ether gave more crystalline material which was recrystallized from ether/pentane yielding fine white needles, m.p. 106–107°, lit. 107° (25), yield 37 mg (10%). Analysis and melting point indicated it to be N-acetyl cyclohexylamine, and this was confirmed by preparation of an authentic sample and comparison of the infrared spectra.

2-Guanidocyclohexanol

2-Guanidocyclohexanol sulphate (500 mg) was acetylated as described above yielding 530 mg of light brown oil which gave two products on chromatography. The first was obtained by elution with 2:1 hexane/benzene, and after recrystallization from pentane yielded colorless crystals, m.p. 69–70°, which analyzed for a triacetyl derivative, the infrared spectrum indicating O,N,N′ substitution. Calc. for $C_{13}H_{21}O_4N_3$: C, 55.11; H, 7.47; N, 14.83. Found: C, 55.04; H, 7.53; N, 14.53%. Yield: 498 mg (79%). The second product which was eluted with 1:1 ether/chloroform, appeared from analysis, infrared spectrum, and m.p. 117–118°, lit. 117° (26), to be O,N-diacetyl *trans*-2-aminocyclohexanol. Yield: 26 mg (5%). Verification was obtained by synthesis of the compound and comparison of the infrared spectra.

N,N-Dimethylguanidine

N,N-Dimethylguanidine sulphate (475 mg) was acetylated as above and the crude material chromatographed on neutral alumina yielding two products. The first product was obtained by elution with 1:1 pentane/benzene and after recrystallization from benzene/ether gave colorless prisms, m.p. 115–117°, which analyzed for 4-acetamido-2-dimethylamino-6-methyl-1,3,5-triazine. Calc. for $C_8H_{13}ON_5$: C, 49.22; H, 6.77; N, 35.88. Found: C, 49.44; H, 6.83; N, 35.83%. Yield: 77 mg (32%). The infrared spectrum was in agreement with this assignment. A second substance was obtained by elution with 2:1 chloroform/ether which gave colorless prisms after recrystallization from methanol/ether, m.p. 176–178°, and analyzed for diacetyl N,N-dimethylguanidine. Calc. for

$C_8H_{13}O_2N_5$: C, 49.11; H, 7.65; N, 24.55. Found: C, 49.24; H, 7.74; N, 24.90%. Yield: 92 mg (31%).

2-Iminoimidazolidine

2-Iminoimidazolidine hydrochloride (500 mg) was acetylated as above and the oily product remaining after removal of the acetic anhydride slowly crystallized. Further recrystallization from acetone gave long white needles, m.p. 141–142°, which, from its analysis, appeared to be triacetyl 2-iminoimidazolidine. Calc. for $C_9H_{13}O_3N_3$: C, 51.17; H, 6.20; N, 19.9; CH_3CO, 61.13. Found: C, 51.25; H, 6.33; N, 19.85; CH_3CO, 60.82%. Yield: 441 mg (51%).

Warming the triacetyl derivative with methanol for 20 minutes at 50° gave a quantitative yield of the methanol adduct, which was recrystallized from the same solvent, giving white rhombohedral crystals, m.p. 165–167°. Calc. for $C_{10}H_{17}O_4N_3$: C, 49.39; H, 7.04; N, 17.28; CH_3CO, 53.60; CH_3O, 12.77. Found: C, 49.56; H, 7.00; N, 17.06; CH_3CO, 53.63; CH_3O, 12.43%.

2-Iminohexahydropyrimidine

2-Iminohexahydropyrimidine acetate (500 mg) on acetylation under the usual conditions gave an oily product which distilled at 105–110° at 0.01 mm, giving a clear oil which slowly crystallized. Recrystallization from pentane/ether gave colorless thick prisms, m.p. 61–63°, which after drying *in vacuo* analyzed for diacetyl 2-iminohexahydropyrimidine. Calc. for $C_8H_{13}O_2N_3$: C, 52.44; H, 7.15; N, 22.94. Found: C, 52.70; H, 6.91; N, 22.61%. Yield: 371 mg (65%).

Attempts to chromatograph the crude product on neutral alumina or to recrystallize the diacetyl derivative from solvents containing alcohol led to the isolation of monoacetyl 2-iminohexahydropyrimidine, m.p. 187–189°, identified by its infrared spectrum.

2-Imino-5-hydroxyhexahydropyrimidine

The acetate salt (500 mg) was acetylated in the usual manner giving an oily product which distilled at 115–125° at 0.01 mm. The oil crystallized from pentane/ether giving fine white needles, m.p. 117–119°, which analyzed for a triacetyl derivative, with the infrared spectrum indicating O,N,N′ substitution. Calc. for $C_{10}H_{15}O_4N_3$: C, 49.78; H, 6.27; N, 17.42. Found: C, 49.49; H, 6.92; N, 17.62%. Yield: 325 mg (57%).

Recrystallization of the triacetyl derivative from solvents containing alcohol, or chromatography on alumina, caused decomposition. The resulting product could be purified either by sublimation *in vacuo* at 140–150° at 0.01 mm or by recrystallization from methanol/ether, which gave white microprisms, m.p. 230–232°, analyzing for a diacetyl derivative. The infrared spectrum indicated the compound to be the O,N-diacetyl derivative. Calc. for $C_8H_{13}O_3N_3$: C, 48.23; H, 6.58; N, 21.18. Found: C, 48.28; H, 6.53; N, 21.40%.

Methylguanidine

Methylguanidine acetate (500 mg) was acetylated at 100° for only 15 minutes, and the oily product was chromatographed on neutral alumina. Elution with benzene, followed by recrystallization from ether/pentane furnished colorless thick needles, m.p. 80–82°, analysis of which indicated diacetyl methylguanidine. Calc. for $C_6H_{11}O_2N_3$: C, 45.85; H, 7.05; N, 26.74. Found: C, 46.15; H, 6.91; N, 26.99%. Yield: 289 mg (49%). Further elution with 1:1 chloroform/benzene gave a solid, which, after recrystallization from methanol/ether, had m.p. 158–160° and was identified as monoacetyl methylguanidine by comparison of infrared spectra. Yield: 53 mg (12%).

Guanylpiperidine

Guanylpiperidine hydrochloride (500 mg) was converted to the acetate salt by ion exchange, after which it was acetylated with excess acetic anhydride for 30 minutes at 100°. The resulting yellowish oil was chromatographed on Woelm IV neutral alumina yielding only one product which was eluted with 1:1 pentane/ether and gave colorless crystals, m.p. 147–148°, from acetone/hexane. Comparison of its infrared spectrum with that of an authentic sample (1) together with its analysis proved it to be 4-acetamido-6-methyl-2-piperidino-1,3,5-triazine. Yield: 202 mg (56%).

Guanylpyrrolidine

Guanylpyrrolidine acetate (500 mg) was acetylated as described above producing a dark red oil together with some crystals. Treatment with cold acetone removed the oil leaving yellow needle-like crystals, which after recrystallization from methanol/ether had m.p. 173–175° and analyzed for 4-acetamido-6-methyl-2-pyrrolidino-1,3,5-triazine. Calc. for $C_{10}H_{15}ON_5$: C, 54.28; H, 6.83; N, 31.66. Found: C, 54.40; H, 6.25; N, 31.38%. Yield: 203 mg (67%).

N,N'-Dimethylguanidine

Dimethylguanidine acetate (500 mg) was acetylated in the usual manner, giving a clear oily product. Chromatography on neutral alumina caused decomposition so the product was purified by distillation at 100–110° at 0.05 mm, giving a colorless oil which analyzed for the triacetyl derivative. Calc. for $C_9H_{15}O_3N_3$: C, 50.69; H, 7.09; N, 19.71. Found: C, 50.39; H, 7.32; N, 19.92%. (λ_{max} 234 mμ, log ϵ 4.2.) Yield: 444 mg (61%).

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